Introductory overview on existing prioritization schemes and approaches

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Outline

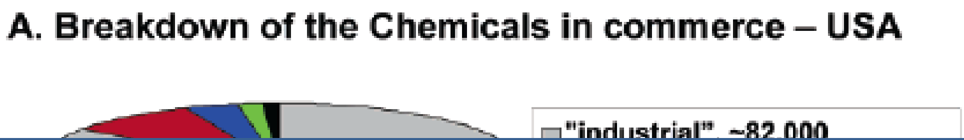
Part I

- Introduction
- The risk assessment process
  - Exposure
  - Effects
- Regulatory issues
- Some Limitations of current approach
- Concluding remarks

Chemicals in the environment

Growing use of chemicals by our technological society:

***CAS:* ~8,400,000** registered compounds (**~240,000** requiring evaluation)
***European Union:* ~100,000** compounds available *[EINECS, 2011].*
***REACH :* ~30,000 compounds (10,000 already registered)**



- These chemicals can potentially reach the environment, being their environmental and health effects difficult to predict.

- Progress achieved on analytical methods allow to quantify many of these compounds (+ their transformation products) at their environmental occurrence levels.

- Pollution in surface waters is considered one of the main causes of impairment of aquatic ecosystems and biodiversity loss

Vörösmarty et al., Nature, 2010, 468, 334
Malaj et al., PNAS, 2014, doi/10.1073/pnas.1321082111

WHAT TO ANALYZE? NOT ALL THAT CAN BE ANALYZED IS WORTH TO BE ANALYZED

SOME KIND OF PRIORITIZATION IS REQUIRED

REGULATORY CONSEQUENCES

Risk Assessment

Prioritization:

Definition:

Methodologies aiming to **identify hazard**s posed by **chemicals** and to **quantify** the associated **risk** concerning:

- **Human health**
- **Ecosystems impairment**

What is risk?

General:

Risk = Occurrence probability × Adverse Effects

Chemical:

Environmental Exposure

Measured concentration (MEC)

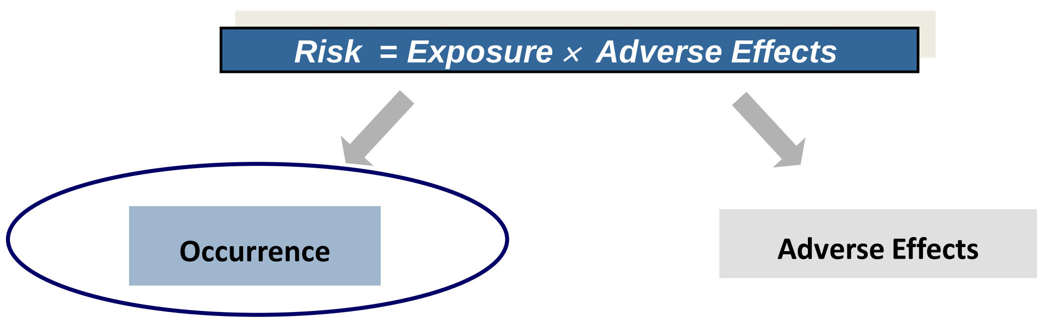
Predicted concentration (PEC)

Adverse Effects

Ecosystem effects

Health effects

Exposure Characterization



Influence Factors

- **Intrinsic to the compound**

  Physico-chemical properties:

  Solubility, Vapor Pressure, Partition Behavior (Kow , Henry, Adsorption Isotherms), Reactivity etc.

- **Environmental conditions**

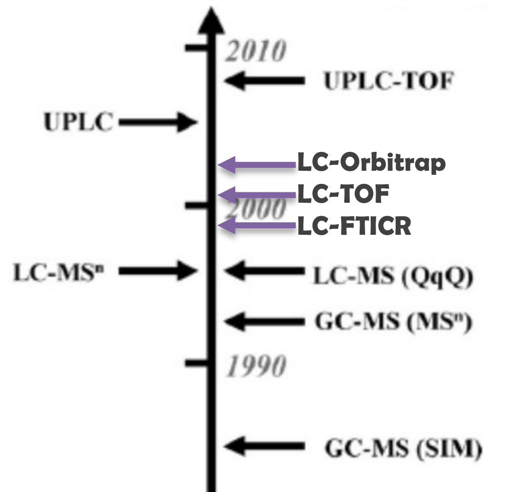
  Temperature, flow, wind velocity, humidity, rainfall, solar radiation etc.

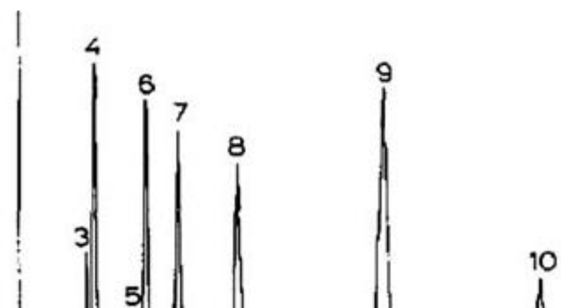
- **Anthropogenic**

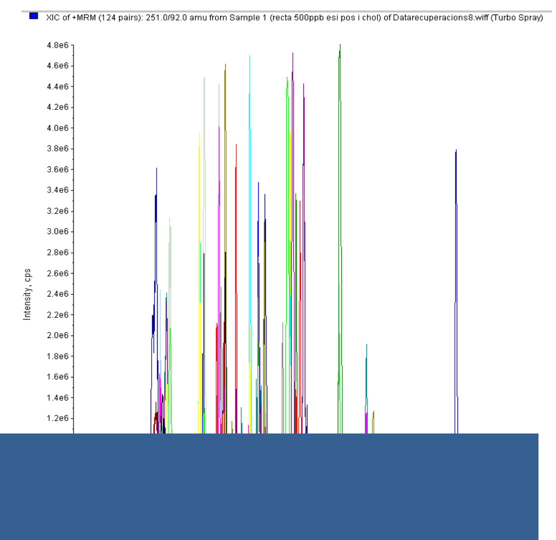
  Volume produced, mode of use, emission factors, waste treatment, recycling and recovery practices etc.

Exposure characterization: Environmental monitoring

Progress in **analytical capabilities** has taken place, thus allowing to identify and quantify majority of emerging compounds at their environmental (trace) levels.







HPLC

TLC

modi
Chro

Improving limits of detection

LC- MS: Every decade roughly 2 orders of magnitude are decreased

1985 → 5 ng ***2005 → 0.1 pg*** ***(factor of 10^4)***

Development of advanced chemical analysis methodologies have led to the “discovery” of

We are nowadays able to reach the environmental levels of many contaminants!

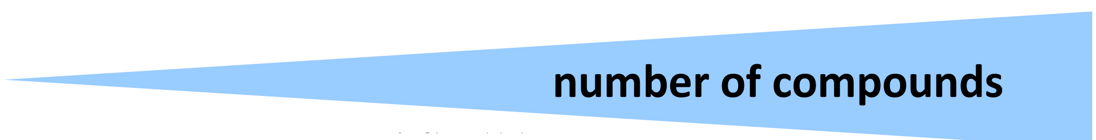
commercially

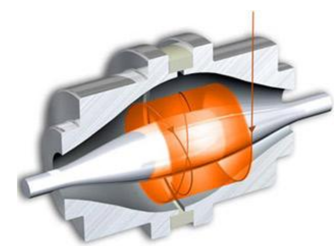
Environmental monitoring strategies

- TARGET ANALYSIS: What you see depends on what you look for (target analysis)
- Those compounds not targeted will elude detection

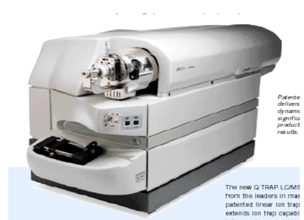
(UHP)LC-MS/MS (QqQ)

Target analysis | **Suspect screening** | **Non-Target screening**





LC-Orbitrap
(UHP)LC-(Qq)TOF



(UHP)LC-MS/MS (QqLIT)

Exposure characterization: Predicting (Modelling)

- Developed in parallel to computation facilities
- Spatial models for chemical fate and transport
  - Multiple 'box' models (equilibrium)

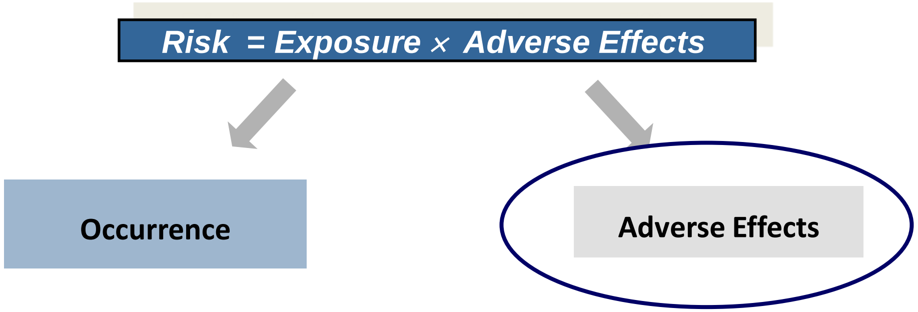
    (Ex.: Fugacity models)
  - Advection-dispersion-reaction time dependent models
  - Spatial explicit multimedia models. ***GIS*** based models

Pistocchi A, Sarigiannis DA, Vizcaino P. Spatially explicit multimedia fate models for pollutantsin Europe: state of the art and perspectives. Sci Total Environ 2010;408:3817–30.

Environmental Expossure Characterization:
Measuring vs. Predictig (Modeling)

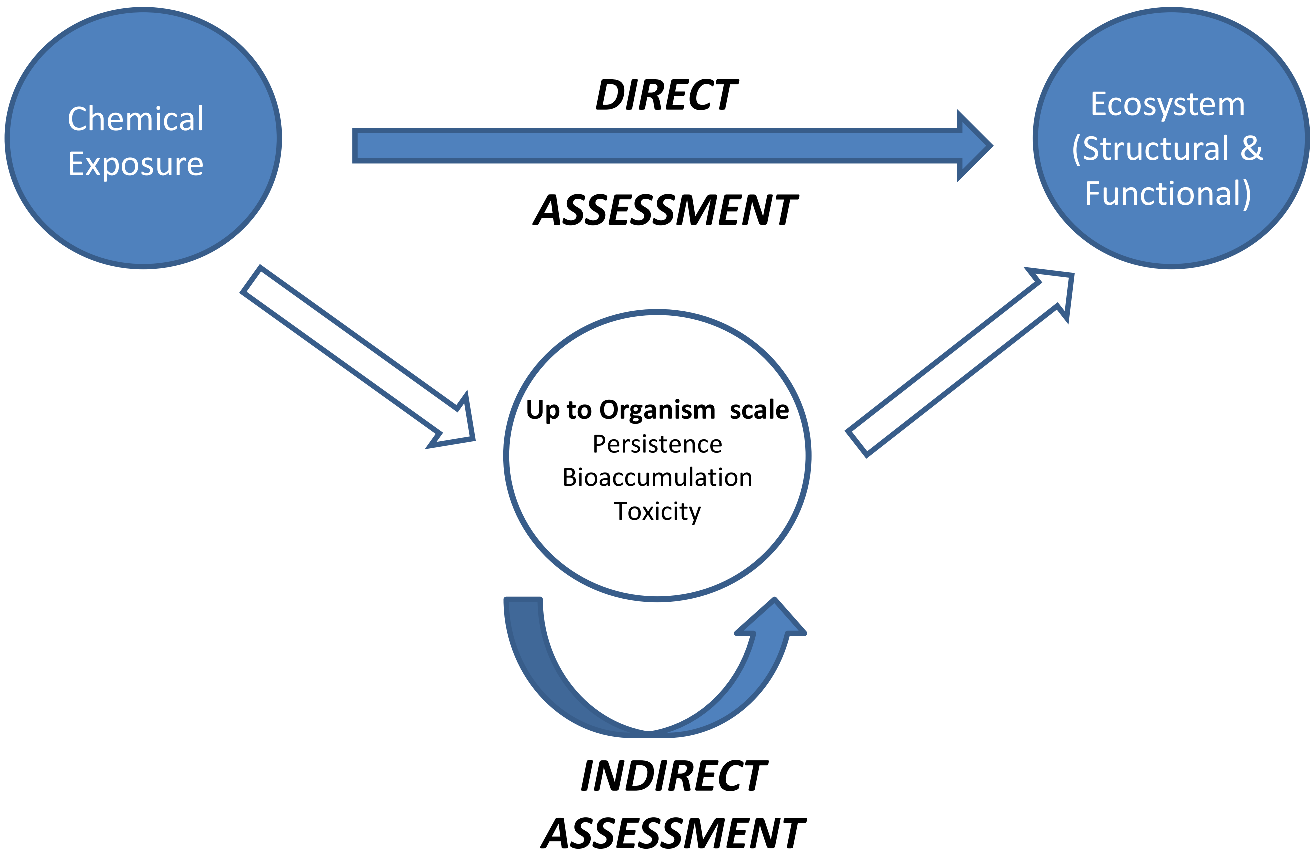
MEC	**Pros**	- Results reflect well reality. - Repeatability and reproducibility of results (good qualified labs)". - Measurements are independent of information/data sources. - Multipurpose analytical methods can cover many compounds on a single run. - Even the best model will ultimately need to be experimentally checked. - Discovery of new emerging contaminants is possible *(Non-target analysis*).
	Cons	- Determination of compounds at very low quantities may be difficult. - Time and space coverage require expensive monitoring campaigns. - Sampling campaigns may miss crucial episodes. - Analytical measurements give a snapshot, rather than a continuous picture. - Expensive analytical equipment and method development. - Target monitoring may miss pollutants: *"you only find what you are looking for"*
PEC	**Pros**	- Very good coverage capabilities on time and space. - Computation equipment is affordable. - Possibility of application to hypothetical scenarios: *"What if?"* - Useful for extrapolations to future (predictions on space and time, even for products not yet in the market). - Simultaneous modelling of many compounds. - Once the model is set up are fast and cheap to use.
	Cons	- Different models may render very different results. - Models are strongly dependent on parameter and data input. - Diffuse sources of pollution may be very difficult to model.

Adverse Effects Characterization



Adverse Effects Characterization:

Two approaches:



Adverse Effects Characterization:

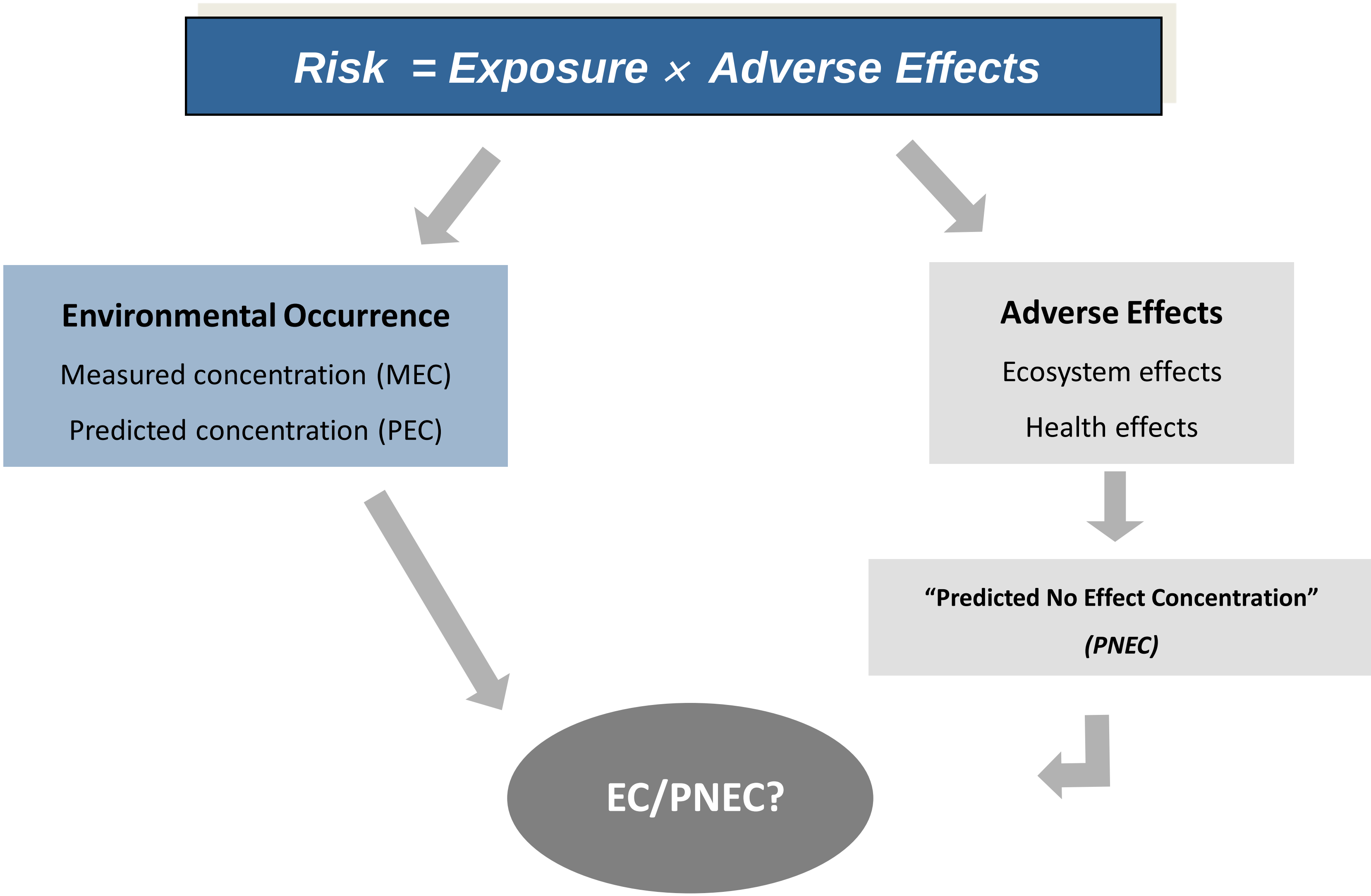
Experimental

- **In vitro (gene, cell, organ response)**
  - Biotransformation assays
  - Gene assays
  - Cell based assays
  - Histopathology
- **In vivo (organism)**
  - **PBT – CMR – ED**
    - **P**ersistence
    - **B**ioaccumulation
    - **T**oxicity
  - **C**arcinogenic – **M**utagenic – **R**eproduction Effects
  - **E**ndocrine **D**isruption
  - Biomarkers
  - Other
- **Population, Community and Ecosystem**
  - Structural and functional indicators

Modelling

- **Property prediction**
  - QSAR, QSPR
  - Read across
  - Computatinal Chemistry
  - ...
- **TKTP models**
- **Survival**
- **Population, Community and Ecosystem**
  - Multivariate analysis models

The classical approach: PEC/PNEC



Classical approach method for ecotoxicology based chemical risk

Ecotoxicological Risk associated to a *single* compound:

- **Hazard Quotients HQ (or Toxic Units, TU):**

$$HQ_i = \frac{c_i}{C(ref)_i}$$

If *HQ* > 1

potential *RISK* situation !

The higher HQ the higher the risk

C(reference site)

Classical approach method for ecotoxicology based chemical risk: Mixture Toxicity

RISK AGGREGATION MODELS:

1) Concentration Addition model (CA):

- All components are assumed to share similar mode of action mechanisms

If $HQ_{mixture}$ > 1
potential *RISK* situation !

(Loewe and Muinschnek, 1926)

2) Independent Action (IA) :

- All components are assumed to act by dissimilar mechanisms
  - Response (i.e., effects) addition

$$HQ_{mixture} = 1 - \prod_{i=1}^{n} \left[1 - HQ_i \right]$$

(Bliss, 1939)

Classical approach : Mixture Toxicity

- When compared to experimental values, often **IA** tends to underestimate whereas **CA** tend to overestimate toxicity
- Even though **IA** and **CA** models are conceptually very different, results are no so much.
- Modes of action are unknown for many contaminants
- **IA** and **CA** should be better seen as defining a kind "window" or "frame" where experimental results fit.
- **CA** ***(expressed as HQ or TU) is often recommended as first tier due to its calculation simplicity***.

[Backhaus T., Faust M. "Predictive environmental risk assessment of chemical mixtures: a conceptual framework". Environ. Sci. Technol. 2012, 46, 2564-2573]

Limitations of the current methodological approach

- **Direct dependence of HQ on ecotoxicity data can be a limitation:**
  - Ecotoxicity data are not available for all compounds
  - Need to use HQ at different trophic levels in order to have a meaningful ecological interpretation
  - Ecotoxicity depends on the organism, time exposure, end point etc. There is a dispersion of data in the literature (data available are not always consistent !)

- **On real samples calculated and experimental toxicities do not always coincide**

- **Due to the additive aggregation (CA), the more compounds we analyze the higher is HQ.**

  HQ values are only comparable for the same analytical profiles.

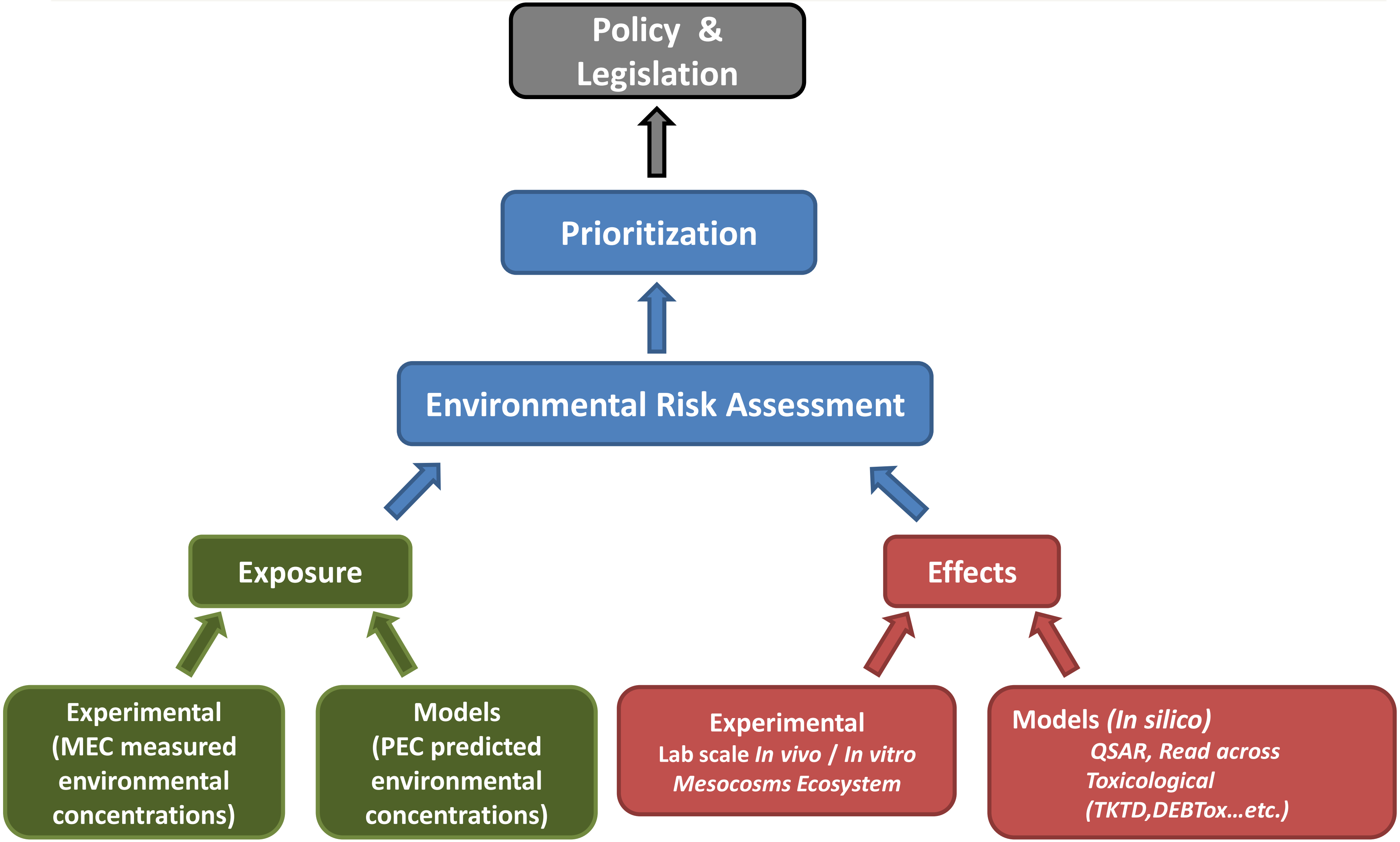
- **The extrapolation from ecotoxicology (experimental or calculated) to ecosystem effects is not straightforward.**

Policy & Legislation : the ultimate goal of Prioritization

Priority/ranking lists of compounds are essential to legislations concerning environmental and health risks related to chemicals

- **International Conventions:**
  - Oslo-Paris Convention for the protection of the marine environment of the North-East Atlantic (OSPAR 1992)
  - Stockholm Convention on Persistent Organic Pollutants (2001)
- **Water Framework Directive: *Directive 2000/60/EC***
  - Decision No 2455/2001/EC *[partially repealed]*
  - Directive 2008/105/EC *[partially repealed]*
  - Directive 2013/39/EU
- **REACH: Regulation (EU) No.1907/2006**
- **Plant Protection Products (PPP): Regulation (EC) N. 396/2005**
- **Biocidal Products: Regulation (EU) No. 528/2012**

Environmental Risk Assessment process leading to legislation



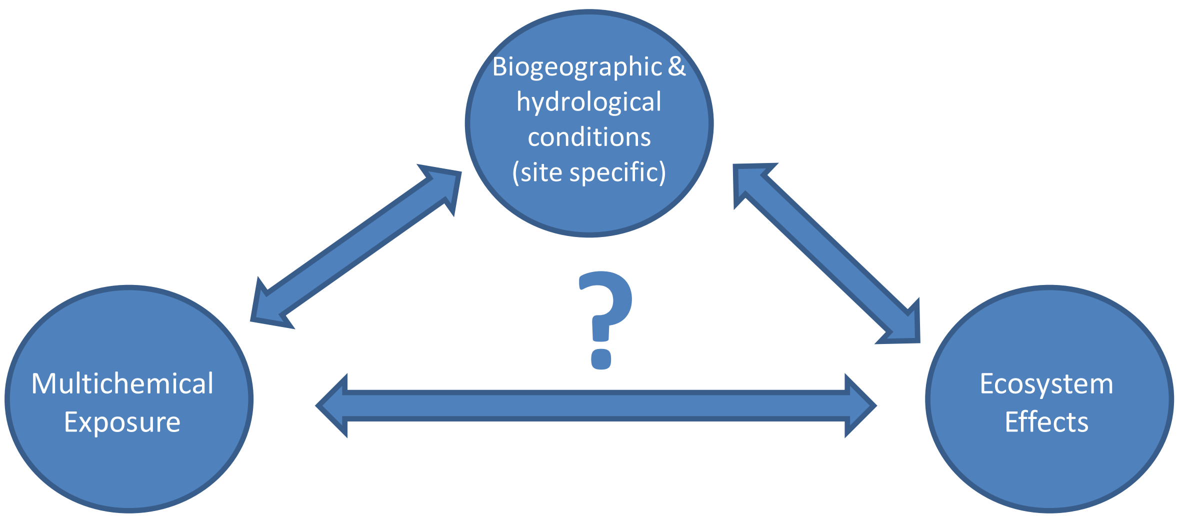
D. Guillén *et al*. Sci. Tot. Env. 440(2012) 236-252

Concluding Remarks: The Challenge

...Our task ahead:

In short, and quoting A.J. Hendriks (2013) :

"How to deal with > 100,000 Substances, Sites and Species: Overarching Principles in Environmental Risk Assessment". A. J. Hendriks, Environ. Sci. & Technol. 2013, 47, 3546-3547



... and how to translate into sound policy, legislation and management practices in due time

Thank you for your attention !

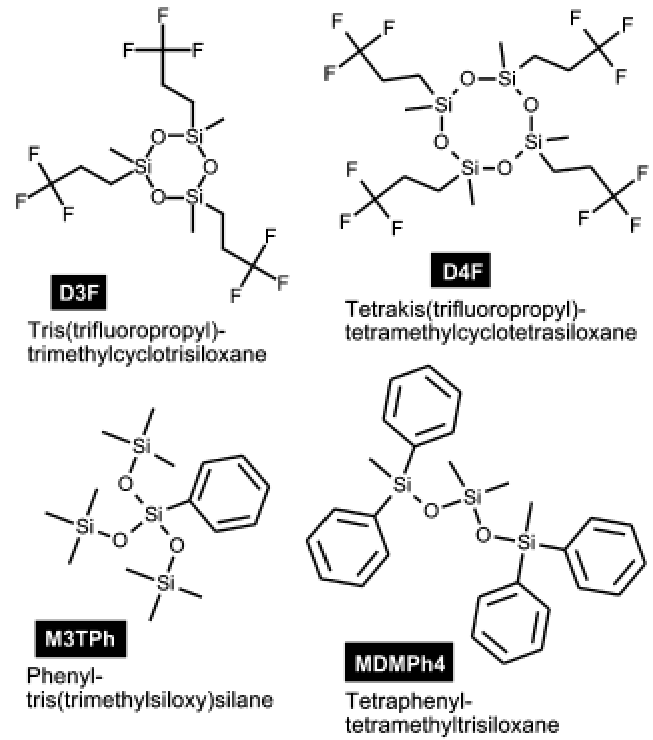
Part II

Some open questions, comments & challenges

Exposure: Prospective on new pollutants

- New emerging families of chemicals of concern:
  - DBPs, Perfluorinated, organosilicon etc.

    Muir DCG, Howard PH. Environ Sci Technol 2006;40:7157–66.
    Mc Lachlan et al. Environ. Sci. Technol. 2014. dx.doi.org/10.021/es5010544
    Richardson SD, Ternes TA. Anal Chem 2011;83:4614–48



- New materials
  - Nanomaterials, microplastics etc.

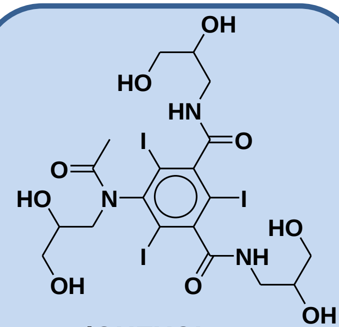
    Wiesner et al.Environ .Sci. Technol . 2006;40:4336–45

- Transformation products

  Escher and Fenner. Environ. Sci. Technol.2011, 45, 3855-3847

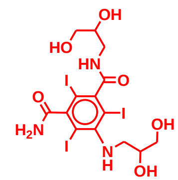
Mc Lachlan et al. Env. Sci. Technol. 2014.
dx.doi.org/10.021/es5010544

IOHEXOL: Phototransformation processes

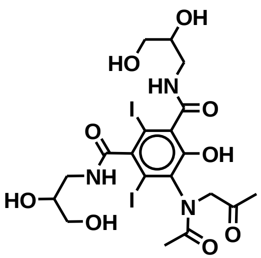


IOHEXOL

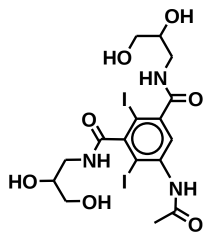
UPLC-(+)ESI-Q Exactive-MS



$C_{14}H_{19}I_3N_3O_6^+$
Exact Mass: 705.8402
Mol. Wt.: 706.03

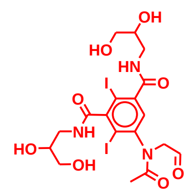


$C_{19}H_{26}I_2N_3O_9^+$
Exact Mass: 693.9753
Mol. Wt.: 694.2328

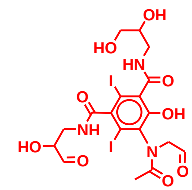


$C_{16}H_{22}I_2N_3O_7^+$
Exact Mass: 621.9542
Mol. Wt.: 622.1702

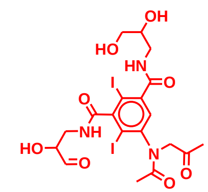
28



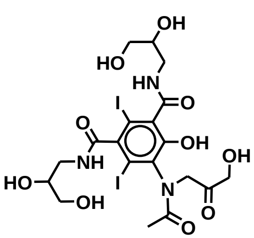
$C_{18}H_{24}I_2N_3O_8^+$
Exact Mass: 663.9647
Mol. Wt.: 664.2069



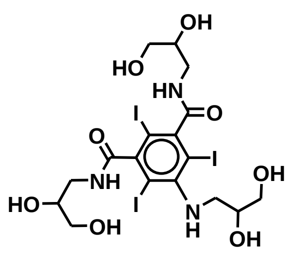
$C_{18}H_{22}I_2N_3O_9^+$
Exact Mass: 677.944
Mol. Wt.: 678.1904



$C_{19}H_{24}I_2N_3O_8^+$
Exact Mass: 675.9647
Mol. Wt.: 676.2176

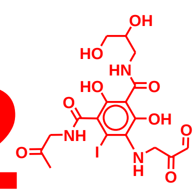


$C_{19}H_{26}I_2N_3O_{10}^+$
Exact Mass: 709.9702
Mol. Wt.: 710.2322

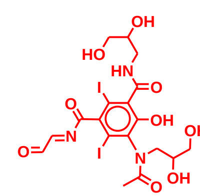


$C_{17}H_{25}I_3N_3O_8^+$
Exact Mass: 779.877
Mol. Wt.: 780.1086

102



$C_{17}H_{21}IN_3O_9^+$
Exact Mass: 538.0317
Mol. Wt.: 538.2673



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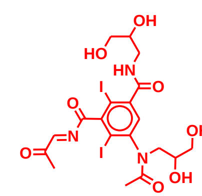

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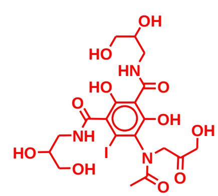
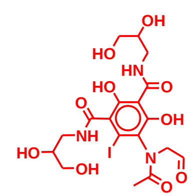
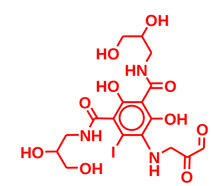
Mol. Wt.: 676.2176



$C_{19}H_{27}IN_3O_{11}^+$
Exact Mass: 600.0685
Mol. Wt.: 600.3351

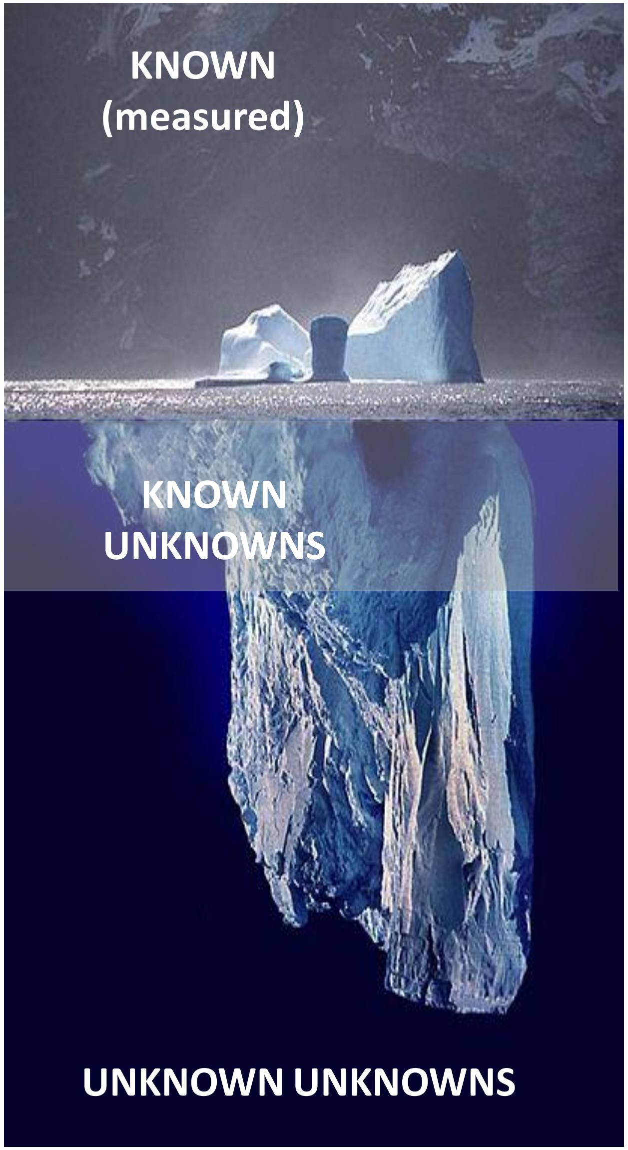


$C_{18}H_{25}IN_3O_{10}^+$
Exact Mass: 570.0579
Mol. Wt.: 570.3091



$C_{17}H_{23}IN_3O_{10}^+$
Exact Mass: 556.0423
Mol. Wt.: 556.2825

Limitations of the current methodological approach



Exposure:

- *Compounds occur in the environment as complex mixtures*
- *We actually ignore a large part of them*

The range of contaminants identified in a sample is just a portion of those present, and their significance in term of risk is essentially unknown !

Example of a Pareto distribution

Vilfredo Pareto (1848-1923) italian economist who stated in 1906 the so called “**80:20**" (*Pareto Principle*)

Sociology: “20 % of people own 80% of wealth”

Quality Control: “20 % of causes account for 80% of failures”

“Few compounds are responsible for most of the risk”

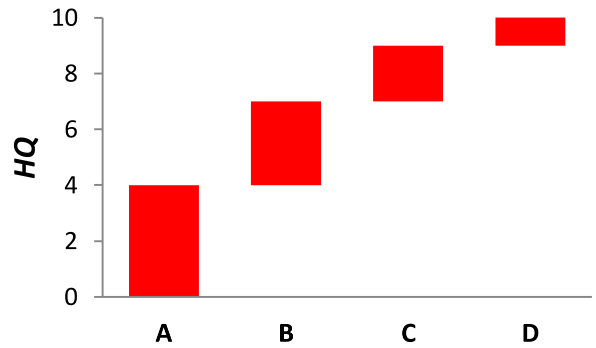
5 chemicals explain 80% of the risk.
Efficient management needs to focus on these chemicals

W. Brack et al. 2013. Solutions Project kick-off Presentation

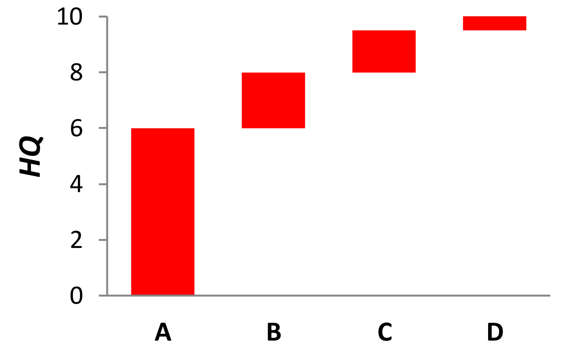
Complexity embedded within the HQ distribution:

Assuming valid the *CA* model and

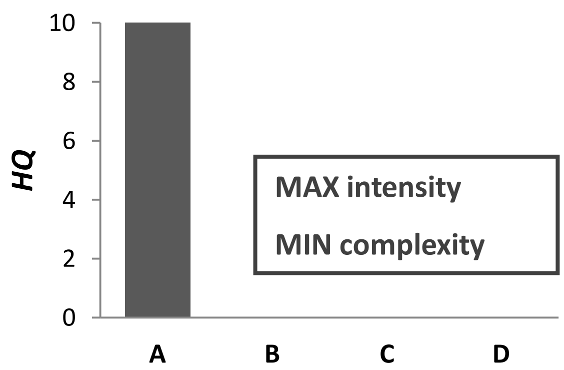
Given a certain value of *HQ*, it may be obtained from different distributions



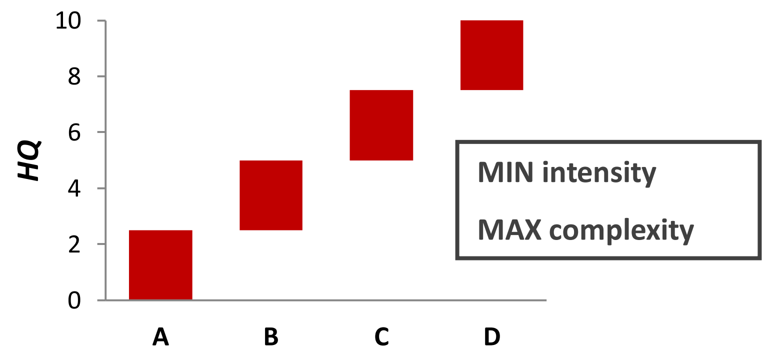
HQ = 4 + 3 + 2 + 1 = 10



HQ = 6 + 2 + 1.5 + 0.5 = 10



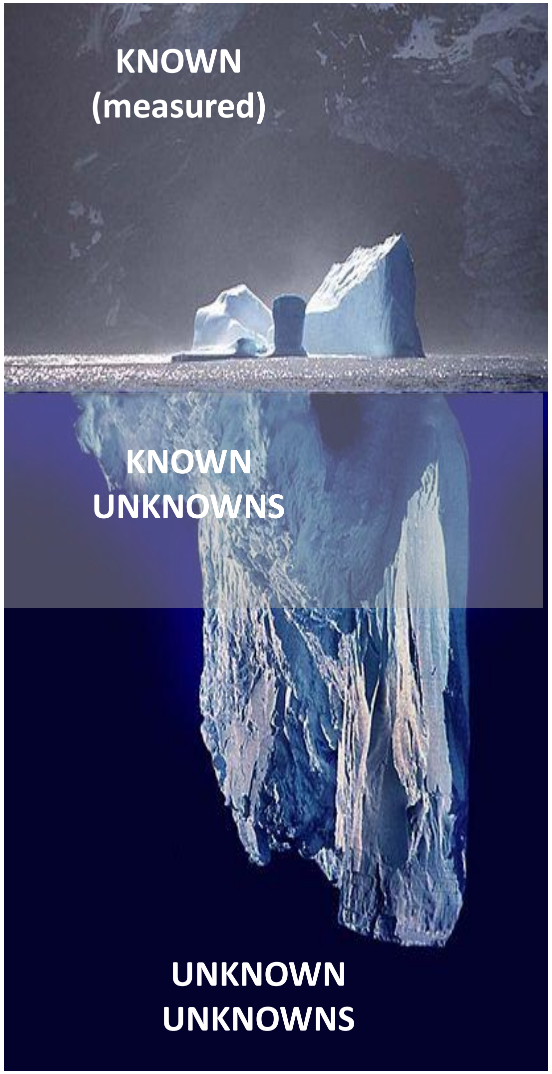
HQ = 10 + 0 + 0 + 0 = 10



HQ = 2.5 + 2.5 + 2.5 + 2.5 = 10

Same HQ but different pattern distributions

Coping with the "hidden part of the Iceberg":
Statistical characterization of multichemical environmental mixtures



Hypothesis:

- We assume that the "known part" is a **representative statistical** sample of the whole system (the usual process in statistical inference).

Process:

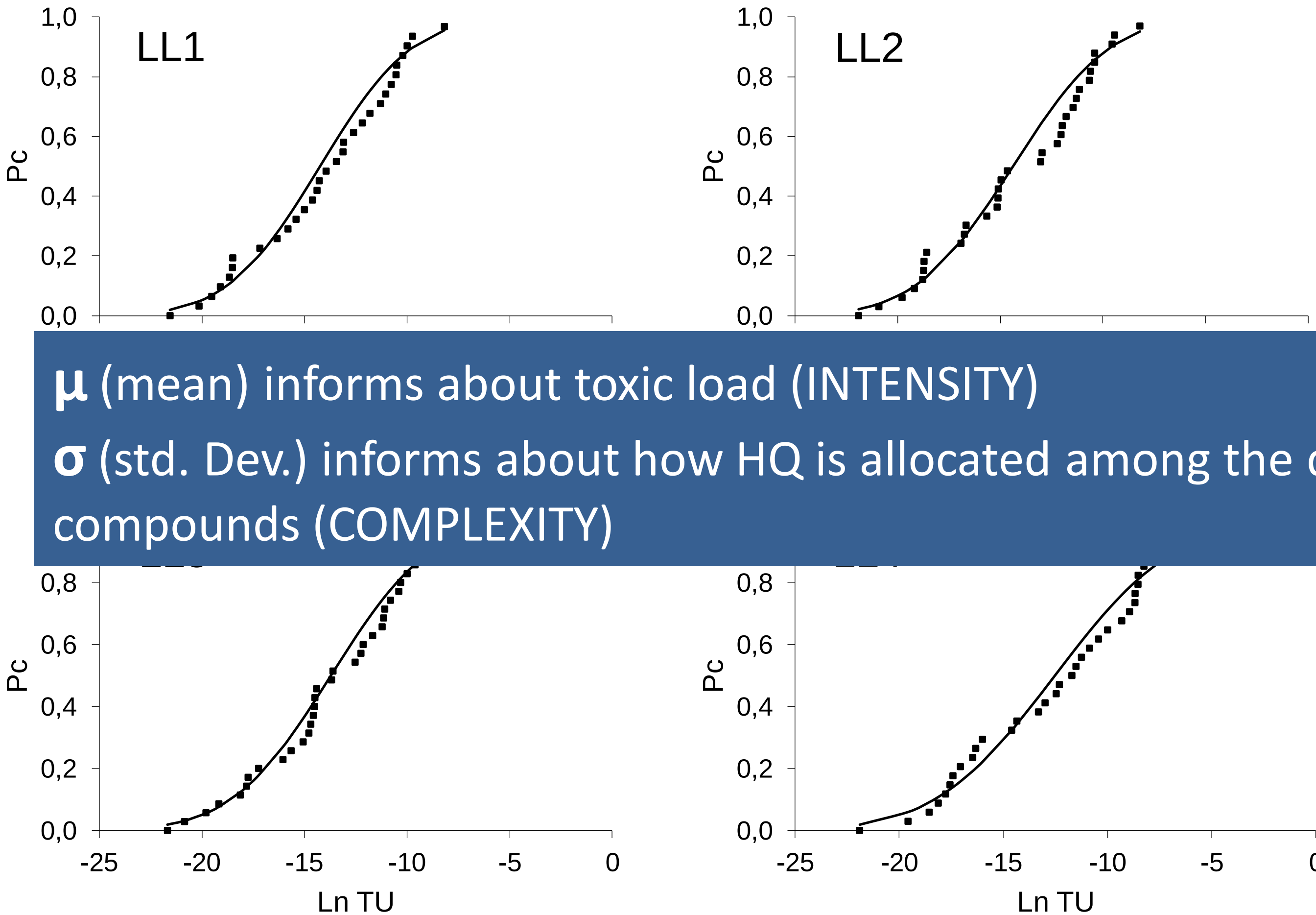
- The **probability density function** of HQ of each sample is obtained
- Parameters characterizing the pdf provide information about the whole sample

Comments:

- We argue that the inclusion of more compounds eventually analyzed would not alter the statistics to a great extent.
- The assumption seems reasonable at least for those unknown compounds showing environmental levels and structural features similar to those analyzed, such as metabolites and transformation products.
- Using the **probability density function** and some statistical criteria, it is possible to prioritize the compounds with highest risk (HQ) contribution

The Llobregat river basin case study

Some examples of Log-nomal distributions for TU(Daphnia)



μ (mean) informs about toxic load (INTENSITY)

σ (std. Dev.) informs about how HQ is allocated among the different compounds (COMPLEXITY)

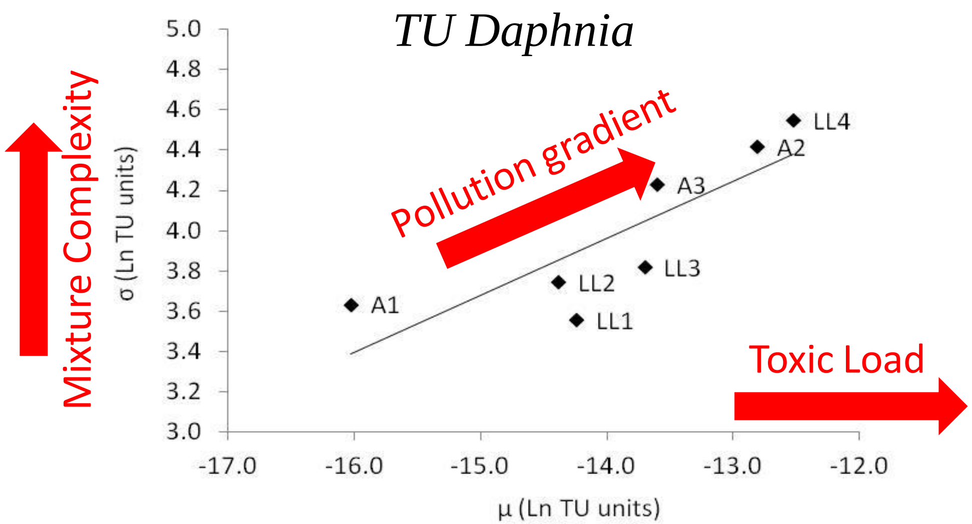
51 organic microcontaminants:

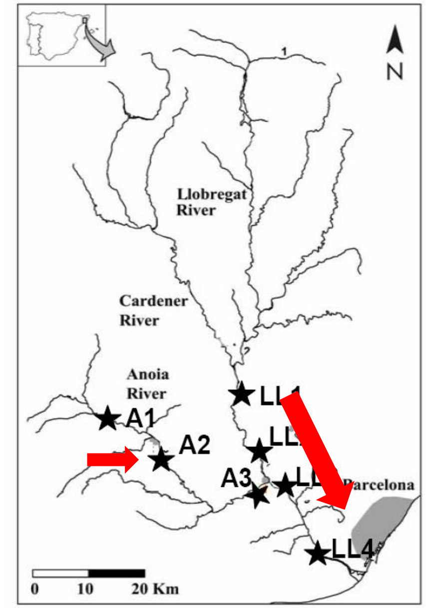
22 pharmaceuticals

29 pesticides

Ginebreda et al., Sci. Tot. Env., 468-469, (2014), 715-723

The Llobregat river basin case study





Assessment of pollution risk vs. *Daphnia* in the different sites as a function of the statistical parameters **μ** and **σ**

COMPOUND PRIORITIZATION (vs. *Daphnia*)

Diazinon, Fenitrothion, Linuron

Diclofenac, Gemfibrozil, Ibuprofen, Erythromycin, Clofibric

From ecotoxicity to Ecosystem effects

- Bridging the gap between chemical exposure, ecotoxicity and whole ecosystem effects.
- Functional & structural aspects of ecosystems need to be covered
- Joint effect of pollution and other stressors (hydrologic, hydromorphologic etc.)
- Different taxa show different sensitivities and vulnerabilities
  - SPEAR

    Von der Ohe and Liess. Environ. Toxicol. Chem. 2004, 23, 150-156
  - SSD
  - msPAF
- Interrelation of species may lead to indirect effects (network character): shifting points

Priotization in practice: Management issues

- Compounds to be monitored: general '*a priori*' lists *vs* basin taylored list
  - Different biogeographical characteristics (biophysical, land use, socio-economic conditions) may involve different priority substances
- Prioritization should cover all relevant environmental compartments
  - Water, sediments, suspended solids, biota
  - Different lists
- Extent (intensity) but also frequency of excedance

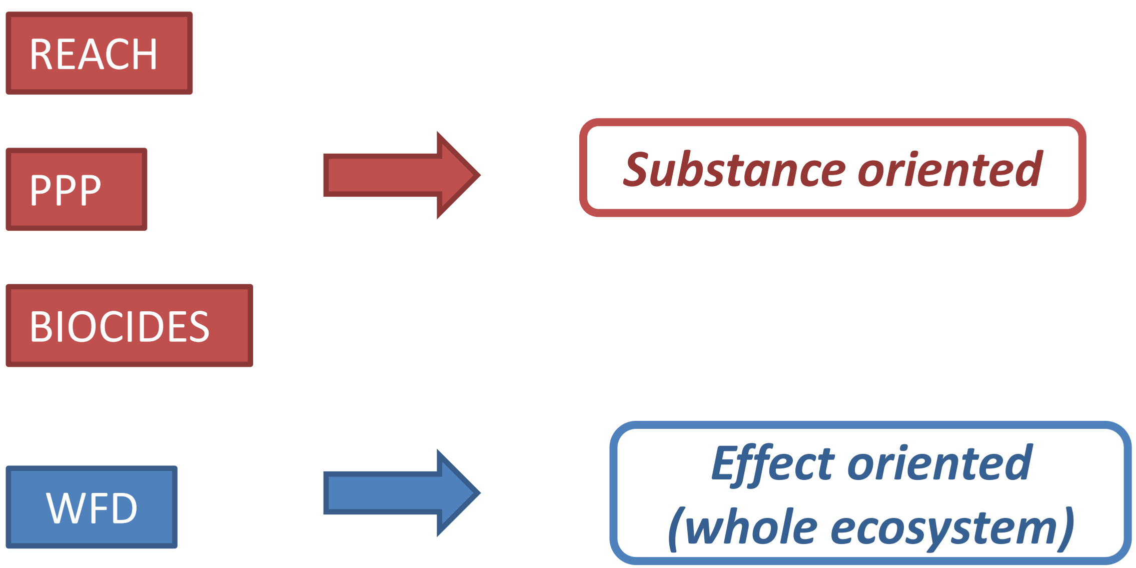
Von der Ohe et al. Sci. Tot. Env. 2011, 409(11), 2064-2077

- Space and time coverage

Prioritization strategies

- **Substance-oriented *vs.* effect-based prioritisation approaches?**

The answer should be mostly dictated by the legislation to which the prioritization exercise is providing support:

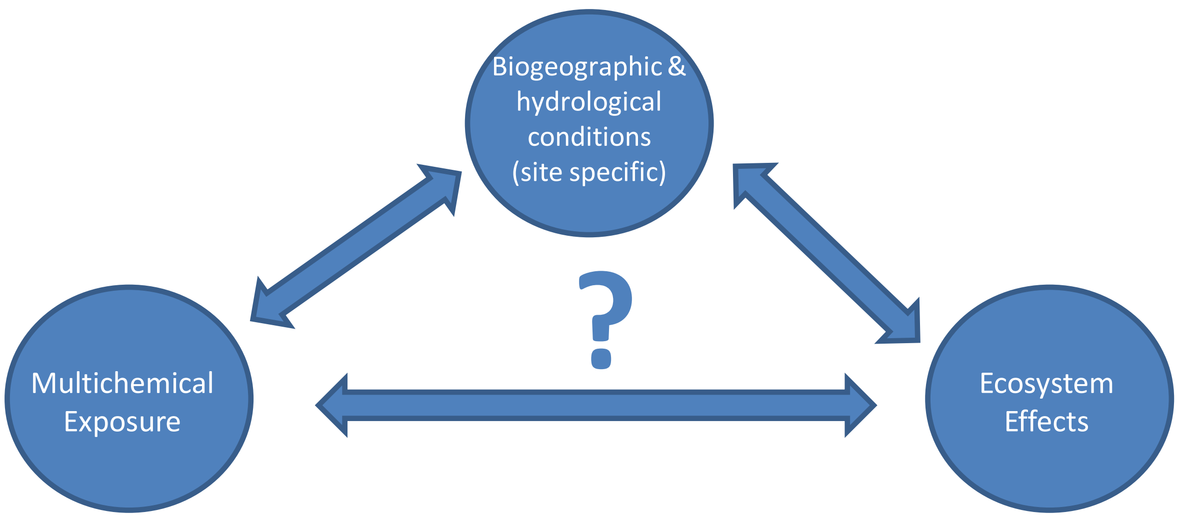


Concluding Remarks: The Challenge

...Our task ahead:

In short, and quoting A.J. Hendriks (2013) :

"How to deal with > 100,000 Substances, Sites and Species: Overarching Principles in Environmental Risk Assessment". A. J. Hendriks, Environ. Sci. & Technol. 2013, 47, 3546-3547



... and how to translate into sound policy, legislation and management practices in due time

Thank you for your attention !

norman

solutions

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