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FACULTÉ DE PHARMACIE

Health risk assesment process for chemicals

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Health Risk Assessment (HRA) - Context

- Often for low-dose but multiple and chronic exposure problems
- With low individual risks, but strong collective impacts!
- Pathologies that are often non-specific and multifactorial and can occur over the long term
- Lack of or incomplete knowledge about the effects of a type of pollution
  - Pollutant little studied, latency...
  - Future pollution
- A need to decide
- A need to inform (social pressure)

A PREDICTIVE APPROACH IN PUBLIC HEALTH

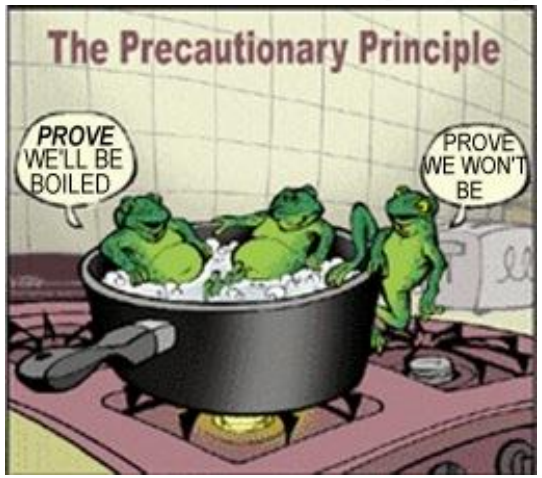
... as little harm as possible in a situation of uncertainty!

Health Risk Assessment (HRA) - Objective

Definition **"Using (scientific) facts to define the health effects of exposure of individuals or populations to hazardous materials or situations"** *(US National Research Council, 1983)*

Purpose: Alternative to "all or nothing" decisions

1. **Apply the PRECAUTIONARY PRINCIPLE**
   "The lack of certainty should not delay the adoption of measures"

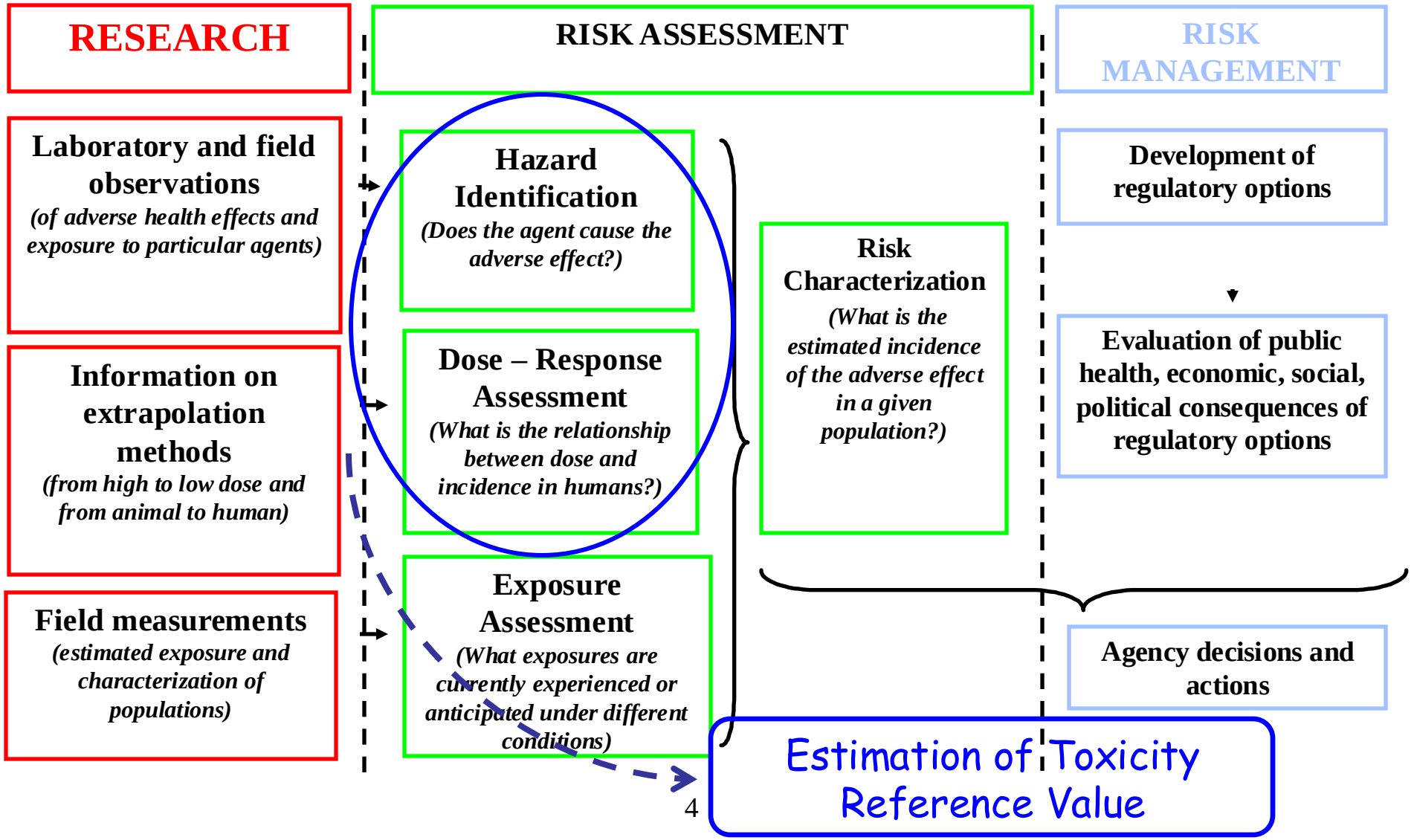


2. **Structure knowledge by associating it with its uncertainties**

3. **Size the intervention based on risk:**
   - Clean-up targets, relevance
   - Screening relevance

4. **To present to the various parties, explicitly, the elements of analysis on which decision-making can be based**
   - Authorization of products, activities or substances
   - Maximum allowable concentrations, emission limits
   - Occupational Exposure Limit Values

Health Risk Assessment (HRA) - Framework



(US National Research Concil, 1983)

Health Risk Assessment (HRA) – A four step process

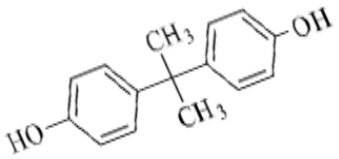
- (1) Hazard identification
- (2) Dose-response assessment
- (3) Exposure assessment
- (4) Risk characterization

HRA – (1) Hazard identification

- 1) Define the NATURE OF THE HAZARDOUS AGENT that may pose health hazards at environmentally relevant concentrations
  - Biological: bacteria, viruses, parasites …
  - Physical: ionazing radiation, temperatures, noise, vibrations
  - Chemical: particulate or gaseous, inorganic or organic

  ➡ **Method presented here**

- 2) Describe the effects that may occur in humans, i.e. the HAZARDOUS POTENTIAL of chemical, physical or biological agents



Qualitative step

(1) Hazard identification - Definitions

- Hazard = Adverse health effect
  - «Adverse health event or any toxic effect: change in the appearance of an organ or transient or permanent impairment of its functions, behavioural disorders, fetal malformation or growth retardation, genetic mutation, benign or malignant tumour, at worst, death »

- Hazard identification
  - « Identification of the undesirable effects that a substance is intrinsically capable of causing in humans »

DANGER ≠ RISK

Interested in the intrinsic properties of the molecule, the product, the material

Interested in properties under the conditions of use

⇒ Review of the benefit-risk ratio

e.g.: oxygen

(1) Hazard identification - Determinants

- Depending on the INTENSITY and DURATION of contact with the organism

  - Acute effect
    - related to a short exposure (from a few seconds to a few days) but at a high dose
    - immediate and disappear when the exposure ends
    - e.g.: cough, mucous membrane irritation, neurological disorders, diarrhea

  - Sub-chronic or chronic effect
    - related to prolonged low-dose exposure
      - **Sub-chronic:** from a few days to one year or more years
      - **chronic:** from a few years to a lifetime
    - e.g.: organ damage, cancers, blood diseases

(1) Hazard identification - Determinants

- Depending on the gateway to the human body (the ROUTE of exposure) (oral, dermal, respiratory)
  - Local effect
    - directly on tissues in contact with the substance (irritation, skin cancer...)
  - Systemic effect
    - if the substance acts on organs distant from the point of contact

- According to the intrinsic characteristics of the exposed SUBJECT
  - Immunological sensitivity
  - Biological capacities of detoxification and repair of aggressions

(1) Hazard identification – Data collection

- **Physical and chemical properties**
  - Chemical formula, structure, solubility
    - ⇨ behaviour in the environment: bio-persistence, degradation, metabolism (ADME)

- **Toxicological properties**

Interest: to establish the risk incurred by humans, before any contact with the agent under study

  - *In vitro* studies (organs, cells, cell fractions)
    - Cytotoxicity
    - Genotoxicity, etc…
  - *In vivo* studies (whole animal) : chronic toxicity
    - Reprotoxicity
    - Carcinogenicity …

Bibliographical work

- **Epidemiological data**

(1) Hazard identification - Epidemiological studies

- Objective of epidemiological studies
  - To assess the distribution of disease in a human population and the FACTORS that contribute to it
  - Attempt to establish an ASSOCIATION between various factors (place of residence, lifestyle, exposure to certain substances, etc.) and the occurrence of diseases

→ Identify factors that affect the likelihood of disease occurrence

Epidemiology ≠ HRA

↳ Not a risk prediction tool!

(1) Hazard identification - Epidemiological studies

- Observational science in a population
  - Is there an association between risk factor and disease?
    - The risk of lung cancer in smokers is 18 times higher than in non-smokers (RR=18)
  - Importance of this risk factor in public health? (impact measure)
    - Lung cancer: 123/100,000 smokers
- Cohort study
  - Evaluation of individuals selected on the basis of their exposure to a target agent, registration over the time of the occurrence of an event to determine the rate of those who develop the disease
- Case-control study
  - Both disease-free individuals and thoses with diseases are selected, and the two groups are then compared to determine key exposure factors

(1) Hazard identification - Epidemiological studies

- E.g. : ELFE Cohort (*Etude Longitudinale Française depuis l'Enfance* - French Longitudinal Study since Childhood)
  - Representative cohort of 20,000 children, born in 2011, born during 4 periods of 6 days each
  - Follow-up from birth to adulthood
  - Analyzes the child's physical, psychological and social development
  - Multidisciplinary project with health, health-environment and social-demographic dimensions
  - multi-institutional project: public health french agency, family allowances, ...
- Biological sampling in maternity wards
  - Cord blood: lead
  - Maternal serum: PCB-dioxins-furans, perfluorinated/polybrominated
  - Mother's urine: cretatinin, phthalates, bisphenol A, pesticides, metals...
  - Mother's hair: mercury

(1) Hazard identification - Epidemiological studies

- Advantages
  - Avoid the uncertainty related to the transposition to humans of a toxicity only proven in other species
  - Quantification of the impact of a risk factor
  - Consideration of pollutant mixtures

- Disadvantages
  - Data often established in occupational settings (high and controlled exposures)
  - Low, unstable RRs that require statistical power
  - Pathologies often multifactorial (sensitivity to confounding factors)
  - Difficulties in measuring exposure
  - Length, difficulty and cost of studies
  - Unsuitable for forecasting
  - Studies with conflicting results (bias)

(1) Hazard identification - 2 key disciplines

	Epidemiology	*In vivo* toxicology	*In vitro* toxicology
Relevance	Strong	Uncertain	Uncertain
Exposure measurement	Difficult	Good	Good
Third-party control	Difficult	Good	Good
Judgement of causality	Difficult	Good	Good
Population size and power	May be important	Limited	-
Sensitivity to low doses	Low	Low	Good
Specificity	Stress effect	Uncertain	Strong
Mechanism of action	Ignored or indirectly known	Directly studyable	Partial but good
Cost	High	High	Low
Situation in relation to the prevention	Downstream	Upstream	Upstream

(1) Hazard identification - Summary of difficulties

- Relevance for low doses
- Cases of mixing of toxic substances
- Degradation by-products
- Sensitive populations
- Power of studies
- Not always data in humans or even in animals

(1) Hazard identification – In practice

- If a toxic molecule is responsible for several hazards and reaches different organs for the same route and intensity of exposure
  - Retain the effect that occurs at the lowest dose and/or the most severe hazard (tumor or hematological malignancy)

- If epidemiological studies are lacking
  - Suspect a harmful effect on humans if the substance has been shown to be dangerous, in animal studies, on one or more species considered to be as sensitive as humans

- If there is a total lack of knowledge about a substance
  - Schedule appropriate studies

(1) Hazard identification – In practice

- Literature review and consultation of specialized databases

  - The French National Agency for Food, Environmental and Occupational Health & Safety (*Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail*, ANSES)
  - French health authority (*Santé Publique France*, SPF)
  - National Agency for the Safety of Medicines (*Agence Nationale de Sécurité du Médicament*, ANSM)
  - Official Journal of the European Community (OJEC)
  - International Agency for Research on Cancer (IARC)
  - World Health Organization (WHO)
  - Health Canada
  - American Environmental Protection Agency (US-EPA, Cal-EPA)
  - Agency for Toxic Substances and Disease Registry (ATSDR)
  - Integrated Risk Information System (IRIS)
  - Toxicology Excellence for Risk Assessment (TERA)
  - Hazardous Substances Data Bank (HSDB)
  - Institut National de l'Environnement et des Risques (INERIS)
  - RijksInstituut voor Volksgezondheid en Milieu (RIVM)
  - …

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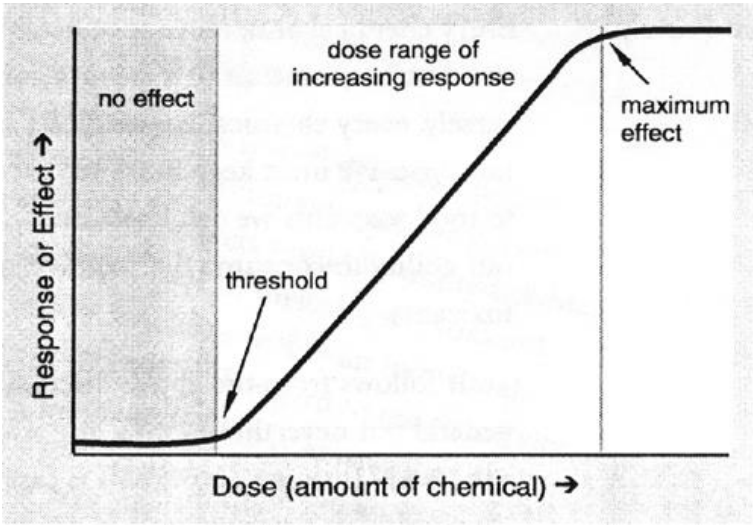
HRA – (2) Estimation of dose-response relationship

- Choice of toxicity reference value (TRV)
- Building TRV: Extrapolation from high to (very) low doses
  - *« nothing is poison, everything is poison, what makes poison is the dose »*
    (Paracelse, 16th century)

DOSE-RESPONSE relationship	≠	**DOSE-EFFECT relationship**
Relationship between a level of exposure and the observed response (incidence) for a given effect		Relationship between the level of exposure and the observed effect (which may vary in severity)



Quantitative step

(2) Dose-response – Definitions

- Relation dose – response relationship
  - « estimating the relationship between the dose of a hazardous substance in contact with the body and the occurrence of a toxic effect »

- Toxicity reference value (TRV)
  - **« estimating of the amount of substance to which an individual can theoretically be exposed for a given period of time without any finding of adverse effect on the body »**
  - It is defined for a **given exposure pathway, exposure time and type of effect**
  - Results from animal toxicological or epidemiological studies
  - Established by national and international specialized agencies
  - Two types of value:

SAFE DOSE

TRV with a threshold dose

TRV without a threshold dose

(2) Dose-response – Objectives of reference value use

- Toxicity Reference Value (TRV)
  - for **impact studies** ➔ installation classified for the protection of the environment (ICPE) (anticipation)
  - for **risk assessment works** ➔ risk reduction strategy
  - **for investigation studies** ➔ decision support in degraded local situations (management at a given time or retrospectively)
- Occupational Exposure Limit Value (OELV)
  - values designed **to protect workers** exposed to chemical substances from possible pathologies of occupational origin. They are designed to allow the monitoring of **work atmospheres** for **prevention purposes**
- Guide value (GV)
  - « concentrations in air or water of a chemical substance below which no health effects or adverse health effects are expected for the general population » ➔ **environmental quality** (**Indoor Air Guide Values, limit value in drinking water**)

Risk assessment, prevention or monitoring

(2) Dose-response – TRV with a threshold dose

- Threshold effects (deterministic effects)

  - «Acute effects, chronic effects, but non-carcinogenic, (carcinogenic) non-genotoxic, non-mutagenic, whose severity is proportional to the dose»

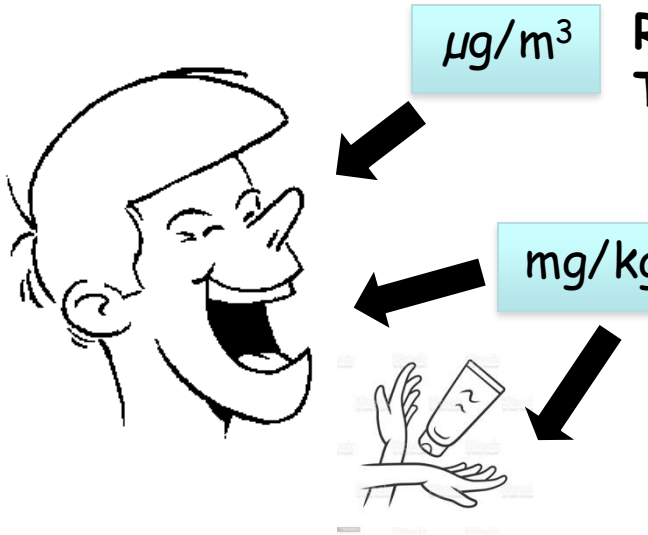
  - The effect only occurs if a certain dose is reached and exceeds the detoxification, repair or compensation capacities of the organism. Above the dose, the intensity of the effects increases with increasing dose

- TRV with a threshold dose

  - « Estimation of the dose of exposure to a chemical substance that is theoretically without adverse health effects, for different durations of exposure »

(2) Dose-response – TRV with a threshold dose

- Expression of TRV according to routes and organizations



µg/m³

RfC (US-EPA), **MRL** (ATSDR), **AAC** (WHO),
TCA (RIVM), **AC** (Health Canada), **REL** (OEHHA)

mg/kg/day

RfD (US-EPA), **MRL** (ATSDR), **TDI** (WHO),
ADI (WHO, RIVM, Health Canada), **REL** (OEHHA)

*RfC (**Reference Concentration**) ; RfD (**Reference Dose**) ; REL (**Reference Exposure Level**) ;*
*MRL (**Minimum Risk Level**) ; ADI (**Acceptable Daily Intake**) ; TDI (**Tolerable Daily Intake**) ;*
*TCA (**Tolerable Concentration in Air**) ; AAC (**Allowable air concentration**) ; AC (**Allowable Concentration**) ; AAC (**Acceptable Air Concentration**)*
OEHHA (California Office of Environemental Health Hazard Assessment)

(2) Dose-response – TRV with a threshold dose

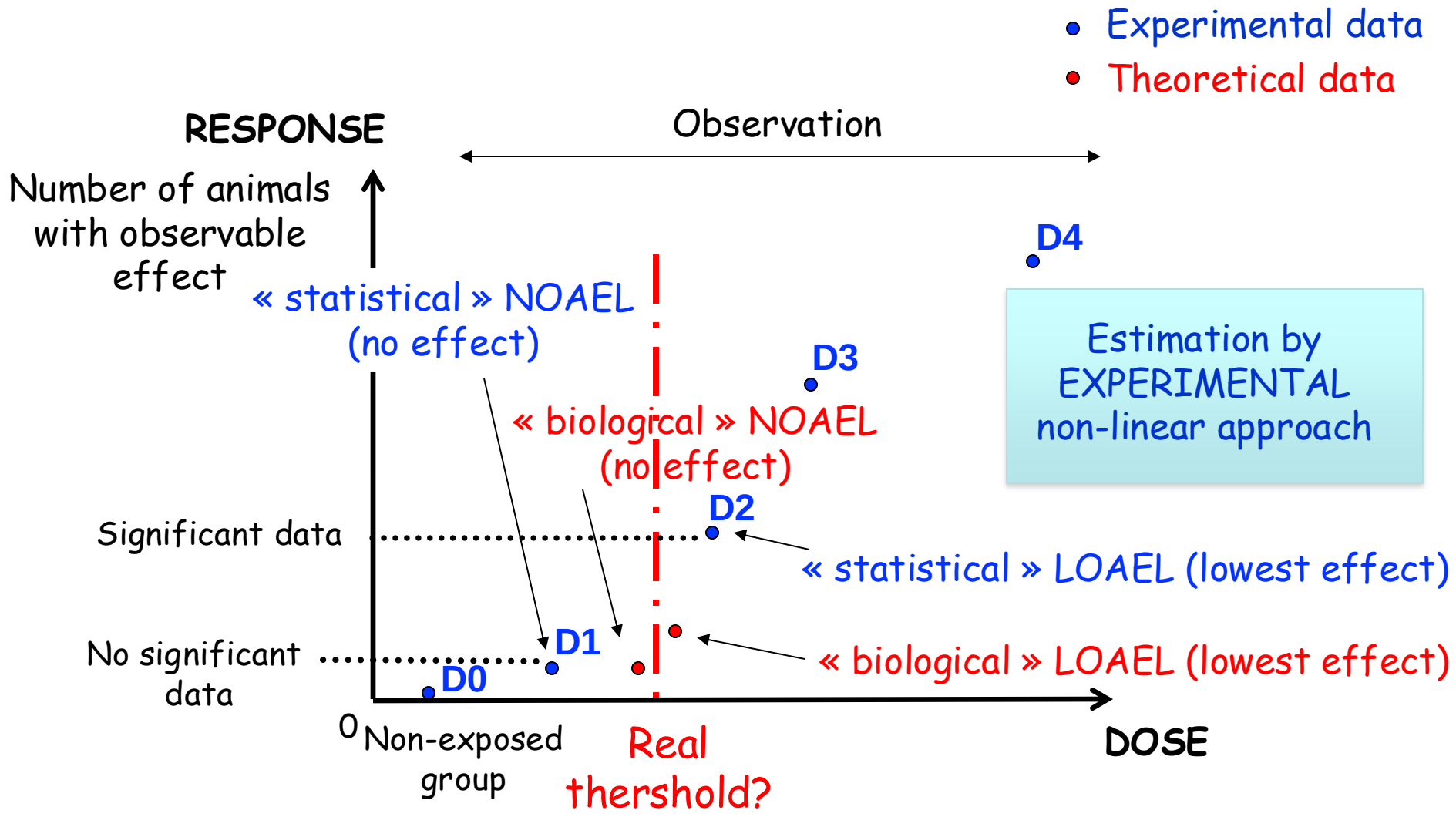
- How to estimate a TRV with a threshold dose ?
  - 1) Determining a critical dose (NOAEL, LOAEL, BMD)
    - To make an approximation of the toxicity threshold observed in the studies (animal, human)
  - 2) Applying uncertainty factors (UF)
    - to obtain an acceptable level of safety exposure and protection for humans
  - 3) Calculating the value (TRV)

$$TRV = \frac{\text{Critical dose}}{(UF1 \times UF2 \times UF3 \times \ldots)}$$

(2) Dose-response – TRV with a threshold dose

- NOAEL: No Observable Adverse Effect Level
  - « Highest level of exposure that did not cause an observable effect »
  - No statistical or no biological significance indicating toxic effect (exposed group / unexposed control group)
  - The highest NOAEL value is used (human or most sensitive species)
- LOAEL: Lowest Observed Adverse Effect Level
  - « Lowest level of exposure resulting in an observable toxic effect »
  - Used if it is impossible to identify a NOAEL
- BMD : BenchMark Dose approach

(2) Dose-response – TRV with a threshold dose



(2) Dose-response – TRV with a threshold dose

- BMD : BenchMark Dose

  - « modeled dose producing a measurable effect corresponding to a given level of response relative to a control group »

  - An alternative method (increasingly recommended) to the use of a NOAEL, allowing to get rid of the variability inherent to animal experiments

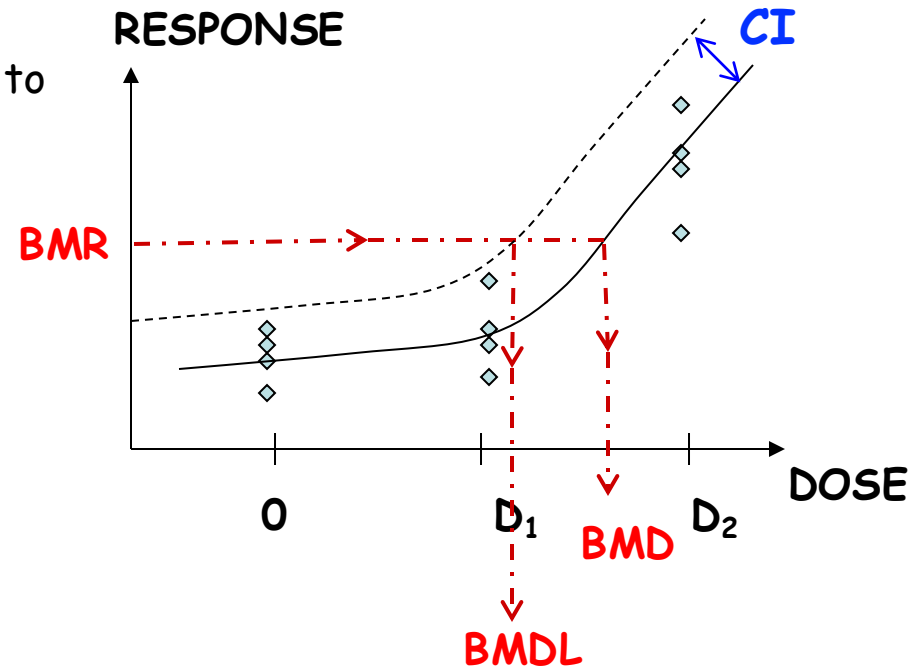
  - The objective is to determine the dose (or the lower limit of the corresponding confidence interval) producing a critical effect with an increase in frequency or severity conventionally set at 1, 5 or 10 %

1- Choice of a theoretical dose-response model fitted to the experimental data

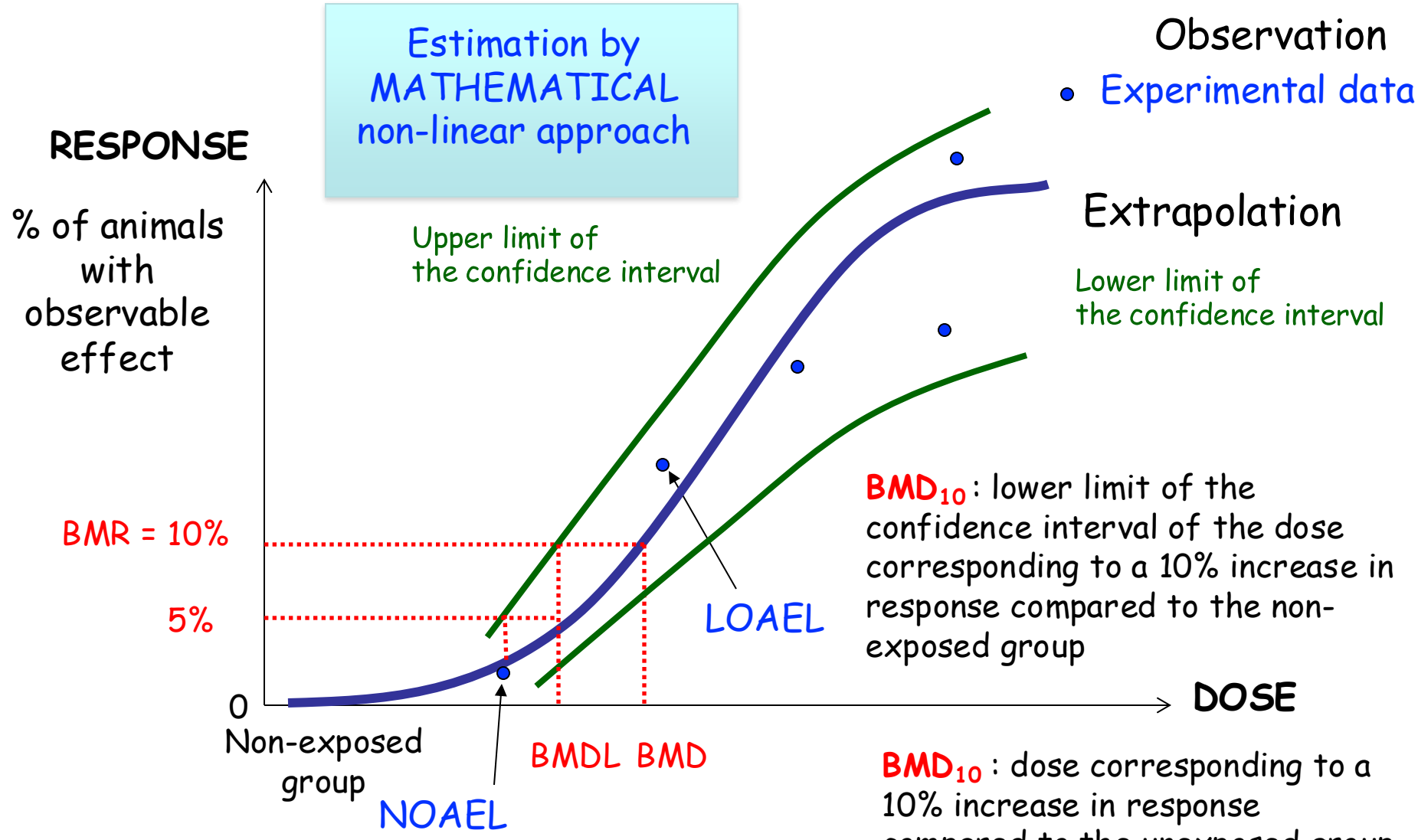
2- Choice of an effect level
BenchMark Response (BMR): 1%, 5%, 10%?

3- Calculation of confidence Interval (CI)

4- Choice of the confidence interval bound for the selected value
e.g. : $BMD_{10}L_{95}$



(2) Dose-response – TRV with a threshold dose



(2) Dose-response – TRV with a threshold dose

- Uncertainty factors (UF) are applied to account for differences when extrapolating data from an experimental study, usually conducted in animals, to a situation of actual environmental exposure in humans

- In general, these factors take into account inter-species and inter-individual variability and the uncertainties associated with experimental protocols

- Value of an uncertainty factor: between 1 and 10
  (usual value by default = 10)

- Five main UF are considered + a « modifying factor »

$$UF = UF_H \times UF_A \times UF_S \times UF_L \times UF_D \times MF$$

(2) Dose-response – TRV with a threshold dose

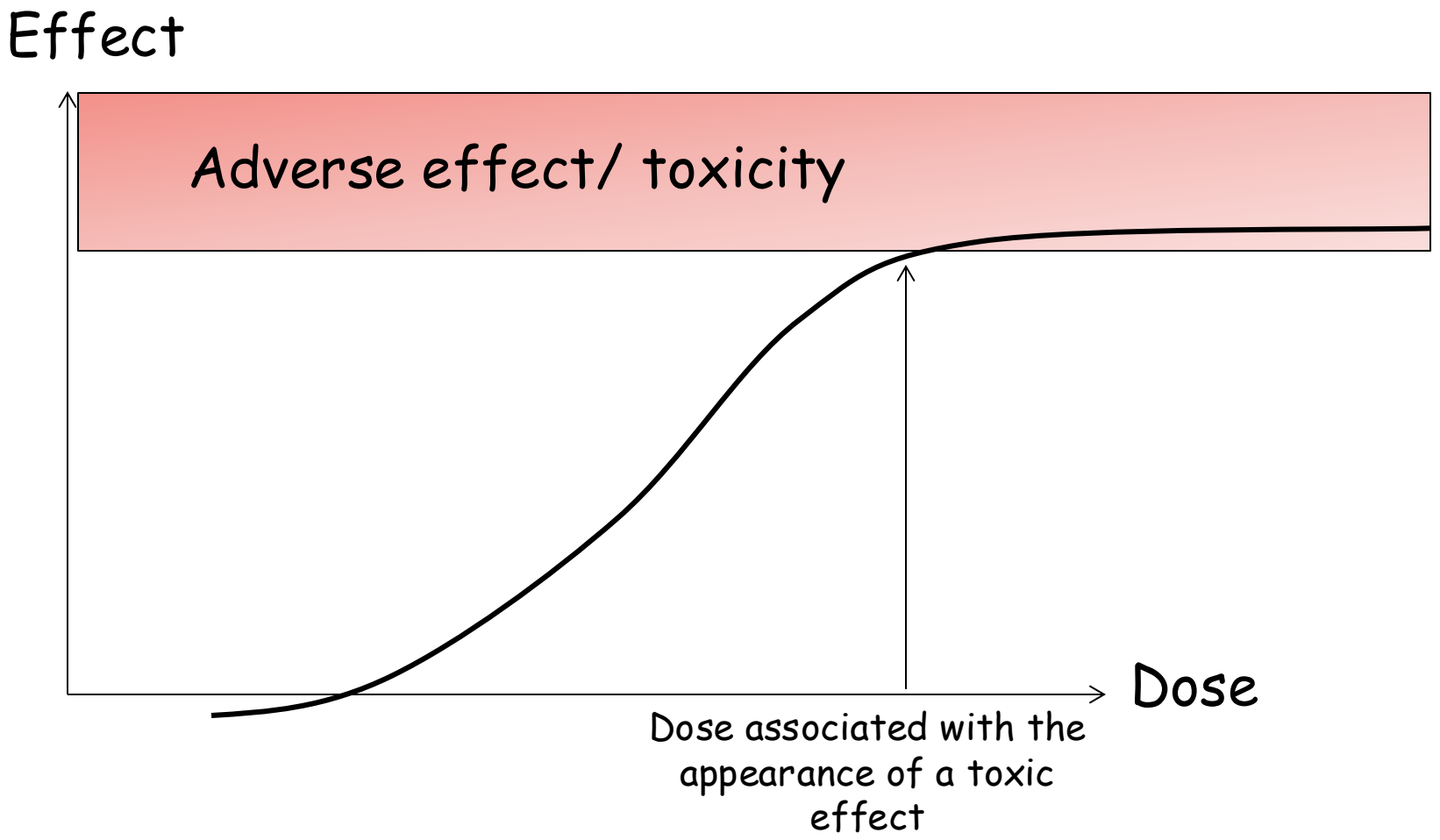
Average Human to Sensitive Human	**1 – UF_H**	Takes into account uncertainty about inter-individual variability. In the absence of data on this variability, a value of 10 is applied, which is conservative by default.

(2) Dose-response – TRV with a threshold dose

Average Human to Sensitive Human

1 – UF_H

Takes into account uncertainty about inter-individual variability. In the absence of data on this variability, a value of 10 is applied, which is conservative by default.



(2) Dose-response – TRV with a threshold dose

Average Human to Sensitive Human

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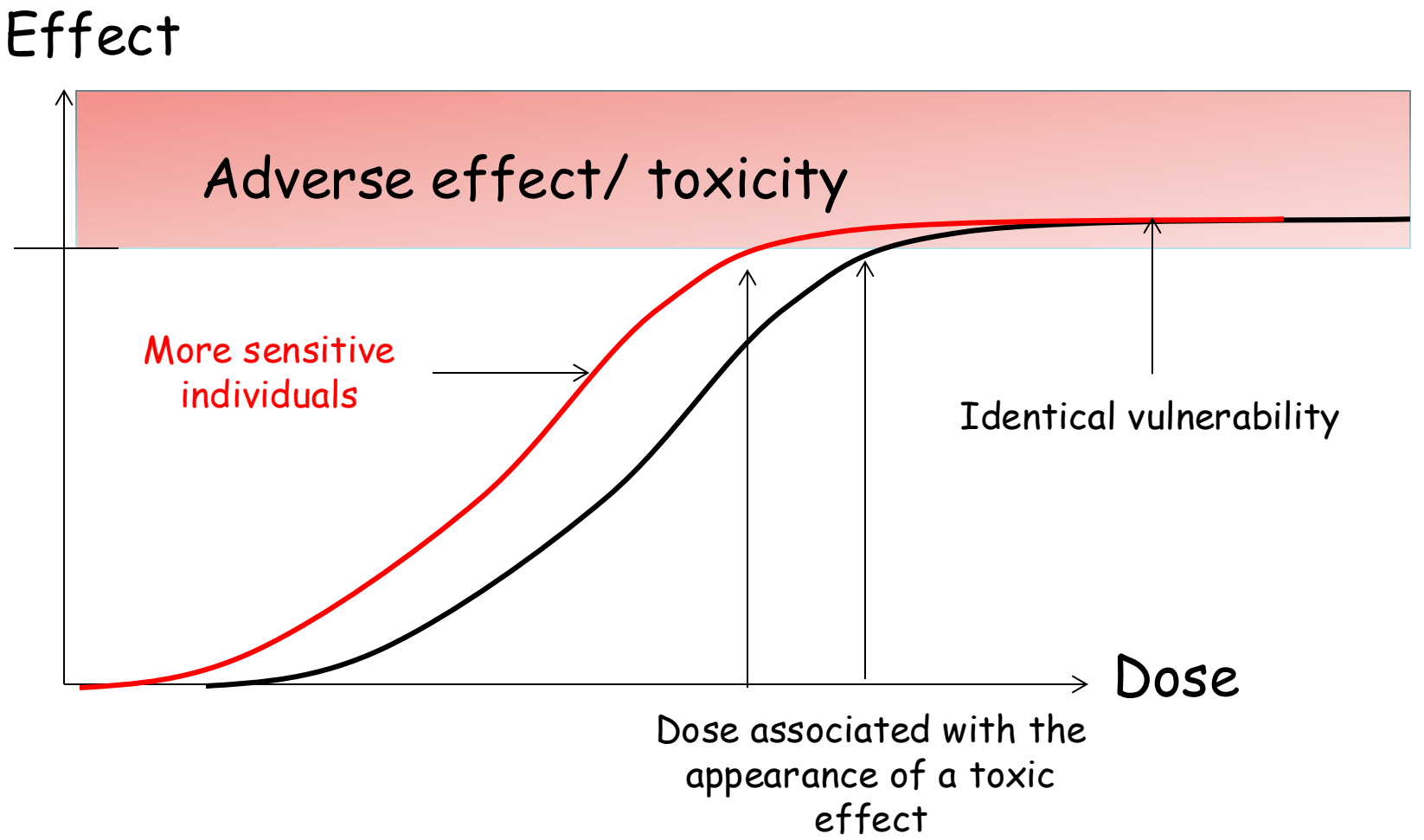

(2) Dose-response – TRV with a threshold dose

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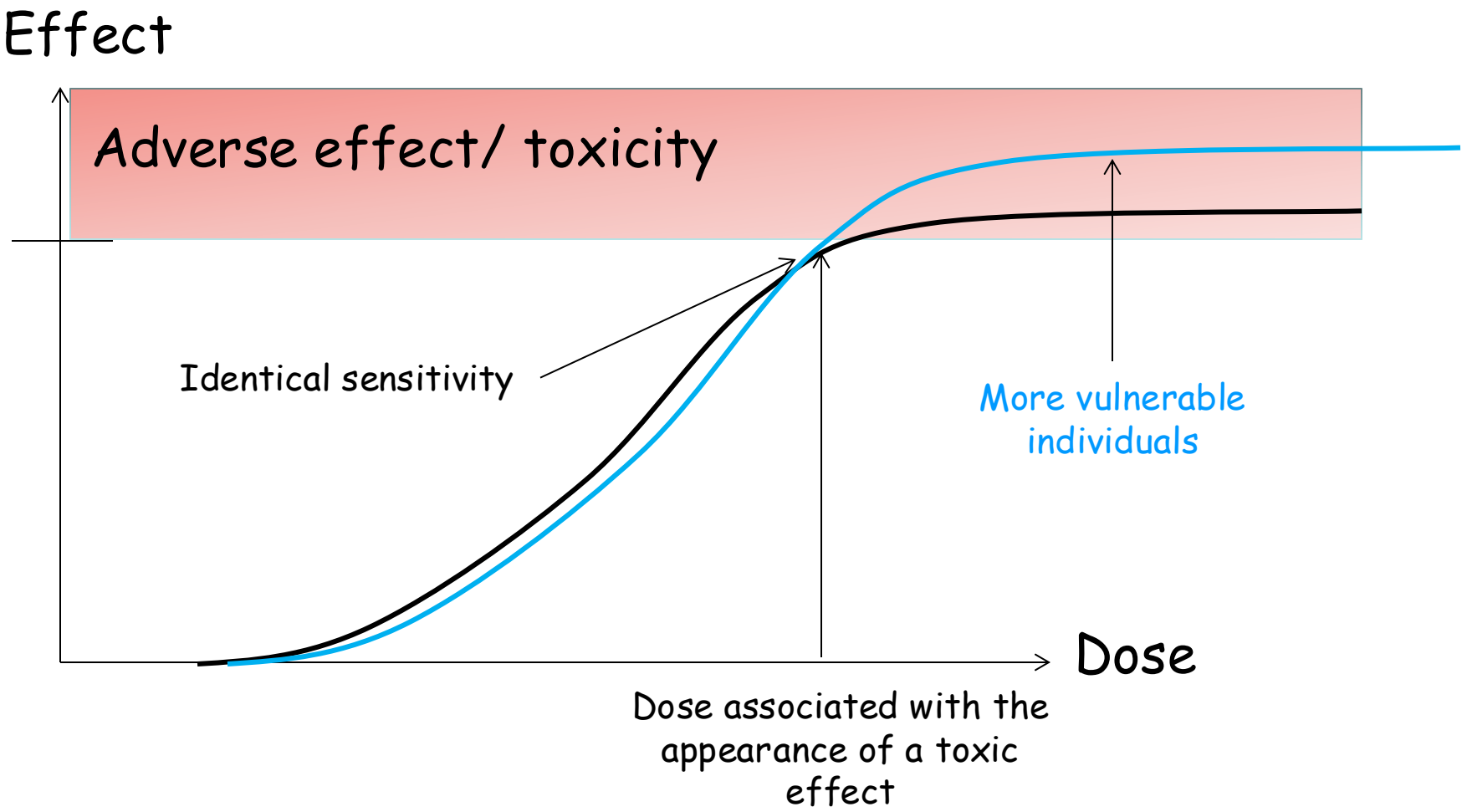

(2) Dose-response – TRV with a threshold dose

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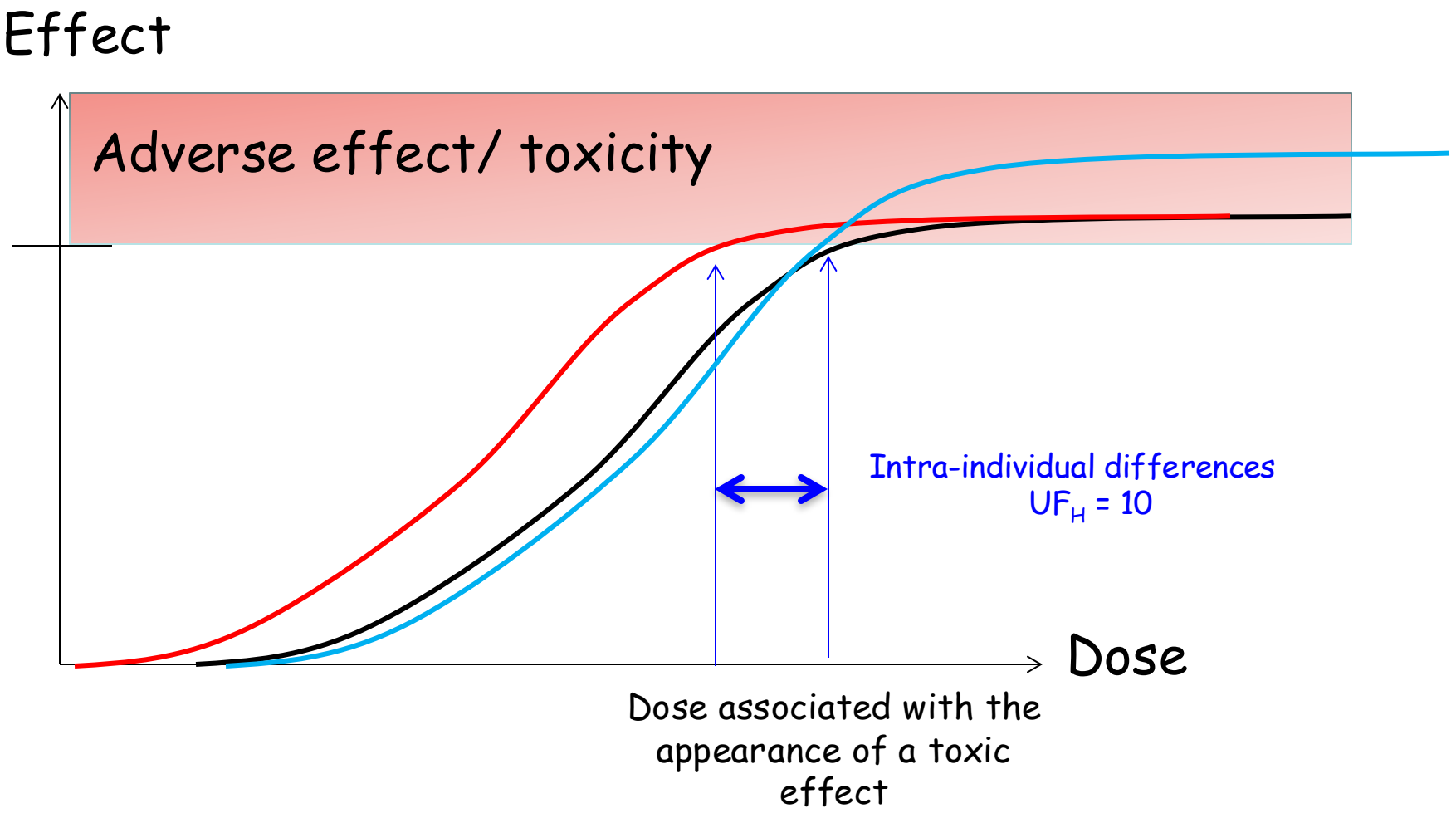


(2) Dose-response – TRV with a threshold dose

Average Human to Sensitive Human	1 – UF_H	Takes into account uncertainty about inter-individual variability. In the absence of data on this variability, a value of 10 is applied, which is conservative by default.
Animal to Human	2 – UF_A	Takes into account inter-species extrapolation, which allows the NOAEL to be estimated in the general human population from animal toxicological data when human epidemiological studies are insufficient. The default factor applied is 10.
Short-term to long-term exposure	3 – UF_S	Takes into account the uncertainty associated with using a NOAEL determined from medium-term studies (approximately 3 months instead of a lifetime) in the construction of the TRV for a lifetime. A factor of 10 is used.

(2) Dose-response – TRV with a threshold dose

4 – UF_L

LOAEL-to-NOAEL

Used when only LOAEL has been determined as the critical dose. It takes into account the uncertainty that the observed LOAEL corresponds to a dose higher than the no-effect level to be estimated. An arbitrarily chosen value of 10 is generally used, or sometimes less when the data permit.

5 – UF_D

Database Insufficiency

A group of other factors that are not routinely used and which take into account the confidence that can be placed in the toxicological studies or effects under consideration. E.g.: a factor ranging from 3 to 10 can be used when toxicological studies are few, to take into account the variability that could have been observed on different results.

MF

Modifying Factor

It is a non-zero factor less than or equal to 10, used by experts who judge the quality of the data and the level of confidence that they can attribute to the construction of the TRV. The factor used by default, or when the data are sufficient and of good quality is equal to 1.

(2) Dose-response – TRV with a threshold dose

100 mg/kg/day LOAEL

/ 10 (estimated LOAEL)

10 mg/kg/day NOAEL

/ 10 (inter-species variation)

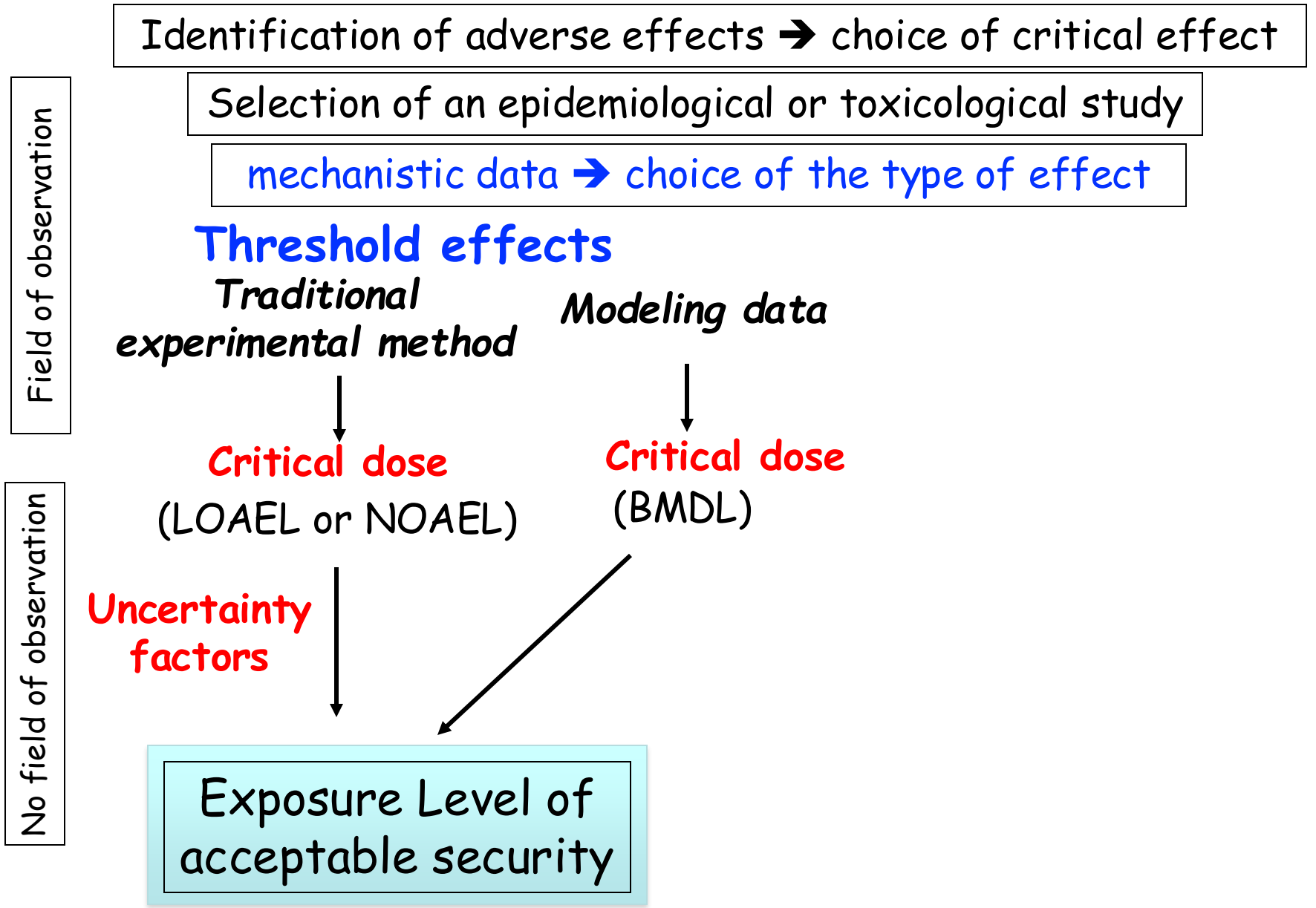
/ 10 (intra-species variation)

0.1 mg/kg/day ADI

acceptable daily intake for humans, including the most sensitive populations

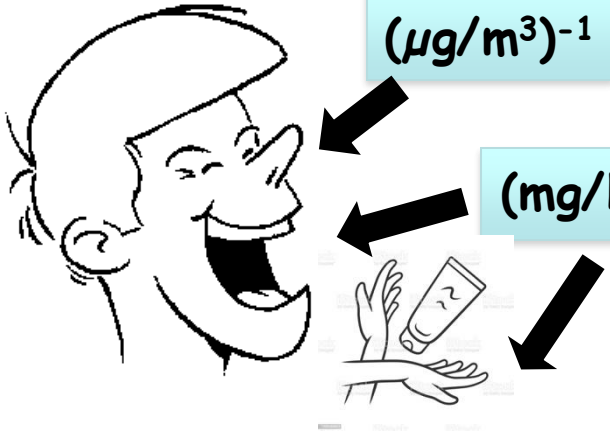
UF = value from 1 to 10 (10 by default)

(2) Dose-response – TRV summary



(2) Dose-response – TRV without a threshold dose

- Non-threshold effects (stochastic effects)
  - « Genotoxic mutagenic and genotoxic carcinogenic effects for which the frequency, but not the severity, is proportional to the dose »
  - The effect appears regardless of the dose received: the probability of occurrence increases with the dose, but the severity does not depend on the dose
- Non-threshold TRV : Excess of Unit Risk (EUR)
  - « additional probability (compared to an unexposed subject) that an individual will develop a pathology (cancer) if exposed to a unit dose of the substance over a lifetime (70 years) »
- Expression of TRV according to routes and organizations



$(\mu g/m^3)^{-1}$

EUR (ANSES, WHO, Health Canada), **SF** (WHO), **$CR_{inhalation}$** (RIVM), **URF** (OEHHA)…

$(mg/kg/day)^{-1}$

EUR (ANSES, WHO, Health Canada), **SF** (WHO), **CR_{oral}** (RIVM), **URF** (OEHHA)…

*CR = **Cancer Risk** ; URF = **Unit Risk Factor** ; SF = **Slope Factor***

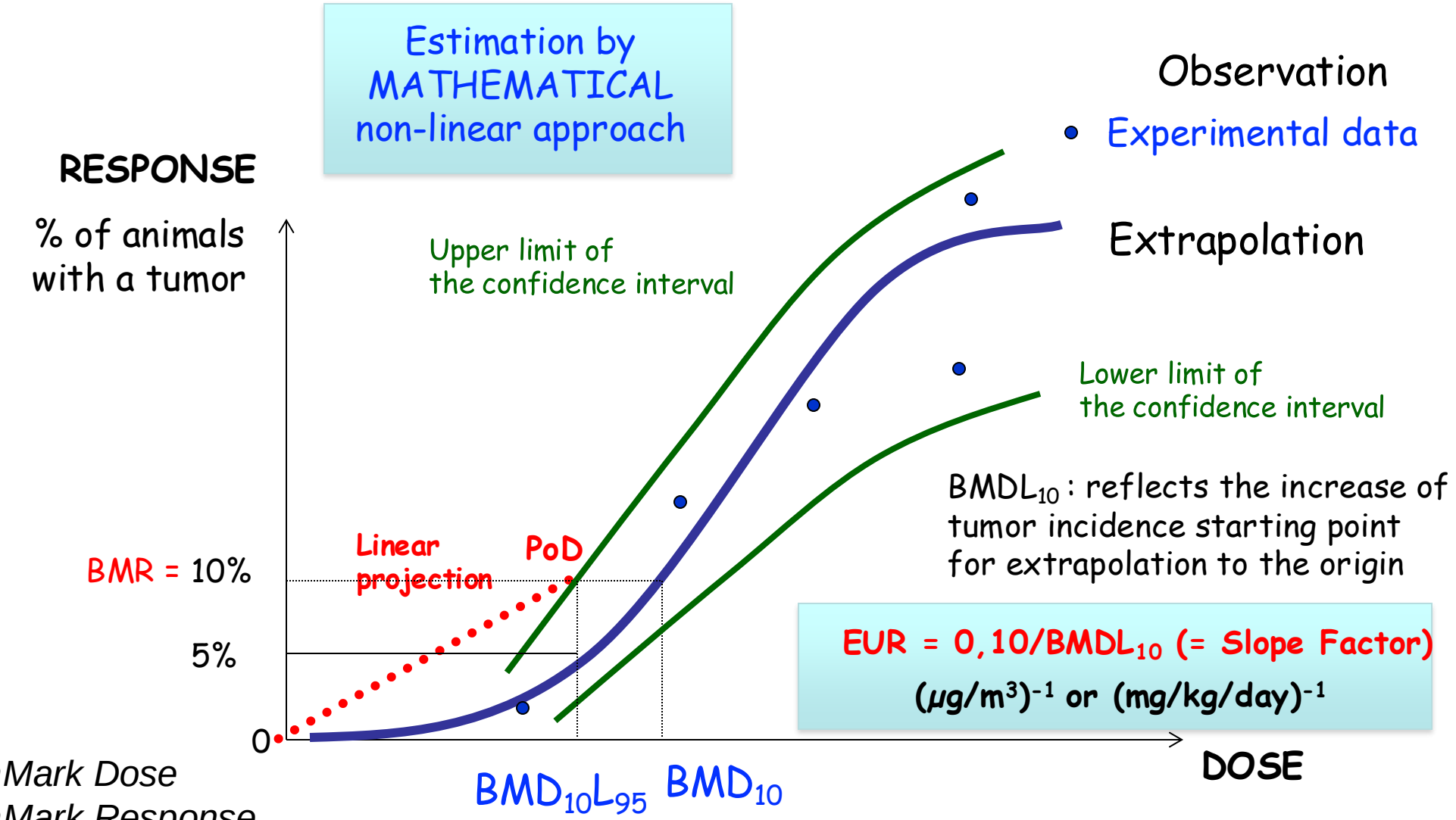
(2) Dose-response – TRV with a threshold dose

How Excess Unit Risk (EUR) is established?

- Non-threshold TRV: **The excess unit risk** is the result of a postulated linear relationship between a low dose of exposure and the probability of occurrence of cancer in a population. Mathematically, it is the slope of the straight line of the linear relationship.
- Established on the basis of dose-response relationships observed in animals, or sometimes in humans: high-dose studies
- Animal-human transposition carried out by adjusting body weight
- Extrapolation of observed data from high doses to low doses, associated with the low risk domain
- E.g. : EUR = 1.8×10^{-3} $(\mu g/m^3)^{-1}$ for Cd
  - 18 excess cancer cases per 10,000 people continuously exposed over a lifetime to 1 $\mu g/m^3$ (EPA 96, occupational cohorts)

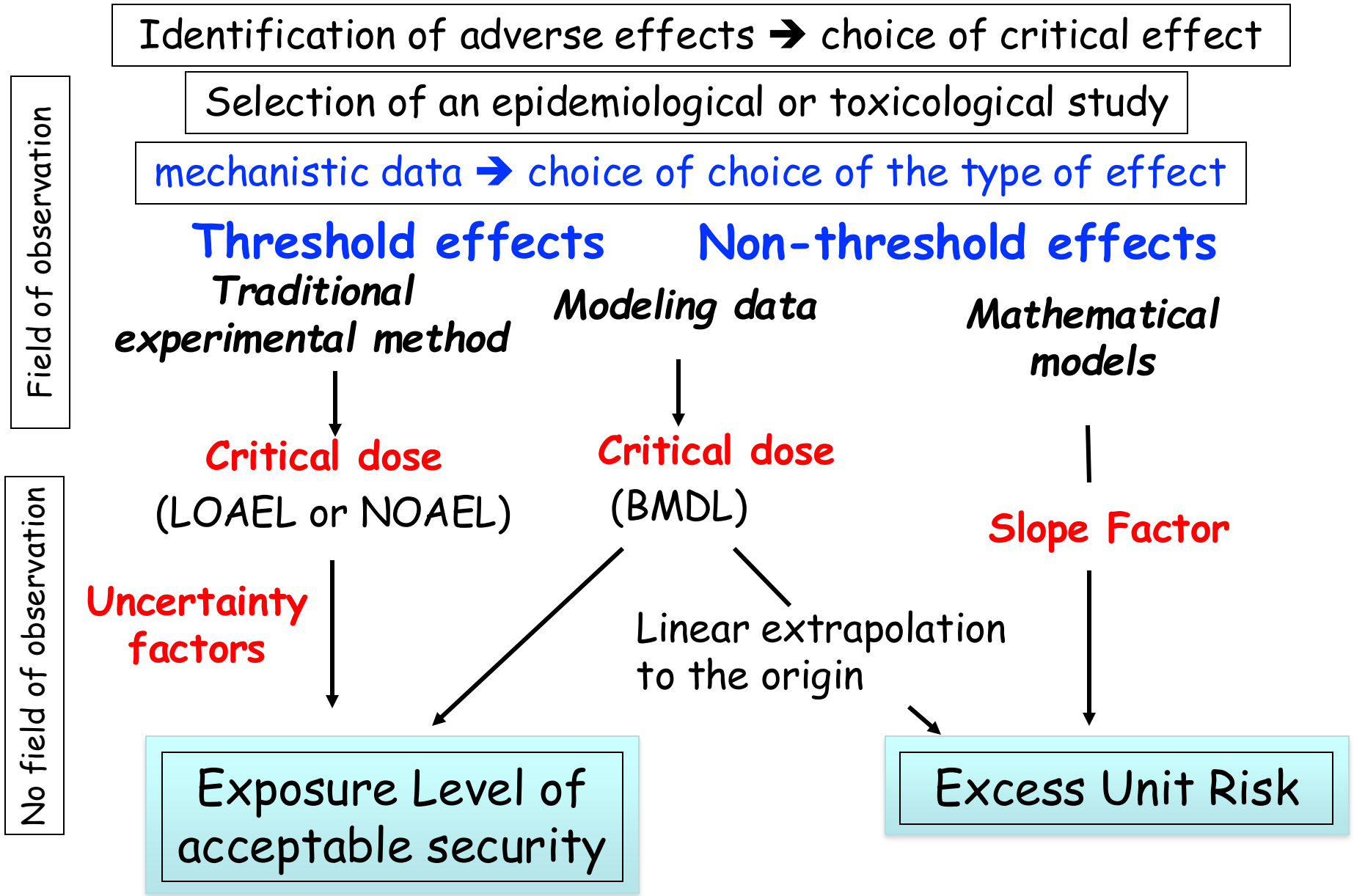
(2) Dose-response – TRV with a threshold dose

How Excess Unit Risk (EUR) is established?



BMD: BenchMark Dose
BMR: BenchMark Response
PoD: Point of Departure

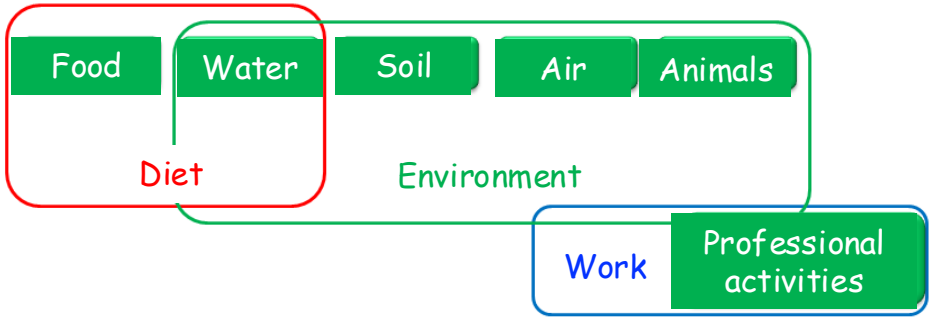
(2) Dose-response – TRV summary



HRA – (3) Exposure assessment

- Principle of exposure assessment

  - « Contact between a dangerous agent and a living organism »
  - «Determination of emissions, pathways and rates of movement of substances and their transformation or degradation in order to assess the concentrations or doses to which human populations are exposed or likely to be exposed »
  - « Determination of relevant exposure pathways, frequency/duration of exposure and level of exposure (concentration/dose) »



Both qualitative and quantitative step

(3) Exposure assessment – Complex step

- Complexity of exposure assessment

  - Relate the concentration of the toxic molecule in the different exposure vectors to the doses presented at the gateways to the body

↓

Construction of

Exposure scenarios

↓

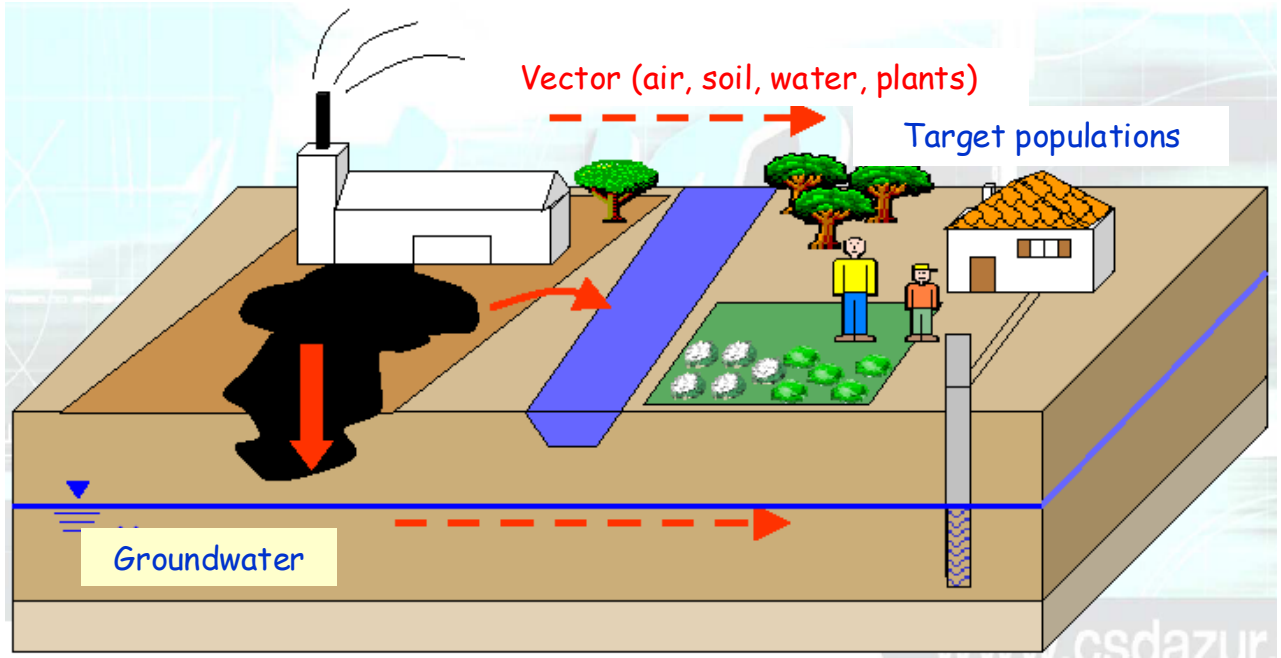
Calculation of

Daily Exposure Dose (Daily dose Intake / Inhaled concentration)

(3) Exposure assessment – Qualitative step

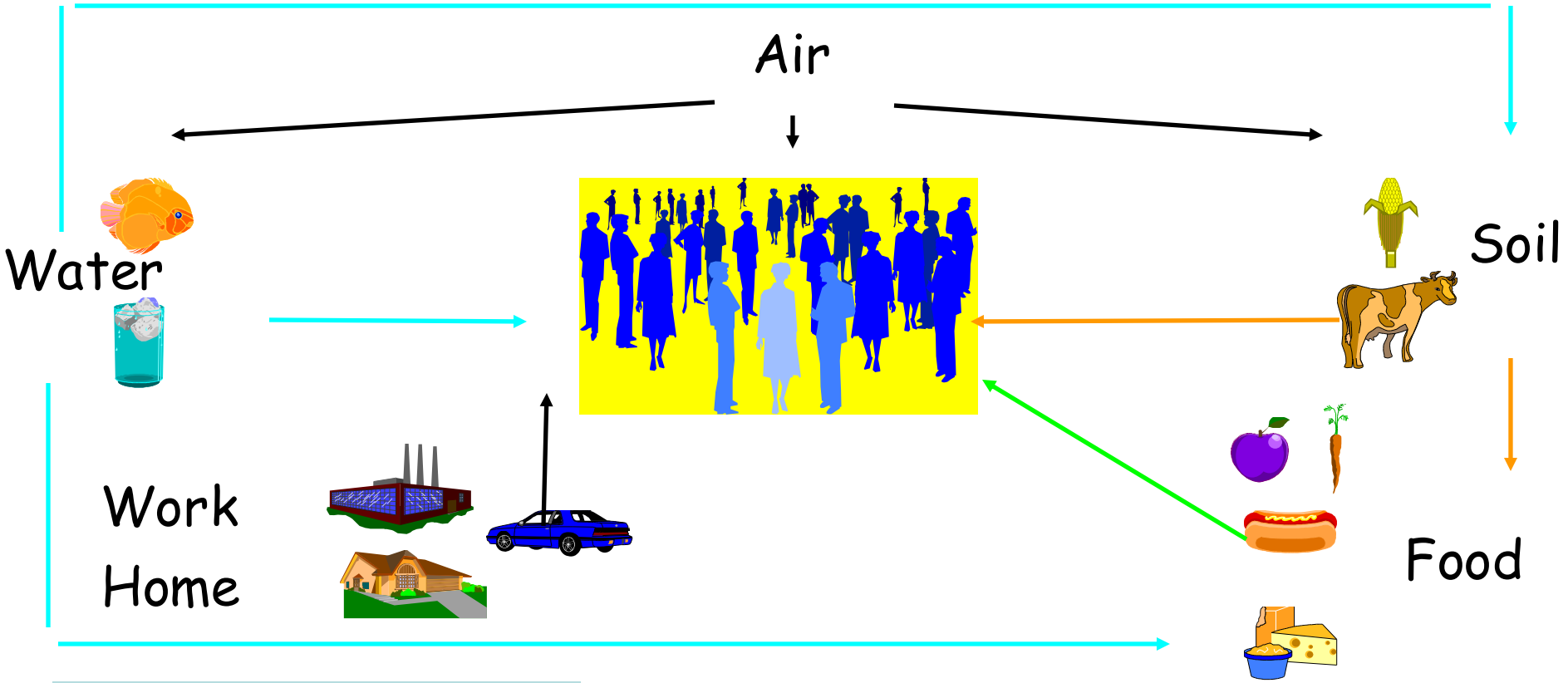
- Establish a concept map
  - « based on the knowledge of discharge emissions, define the pathways of pollutants in the different environmental compartments to the target populations »

SOURCE-VECTOR-TARGET



(3) Exposure assessment – Qualitative step

- Describe possible exposure conditions: vectors /routes



Exposure routes:
ingestion, inhalation, dermal, transplacental

(3) Exposure assessment – Qualitative step

- Identify the modes of transfer of pollutants
  - Fate of a substance in an environmental compartment
    - Transport to another compartment
    - Transformation by various means
      - Physical
      - Chemical
      - Biological
    - Bioconcentration*, bioaccumulation, biomagnification

Physico-chemical characteristics of toxics and media, which condition the transfer and bioavailability of pollutants

***Bioconcentration** is the accumulation of chemicals dissolved in water in fish and aquatic organisms through the gills and body surface directly.

(3) Exposure assessment – Qualitative step

- Describe the individual factors of exposed populations

- **Constitutional/physiological**
  - Ethnic
  - Physiological state
  - Genetic

Especially for epidemiological studies

  - Gender
  - Age
  - Weight
  - Surface area
  - Respiratory rate

- **Lifestyles**
  - Eating habits
  - Life hygiene (alcohol, tobacco…)
  - Medications
  - Space-time budget

(3) Exposure assessment – Qualitative step

- A first descriptive step
  - What is the emission source?
  - Are there other sources?
  - What is the area impacted by this source?
  - What are the polluted environments?
  - Which ones will be in contact with a population?
  - Which population?
  - What are the conditions of exposure?
  - What are the relevant routes of exposure?
  - What are the durations of exposure (acute/chronic)?

(3) Exposure assessment – Quantitative step

- Define the exposure time
  - **CHRONIC exposure** (> 1 year) +++
    - recurring or continuous, corresponding to a significant fraction of the useful life
  - **ACUTE exposure** (< 15 days) +
    - intervening only part of the year: linked to a seasonal activity (swimming...) or to a malfunction of an installation
- Define the exposure frequency
  - Depending on the **SPACE-TIME-ACTIVITY BUDGET**
- Define the exposure level
  - **CONCENTRATION** of a dangerous agent in the polluted environment(s) in contact with humans (eg. µg/L, ng/m^3, pg/g...)
  - **DOSE: quantity of this molecule presented at the biological barrier of the exposed individual (external dose)** or having crossed it (internal dose), per unit of body weight and per unit of time (mg/kg/day)

(3) Exposure assessment – Quantitative step

- Define the exposure dose/concentration

Complementary tools

- **Metrology** (sampling/analysis)
  - Measures to identify the source of pollution
    - air, water and soil sampling and analysis
  - Measures in exposure compartments
    - plants, tap water, air...
  - Measures at the point of contact with the body
    - atmospheric sensor, skin sensor, measurements in consumed food
  - Mesures of internal doses
    - search **for biomarkers of exposure** in biological fluids
- **Modeling** (mathematical representation based on measurements)
  - Estimation of concentrations at exposure points distant from sampling points (transposition)
  - Spatio-temporal evolution of pollutant levels
  - Prediction of low concentrations, < LOD (detection limits)

(3) Exposure assessment – Quantitative step

- Oral exposure (Daily dose intake)

$$D = [(C \times Q \times F) / BW]$$ mg/kg/day

C : Concentration of exposure for a given vector (mg/kg)
Q : Quantity of media ingested by day (kg/day)
F : Frequency of exposure (fraction of days/year, of hour/day…)
BW : Body Weight (kg)

$$X \frac{ED \text{ (exposure duration)}}{AT \text{ (averaging time*)}}$$

- Pulmonary exposure (Inhaled concentration)

$$C = [(\Sigma Ci \times ti) \times F]$$ mg/m³ or µg/m³

C : Average inhaled concentration (mg/m³ or µg/m³)
Ci : Concentration of pollutant in the inhaled air during the fraction of time ti (mg/m³)
ti : Fraction of exposure time
F : Frequency of exposure

Unit of ET and AT = years

For threshod effects ED/AT = 1
For non threshold effects ED/AT ≠ 1

*Period of time over which exposure is averaged (entire life for cancer risk)

HRA – (4) Risk characterization

- Risk
  - « Probability of occurrence of a hazard » under given exposure conditions
    - eg: being exposed for 20 years to 1 f/cm^3 of asbestos can lead to bronchopulmonary cancer

- Risk characterization
  - «estimating the incidence and severity of adverse effects likely to occur in a human population as a result of actual or foreseeable exposure to all emitted substances »

- Two components of risk
  - Probability
  - Severity

Quantitative step

(4) Risk characterization - Principle

THE RISK

relating
to the danger

is a function of

THE PROBABILITY OF OCCURRENCE of the damage

- Frequency and duration of exposure
- Probability of occurrence of a hazardous event
- Possibility to avoid or limit damage

and of

THE GRAVITY

of the damage for the considered danger

Definition of risk according to the standard ISO 14 121

(4) Risk characterization - Quantification

- Threshold effects : Hazard Quotient (HQ)

$$HQ = \frac{\text{Daily exposure}}{\text{TRV (Acceptable daily exposure)}}$$

HQ < 1 ➔ acceptable risk

HQ > 1 ➔ possibility of the toxic effect appearing

Defined for each route of exposure: $D_{ingested}$/RfD ou $C_{inhaled}$/RfC

- Non-threshold effects: Individual excess risk (IER)

« **Probability** that the individual is likely to develop the effect associated with the substance during his or her lifetime as a result of the exposure under consideration » (is in addition to the basic risk)

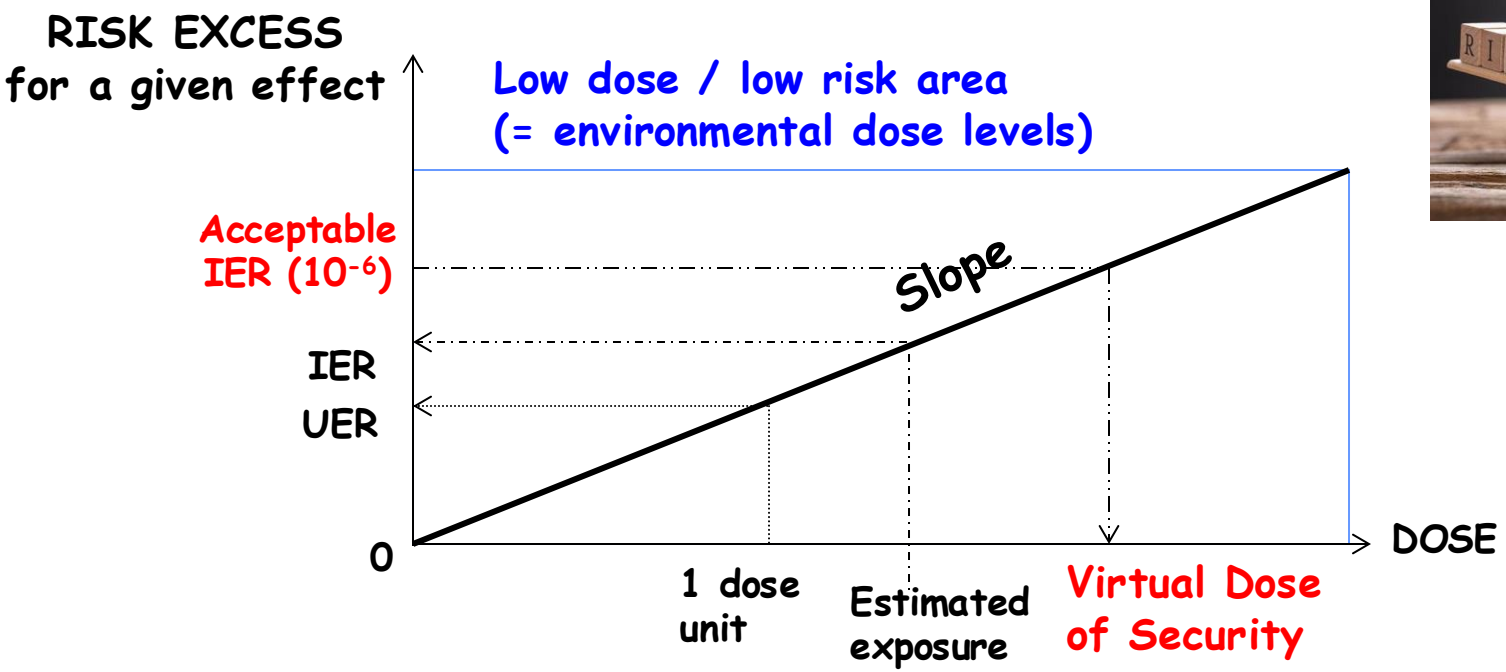
IER = Daily exposure x TRV (SF)

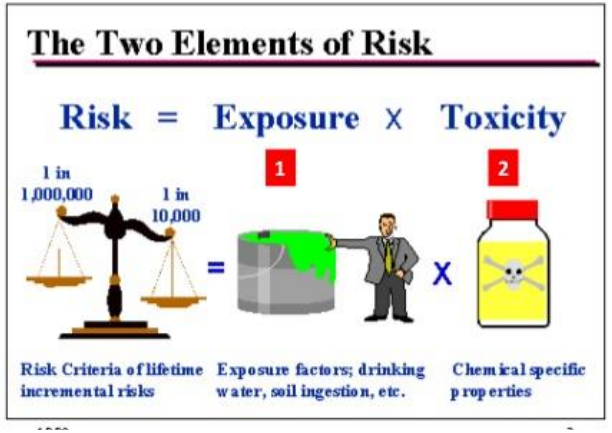
➔ comparison to acceptable risk thresholds

Defined for each route of exposure: $D_{ingested}$ x SF ou $C_{inhaled}$ x SF

(4) Risk characterization - Quantification

- Acceptable risk threshold?
  - A different approach from the "no-effect dose" approach
  - Definition of the virtually no-effect dose after risk/benefit analysis
  - Definition of "socially acceptable" risk





IER between 0 and 1 (0 and 10^{-X})

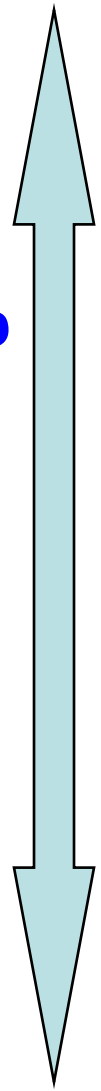
Values commonly recognized as ACCEPTABLE: 10^{-4} à 10^{-6}

(10^{-6}: the adverse event occurs in 1 out of 1 million individuals)

Human Risk Assessment - Summary

- **Hazard identification**
  - Toxicology, epidemiology
- **Dose-response relationship**
  - Reference Toxicity Value
  - With threshold, without threshold
- **Exposure assessment**
  - Daily dose of exposure
  - Inhalation concentration
- **Risk assessment**
  - HQ for threshold effects
  - IER for non-threshold effects

+ INCERTAINTIES EVALUATION



TRANSPARENCY

Principles :

Caution

Proportionality

Specificity

Human Risk Assessment - Summary

Need for a multidisciplinary approach

- Disciplines explaining the link

  Biology, toxicology, medicine...

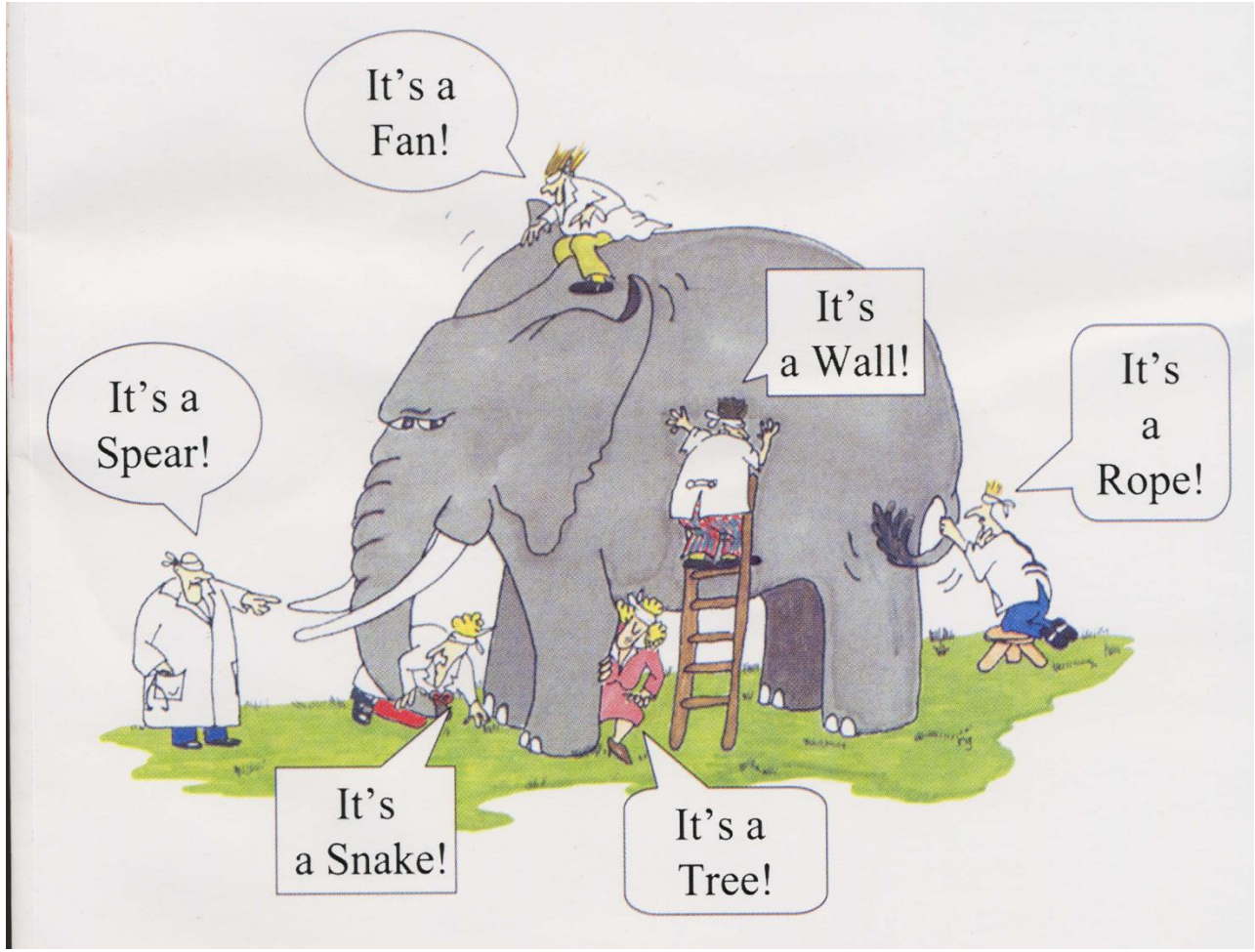
- Disciplines quantifying the link (at collective level)

  Epidemiology, Human Risk Assesment

- And always a key notion: the exposure

Towards the "truth" of the CAUSE-EFFECT LINK...

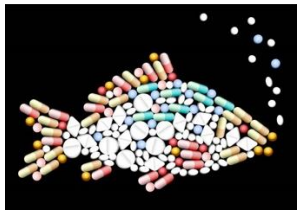
...to MANAGE THE RISKS



ANNEX - Example of endocrine-disrupting drugs

Fate of absorbed drugs in the body

Absorption



Body

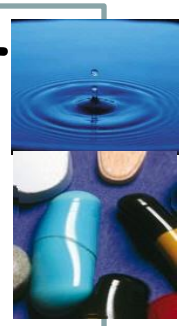
Total degradation (H_2O - CO_2)

Unchanged molecule

Partial degradation

Distribution
Metabolization
Bioaccumulation

Environment



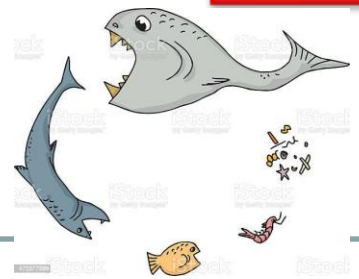
Metabolites and unchanged molecule

Metabolites conjugated or not

Deconjugation

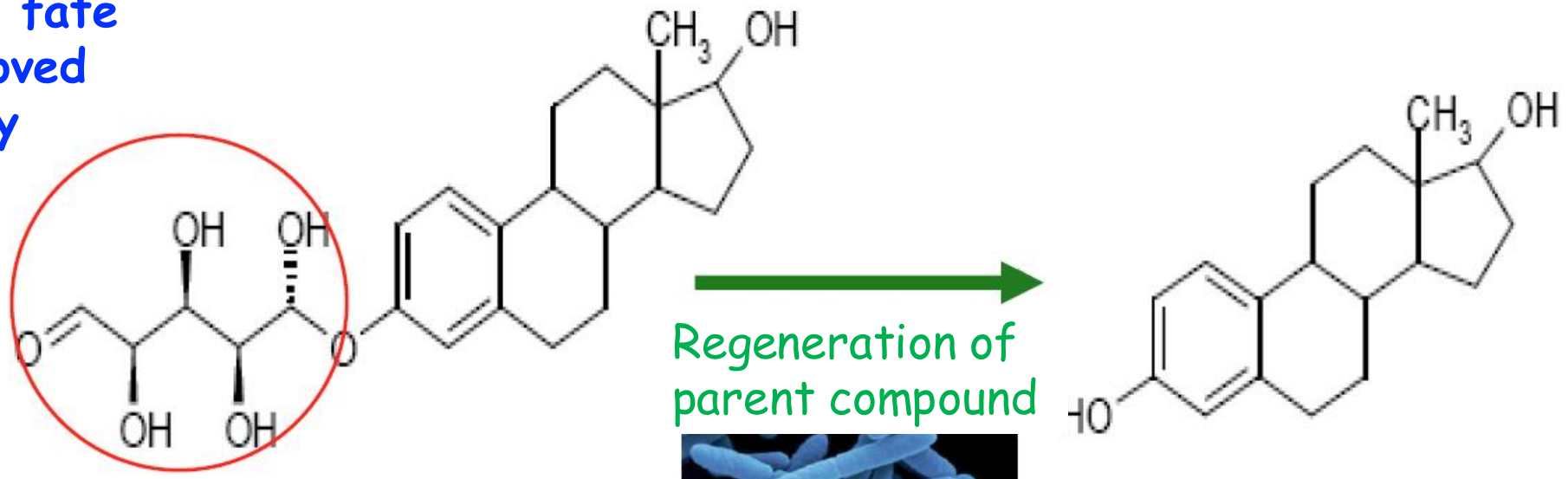
Entry into the food chain

Excretion



ANNEX - Example of endocrine-disrupting drugs

Environmental fate of drugs removed from the body



Glucuronide derivative

17-β-estradiol

Deconjugation of the glucuronoconjugate derivative of 17-β-estradiol by glucuronidases from bacteria *E. coli* in wastewater
(Ascenzo et al., 2003)

ANNEX -Ex. of endocrine-disrupting drugs

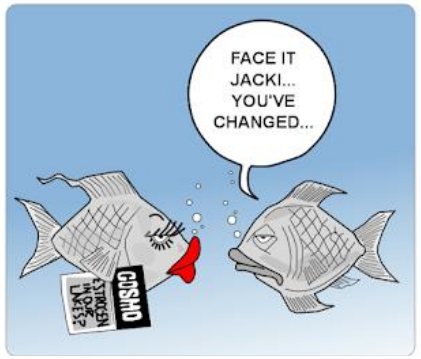
Impact and effected organisms

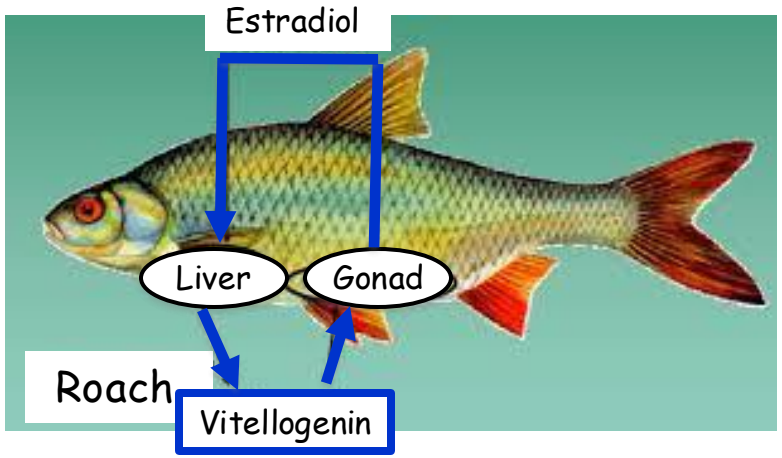
Therapeutic group	Examples of Pharmaceutical	Impact and effected organisms
Analgesics	Diclofenac, Ibuprofen	Organ damage, reduced hatching success (fish) Genotoxicity, neurotoxicity and oxidative stress (mollusk) Disruption with hormones (frog)
Antibiotics	-	Reduced growth (environmental bacteria, algae and aquatic plants)
Anti-cancer	Cyclophosphamide[1], mitomycin C, fluorouracil, cisplatin, doxorubicin	Ecotoxcity, genotoxicity
Antidiabetics	Metformin	Potential endocrine-disrupting effects (fish)
Anti- convulsants	Carbamazepine, phenytoin, valproic acid	Reproduction toxicity (invertebrates), development delay (fish)
Antifungals	Ketoconazole, clotrimazole triclosan	Reduced growth (algae, fish), reduced algae community growth, disruption of hormones (rats)
Antihistamines	Hydroxyzine, fexofenadine, diphenhydramine	Behaviour changes, growth and feeding rate (fish) Behaviour changes and reproduction toxicity (invertebrates)
Antiparasitics	Ivermectin	Growth and reduced reproduction (invertebrates)
Beta blockers	Propranolol	Reproduction behaviour (fish), reproduction toxicity (invertebrates)
Endocrine active pharmaceuticals	E2, EE2, levonorgestrel	Disruption with hormones causing reproduction toxicity (fish, frogs)
Psychiatric dugs	Fluoxetine, sertraline, oxazepam, citalopram, chlorpromazine	Behaviour changes - feeding, boldness, activity, sociality (fish) Disruption with hormones (fish) Behaviour changes - swimming and cryptic (invertebrates) Reproduction toxicity and disruption with hormones (invertebrates)

Examples of measured effects of certain pharmceuticals redisues on aquatic organisms in laboratory studies

ANNEX- Example of endocrine-disrupting drugs

Endocrine disrupting Pharmaceuticals





Egg yolk protein synthesized in the liver of females under the control of E2

Chronic exposure of fishs in a canadian lake to **5–6 ng/L** of 17a-ethinylestradiol (EE2)

Feminization of males with production of vitellogenin
Intersex in males and disrupted oogenesis in females with an ultimate vision of near extinction of the fish species in the lake.

(Kidd et al., PNAS, 2007)

Endocrine disrupting PPCPs

Steroids

Estrogens
- 17 β estradiol
- estrone
- 17 α ethynylestradiol

Progestogens:
- norenthindrone
- progesterone

Estrogen antagonists
- tamoxifen

Androgens and glucocorticoids
- testosterone
- beclometazone
- hydrocortisone

Phytoestrogens
- sequiterpenes
- phytosterols

Veterinary growth hormones
(growth promoters for meat-producing animals)
- zeranol
- trenbolone acetate
- melenogestrol acetate

Personal care products

Disinfectants

Conservation agents

Fragrances
- musk xylol
- musk ketone
- galaxolide
- tonalide
- celestolide

UV screens
- benzophenone-3
- homosalate
- 4-methyl-benzylidene camphor
- octyl-methoxycinnamte
- octyl-dimethyl-PABA

Nonsteroidal pharmaceuticals

Agents used on blood and blood forming organs
- acetylsalicylic acid
- pentoxyfylline

Agents for treatment of heart and circulatory diseases
- clofibric acid

Dermatological drugs
- hydrocotisone

Antibiotics
- penicillin
- amoxicyllin
- tetracyclines

Analgesics
- paracetamol

Anti-inflamatorics
- ibuprofen
- naproxen
- diclofenac

Agent used in treatment of allergy and asthma
- budenoside

Anti-depresants
- fluoxetine

Pharmaceuticals and personal care products (PPCPs) showing endocrine-disrupting potential

(Ebele et al., 2017)

ANNEX- Example of endocrine-disrupting drugs

First definition of Endocrine-disrupting compound (EDC)

"An exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes"

(Kavlock et al., 1996)

Consensual definition of EDC

"An exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations"

(WHO, 2002)

List of main EDCs

Endocrine Disruptors

Arsenic	Insecticides	Fire retardants
Atrazine	Polychlorobiphenyl	Estradiol
Bisphenol A	Cadmium	Estrone
Lead	Parabens	Fungicides
Mercury	Pesticides	Perchlorate
Phytoestrogens	Bis (2-ethylhexyl)phthalate	Triclosan
Glycol ethers	Polycyclic aromatic hydrocarbons	Perfluorinated chemicals

(Dallio et al., 2019)

ANNEX- Example of endocrine-disrupting drugs

Wildlife and human health effects of EDCs

↘ Reproduction of marine invertebrates

Gastropods (tributyltin)

Feminization of reptiles and amphibians

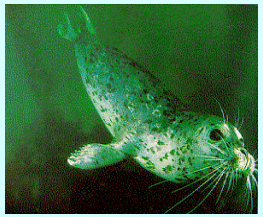
Alligators (dicofol)

Sex change of fish downstream of WTP

Estradiol, EE2

PROVEN IN WILDLIFE

↘ Reproduction and thyroid abnormalities in marine mammals

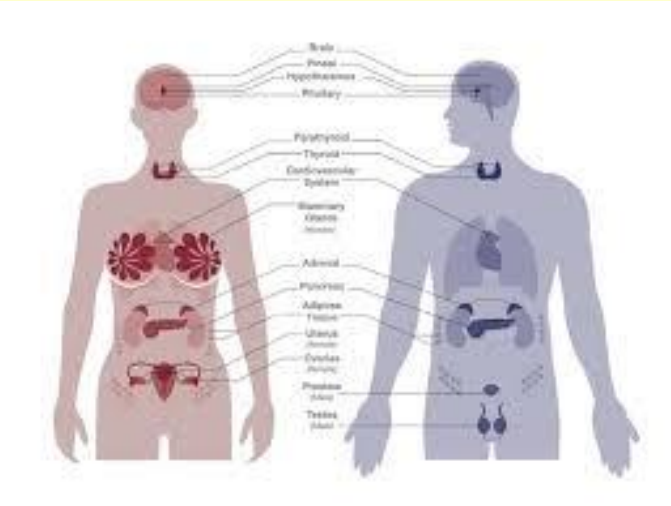


Seals in the North Sea (PCBs)

Thyroid abnormalities and feminization in birds

Falcons, gulls (DDT, PCBs)

Neurodevelopmental impairment
Dysgenesis of the reproductive system
Sex ratio
Fertility alteration



Breast cancer
Endometriosis
Early puberty

Impaired sperm quality
Impaired sperm count
Testicular cancer
prostate cancer
Cases of cryptorchidism
Cases of hypospadias

SUSPECTED IN HUMAN

ANNEX- Example of endocrine-disrupting drugs

Micropollutants with endocrine-disrupting effects

Environmental problem proved

↓

Ecosystem disruption confirmed

↓

In vitro and *in vivo* effets on animals validated

↓

Impact on human health under assesment