Società Italiana di Tossicologia

- **La Società Italiana di Tossicologia** non ha fini di lucro, politici e sindacali ed ha durata illimitata, ha come logo il nome "SITOX" e sede amministrativa a Milano

- **I principali obiettivi** della SITOX sono indirizzati a:
  - promuovere la ricerca scientifica nei diversi ambiti della Tossicologia;
  - stimolare il confronto e rapporti di collaborazione con Istituzioni nazionali e internazionali, Enti di ricerca ed altre Organizzazioni scientifiche responsabili per la tutela della salute e dell'ambiente;
  - diffondere l'informazione tossicologica nell'opinione pubblica attraverso comunicati, eventi e conferenze;
  - promuovere la formazione e l'aggiornamento dei tossicologi attraverso congressi, convegni, seminari e corsi ECM;
  - riconoscere, attraverso l'istituzione del Registro Nazionale dei Tossicologi Certifica (RENTIC) la figura del tossicologo certificato.

Presidente
Corrado L. Galli
Past Presidente
Patrizia Hrelia
Presidente Eletto
Orazio Cantoni

Consiglio Direttivo
Francesca Maffei
Guido Mannaioni
Angelo Moretto
Michele Navarra
Emanuela Testai
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Barbara Viviani

SITOX

410 Soci ordinari

23 soci sostenitori

4 soci onorari

Prof. Lewis Goldfrank,
Prof. Pier Francesco Mannaioni,
Prof. Rodolfo Paoletti,
Prof. Paolo Preziosi

Società Italiana di Tossicologia

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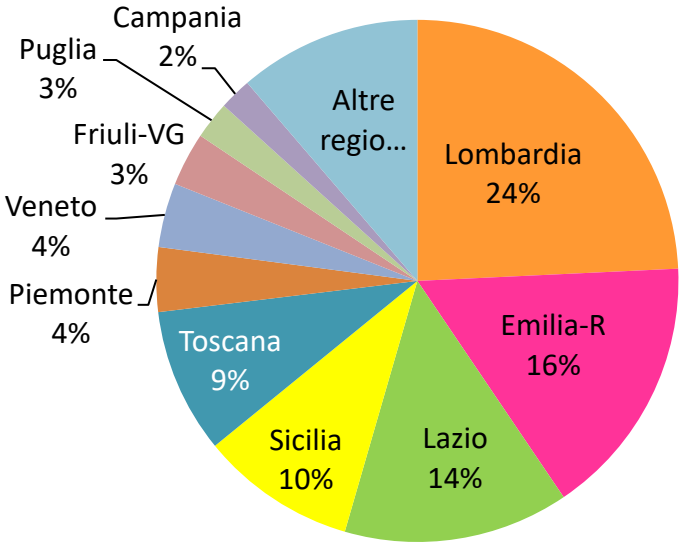

DISTRIBUZIONE DEI 410 SOCI SITOX IN BASE ALLA REGIONE SEDE DELL'ISTITUZIONE DI AFFERENZA

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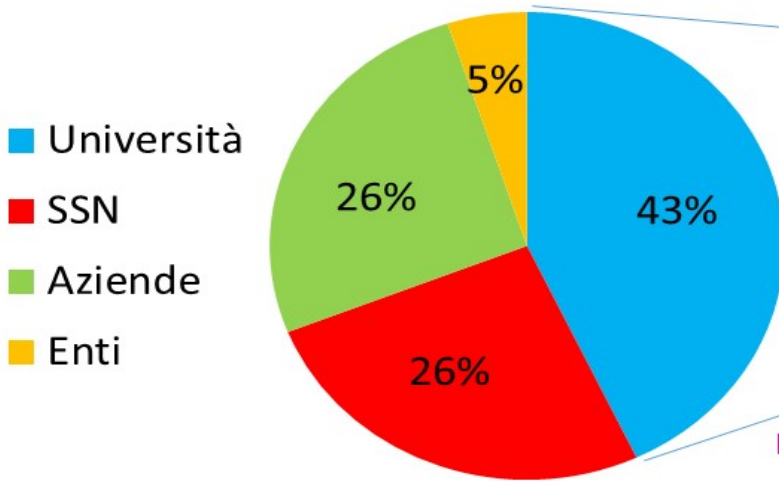


distribuzione dei soci ordinari in base al settore professionale di afferenza

UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE E BIOMOLECOLARI

INTRODUZIONE ALL'ANALISI DEL RISCHIO IN CAMPO ALIMENTARE

CORRADO LODOVICO GALLI - ERT

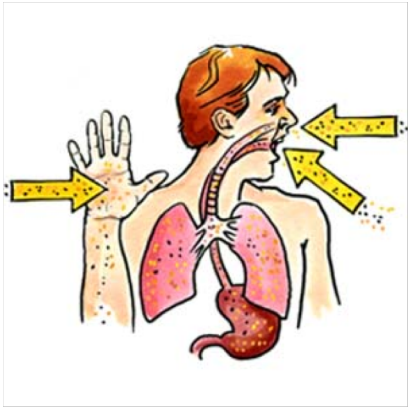
Contaminazione da inquinanti organici persistenti nella catena alimentare: monitoraggio, ricerca e caratterizzazione del rischio

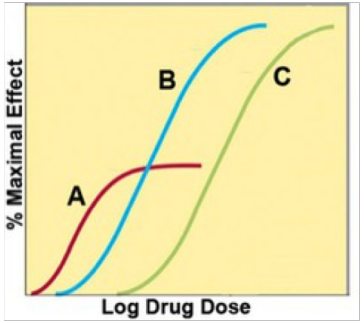
Aula Magna Campus Mattei, Località Crocicchia, 61029 Urbino (PU)

SIMPLE QUESTIONS versus DIFFICULT ANSWERS

What chemical(s)

are we **exposed to**?





At what dose is toxicity observed

- Where do they cause toxicity?
- What are the mechanism of toxicity?
- Who is susceptible?

ENSURING THE SAFETY OF CHEMICALS

- **Synthetic**
- Persistent
- Natural
- Endocrine active

PUBLIC HEALTH and RISK ANALYSIS

RISK ASSESSMENT

① Assess the intrinsic hazard of a chemical and establish a level of safety;

② Determine the level of exposure to a chemical;

③ Compare the daily intake (*exposure*) with the *health based guidance values (HBGVs)* to ensure that the risk is acceptable in light of all the existing scientific evidence.

HAZARD

Hazard is the potencial capacity of producing harm.

RISK

Risk is proportional to both the hazard and the extent of exposure.

REFERENCE POINTS - POINTS OF DEPARTURE

Toxicants or Non DNA reactive-Carcinogens

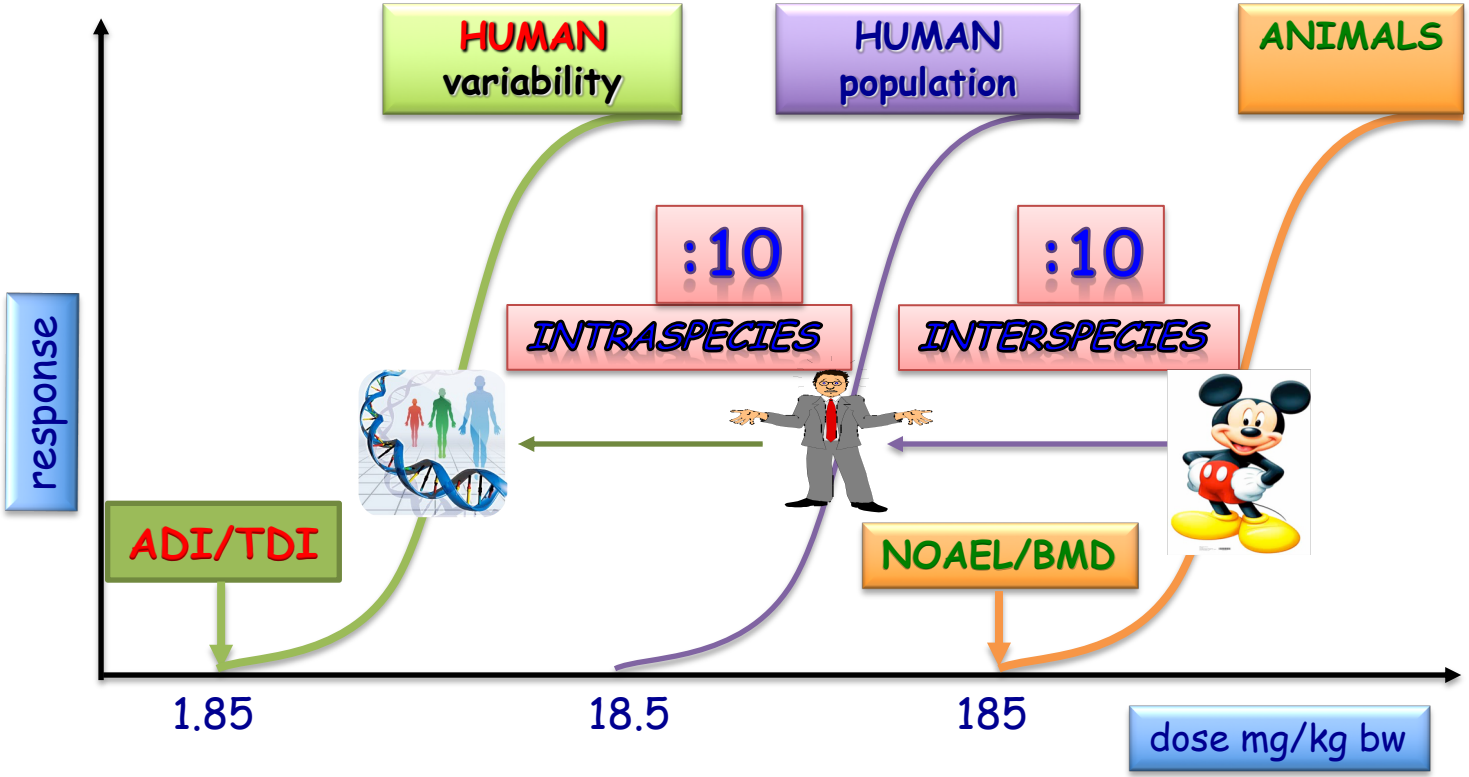
- No-Observed-(Adverse)-Effect-Level (NO(A)EL)
- Benchmark Dose (BMD)

DNA reactive-Carcinogens

- Benchmark Dose (BMD)
- TD25
- TD50

ANIMAL-BASED TOXICOLOGICAL STUDIES

(QUANTIFICATION OF ADVERSE HEALTH EFFECTS)



HEALTH BASED GUIDANCE VALUES (HBGVs)

- NON-DNA-reactive carcinogens
  - ADI (Acceptable Daily Intake)
  - TDI/TWI (Tolerable Daily/Weekly Intake)
  - MoS (Margin of Safety)
- DNA-reactive carcinogens
  - MoE (Margin of Exposure)
  - TTC (Threshold of Toxicological Concern)

ADMISSIBILE DAILY INTAKE

$$ADI = \frac{NOAEL/BMD}{SF}$$

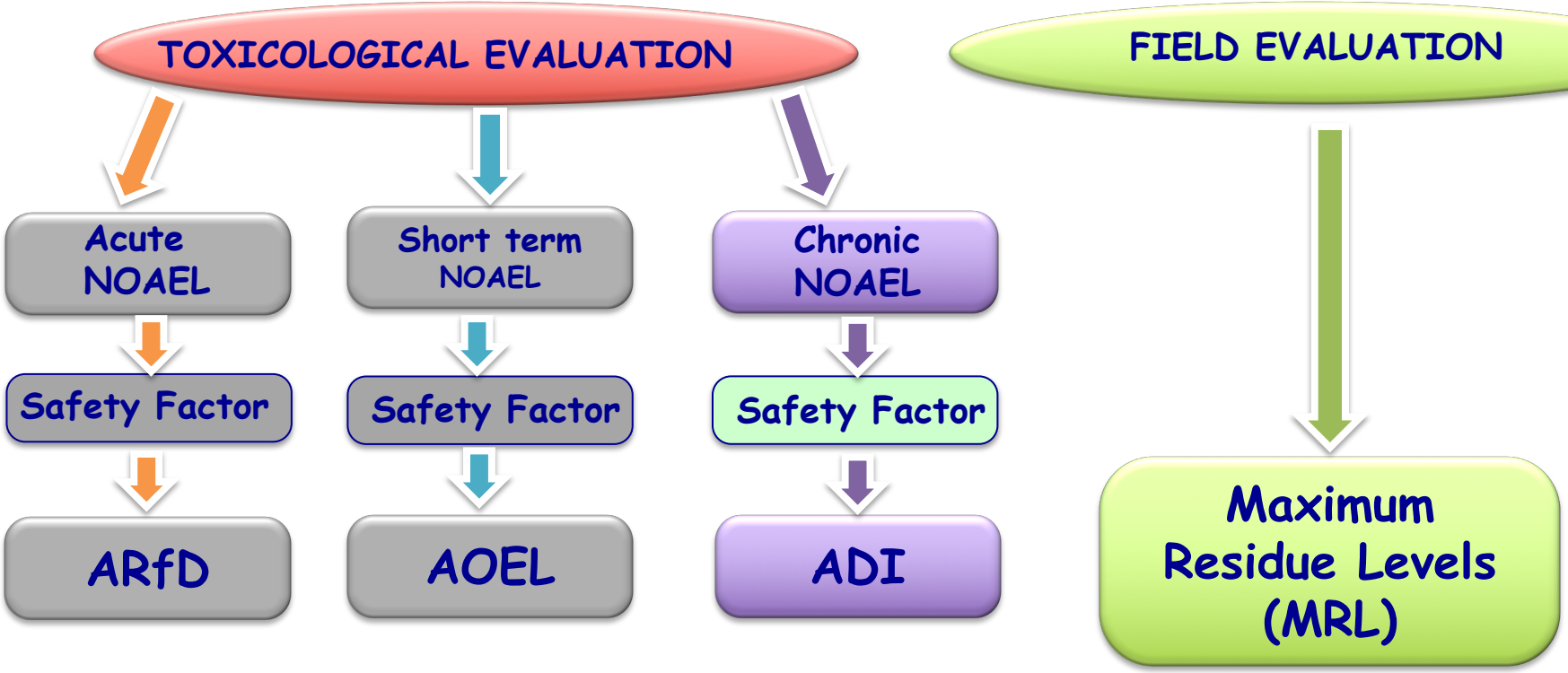
ADI = Admissible Daily Intake mg/kg b.w.

NOAEL = No Observed Adverse Effect Level (mg/kg b.w.)

BMD = Benchmark Dose (mg/kg b.w.)

SF = Safety Factor (10, 100, n)

PESTICIDES HEALTH BASED GUIDANCE VALUES



PESTICIDES CONSUMERS RISK ASSESSMENT

HEALTH BASED GUIDANCE VALUES (HBGVs)

- NON-DNA-reactive carcinogens
  - ADI (Acceptable Daily Intake)
  - TDI/TWI (Tolerable Daily/Weekly Intake)
  - MoS (Margin of Safety)
- DNA-reactive carcinogens
  - **MoE** **(Margin of Exposure)**
  - TTC (Threshold of Toxicological Concern)

MARGIN OF EXPOSURE (MoE)

$$MoE = \frac{NOAEL/BMD}{EXPOSURE}$$

NOAEL/BMD → 25 mg/kg b.w.

EXPOSURE → 0.0005 mg/kg/day

- MoE = > 10,000

ENSURING THE SAFETY OF CHEMICALS

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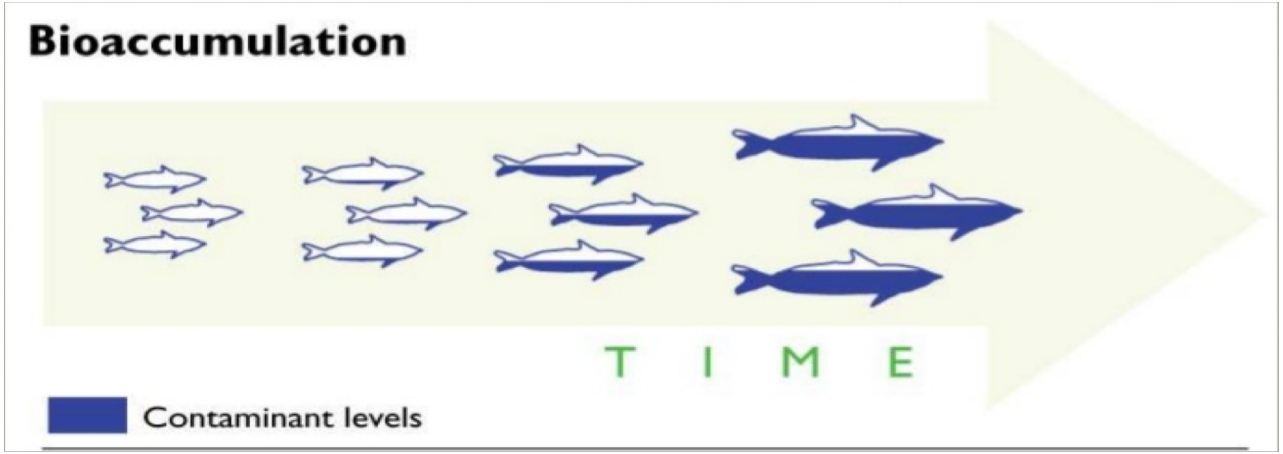
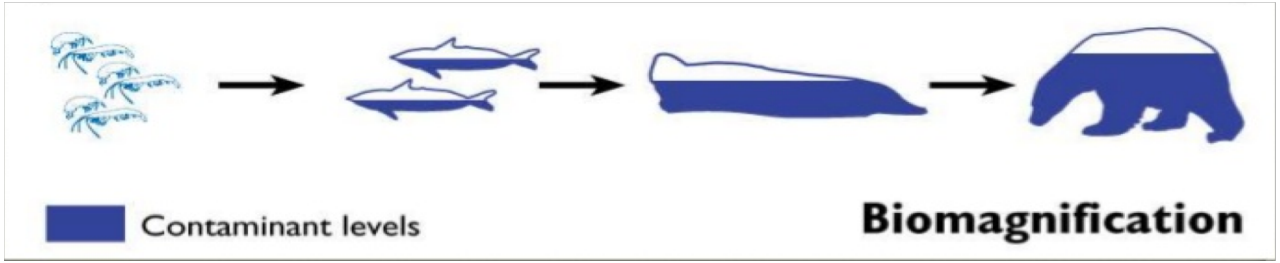
CUMULATIVE EFFECT



Bioaccumulation:

refers to the accumulation of substances, of a chemicals in an organism.

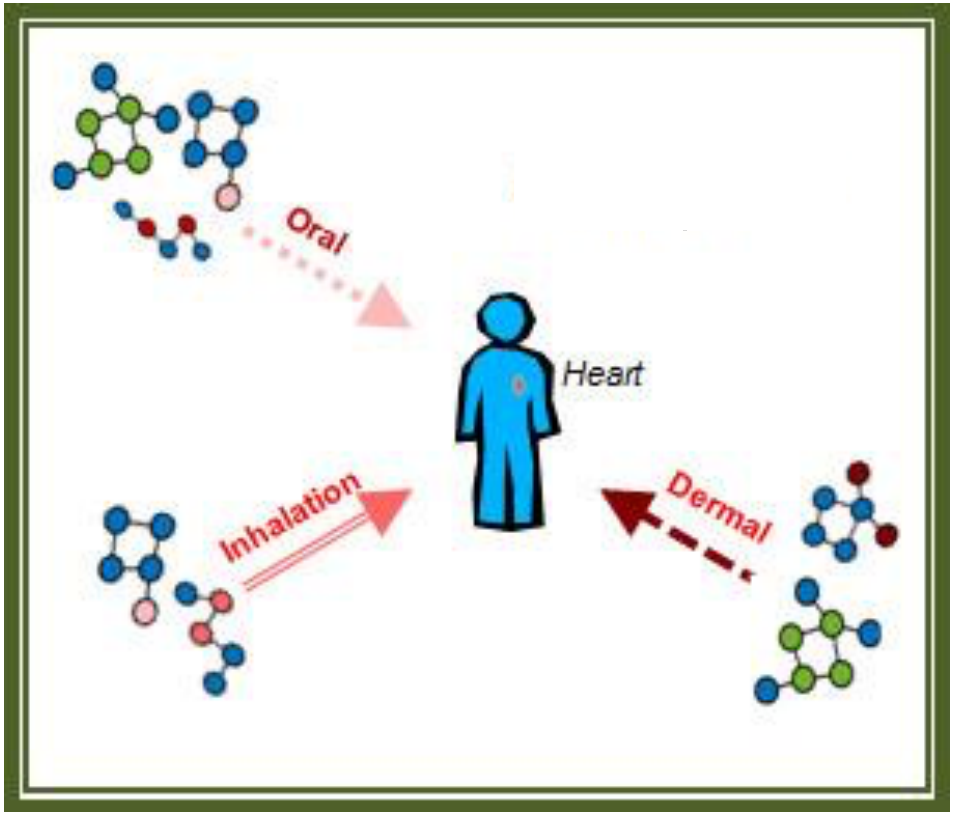
CUMULATIVE EFFECT



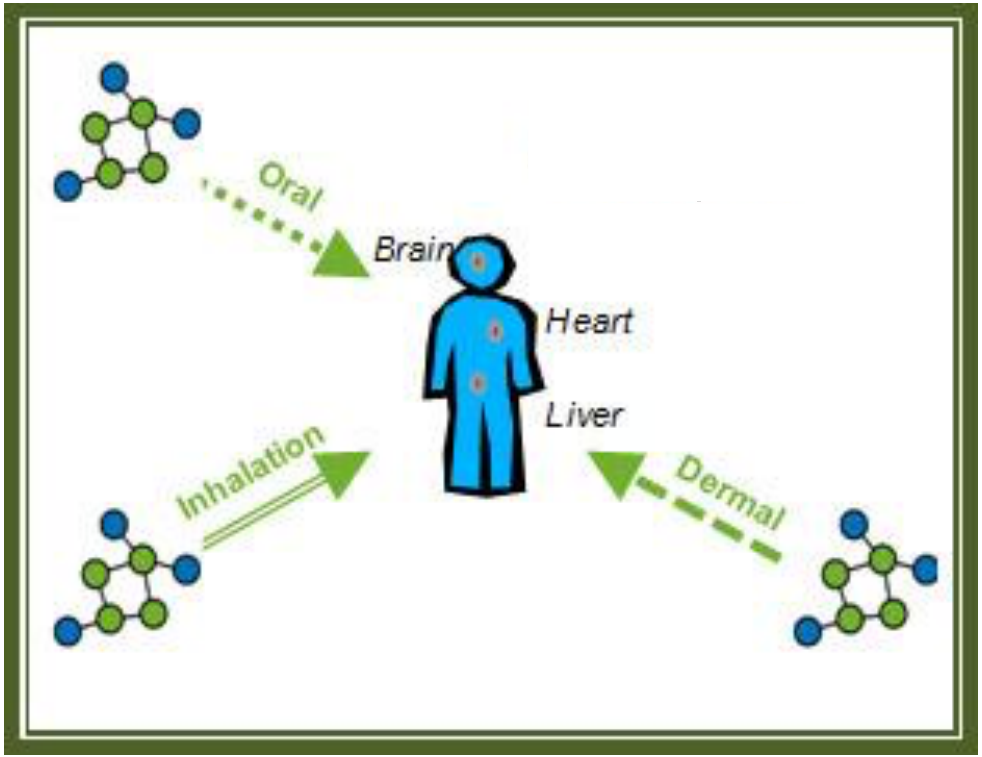
Biomagnification:

increase in concentration of a pollutant from one link in a food chain to another

CUMULATIVE EXPOSURE



AGGREGATE EXPOSURE



POLYCHLORINATED DIBENZO-P-DIOXINS/DIBENZOFURANS (PCDD/FS*)
POLYCHLORINATED BIPHENYLS (PCB)

- **Polychlorinated Dibenzo-p-Dioxins (PCDD) (75)**
- **Polychlorinated Dibenzofurans (PCDF) (135)**
- **(17/210)**

- **Non-Dioxin-like polychlorinated biphenyls (NDL-PCB) (197)**
- **Dioxin-like polychlorinated biphenyls (DL-PCBs/DL-PCBs) (12)**
- **(12/209)**

- 17 PCDD/Fs are relatively persistent in animals and humans and therefore considered relevant.
- ***Considered non-genotoxic carcinogens, bioaccumulative, with very large kinetic differences between animals and humans***

CONGENER	relative effect potency (REP) WHO_{2005} – TEF	pg	total toxic equivalent (TEQ) WHO_{2005} – TEF	pg/kg bw
PCDD				
2,3,7,8 - TCDD	1	20	20	0.29
1,2,3,7,8 - PeCDD	1	60	60	0.86
1,2,3,4,7,8 - HxCDD	0.1	10	1	0.014
1,2,3,6,7,8 - HxCDD	0.1	70	7	0.1
1,2,3,4,6,7,8 - HpCDD	0.01	130	1.3	0.02
1,2,3,4,6,7,8,9 - OCDD	0.0003	600	0.2	0.003
Total		890	89.5	1.3

METALS

- **Metals can neither be created nor destroyed**
  - Problematic environmental contaminants
  - However, chemical form of the metal can be altered
- **Metals are naturally occurring**
  - Natural sources of toxicity
  - Anthropogenic activities increase metal toxicity either because:
    - Metals are moved from biologically inaccessible to accessible compartments in the biosphere.
    - Form of the metal is changed to more bioavailable or toxic form

MERCURY (Hg)

- Elemental
  - liquid at room temperature that volatizes readily
  - rapid distribution in body by vapor, poor in GI tract
- Inorganic
  - poorly absorbed in GI tract, but can be caustic
  - dermal exposure has resulted in toxicity
- Organic
  - lipid soluble and well absorbed via GI, lungs and skin
  - can cross placenta, BBB and into breast milk

MERCURY (Hg)

- Toxicity occurs with long term exposure and effects the CNS.
  - Signs progress from paresthesias to ataxia, followed by generalized weakness, visual and hearing impairment, tremor and muscle spasticity, and then coma and death.
- Teratogen with large chronic exposure
  - Asymptomatic mothers with severely affected infants
  - Infants appeared normal at birth, but psychomotor retardation, blindness, deafness, and seizures developed over time.

NOAEL: 1.5 mg/kg b.w./day

ARSENIC (As)

- As ^{III}:
  - bind to sulfhydryl groups leading to inhibition of enzymatic systems
  - inhibit the Krebs cycle and oxidative phosporylation. These lead to inhibition of ATP production
- As ^{V}
  - can replace the stable phosphate ester bond in ATP and produce an arsenic ester stable bond which is not a high energy bond

- **$BMDL_{10}$:0.0003 mg/kg b.w./day**

LEAD (Pb)

- Lead has affinity for SH groups and is toxic to zinc-dependent enzyme systems
  - Heme synthesis: hemoglobin, cytochromes
  - Steroid metabolism and membrane integrity
  - Interference in vitamin D synthesis in renal tubular cells (conversion of 1-hydroxyvitamin D to 1,25-hydroxyvitamin D)
    - **$BMDL_{10}$: 0.00063 mg/kg b.w./day**

ENSURING THE SAFETY OF CHEMICALS

- Synthetic
- Persistent
- **Natural**
- Endocrine active

SOSTANZE TOSSICHE NEGLI ALIMENTI

NATURALI

- Normali componenti degli alimenti (nutrienti)

- **NATURALI CONTAMINANTI DEGLI ALIMENTI**
  - **TOSSINE NATURALI**
  - Contaminazione di origine microbiologica
  - Tossine presenti negli alimenti animali

MICOTOSSINE

TOSSICITA' MICOTOSSINE

EPATOTOSSINE	CANCEROGENE	NEFROTOSSINE	TERATOGENE	MUTAGENE
Aflatossine	Patulina	**Ocratossine**	**Aflatossina**	**Aflatossine**
Rubratossine	Ac. Penicillico	**Aflatossine**	Rubratossine	Patulina
Sporidesmina	**Aflatossine**	Citrinina	Tricoteceni	Ac. Penicillico
Ocratossine	Tricoteceni		**Ocratossine**	Rubratossina

MYCOTOXINS

• Aflatoxin B_1	<10 ppb (food)
• Aflatoxin M_1	<0.5 ppb (milk)
• Patulin	0.4 µg/kg bw (PMTDI)
• Fumosin B_1	2.0 µg/kg bw (PMTDI)
• Deoxynivalenol	1.0 µg/kg bw (PMTDI)
• T-2 and HT-2toxin	60 **ng**/kg bw (PMTDI)
• Ochratoxin A	100 **ng**/kg bw **(PTWI)**

ENSURING THE SAFETY OF CHEMICALS

- Synthetic
- Natural
- Persistent
- **Endocrine active**

CRITERIA FOR ENDOCRINE DISRUPTION

COMMISSION REGULATION (EU) 2018/605 OF 19TH APRIL 2018

An **active substance** shall be considered as having endocrine disruption properties that may cause adverse effect in humans if, it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effect identified are not relevant to humans:

1. It shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;
2. It has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;
3. The adverse effect is a consequence of the endocrine mode of action

RISK ANALYSIS