Rischi e dose soglia per i prioritari e gli emergenti: luci ed ombre

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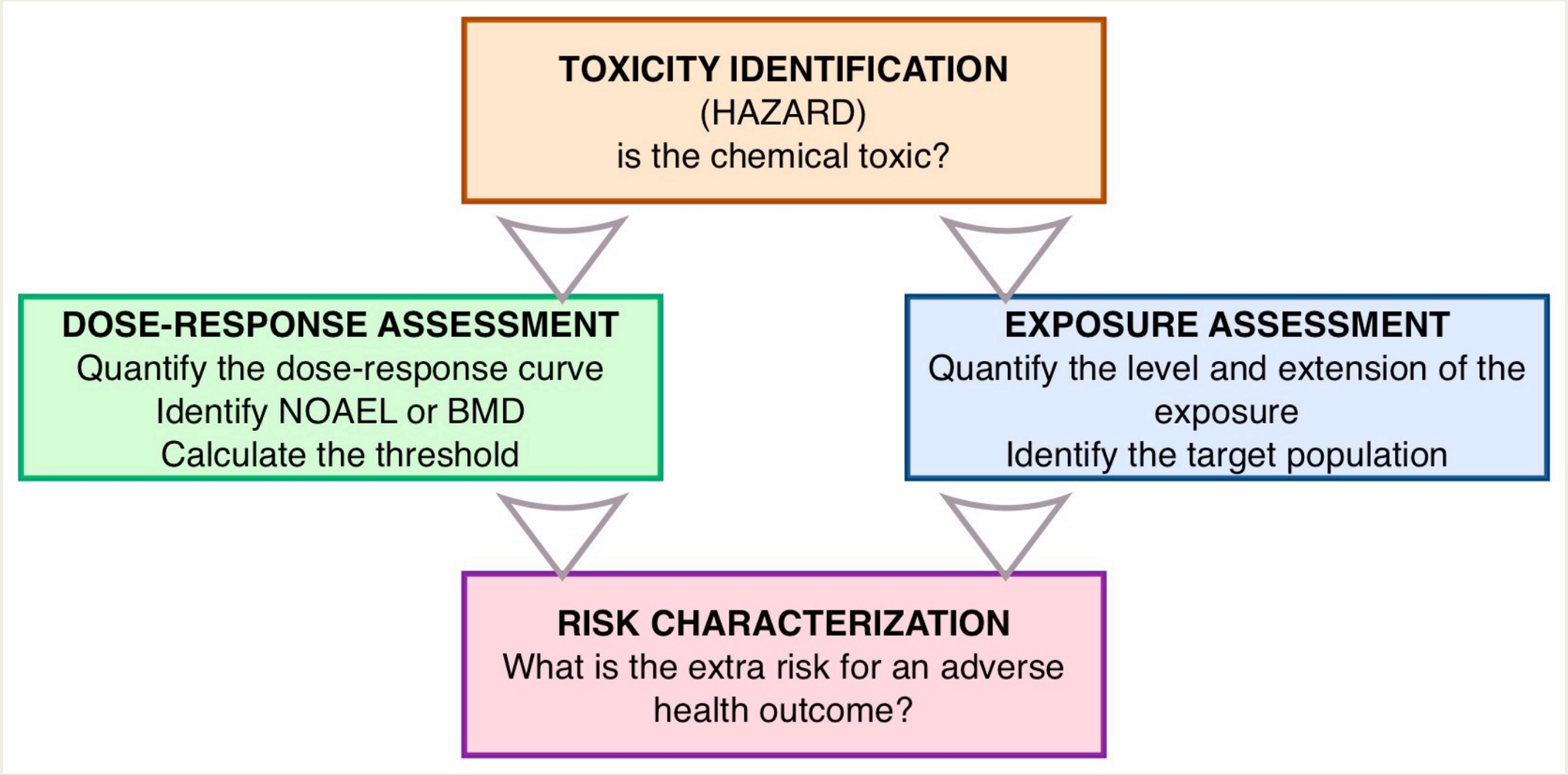
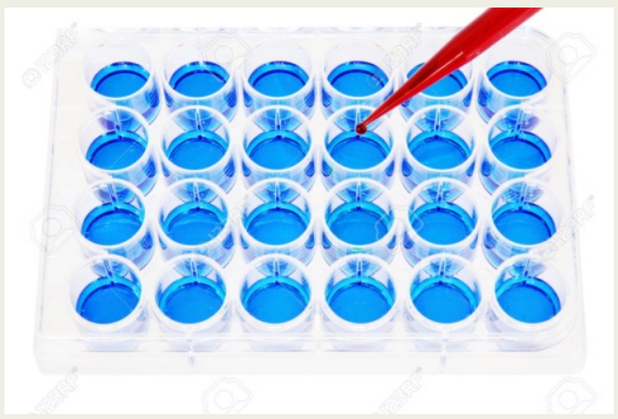
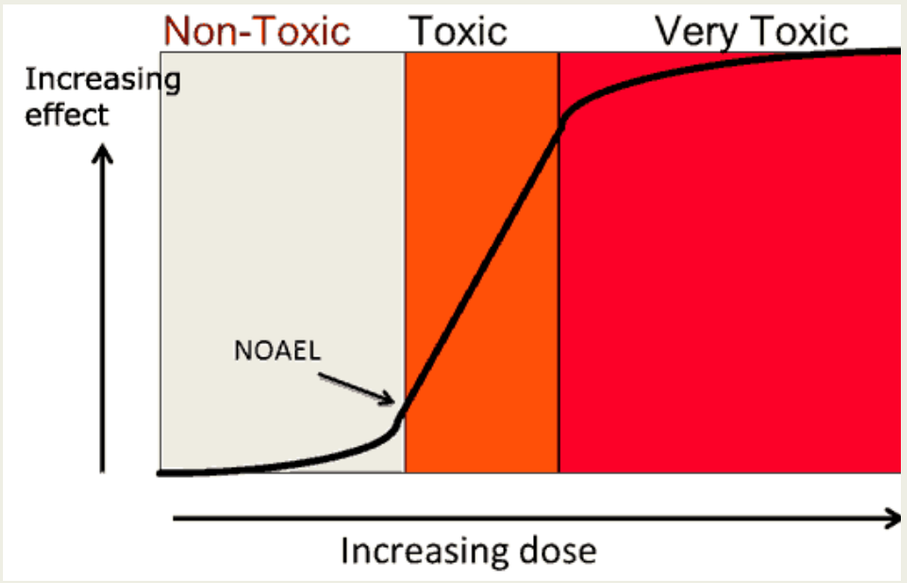
Valutare il rischio per l'esposizione alle sostanze chimiche

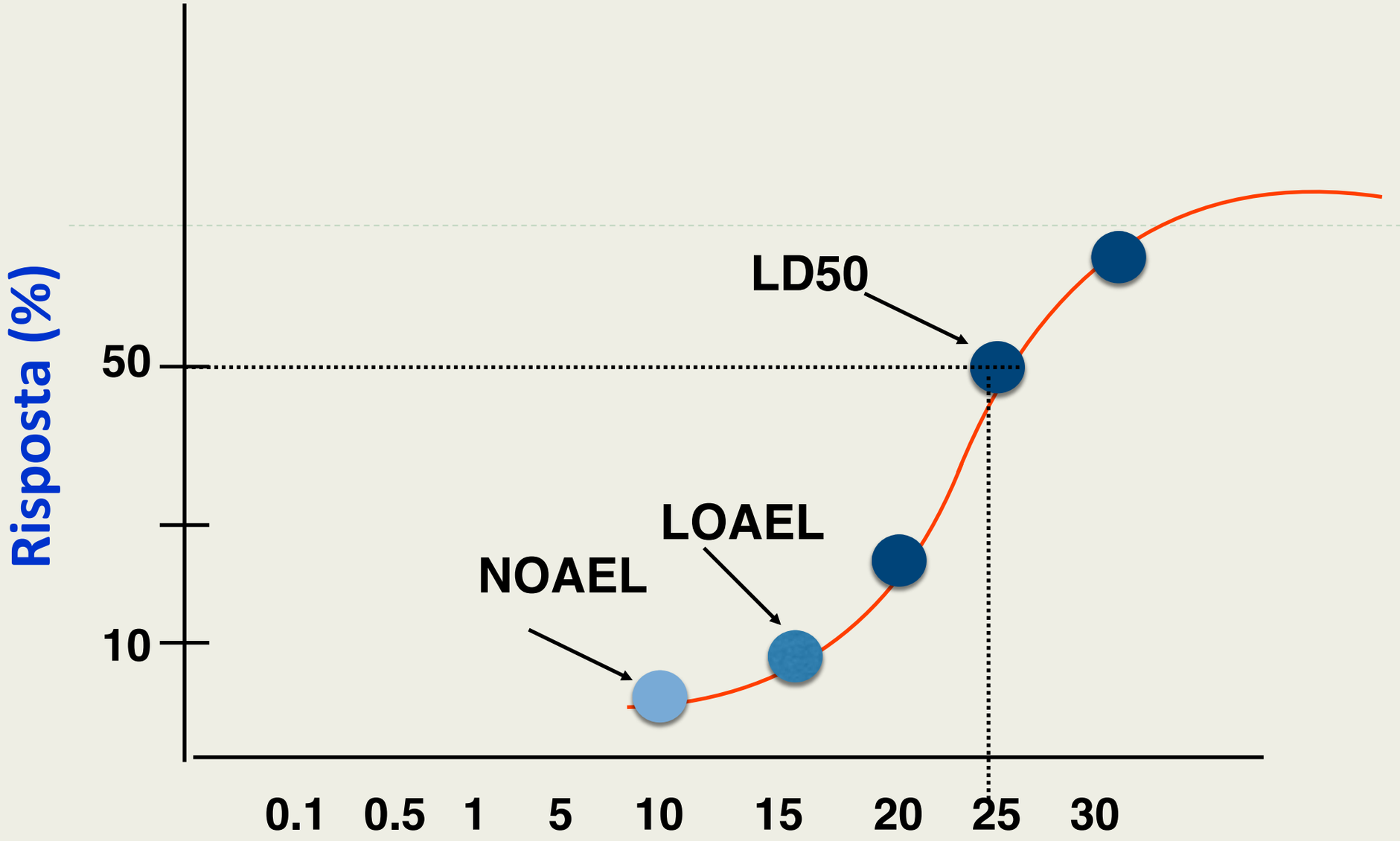




- Tossicità acuta
- Tossicità subcronica
- Tossicità cronica

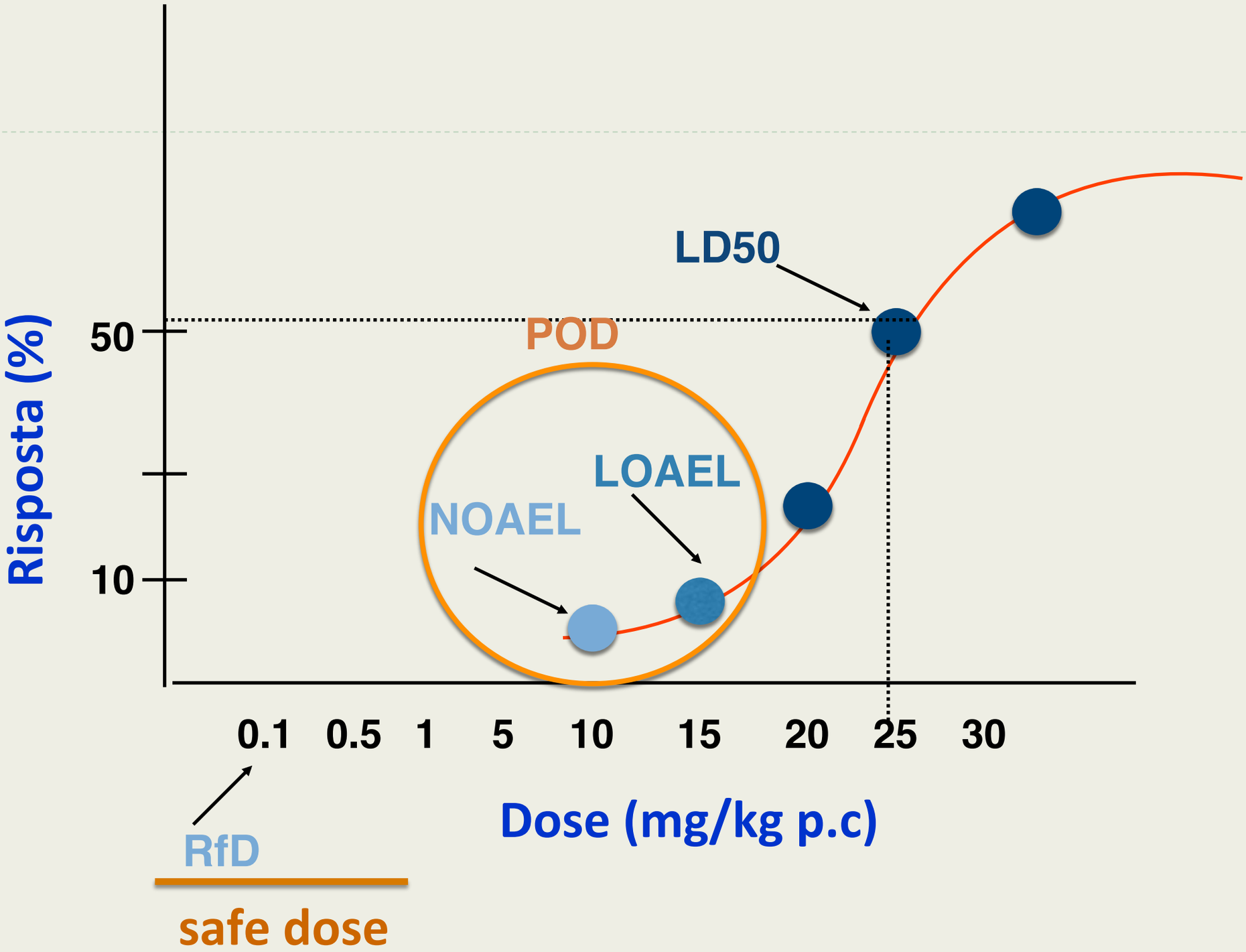


- Studi standard (protocolli convalidati e linee guida)
- Eseguiti in Buona Pratica di Laboratorio
- Mutualmente accettati

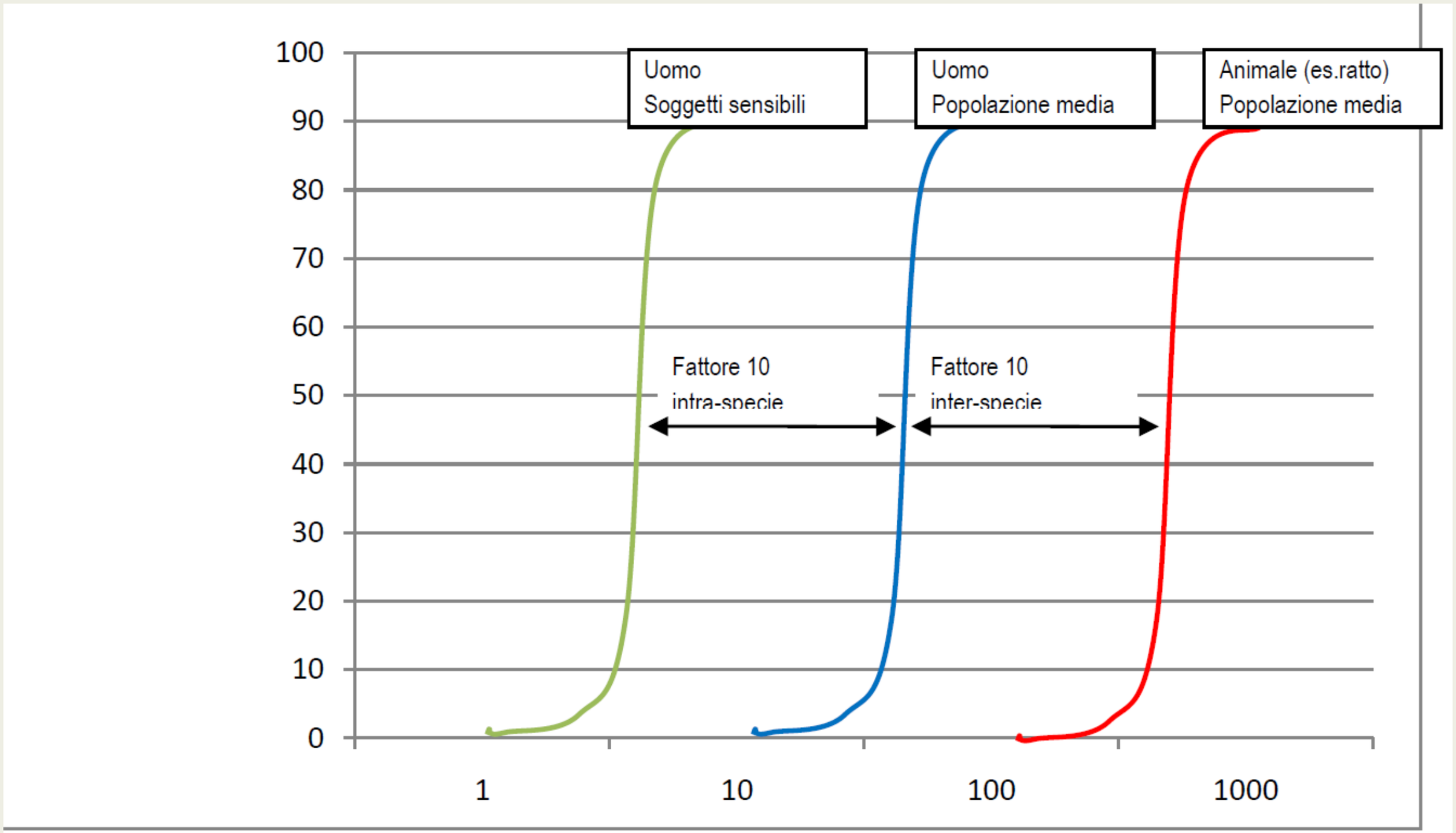


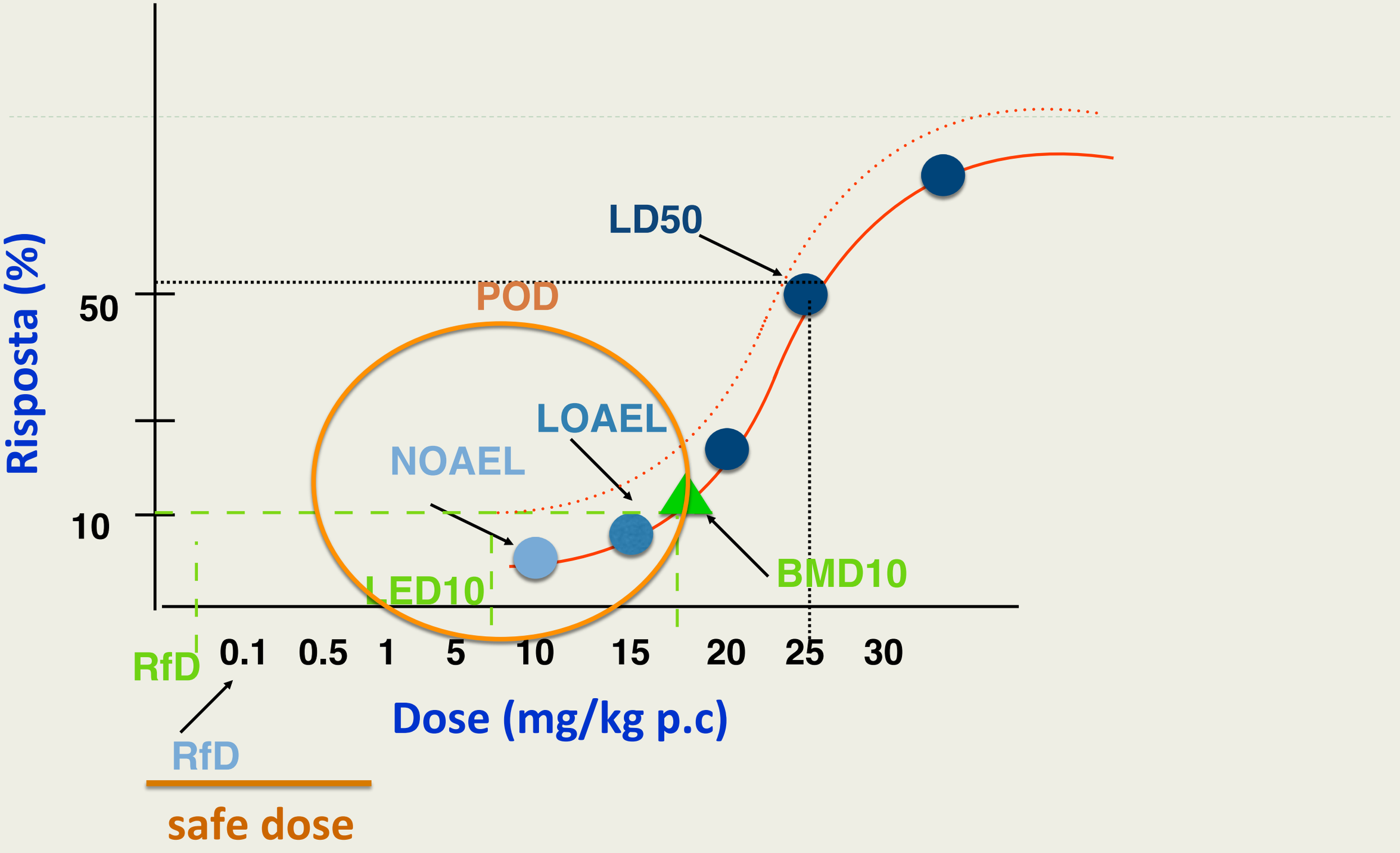
Dose (mg/kg p.c)

Indice	Spiegazione
LD50	lethal dose. Dose letale che uccide il 50% degli esposti in una unica somministrazione
NOAEL	No Observed Adverse Effect Level
LOAEL	Lowest Observed Adverse Effect Level
RfD	Refrence dose

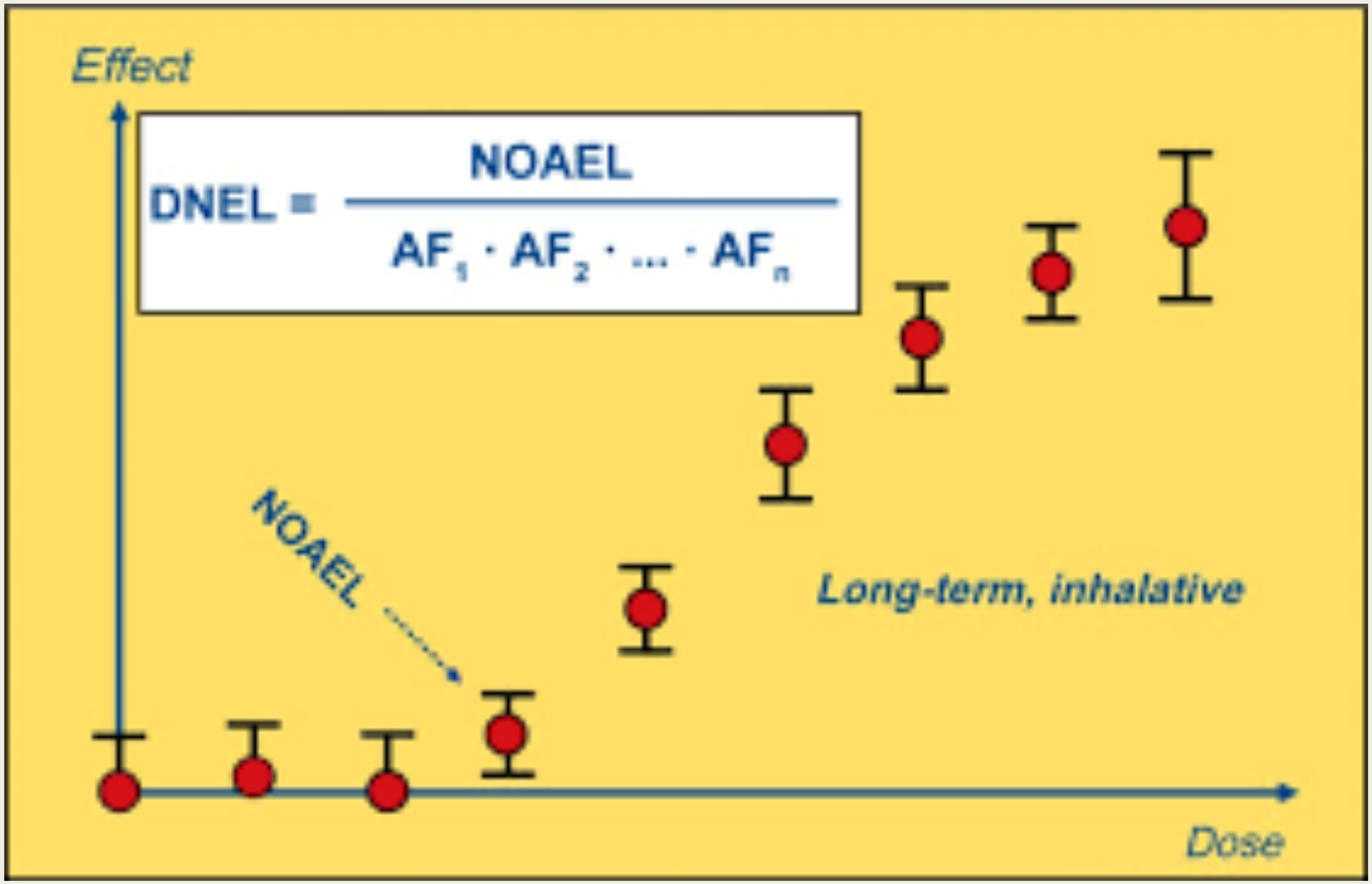


$$RfD = \frac{NOAEL_{\text{critical effect}}}{UF_{\text{interspecies}} \times UF_{\text{intraspecies}} \times MF}$$


100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
Uomo
Soggetti sensibili
Uomo
Popolazione media
Animale (es.ratto)
Popolazione media
Fattore 10
intra-specie
Fattore 10
inter-specie

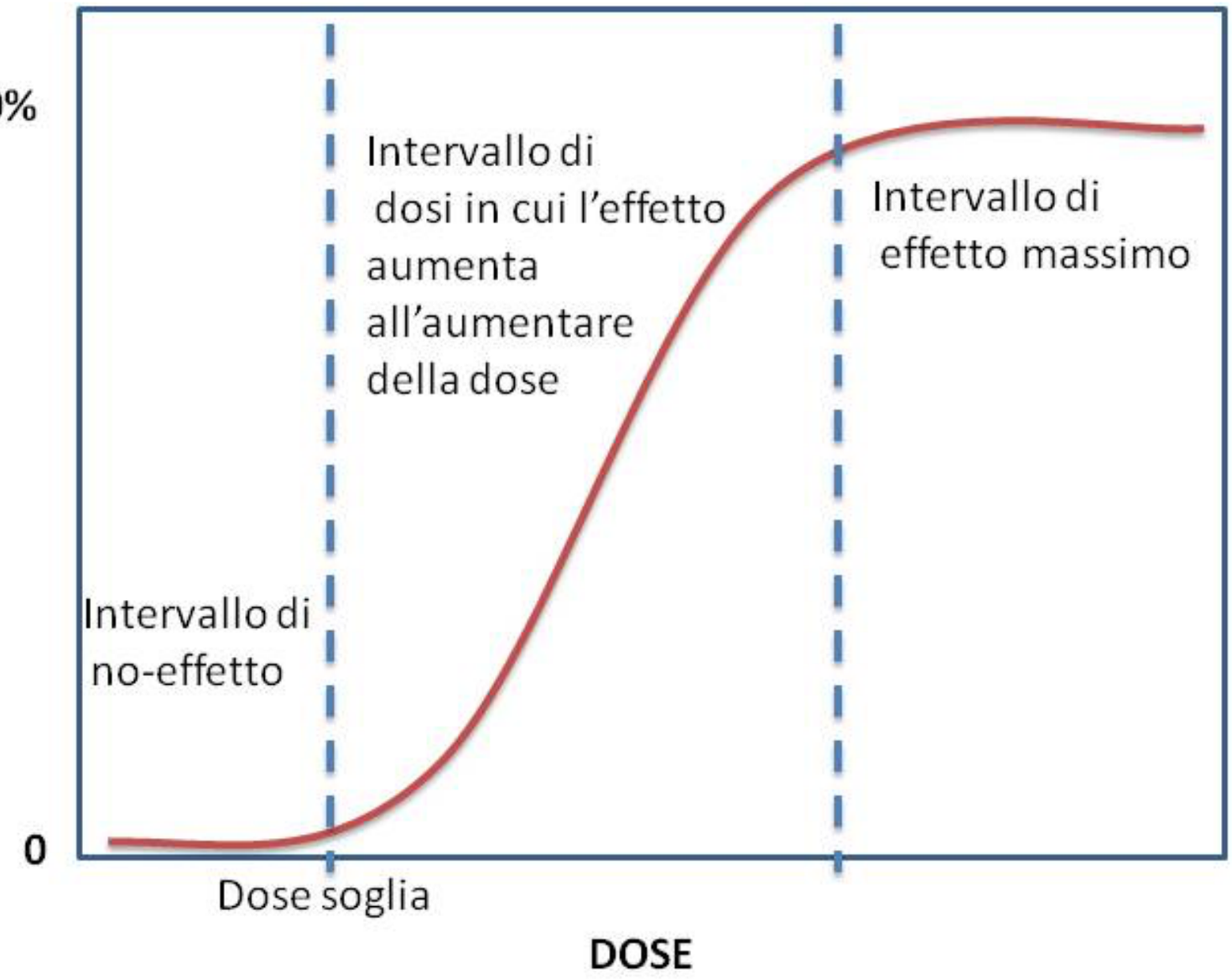

Risposta (%)
50
10
LD50
POD
LOAEL
NOAEL
LED10
BMD10
RfD
0.1
0.5
1
5
10
15
20
25
30
Dose (mg/kg p.c)
RfD
safe dose

Limiti di esposizione: DNEL



Assessment Factors - Differences		Default value – systemic effects	Default value – local effects
Interspecies	- Differences in metabolic rate - Other differences	Allometric scaling factor*(4 for rat) 2.5	- 1 or 2.5
Intraspecies	- Worker - General population	5 10	5 10
Exposure Duration	- Subacute to subchronic - Subchronic to chronic - Subacute to chronic	3 2 6	3 2 6
Dose-response	- LOAEL to NOAEL - Other issues	3-10 1(default)	3-10 1(default)
Data quality	- Case by case	>=1(good quality=1)	>=1(good quality=1)

*Allometric scaling factors: rat (4), mouse (7), hamster (5), rabbit (2.4), monkey(2), dog (1.4). Only to be applied to oral and dermal NOAEL in units (mg/kg bw/day).


100%
EFFETTO
Intervallo di
dosi in cui l'effetto
aumenta
all'aumentare
della dose
Intervallo di
effetto massimo
Intervallo di
no-effetto
0
Dose soglia
DOSE

Curve non monotone (ormesi)

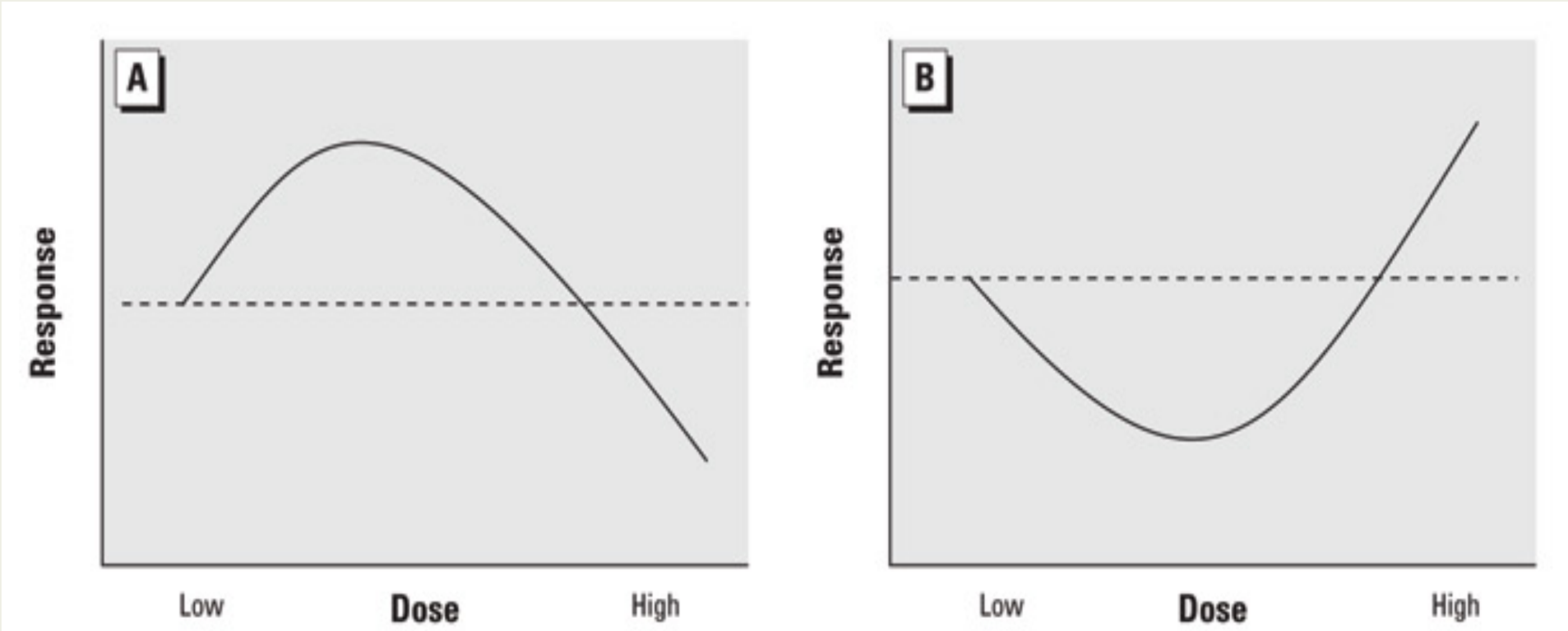
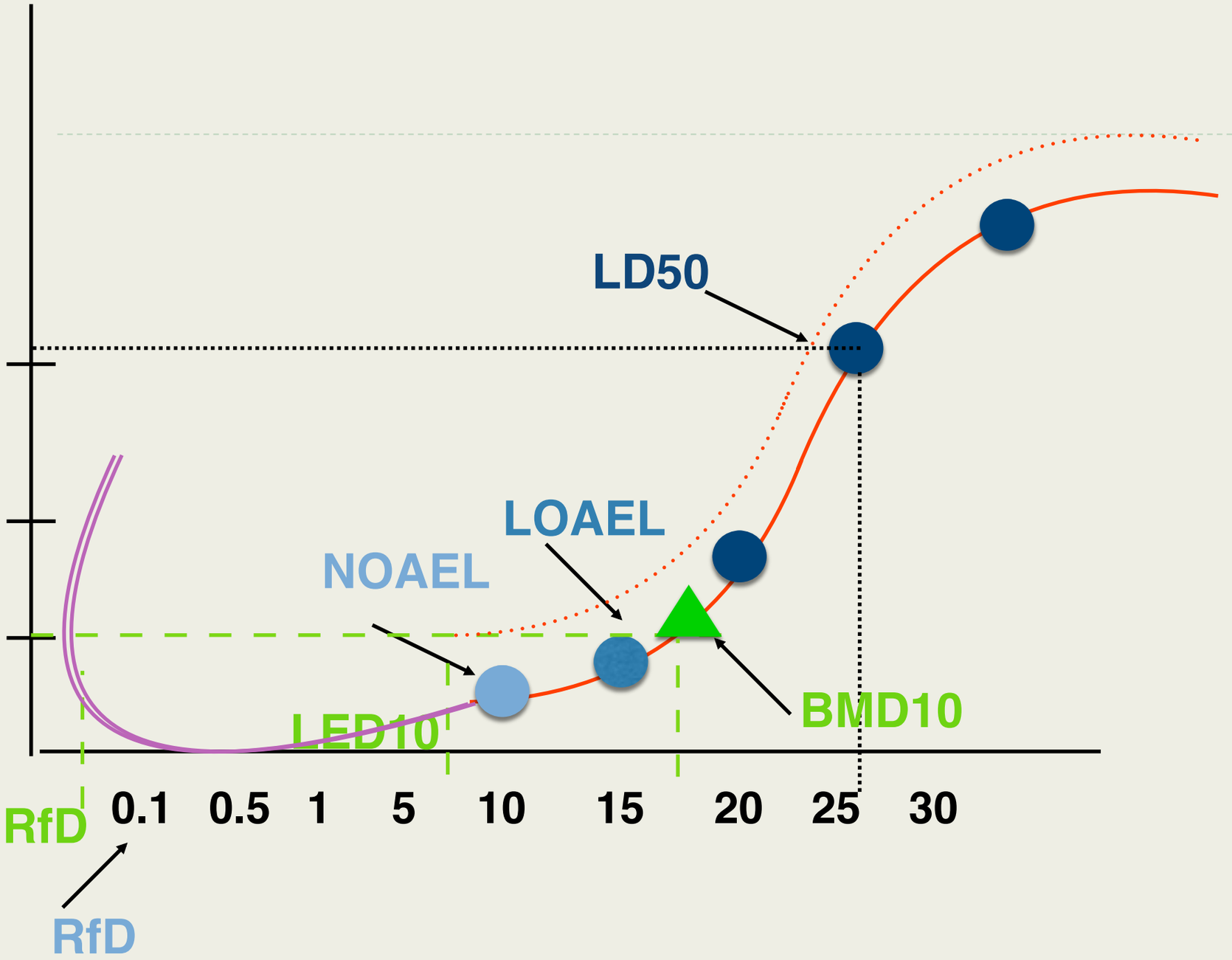
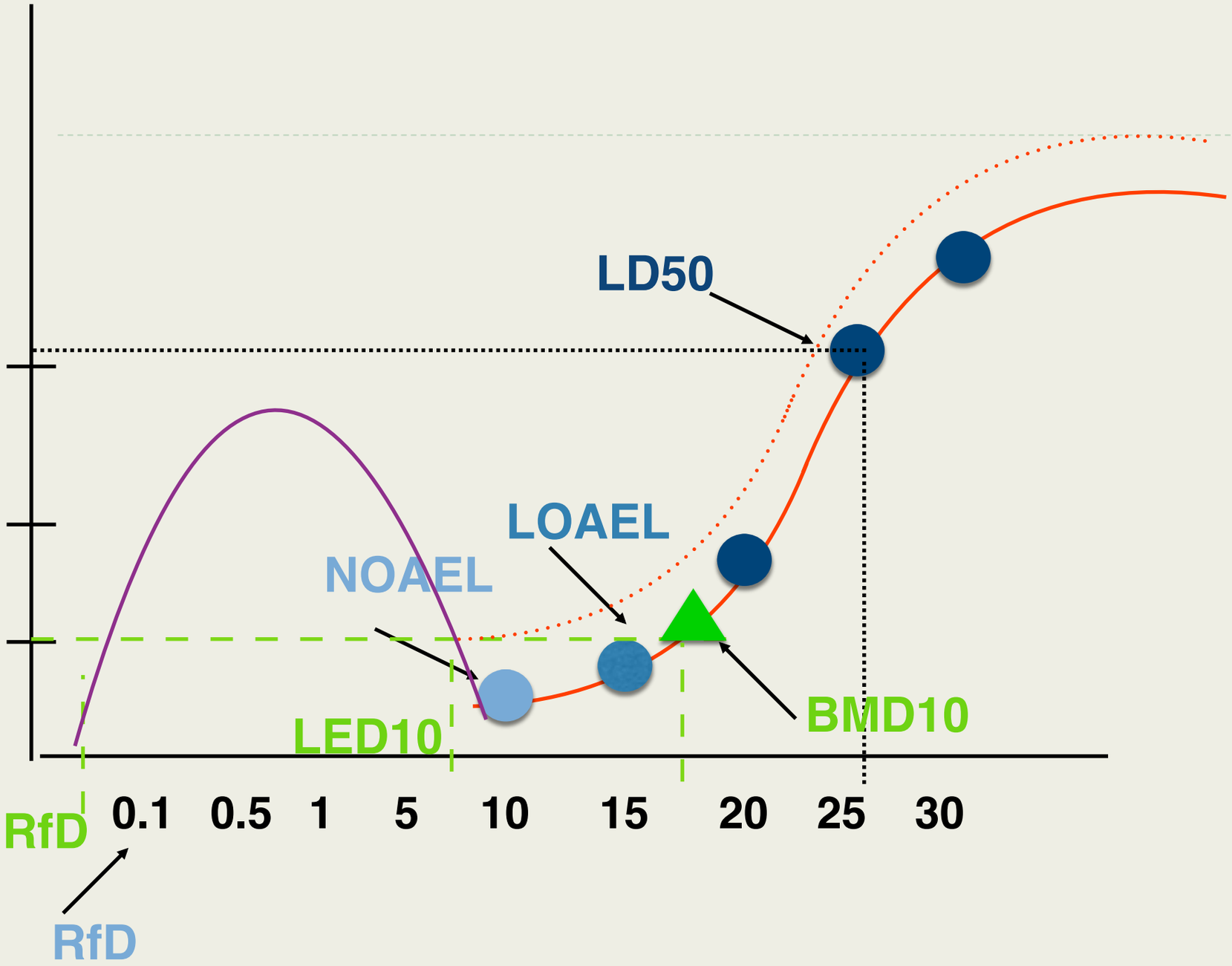


Figure 1. Schematic forms of the hormetic dose response. (*A*) The most common form of the hormetic dose–response curve showing low-dose stimulatory and high-dose inhibitory responses (β- or inverted U-shaped curve). (*B*) The hormetic dose–response curve depicting low-dose reduction and high-dose enhancement of adverse effects (J- or U-shaped curve).

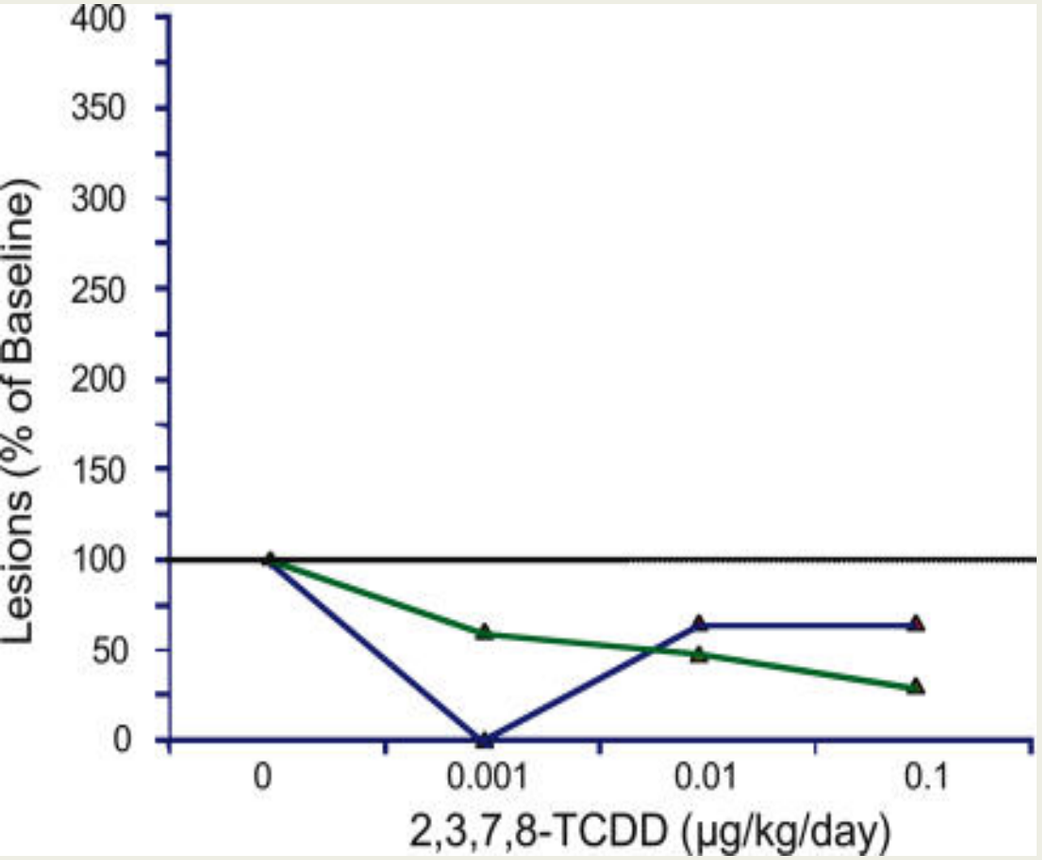
- Dose-risposta bifasica che porta a curve a U, J o U rovesciata


LD50
LOAEL
NOAEL
LED10
BMD10
RfD
0.1
0.5
1
5
10
15
20
25
30
RfD

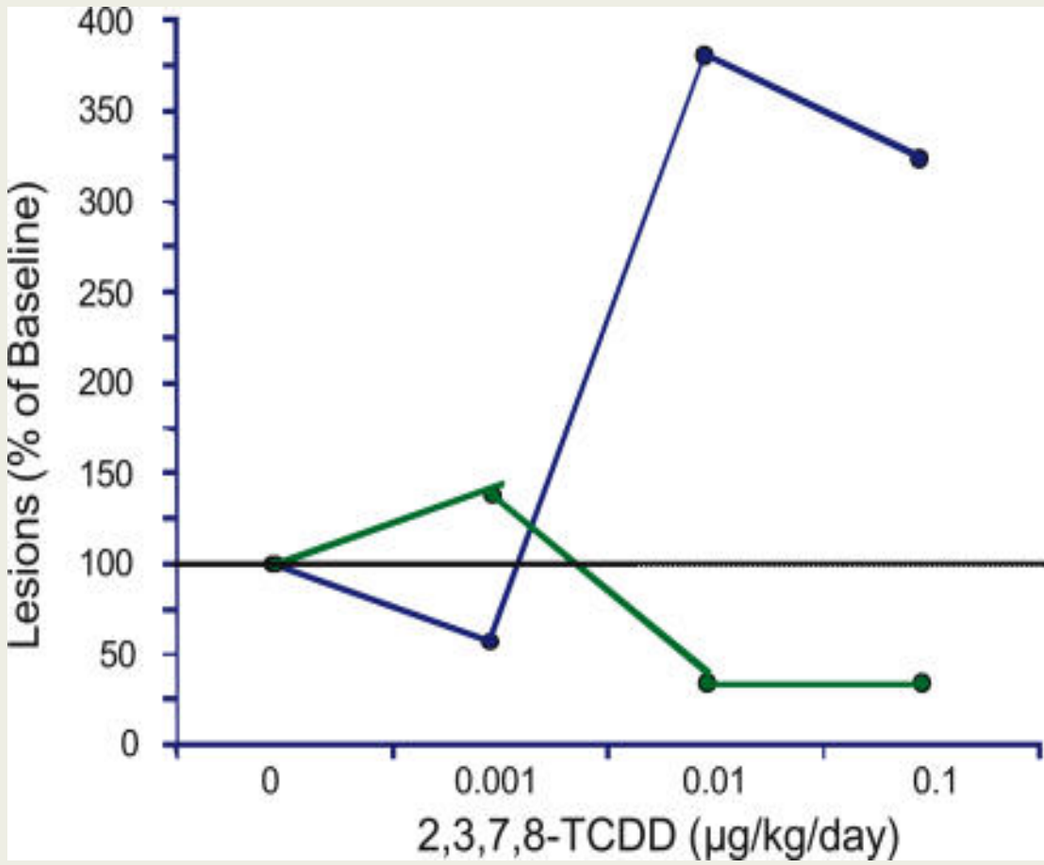

LD50
LOAEL
NOAEL
LED10
BMD10
RfD
0.1
0.5
1
5
10
15
20
25
30
RfD

Effetti della diossina nei ratti (test a lungo termine)

Liver and pancreas tumor in male Sprague Dawley rats

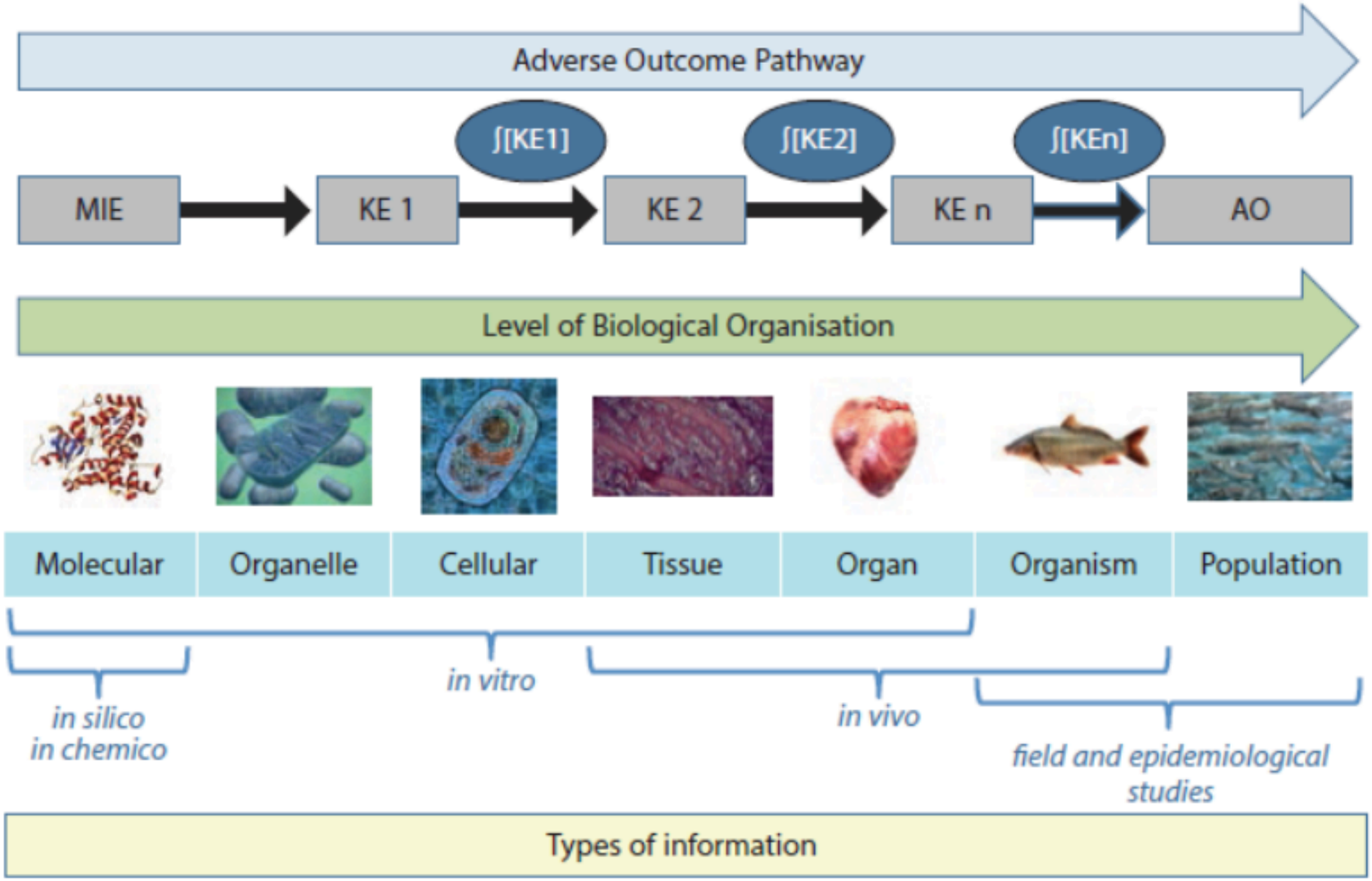


Liver and pancreas tumor in female Sprague Dawley rats



Borak and Siriannim Dose Response, 3 443, 2005

Siamo certi che le curve non monotone a basse dosi siano legate a un effetto avverso?



Courtesy of OECD

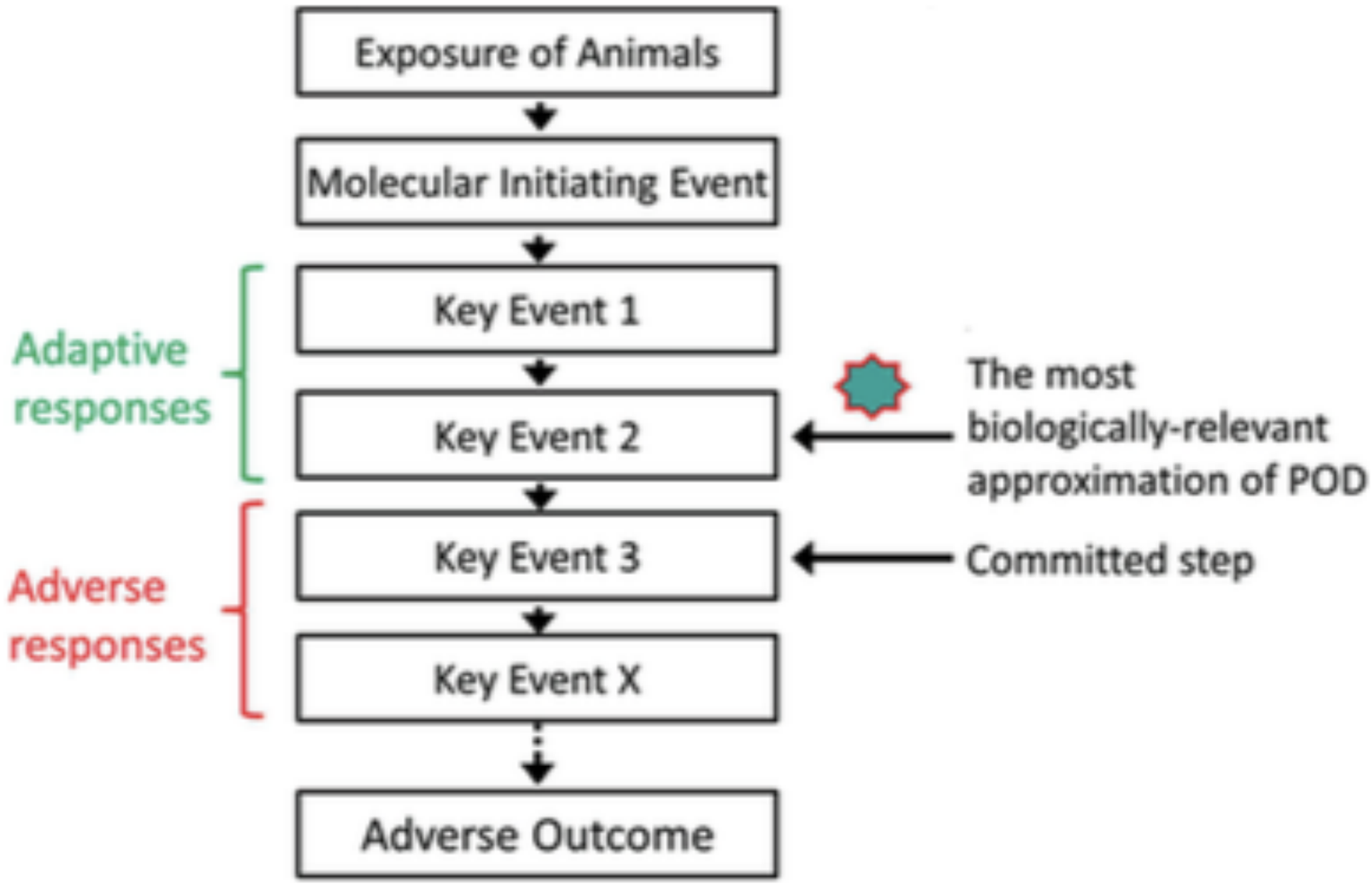


Figure 2. Selection of the most appropriate POD from toxicogenomics data.

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The use of omics-based approaches in regulatory toxicology: an alternative approach to assess the no observed transcriptional effect level

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Rischi e dose soglia per i prioritari e gli emergenti: luci

una dose soglia per composti genotossici

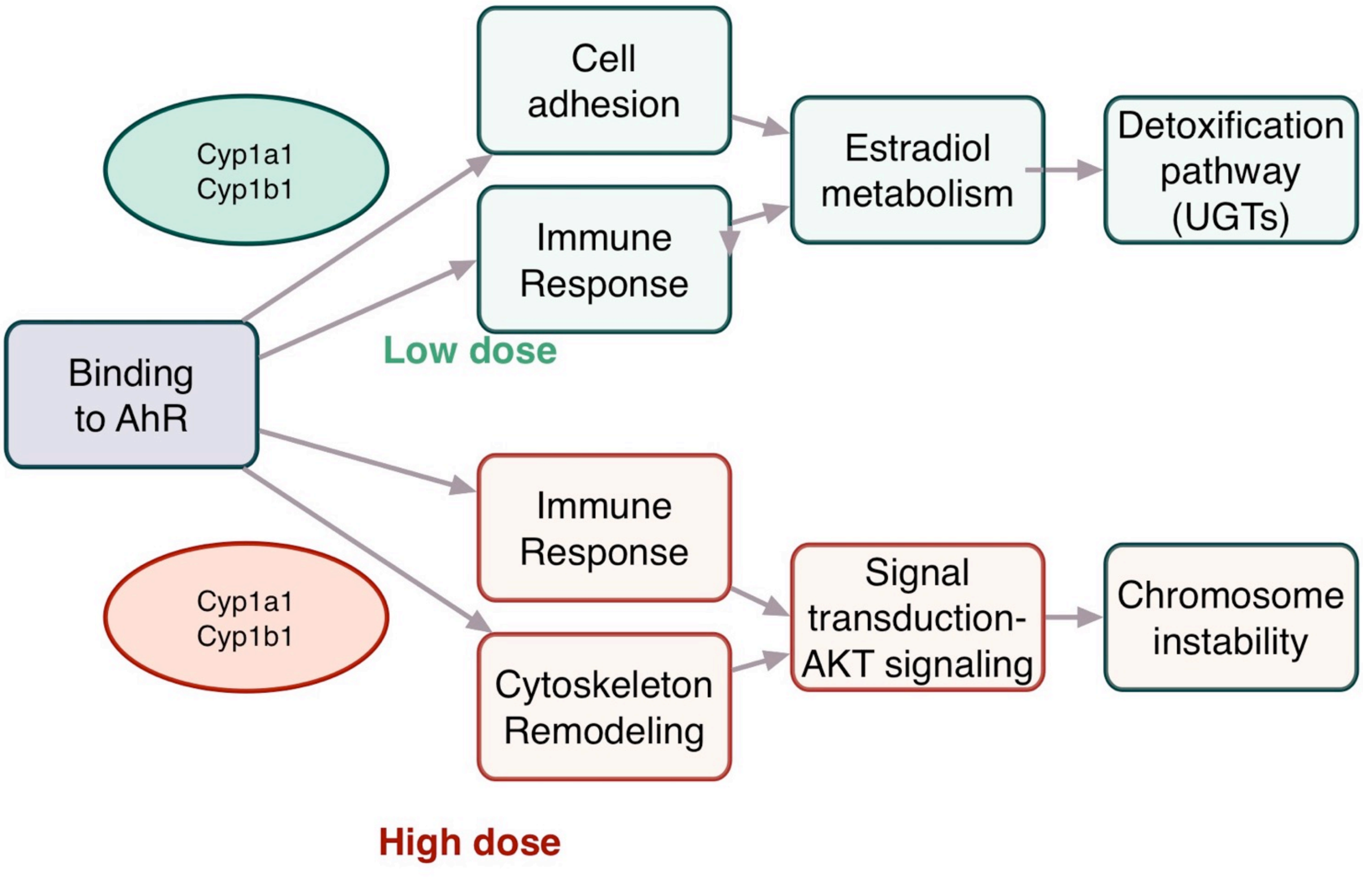
ACCEPTED MANUSCRIPT

The Transformics Assay: First Steps for the Development of an Integrated Approach to Investigate the Malignant Cell Transformation *in vitro*

Maria Grazia Mascolo ✉, Stefania Perdichizzi, Monica Vaccari, Francesca Rotondo, Cristina Zanzi, Sandro Grilli, Martin Paparella, Miriam N Jacobs, Annamaria Colacci ✉

Carcinogenesis, bgy037, https://doi.org/10.1093/carcin/bgy037
Published: 15 March 2018 **Article history** ▾

Abstract

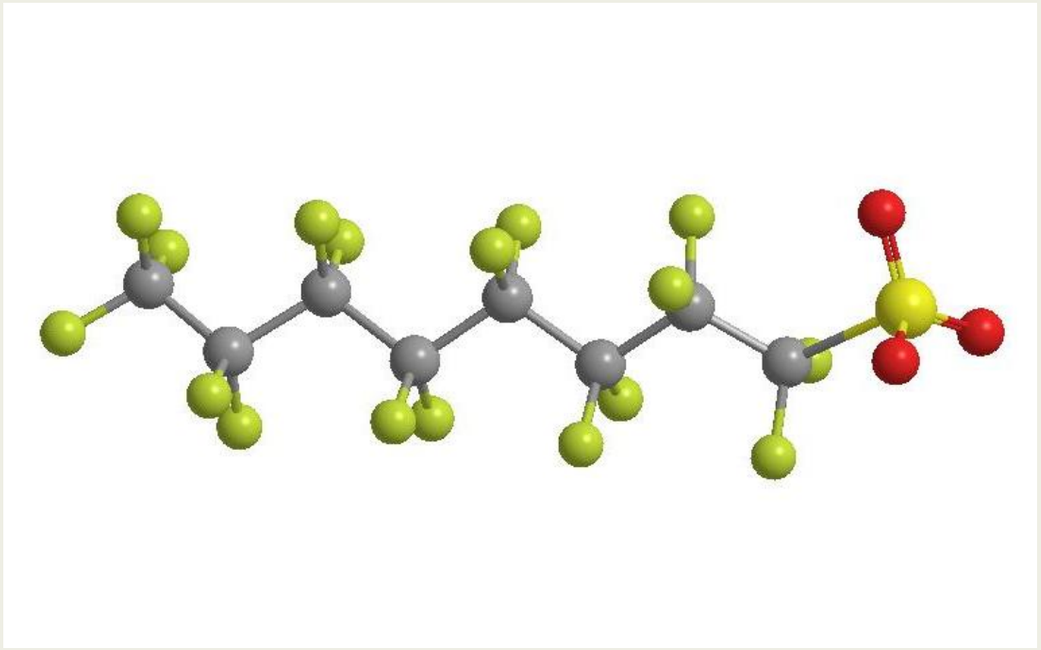

Cell adhesion
Cyp1a1
Cyp1b1
Estradiol metabolism
Detoxification pathway (UGTs)
Immune Response
Binding to AhR
Low dose
Immune Response
Signal transduction-AKT signaling
Chromosome instability
Cyp1a1
Cyp1b1
Cytoskeleton Remodeling
High dose

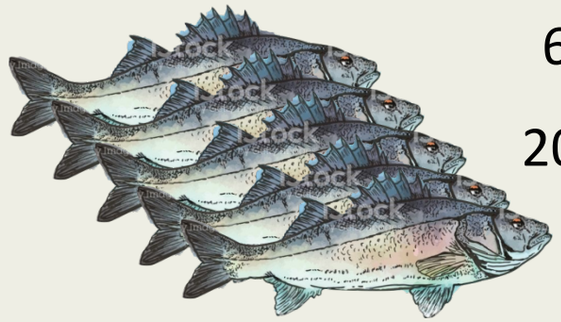
Rischi e dose soglia per i prioritari e gli emergenti: ombre

Sostanze Perfluoroalchilate

Dal poco che sappiamo…..

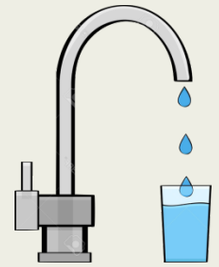
- I PFAS sono composti bioaccumulanti
- Il 17 marzo 2010 la commissione europea ne ha disposto un monitoraggio negli alimenti che costituiscono l'unica fonte significativa di esposizione umana
- Al momento attuale non si conosce il meccanismo d'azione e non ci sono dati sufficienti per una loro classificazione ne' come cancerogeni ne' come distruttori endocrini per l'uomo.
- Effetti avversi ipotizzati
  - Tossicità acuta moderata
  - Tossicita' subcronica e cronica
    - Fegato (accumulo)
    - Tiroide (alterazione del profilo ormoni tiroidei)
    - Lipoproteine
- Dati sperimentali e studi umani mostrano curve non monotone





60 ng/kg p.c/die

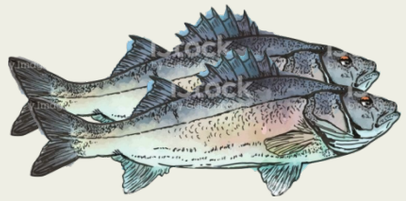
200 ng/kg p.c/die



0,5% totale intake

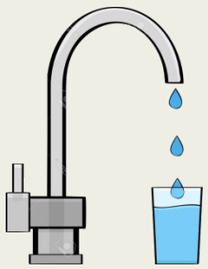
Perffluoro ottano sulfonato (PFOS)

Altro: 2% totale intake



2 ng/kg p.c/die

6 ng/kg p.c/die



< 16 % totale intake

Acido perfluottanoico (PFOA)

Effetti avversi e dose soglia: PFOS

- Dose soglia
  - NOAEL piu’ bassa da studi subcronici (effetti sulla tiroide nelle scimmie)
    - 0.03 mg/kg p.c/die
  - TDI
    - 150 ng/kg p.c./die (NOAEL / 100 * 2)
- Limite precauzionale proposto 0.65 ng/L che consente di consumare 115 grammi di pesce al giorno

A conti fatti….

NOAEL (mg/kg p.c. die)	0.03	Tiroide nella scimmia
AF	4	Estrapolazione animale-uomo sulla base della diversa tossicocinetica
POD	0.0075	
UF	75	(UF 2.5 per tossicodinamica, UF 10 per differenza intraspecie, UF 3 per studio subcronico invece che cronico)
TDI (mg/kg p.c./die)	0.001	

Limite (health based value)

Acqua potabile = 0.001 X 70 X 0.2 / 1.5 L/die = 0.9 **µg/L**

Pesce = = 0.001 X 70 X / 150 g/die = 0.05 **µg/kg**

A conti fatti….

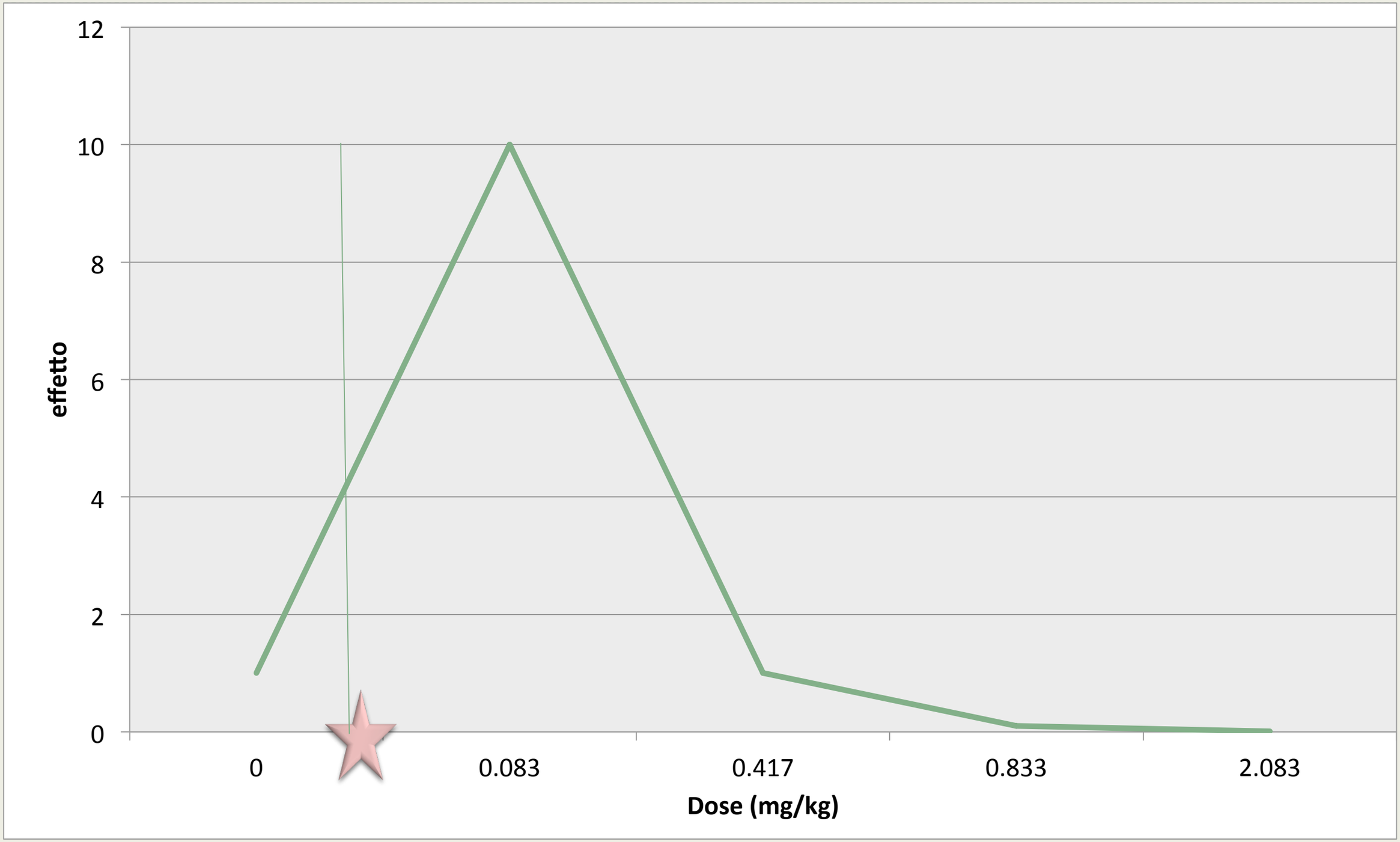
NOAEL (mg/kg p.c. die)	0.021	Ipetrofia epatica nel ratto
AF	14	Estrapolazione animale-uomo sulla base della diversa tossicocinetica
POD	0.0015	
UF	25	(UF 2.5 per tossicodinamica, UF 10 per differenza intraspecie)
TDI (mg/kg p.c./die)	0.00006	

Limite (health based value)

Acqua potabile = 0.00006 X 70 X 0.2 / 1.5 L/die = 0.6 **µg/L**

Pesce = = 0.00006 X 70 / 150 g/die = 0.028 **µg/kg**

Eventi molecolari (livello NK, risposta immunitaria) in topi esposti a PFOS



Effetti avversi e dose soglia: PFOA

- Dose soglia
  - NOAEL piu’ bassa da studi subcronici
    - 0.06 mg/kg p.c/die
  - BMDL10: 0,3 - 0,7 mg/kg p.c/die
  - TDI
    - 1,5 µg/kg p.c./die (NOAEL / 100 * 2)
- Esposizione alimentare
  - 2 – 6 ng/kg p.c/die

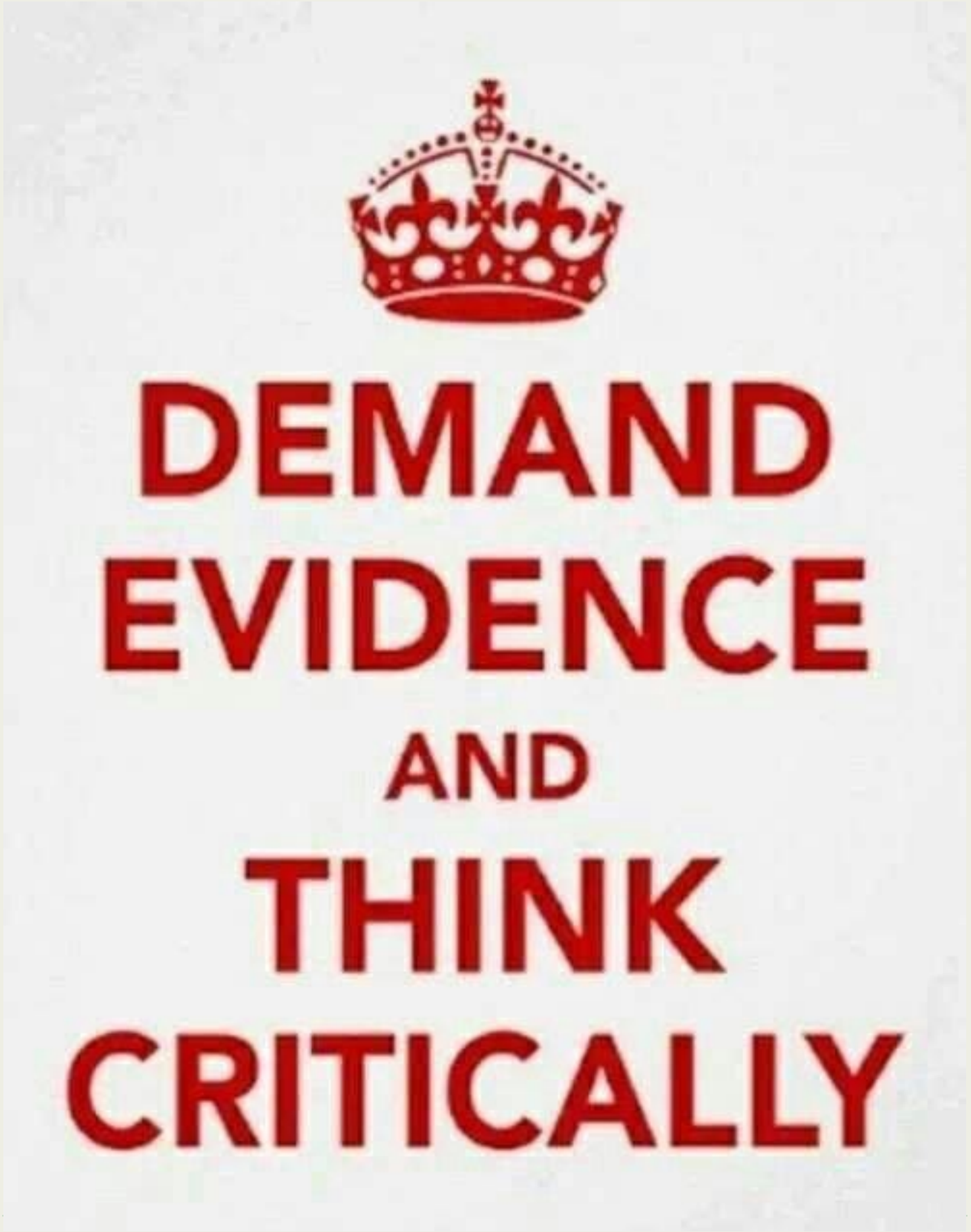
Table 7 Selected toxicity data for PFOS for freshwater species

Fonte: RIVM

Chronic[a]			**Acute**[a]		
Taxonomic group	**NOEC/EC10 [mg/L]**	**[µg/L]**	**Taxonomic group**	**L(E)C50 [mg/L]**	[µg/L]
Algae			**Algae**		
Chlorella vulgaris	8.2[b]	8200	*Chlorella vulgaris*	82[b]	82000
Navicula pelliculosa	191	191000	*Navicula pelliculosa*	283	283000
Pseudokirchneriella subcapitata	53[c]	53000	*Pseudokirchneriella subcapitata*	120[c]	120000
Cyanobacteria			**Cyanobacteria**		
Anabaena flos-aqua	94	94000	*Anabaena flos-aqua*	176	176000
Macrophytes			**Macrophyta**		
Lemna gibba	6.6[d]	6600	*Lemna gibba*	31[d]	31000
Myriophyllum sibiricum	0.56	560	**Crustaceans**		
Myriophyllum spicatum	3.2	3200	*Daphnia magna*	48[i]	48000
Crustaceans			*Daphnia pulicaria*	124	124000
Daphnia magna	7.0[e]	7000	*Moina macrocopa*	18	18000
Moina macrocopa	0.40[f,m]	400	*Neocaridina denticulate*	9.3	9300
Insects			**Platyhelmintes**		
Chironomus tentans	$< 2.3 \times 10^{-3}$[m]	< 2.3	*Dugesia japonica*	18[j]	18000
Enallagma cyathigerum	$< 1.0 \times 10^{-2}$[m]	< 10	**Mollusca**		
Fish			*Physa acuta*	165	165000
Oryzias latipes	$< 1.0 \times 10^{-2}$[m]	< 10	*Unio complamatus*	59	59000
Pimephales promelas	2.8×10^{-2}[g]	27	**Fish**		
Amphibians			*Lepomis macrochirus*	6.4	6400
Xenopus laevis	5.0[h]	5000	*Pimephales promelas*	6.6[k]	6600
			Oncorhynchus mykiss	13[l]	13000

Conclusioni

- E’ sempre possibile definire una dose-soglia, per piccola che sia, riferita anche a eventi precoci nel percorso che porta all’effetto avverso, che il piu’ delle volte sono riferiti a risposte adattative
- E’ solo sulla base di questi eventi, messi in luce con studi standard e/o tecnologie altamente performanti che e’ possibile effettuare delle stime scientificamente difendibili e basate sull’evidenza, che tengano anche conto di comportamenti anomali alle basse dosi


DEMAND
EVIDENCE
AND
THINK
CRITICALLY

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