Curso Sobre Protección Vegetal y Ecotoxicología 2023

Maestría en Protección Vegetal
Facultad de Ciencias Agrarias y Forestales
Universidad Nacional de la Plata (UNLP)

Clase 4. Biodisponibilidad, Bioacumulación y Mecanismos de acción tóxica

Dr. Pedro Carriquiriborde
Maestría en Protección Vegetal 2023, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de la Plata (UNLP)

Las tres fases de la acción tóxica

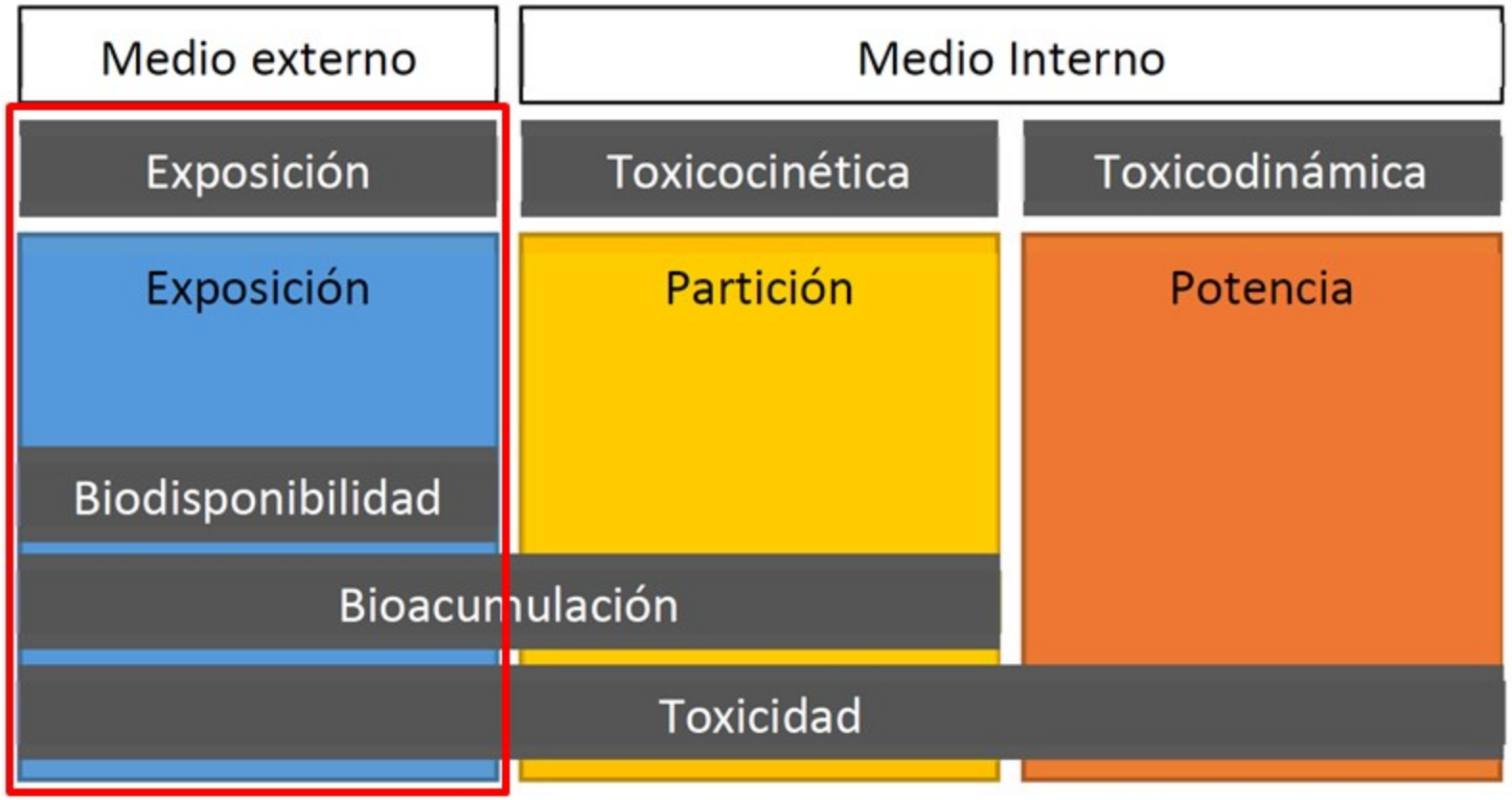
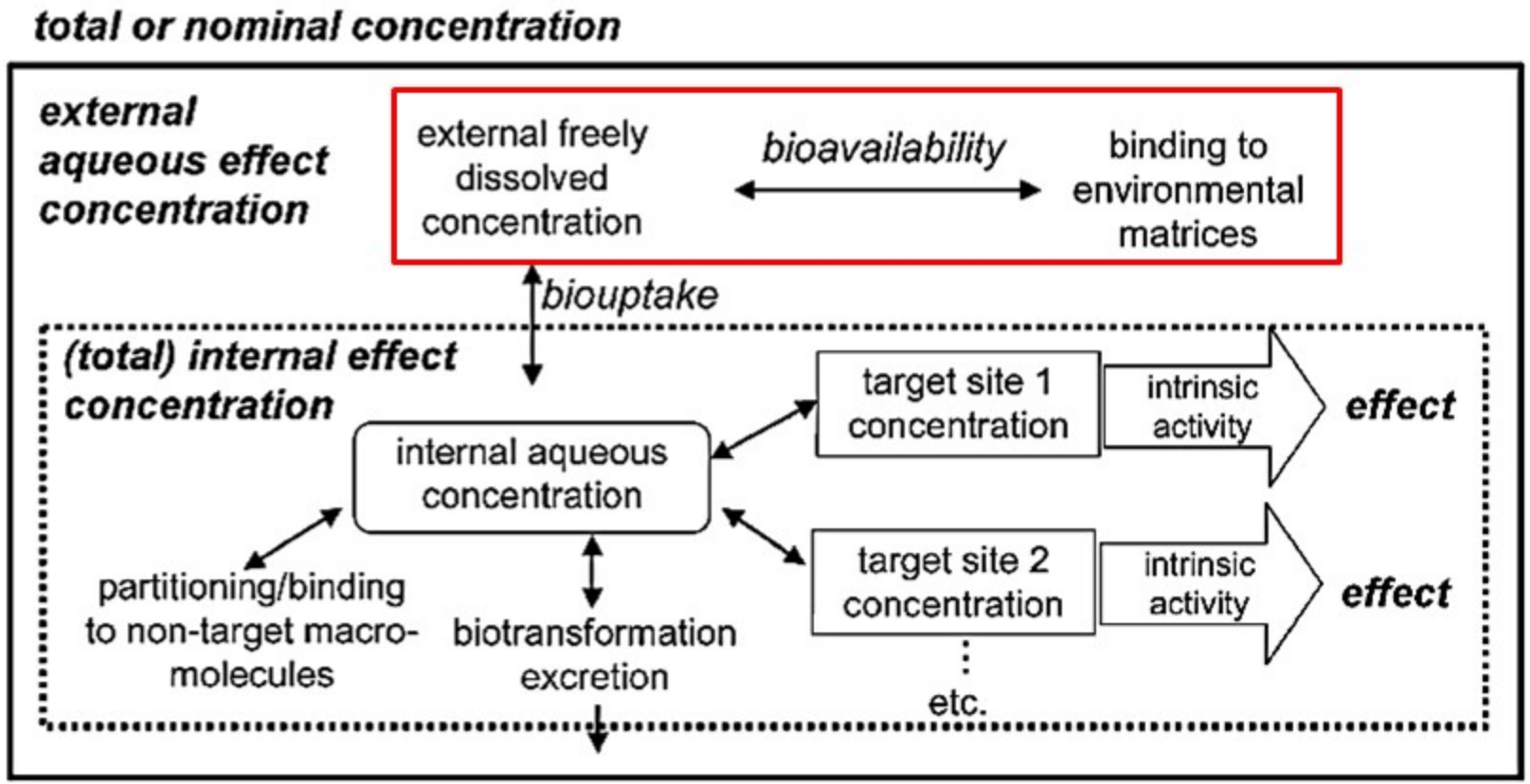


Figura 3.1: Las tres fases de la acción tóxica propuesta por McCarty (1990)

Concentración interna efectiva y acción tóxica



(Escher & Hermens 2002)

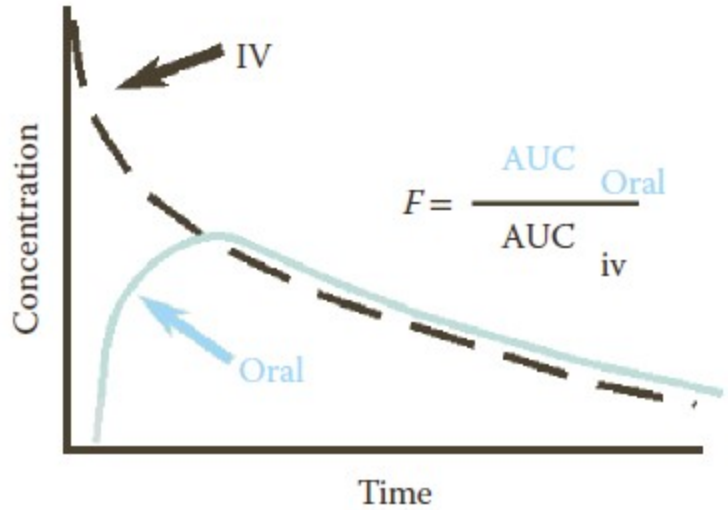
Exposición

- <u>Biodisponibilidad</u>

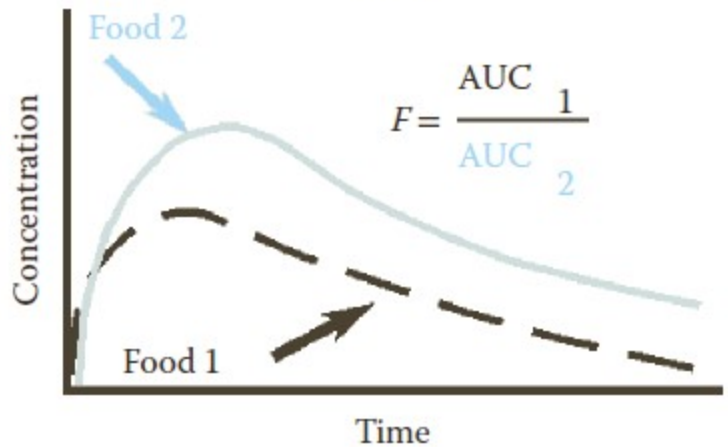
  - El grado en que un contaminante en una fuente está libre para incorporarse e inducir un efecto en su sitio de acción (Newman 2002)

  - La porción de un contamínate en el ambiente que se encuentra en una forma asequible para causar una acción biológica, como ser absorbido o ingresar al organismo (Rand 1995)

- Absoluta



- Relativa

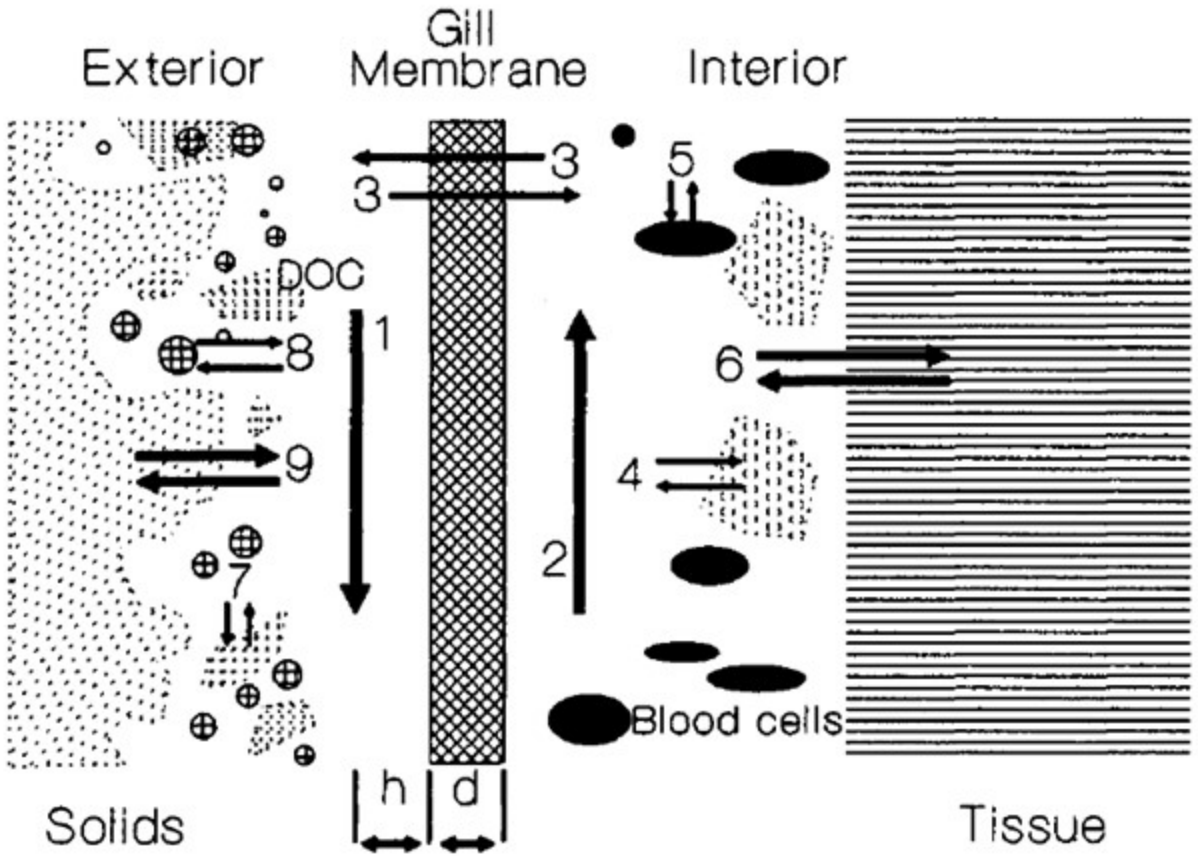


Biodisponibilidad

Compuestos Orgánicos

1. Flujo medio externo
2. Flujo medio interno
3. Difusión
4. Complejación proteínas séricas
5. Adsorción células
6. Transferencia a tejidos
7. Complejación con DOM
8. Adsorción POC
9. Adsorción grandes moléculas con difusión interna

h. lámina de medio estancado
d. distancia de difusión



Biodisponibilidad

Compuestos Orgánicos

Ej. Cipermetrina

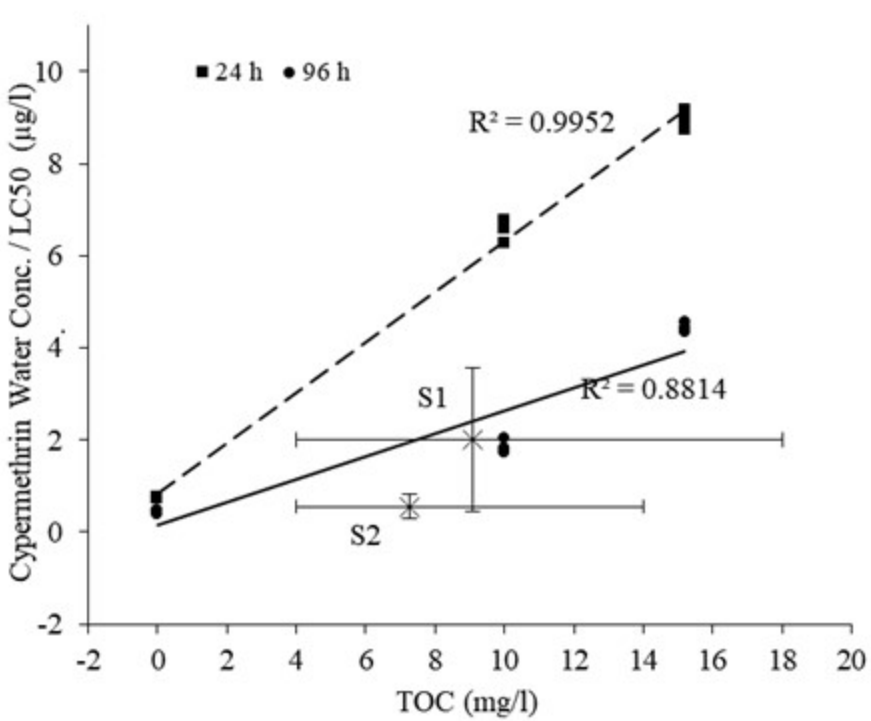
ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect
Chemosphere 68 (2007) 613–621

CHEMOSPHERE
www.elsevier.com/locate/chemosphere

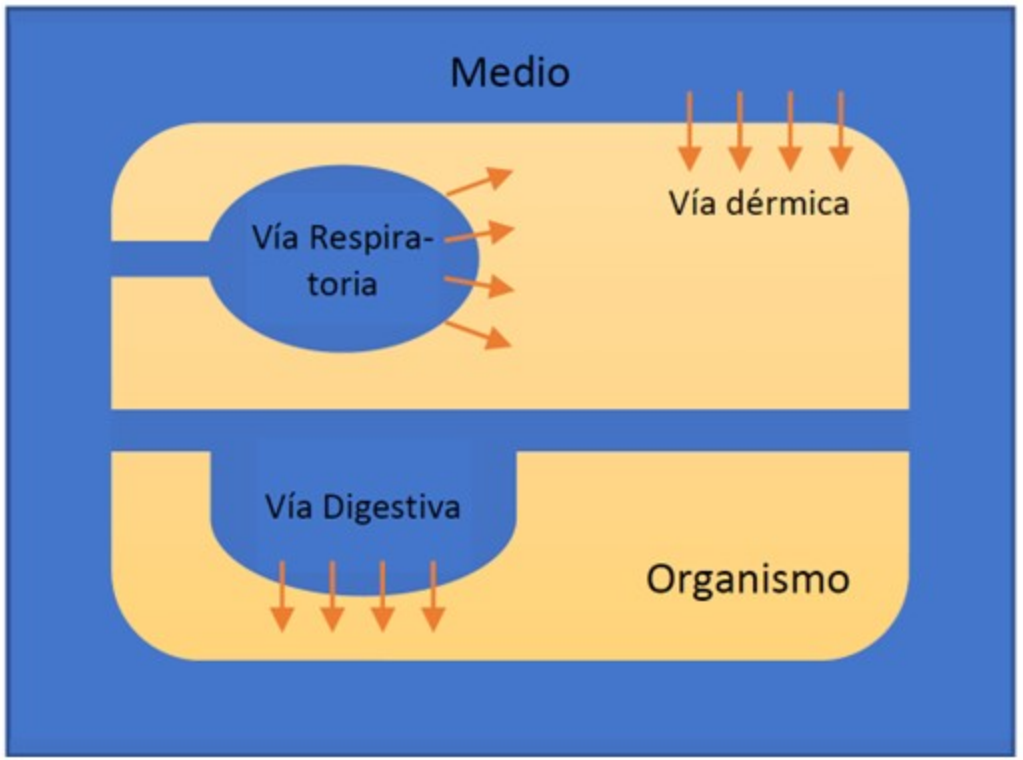
Impact of cypermethrin on stream fish populations under field-use in biotech-soybean production

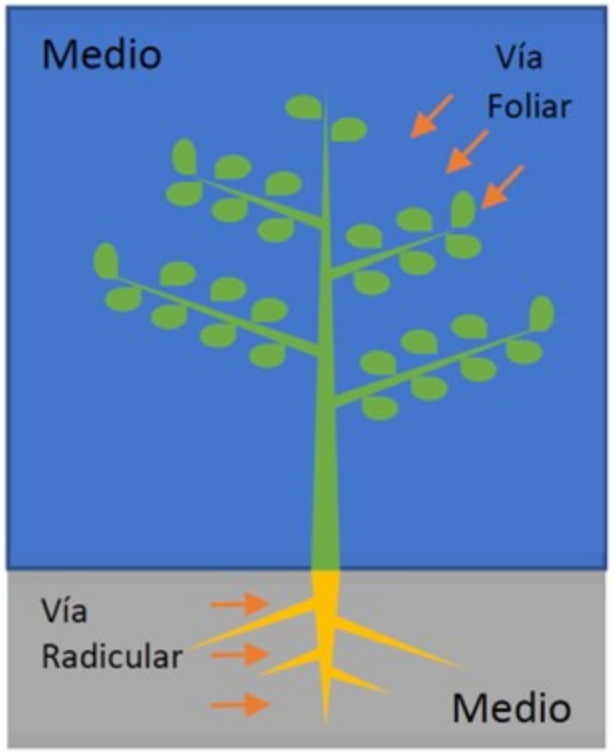
Pedro Carriquiriborde [a], Juan Díaz [a], Hernán Mugni [b], Carlos Bonetto [b], Alicia E. Ronco [a,*]



Exposición

- Vías de exposición





Exposición

- Vías de exposición

Major Routes of Uptake for Organic Pollutants

Organisms	Uptake Route	Sources
Terrestrial vertebrates	Alimentary tract	Food and ingested water
	Skin	Contaminated surfaces
	Lungs	Droplets and particles in air, vapor
Terrestrial invertebrates	Alimentary tract	Food and water
	Cuticle (insects)	Contaminated surfaces
	Body wall (slugs, worms)	Contaminated environment, e.g., soil
	Tracheae	Droplets and particles in air, vapor
Fish	Gills	Pollutants dissolved or suspended in ambient water
	Alimentary tract	Food
Aquatic mammals and birds	Alimentary tract	Food Small amounts from ambient or ingested water
Aquatic amphibians	Alimentary tract	Food
	Skin	Small amounts from ambient water
		Pollutants in ambient water dissolved or suspended
Aquatic invertebrates	Alimentary tract	Food; some from ambient water
	Respiratory surfaces	Pollutants dissolved or suspended in ambient water
Plants	Leaves	Pollutants in droplets or particles[a]
		Vapors
	Roots	Pollutants dissolved in soil water[a]

Las tres fases de la acción tóxica

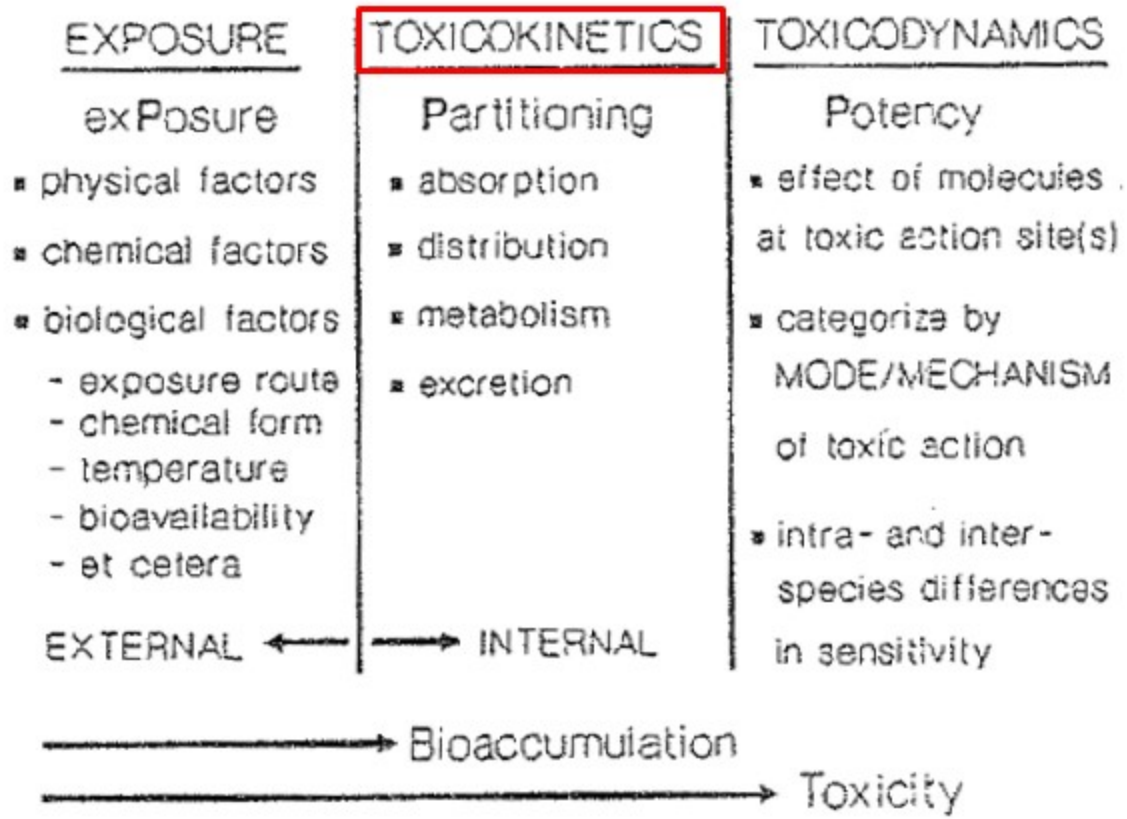
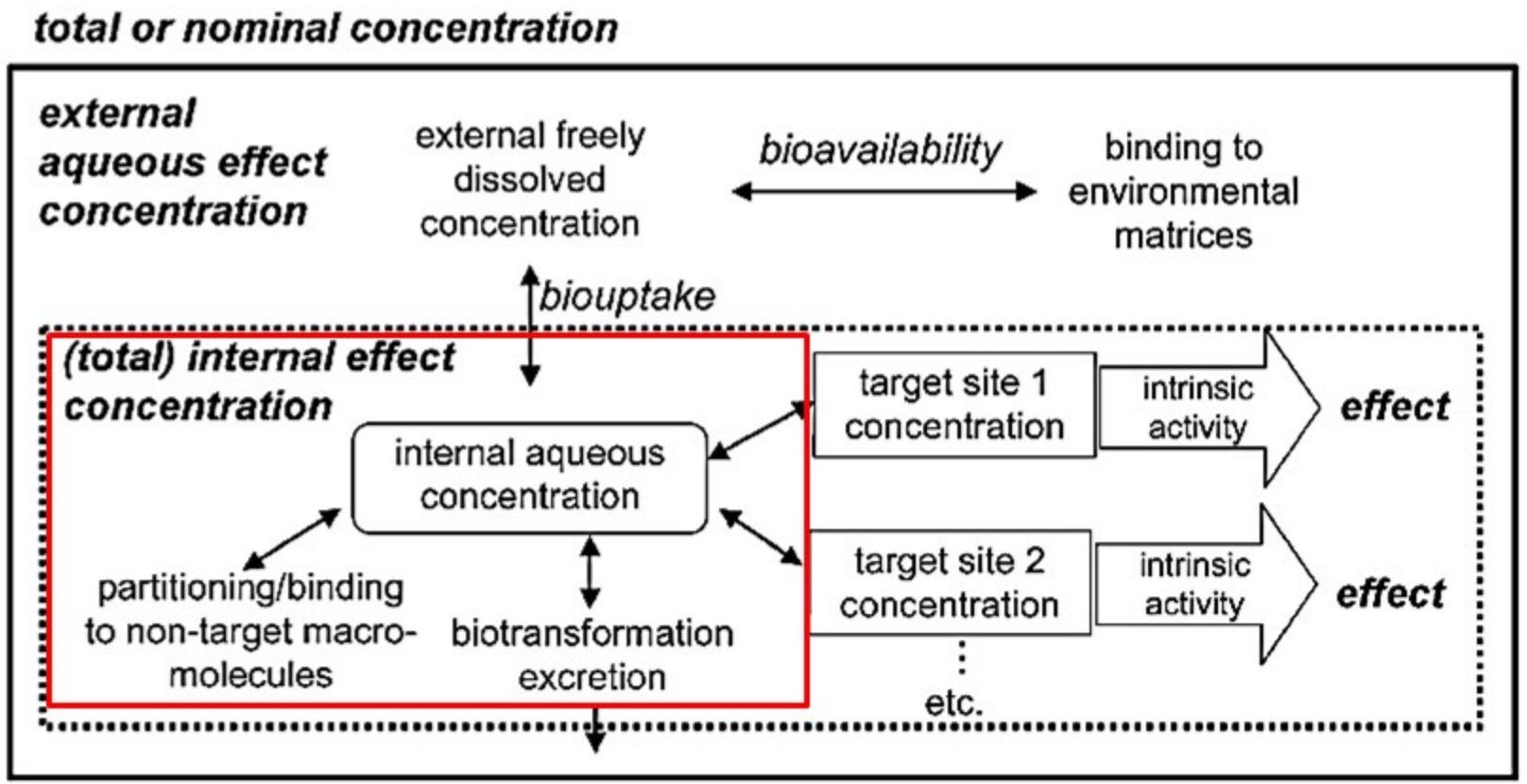


Figure 4. The Three Phases of Toxic Action. (Modified from McCarty, 1990, used with permission.)

- Concentración interna efectiva y acción tóxica



(Escher & Hermens 2002)

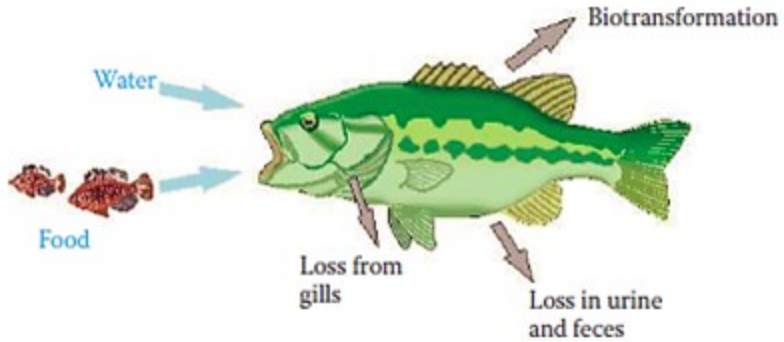
Toxicocinética

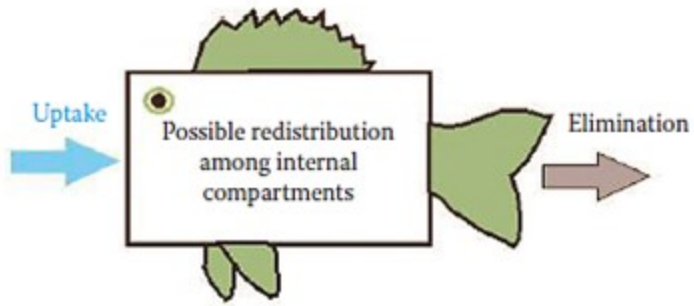
- Incorporación
- Distribución
- Biotransformación
- Acumulación
- Eliminación

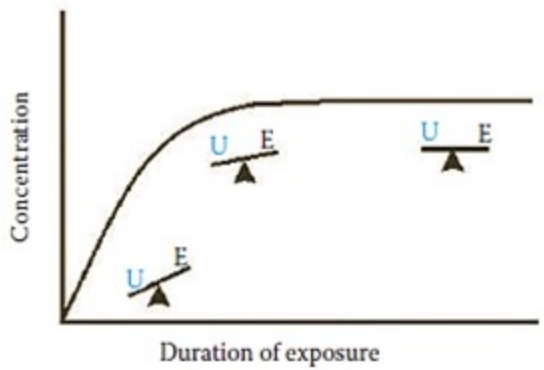
- Bioacumulación: relación entre la concentración de un contaminante en el organismo y en la sumatoria de todas las vías de exposición.

- Bioconcentración: relación entre la concentración de un contaminante en el organismo y el medio circundante.

- Biomagnificación: incremento en la concentración de un contaminante a través de los niveles tróficos.

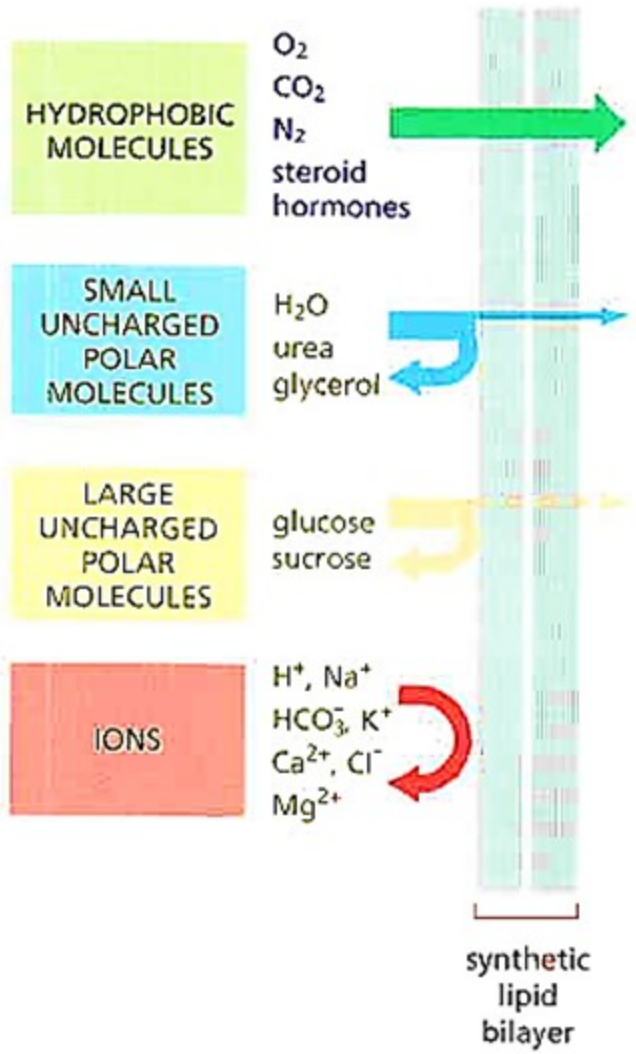






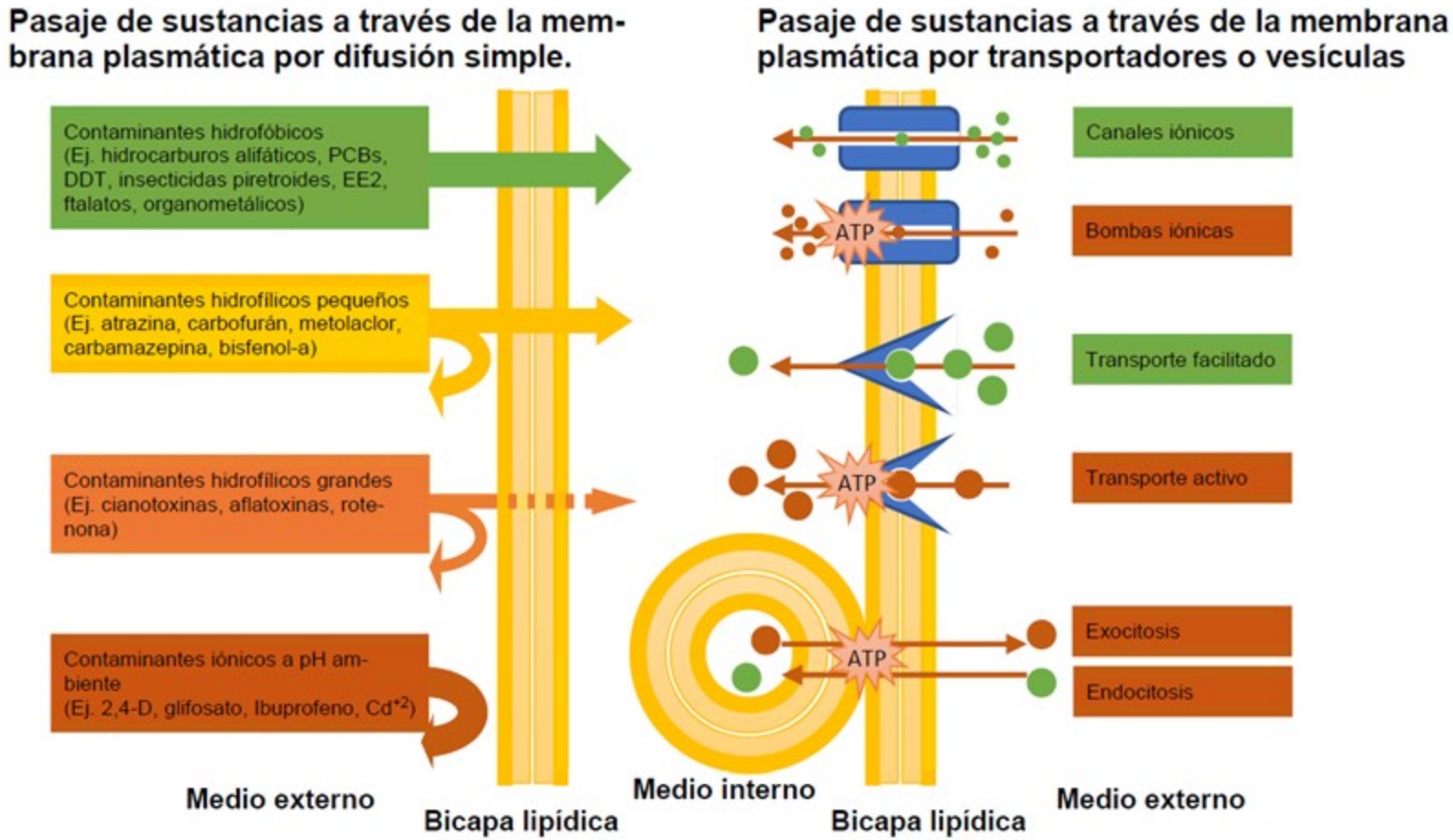
Toxicocinética

- Incorporación



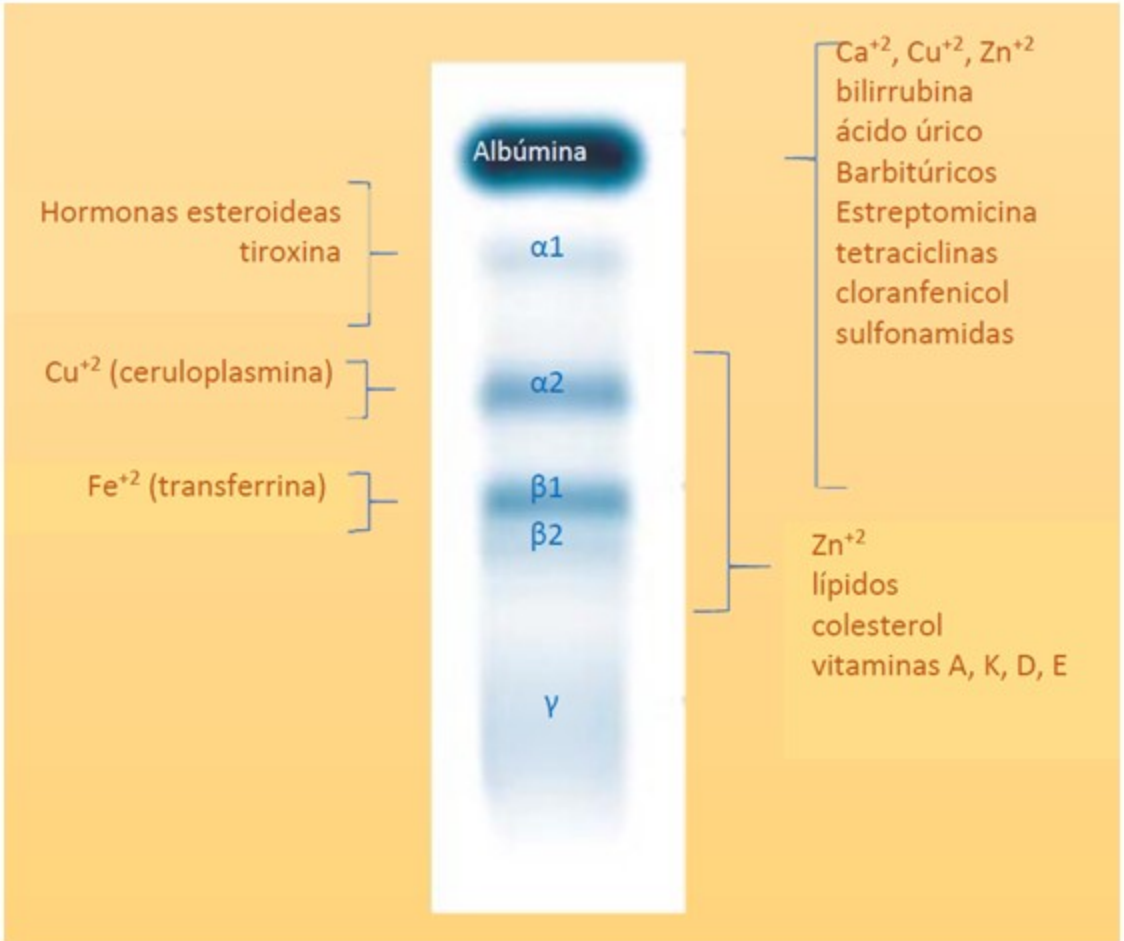
Toxicocinética

- Incorporación



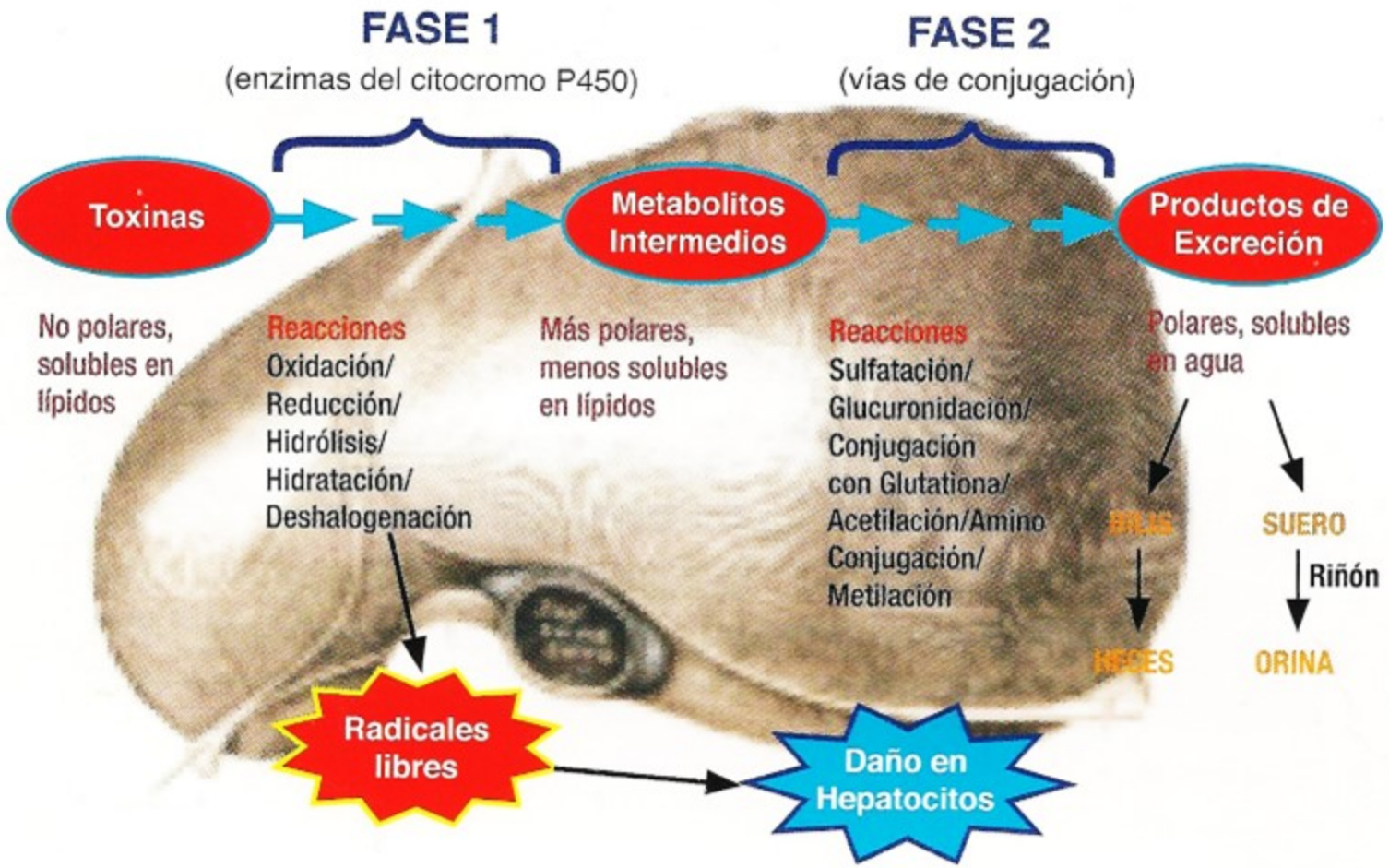
Toxicocinética

- Distribución



Toxicocinética

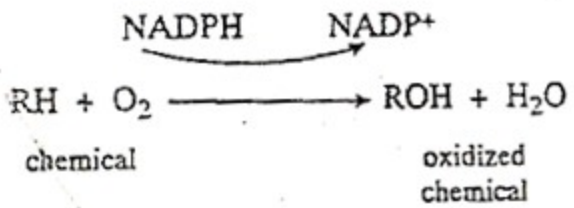
- Biotransformación

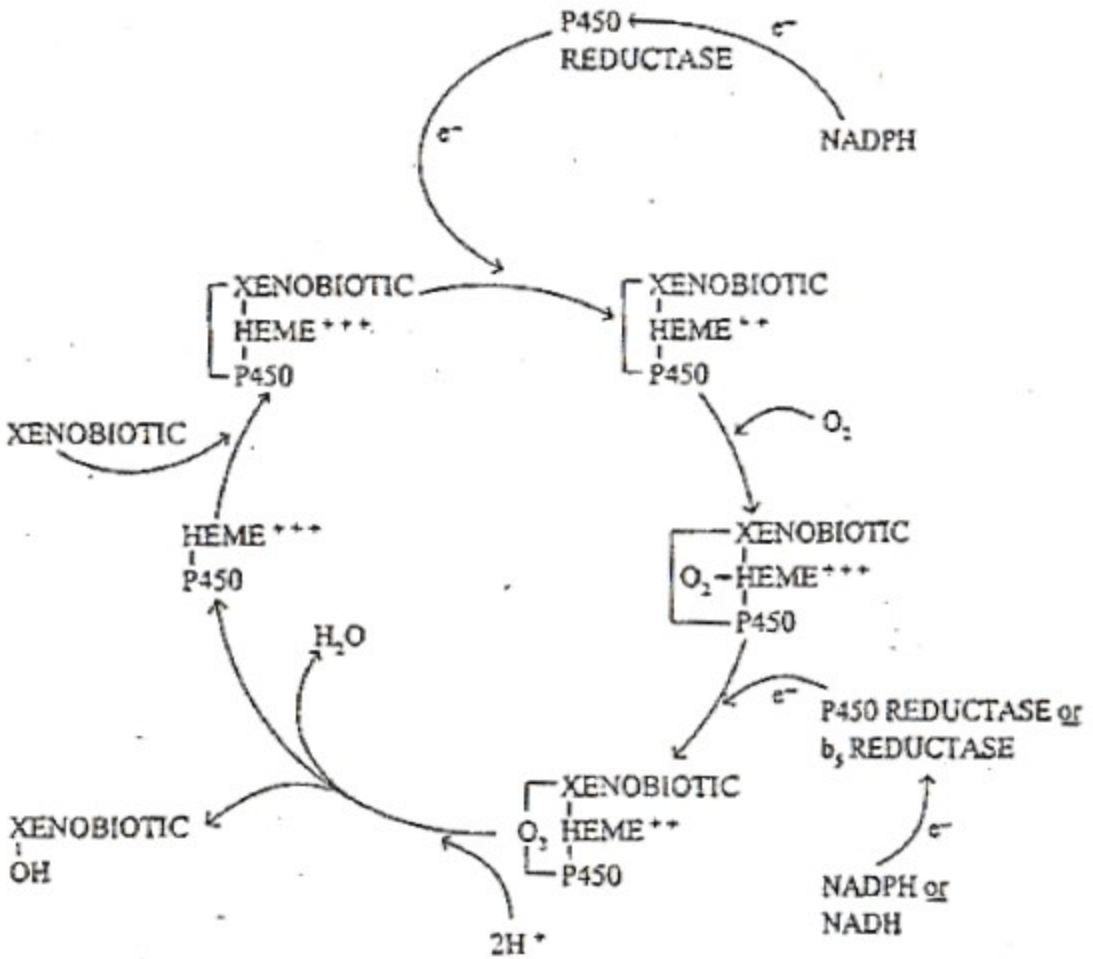


Toxicocinética

- Biotransformación

  - Biotransformación de fase I
    (Citocromo P450, fracción microsomal)

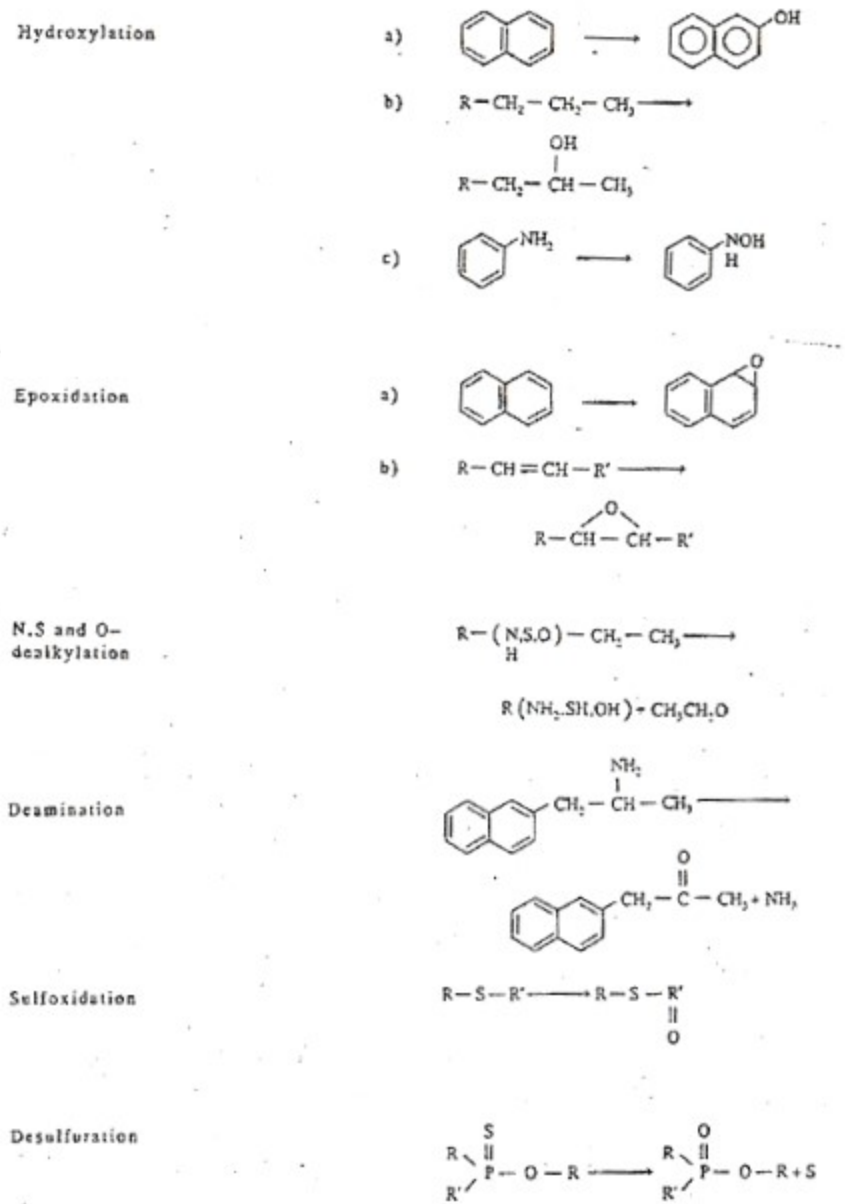




Toxicocinética

- Biotransformación

  - Biotransformación de fase I
    (Citocromo P450, fracción microsomal)



Toxicocinética

- Biotransformación

  - Biotransformación de fase I (Otras)

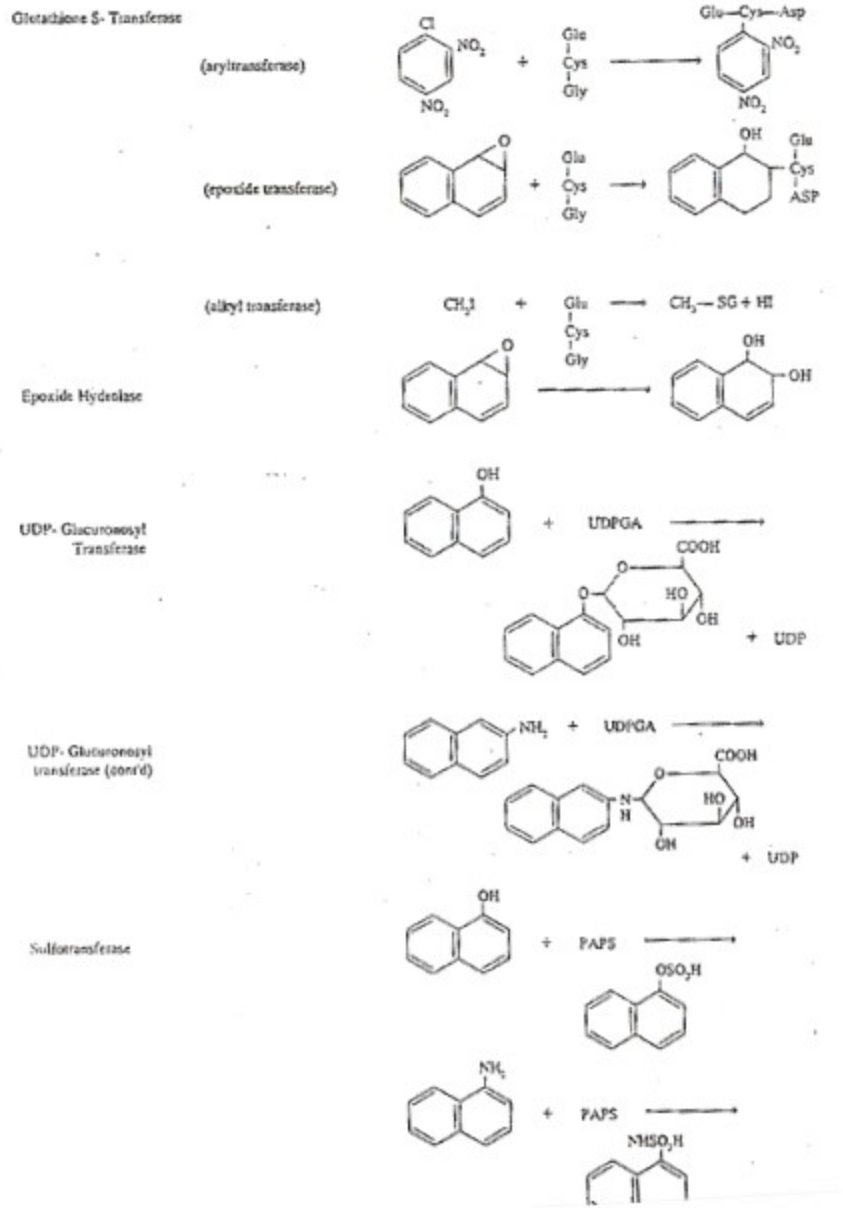
Enzymes That Metabolize Lipophilic Xenobiotics (Phase I)

Name	Principal Location	Cofactors	Substrates
Microsomal monooxygenases (mixed function oxidases)	Endoplasmic reticulum of many animal tissues, especially liver of vertebrates, hepatopancreas, fat body, and gut of invertebrates	NADPH/NADH, O_2	Most lipophilic xenobiotics of molecular weight < 800
Carboxyl esterases	Endoplasmic reticulum of many animal tissues; also found in cytosol and in serum/plasma of vertebrates	None known	Lipophilic carboxyl esters
A esterases	Endoplasmic reticulum of certain cell types of vertebrates; mammalian serum/plasma (associated with high-density lipoprotein)	Ca^{2+}	Organophosphate esters
Epoxide hydrolases	Principally endoplasmic reticulum of animal cells; some in cytosol	None known	Organic epoxides
Reductases (a number of different enzymes can express this activity at low levels of dissolved oxygen, including certain flavoproteins and hemoproteins)	Endoplasmic reticulum and cytosol of a number of types of animal cell	NADH/NADPH	Organonitro-compounds, some organohalogen compounds, e.g., *p,p'*-DDT

Toxicocinética

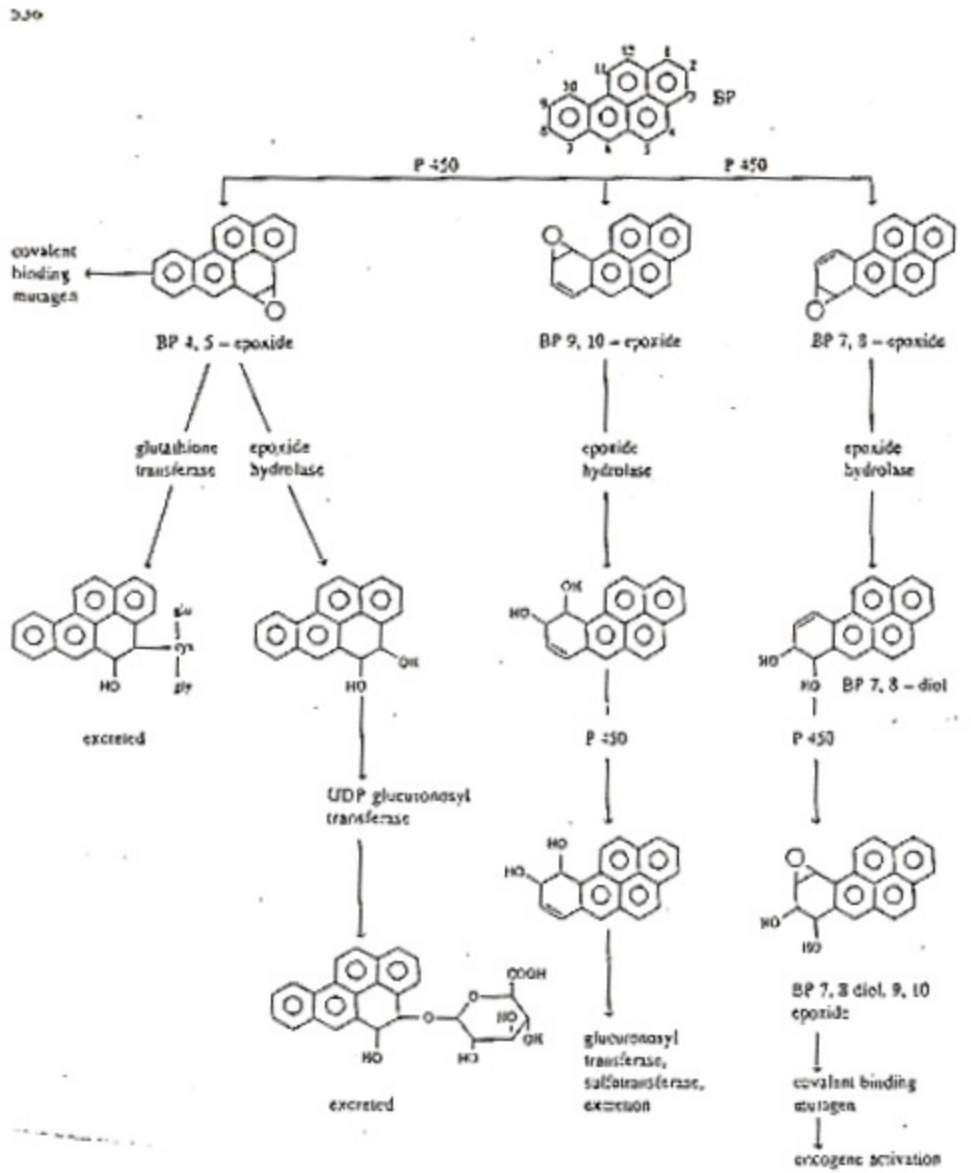
- Biotransformación

  - Biotransformación de fase II (conjugación, citosol)



Toxicocinética

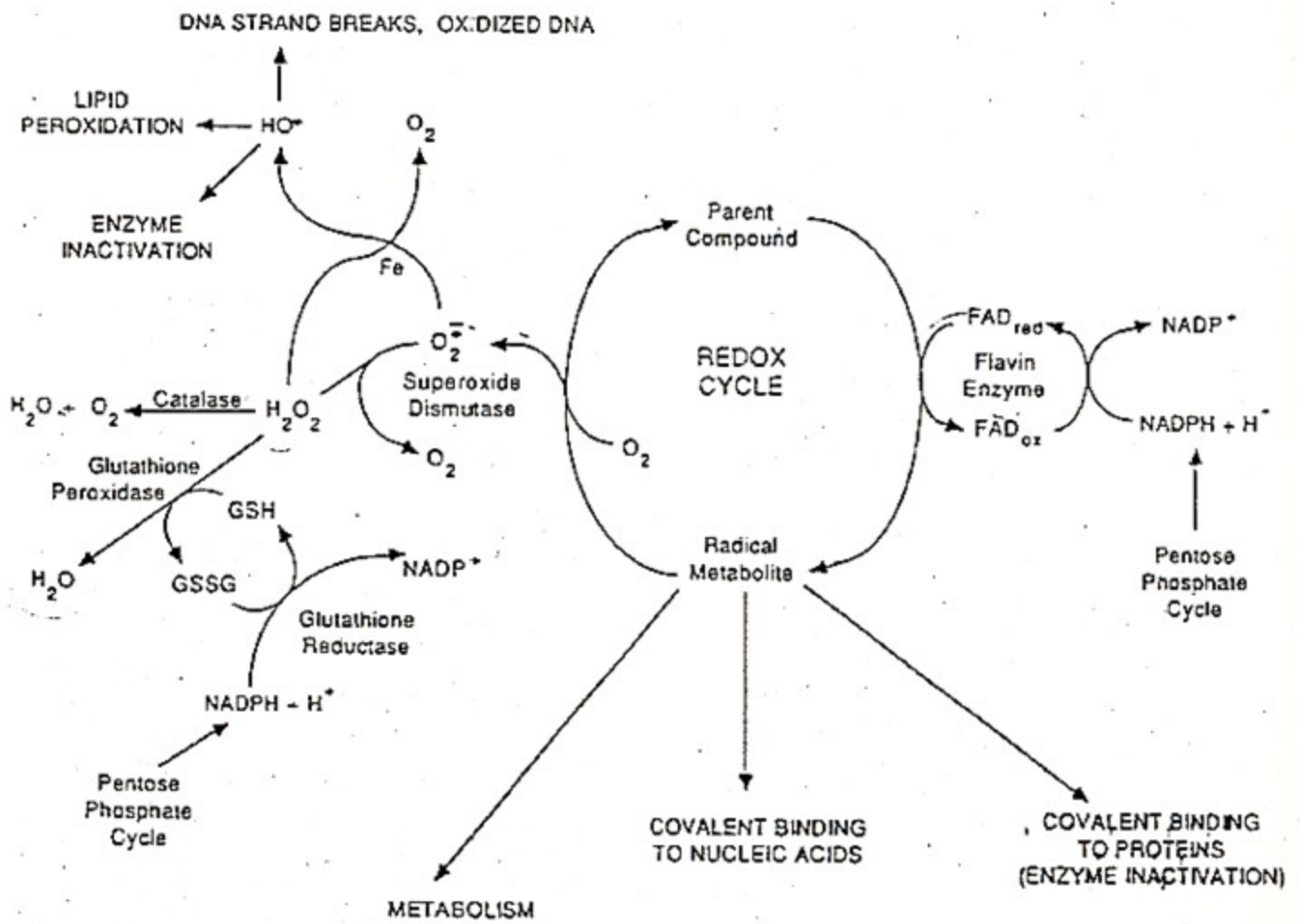
- Biotransformación
  - Ej. biotransformación de benzo-a-pireno



Toxicocinética

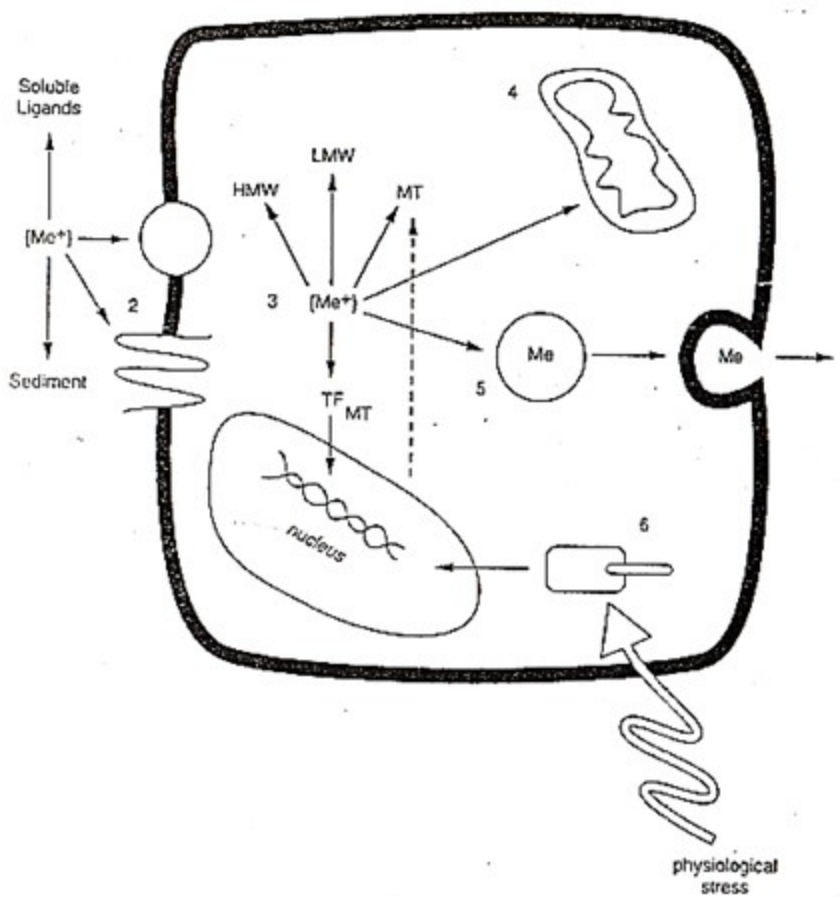
- Biotransformación

  - Especies reactivas de oxígeno, sistema antioxidante y estrés oxidativo



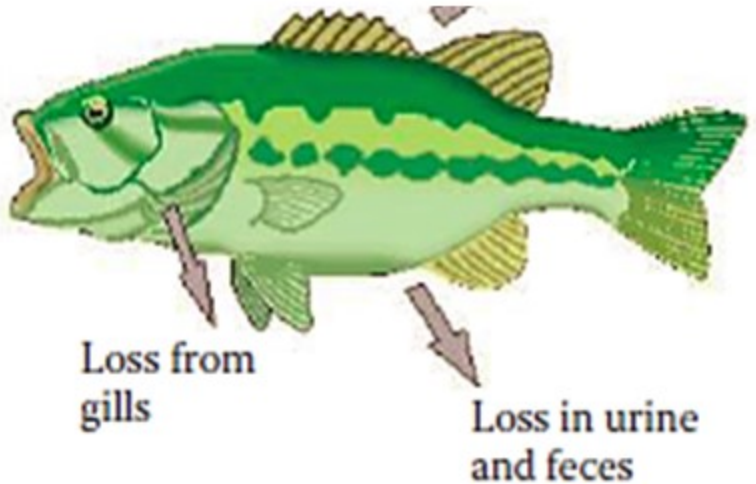
Toxicocinética

- Acumulación



Toxicocinética

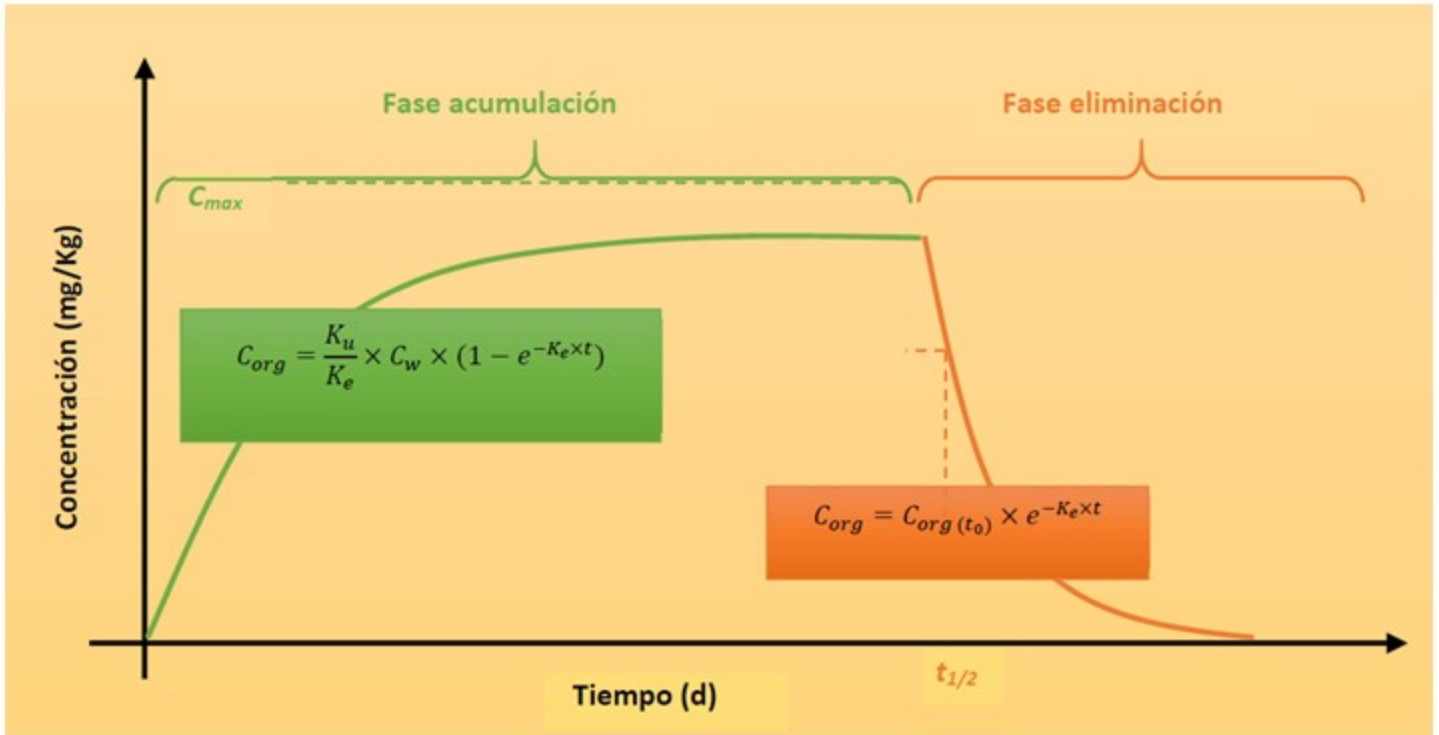
- Eliminación

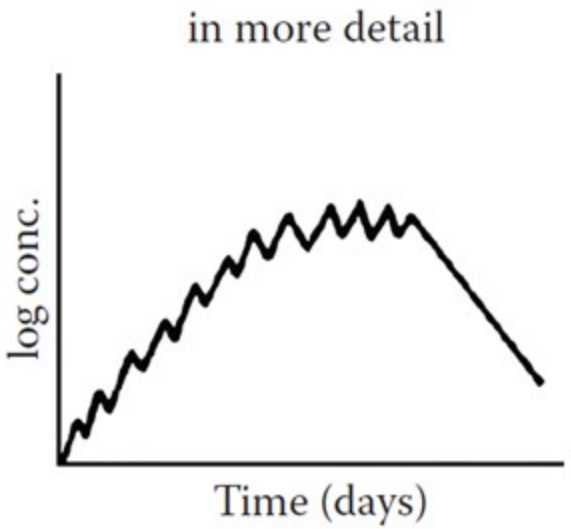


Toxicocinética

$$C_{org} = \frac{\sum_{j=1}^{m} C_j \times K_{uj}}{\sum_{i=1}^{n} k_{ei}} \times \left(1 - e^{-\sum_{i=1}^{n} K_{ei} \times t}\right) + C_{org(t_0)} \times e^{-\sum_{i=1}^{n} K_{ei} \times t}$$

- Modelo toxicocinético de un compartimiento



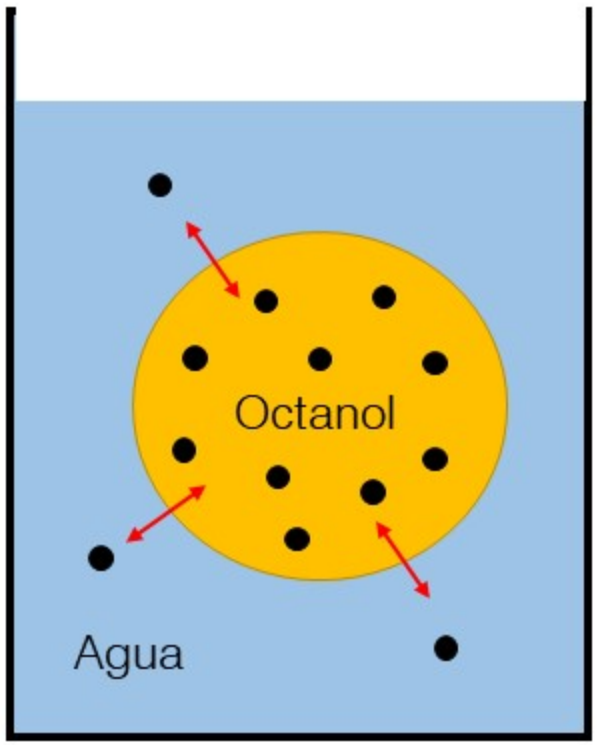


Bioacumulación, bioconcentración, biomagnificación

Modelización del proceso

Modelo de Partición para Contaminantes Orgánicos (equilibrio termodinámico)

$$K_{ow} = \frac{C_{octanol}}{C_{water}}$$

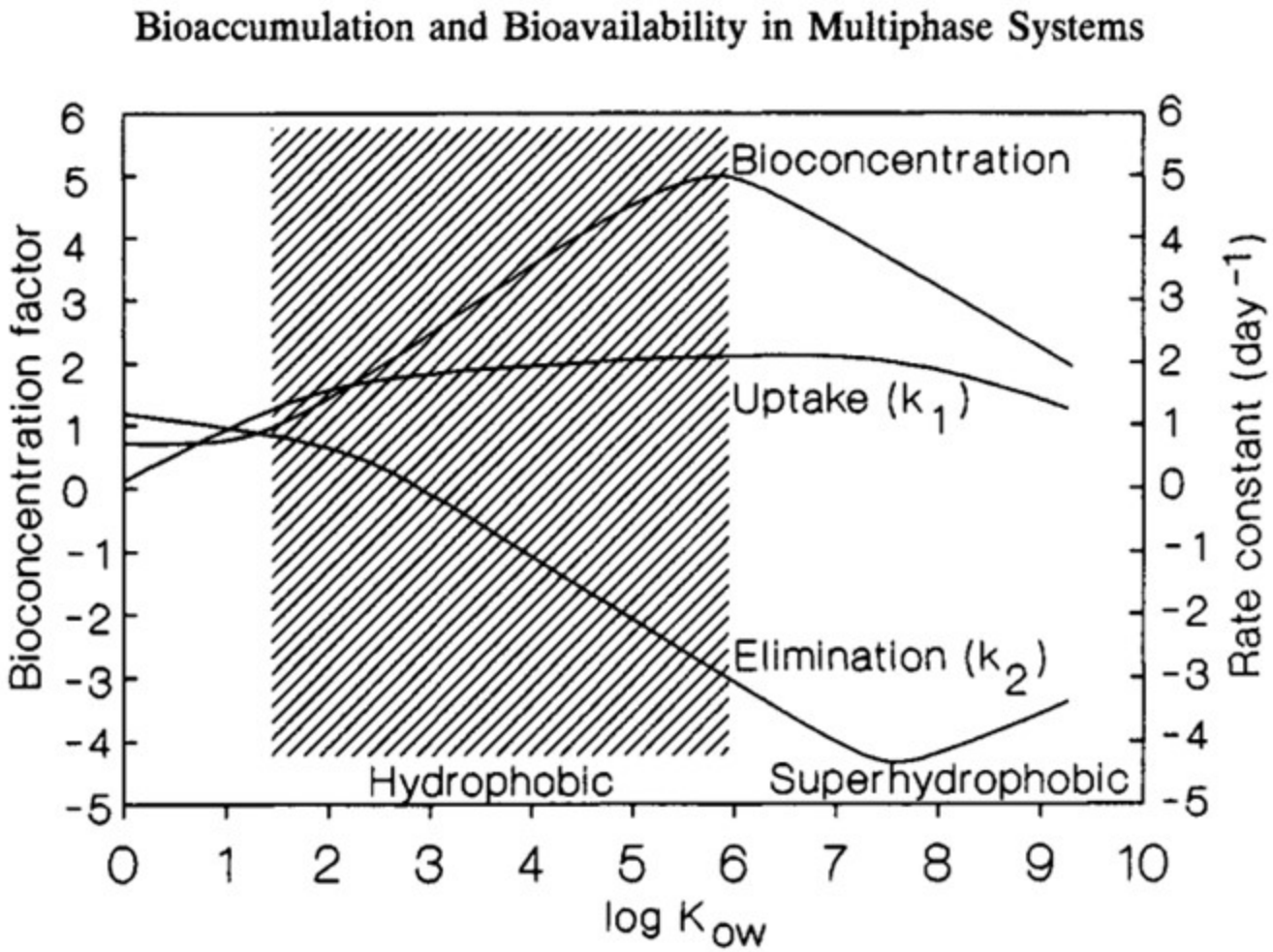


$$Z_i * f_i = C_i \qquad K_{ow} = \frac{C_{octanol}}{C_{water}} = \frac{Z_{octanol}}{Z_{water}}$$

Bioacumulación, bioconcentración, biomagnificación

Modelización del proceso

Modelo de Partición para Contaminantes Orgánicos (equilibrio termodinámico)



Bioconcentración

ELSEVIER

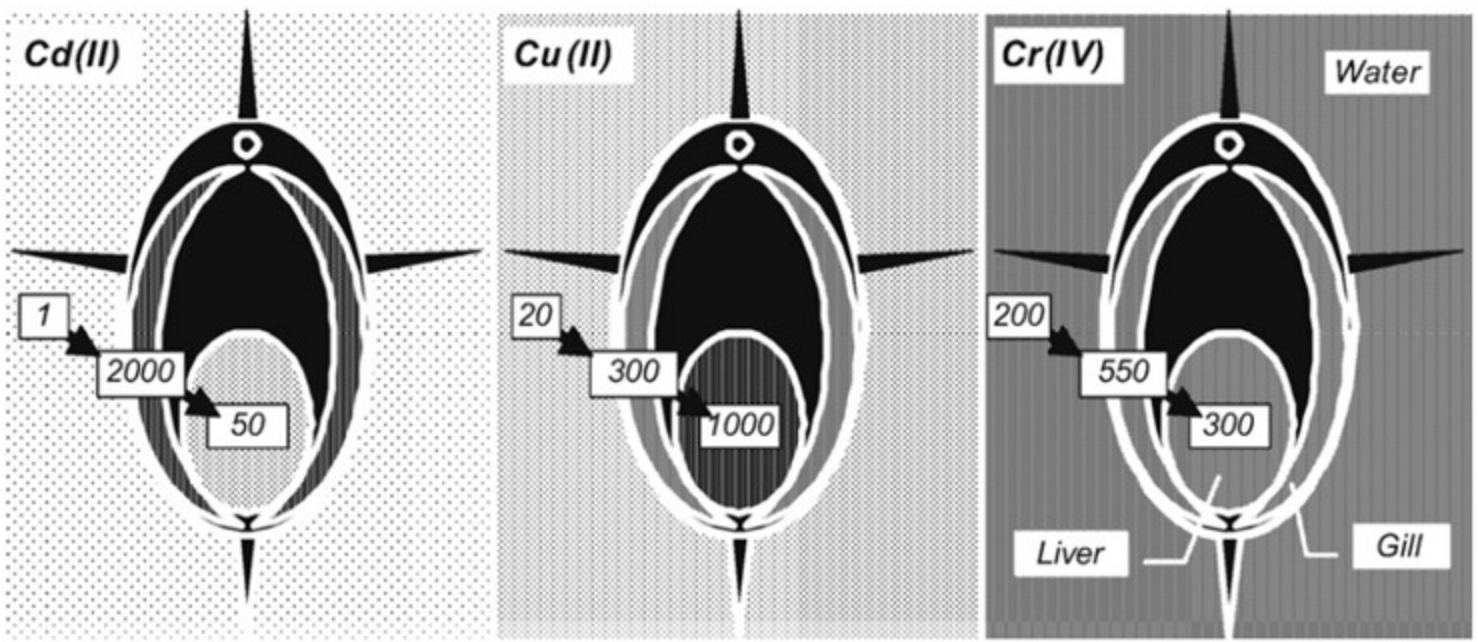
Aquatic Toxicology 86 (2008) 313–322

AQUATIC TOXICOLOGY

www.elsevier.com/locate/aquatox

Distinctive accumulation patterns of Cd(II), Cu(II), and Cr(VI) in tissue of the South American teleost, pejerrey (*Odontesthes bonariensis*)

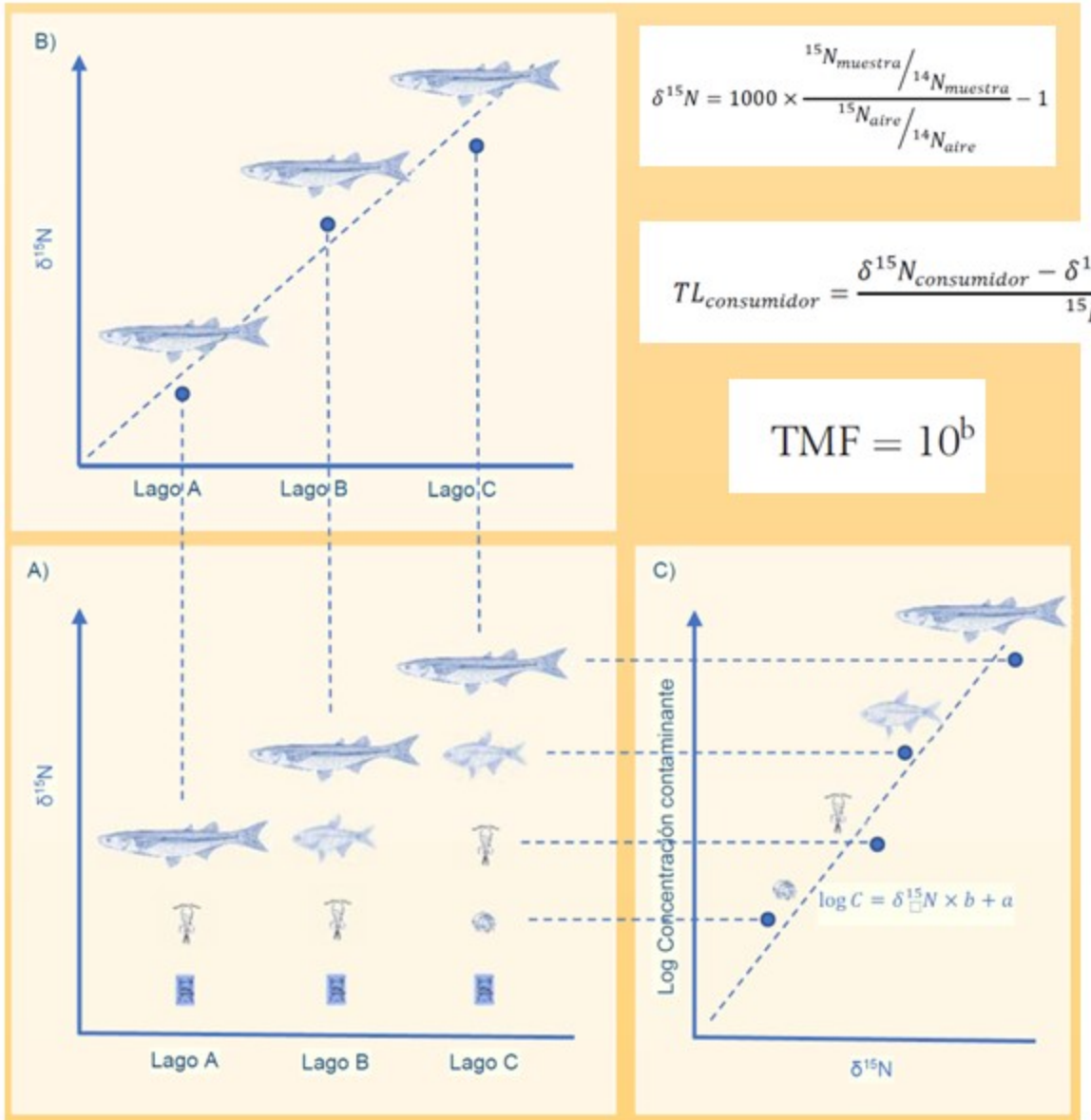
Pedro Carriquiriborde, Alicia E. Ronco*



Biomagnificación

$$B = \frac{C_n}{C_{n-1}}$$

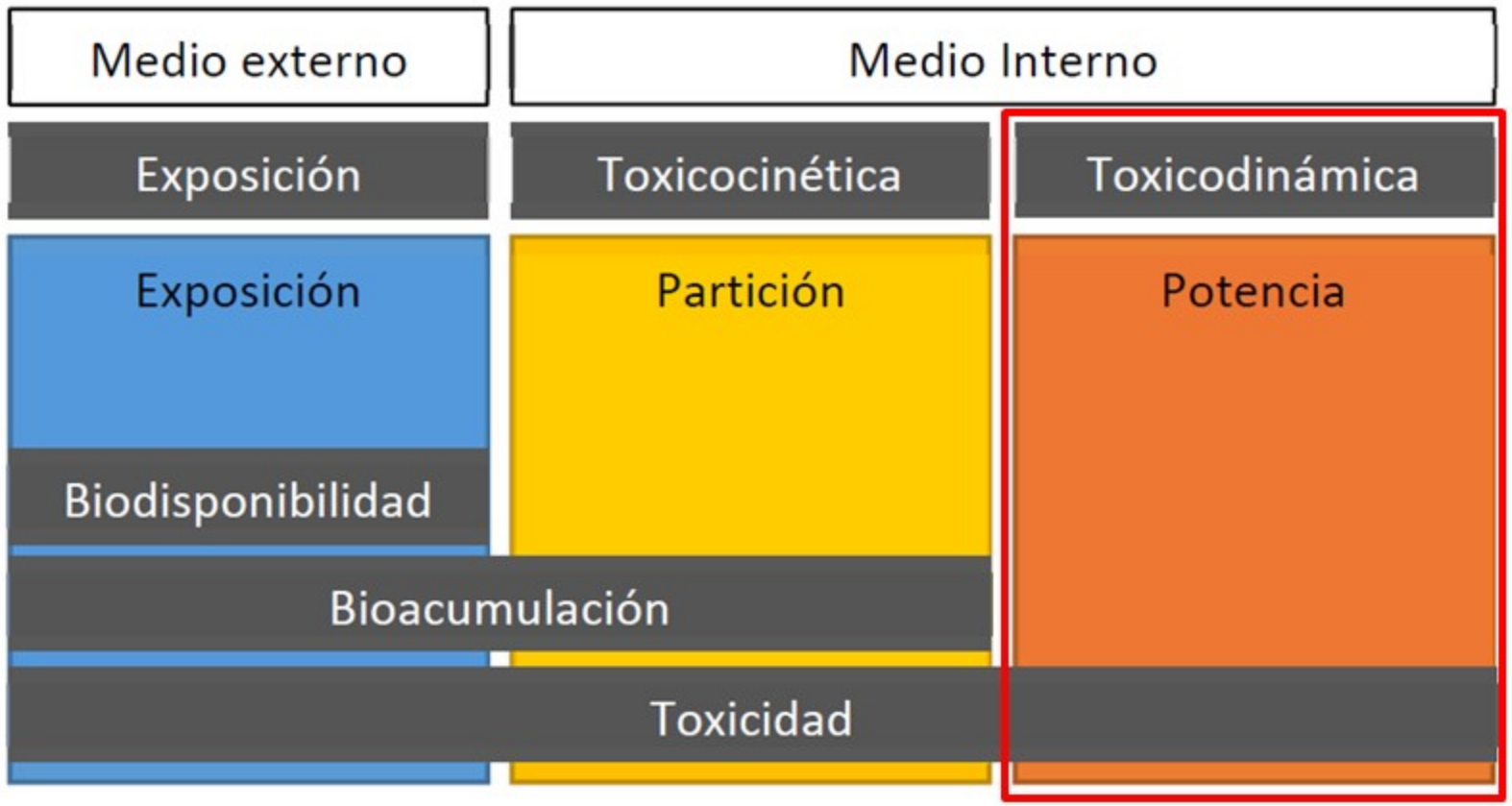
$$B = \frac{\alpha R}{K_e}$$



Clase 3. Mecanismos de toxicidad y efectos a nivel subindividual

Dr. Pedro Carriquiriborde
Maestría en Protección Vegetal 2023, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de la Plata (UNLP)

Las tres fases de la acción tóxica

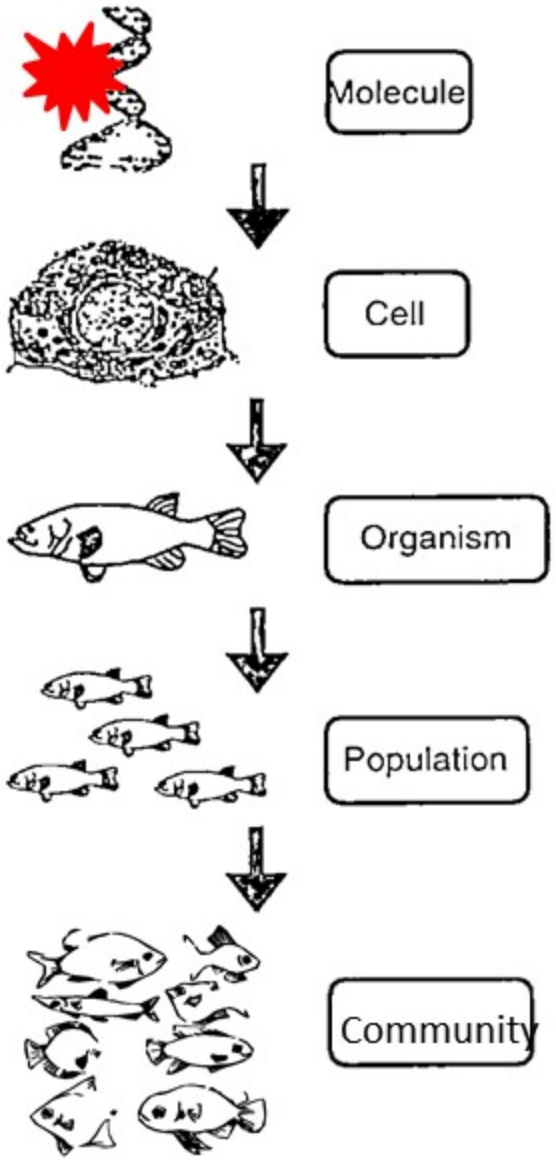


Concentración interna efectiva y acción tóxica

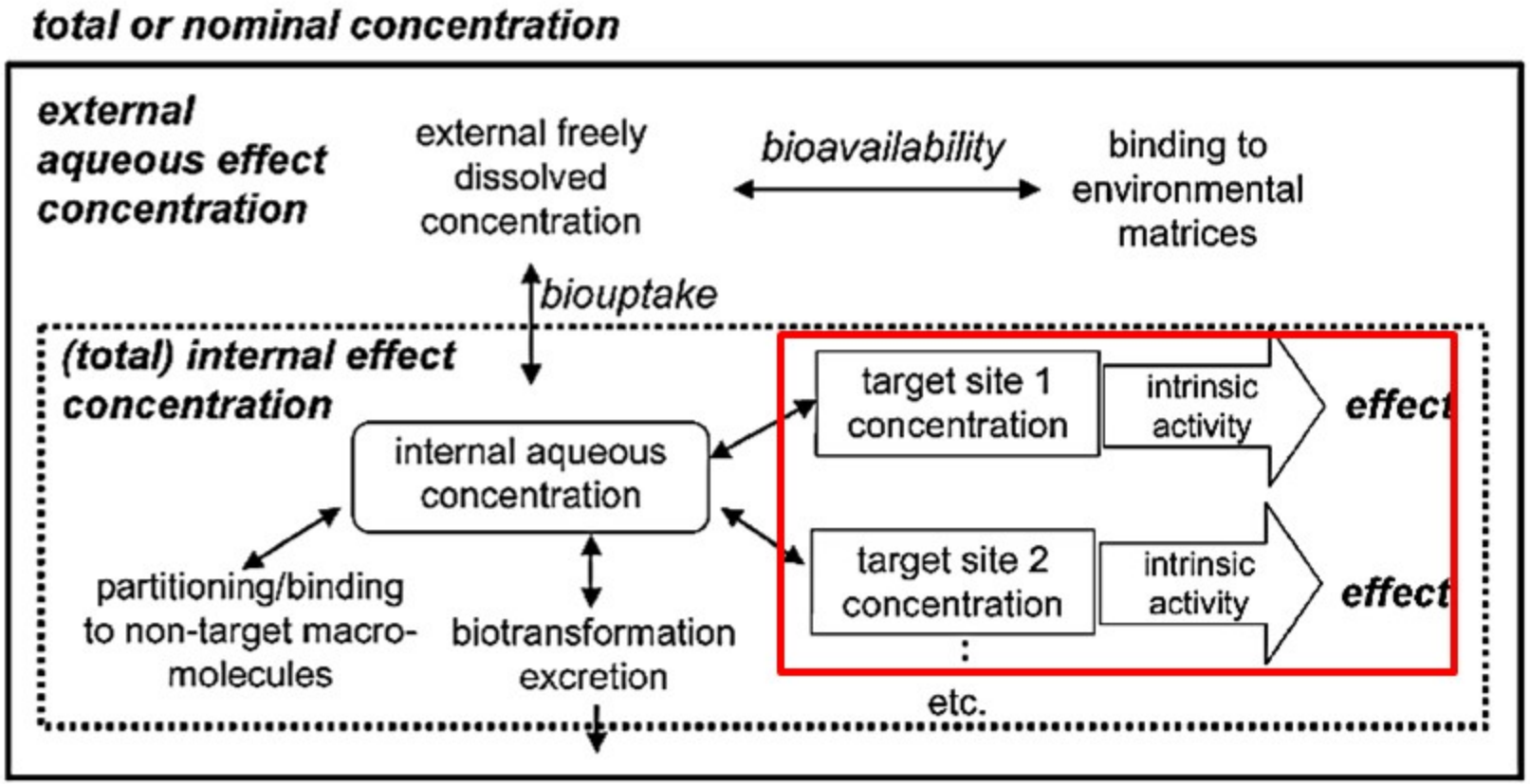
Definición

Modo de acción: conjunto de signos fisiológicos y de comportamiento que caracterizan un tipo de respuesta biológica adversa.

Mecanismo de acción: procesos bioquímicos cruciales y/o la interacción xenobiótico-biológica subyacente a un modo de acción dado

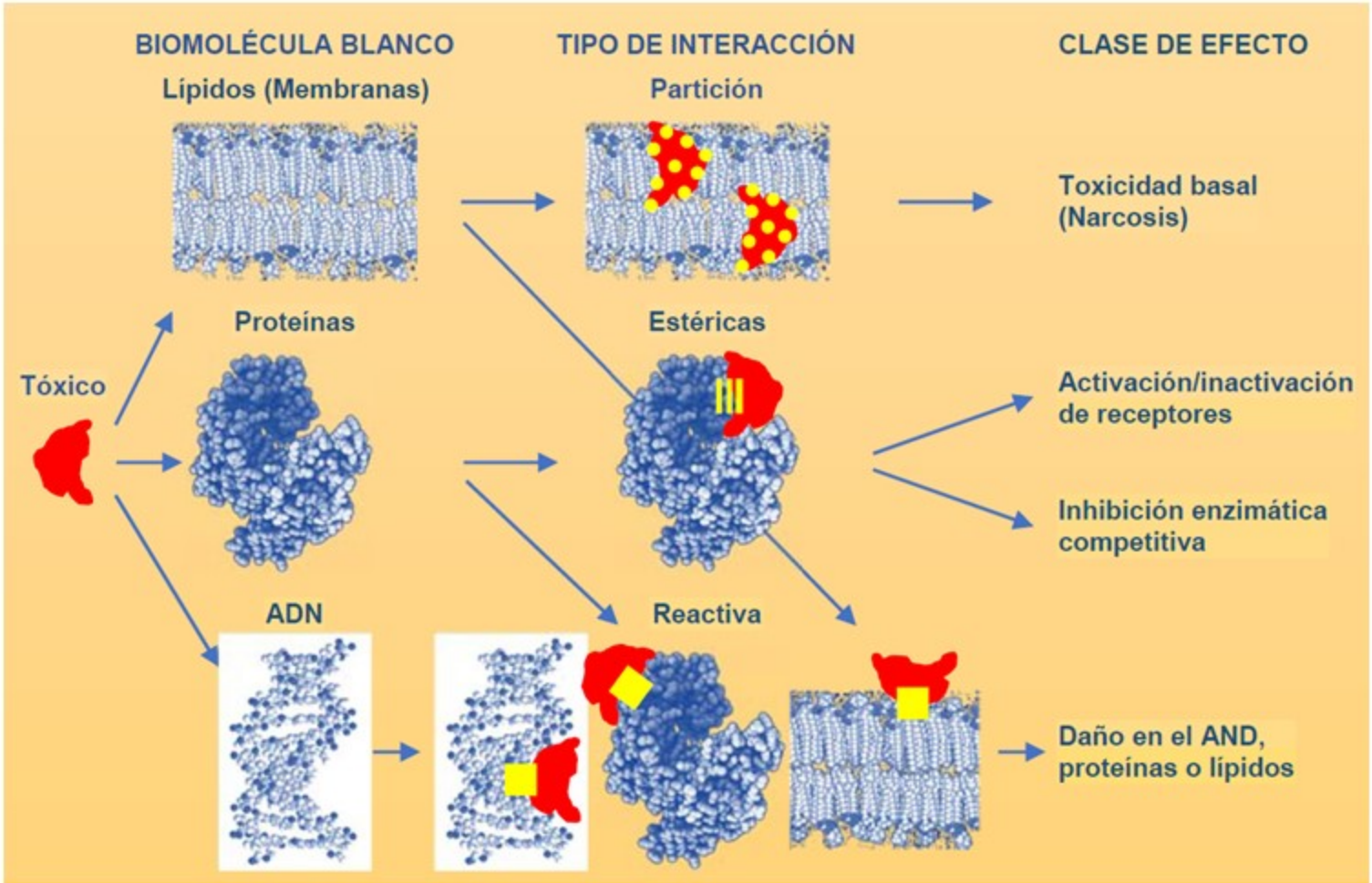


Concentración interna efectiva y acción tóxica



(Escher & Hermens 2002)

Concentración interna efectiva y acción tóxica



Clase 4. Biodisponibilidad, Bioacumulación y Mecanismos de acción tóxica

TABLE 1. Classification According to Targets, Interaction with Targets and Mechanisms Relevant in Ecotoxicology

site of action	subclass	domain[a]	interaction[b]	molecular mechanism(s)		mode of action	selective test system (examples)
biological membrane	general	m	ns	nonspecific disturbance of membrane structure and functioning	1	baseline toxicity	neutral red assay (*40*) Kinspec (*59*)
	general	m	s	formation of reactive intermediates (e.g., ROS[c]) causing peroxidation of membrane lipids and proteins	2	degradation of membrane lipids and membrane proteins	reaction of reaction product (malondialdehyd) with thio-barbituric acid (*211*)
	energy-transducing	m	ns, s	ionophoric shuttle mechanisms	3	uncoupling	O_2-consumption in mitochondria (*40*) Kinspec (*109*)
		m	s	blocking of quinone and other binding sites etc.	4	inhibition of the electron transport chain	O_2-consumption in submitochondrial particles (*40*) Kinspec (*109*)
		m	s	blocking of proton channels and other transport channels	5	inhibition of ATP synthesis/ depletion of ATP	ATP assay, e.g. with luciferin/ luciferase (*212*)
	photosynthetic	m	s	blocking of photo-synthetic electron transport	6	photosynthesis inhibition	O_2-production in chloroplasts (*40*) chlorophyll fluorescence (*213*)
proteins, peptides	general	m, c	ns, s	electrophilic reactivity, alkylation and oxidation of proteins and glutathione (GSH)	7	damage and depletion of biomolecules	GSH depletion (*173*)
	specific enzymes and receptors	m, c	s	noncovalent or covalent binding to enzymes and receptors	8	inhibition or competition, e.g.,: 1. acetylcholine esterase 2. estrogen receptor 3. A_h receptor, etc.	receptor binding studies or enzyme activity measurements; e.g.,: 1. enzyme activity (*40*) 2. yeast estrogen screen (*214*) 3. CYP1A induction (*215*)
	specific enzymes and receptors	c	s	noncovalent or covalent binding to enzymes of the nucleic acid metabolism, replication or repair	9	indirect mutagenicity (DNA repair, recom-bination, regulation)	induction of repair mechanisms, e.g., SOS chromotest, or bacterial revertants, e.g., Ames test (for review see ref *216*)
DNA, RNA	general	c	ns, s	base modification and damage: electrophilic (alkylation) and oxidative damage, bulky adducts	10	direct mutagenicity (frameshift, cross-links, strand breaks, deletion, etc.)	measurement of DNA adducts (*173*), induction of repair mechanisms (for review see ref *216*)

[a] Cellular environment: m = membrane, c = cytosol and other aqueous compartments in the cell. [b] Selectivity: ns = nonselective, s = selective. [c] ROS = reactive oxygen species.

(Escher & Hermens 2002)

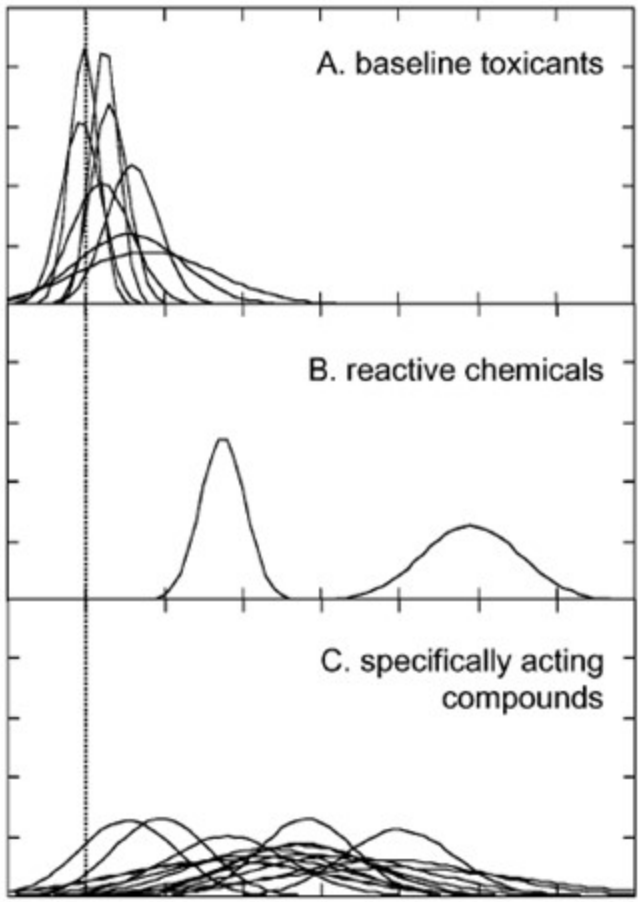
Concentración interna efectiva y acción tóxica

- Distribución de sensibilidad entre especies de acuerdo al tipo de modo de acción

A: acetone, o-cresol, ethyl acetate, heptanol, phenol, propanol, pyridine, and trichloroethylene

B: salicylaldehyde and propenal

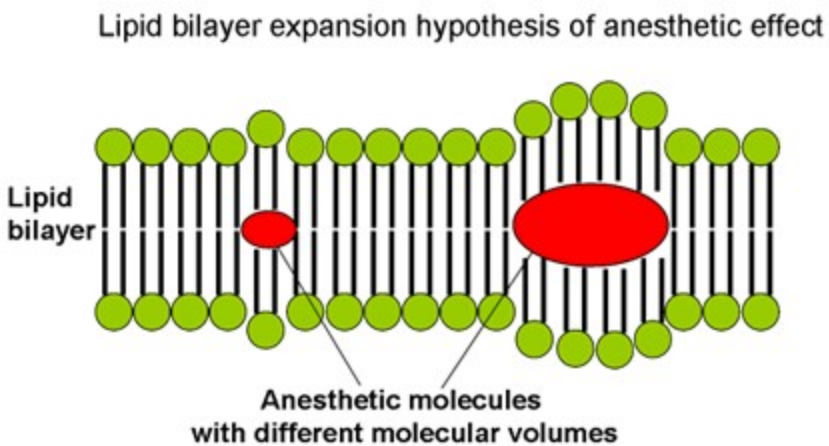
C: methomyl, carbaryl, parathion, dibrom, fenthion, malathion, dichlorvos, diazinon, aldrin, dieldrin, endrin, heptachlor, lindane, and toxaphene

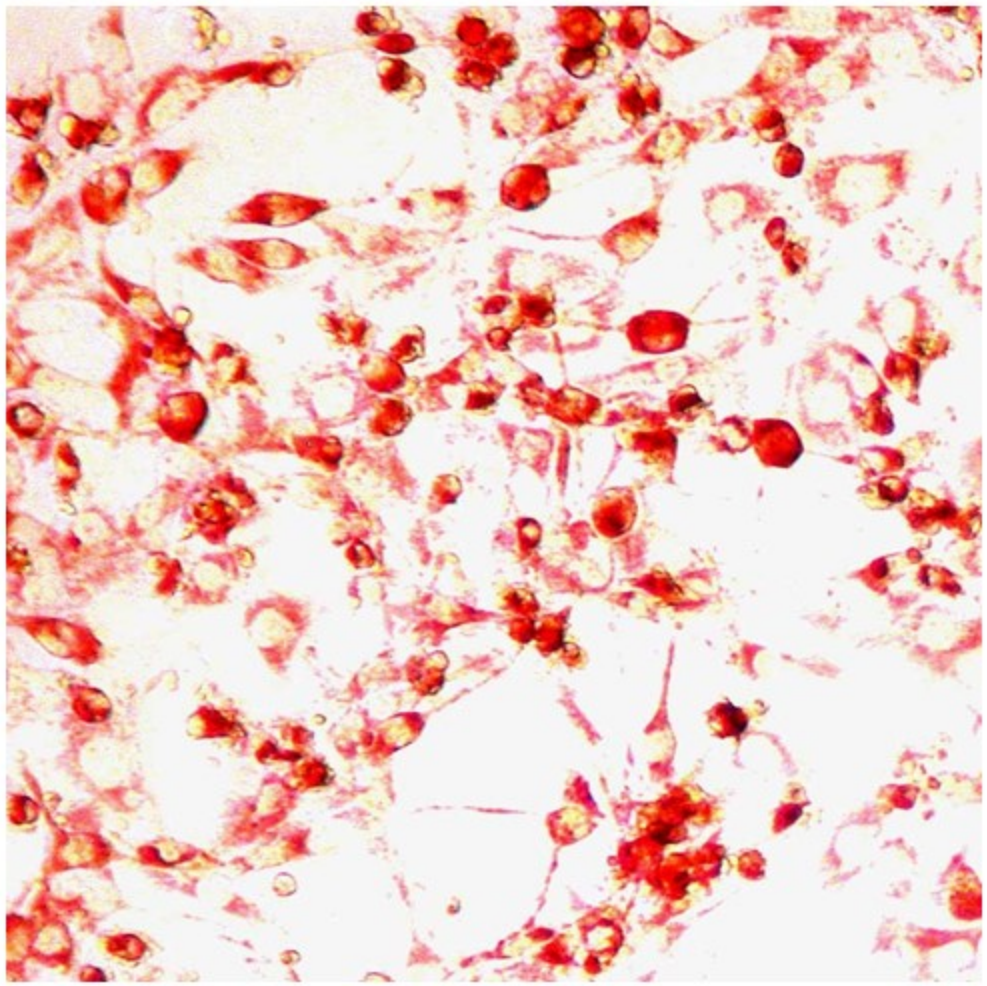


(Escher & Hermens 2002)

Concentración interna efectiva y acción tóxica

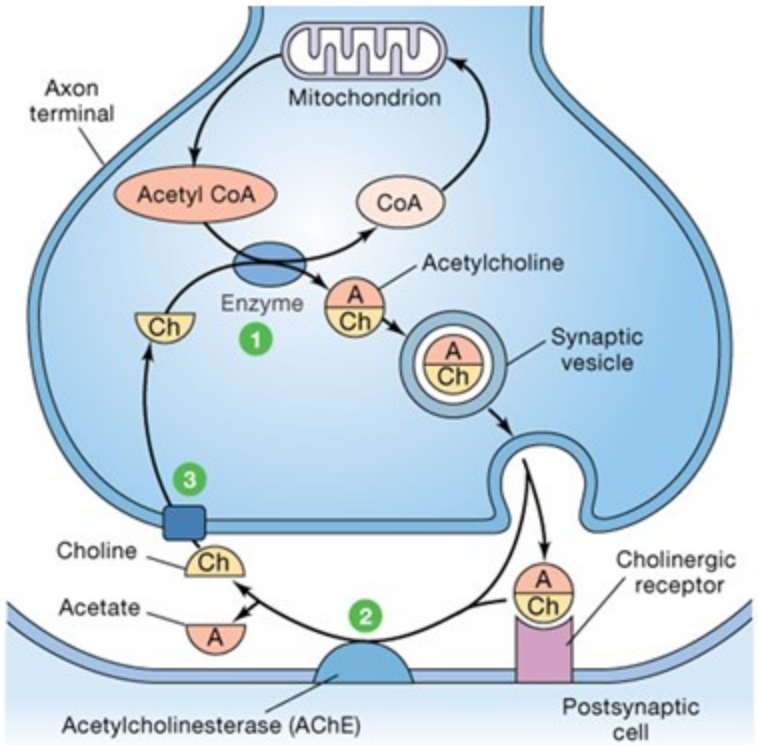
- Toxicidad basal o narcosis (ensayo de rojo neutro)

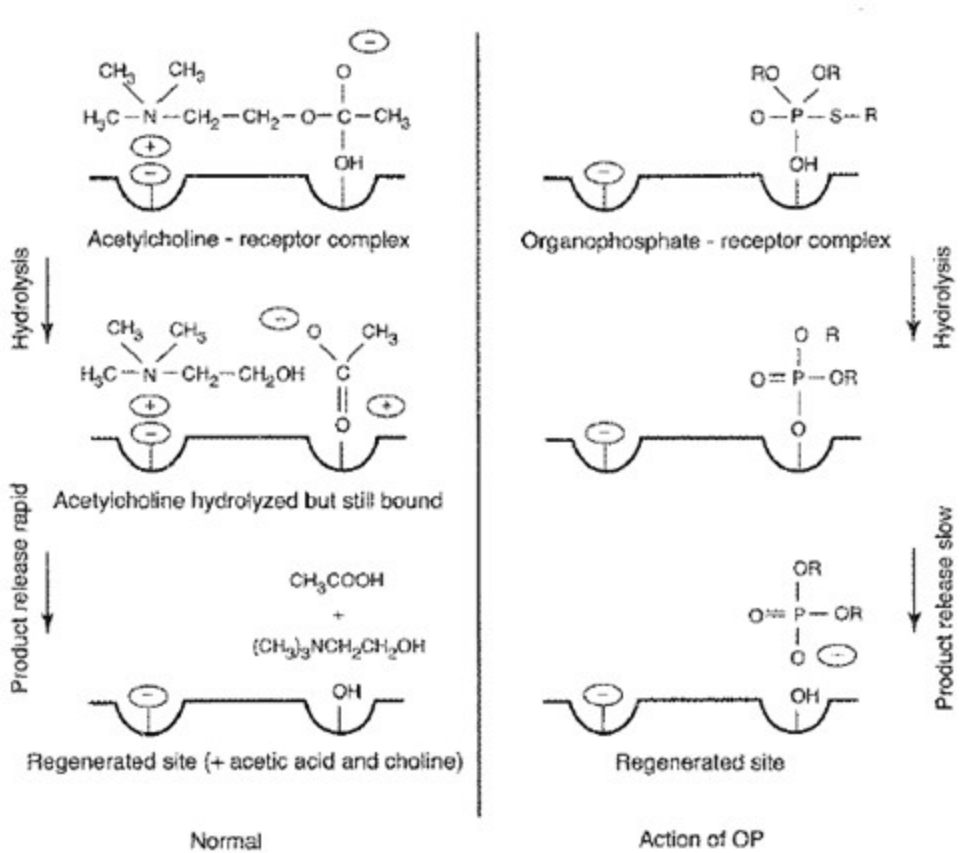




Concentración interna efectiva y acción tóxica

- Uniones covalentes o especies reactivas (Daño en el ADN, proteínas o lípidos)





Inhibición de la AchE

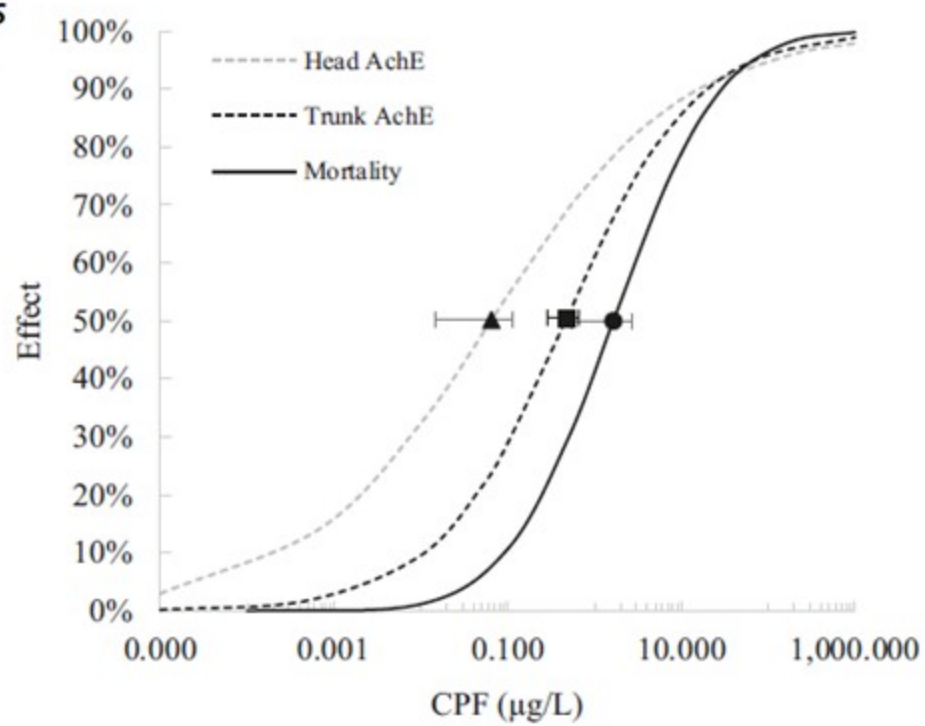
Concentración interna efectiva y acción tóxica

- Uniones covalentes o especies reactivas (Daño en el ADN, proteínas o lípidos)

Ecotoxicology (2018) 27:968–979
https://doi.org/10.1007/s10646-018-1941-5

Lethal and sublethal responses in the fish, *Odontesthes bonariensis* exposed to chlorpyrifos alone or under mixtures with endosulfán and lambda-cyhalothrin

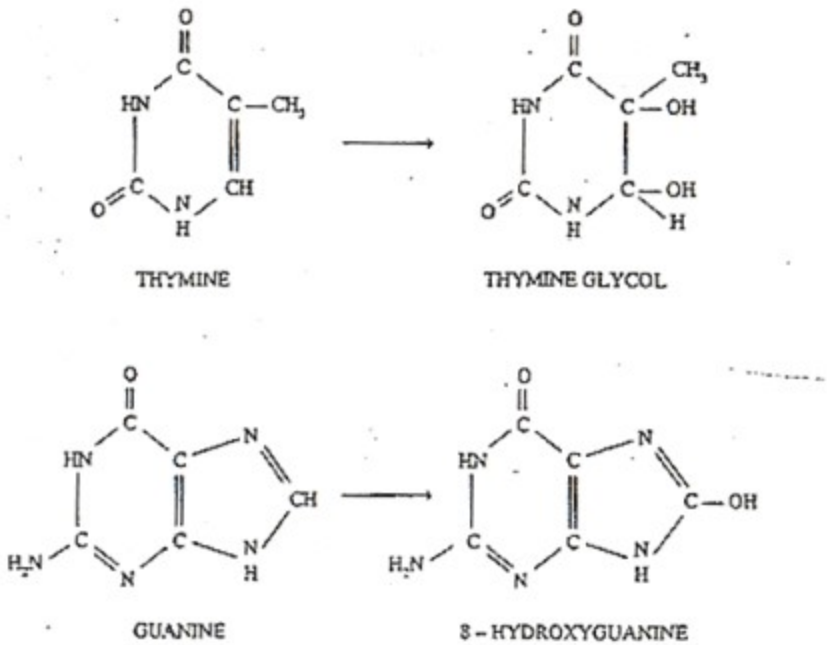
Viviana López Aca[1] · Patricia Verónica Gonzalez[1] · Pedro Carriquiriborde[1]



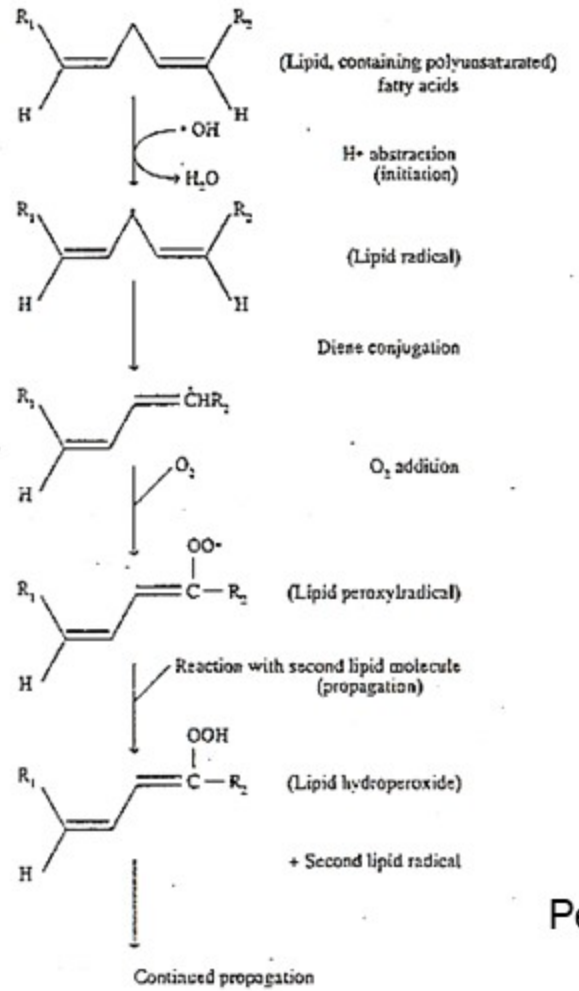
Inhibición de la AchE

Concentración interna efectiva y acción tóxica

- Uniones covalentes o especies reactivas (Daño en el ADN, proteínas o lípidos)



Oxidación bases nitrogenadas del ADN



Peroxidación lipídica

- Uniones covalentes o especies reactivas (Daño en el ADN, proteínas o lípidos)

Pesticide Biochemistry and Physiology 105 (2013) 102–110

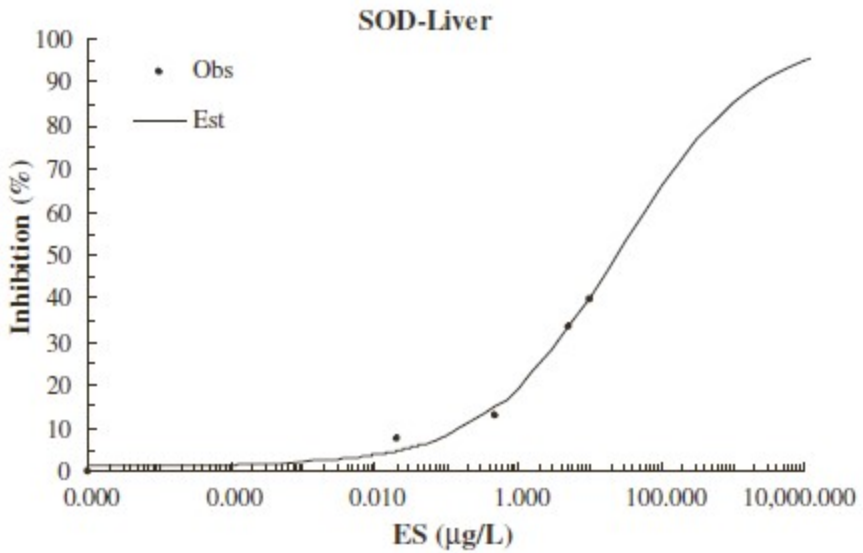
Contents lists available at SciVerse ScienceDirect

Pesticide Biochemistry and Physiology

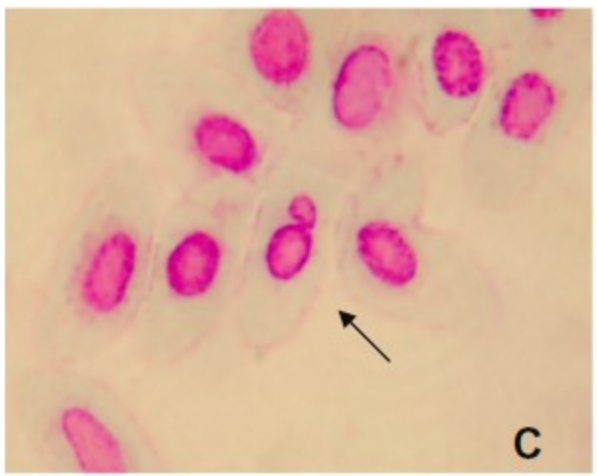
journal homepage: www.elsevier.com/locate/pest

Oxidative stress and genotoxicity in the South American cichlid, *Australoheros facetus*, after short-term sublethal exposure to endosulfan

Andrea C. Crupkin [a,*], Pedro Carriquiriborde [b,c], Julieta Mendieta [d], Ana M. Panzeri [e], María L. Ballesteros [a,b,f], Karina S.B. Miglioranza [a,b,f], Mirta L. Menone [a,b,f]



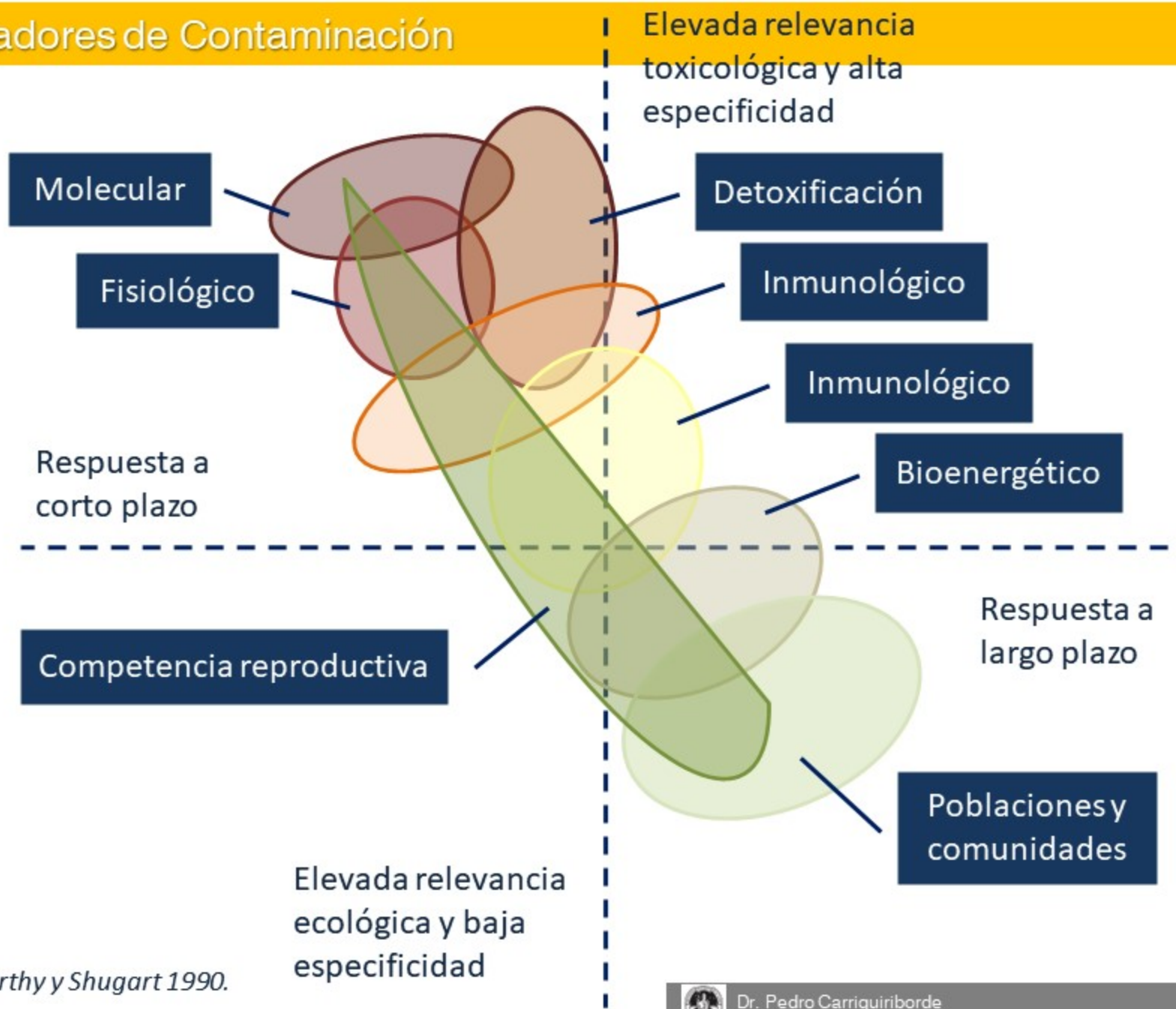
Obs: observed data, Est: estimated curve



Estrés oxidativo y daño en el ADN

Clase 4. Biomarcadores de Contaminación

Dr. Pedro Carriquiriborde
Maestría en Protección Vegetal 2023, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de la Plata (UNLP)



McCarthy y Shugart 1990.

Que son los Biomarcadores?

"mediciones de fluidos corporales, células o tejidos que indican, en términos bioquímicos ó celulares, la presencia de contaminantes o la magnitud de la respuesta biológica a estos" (McCarthy y Shugart 1990)

"cambios a nivel fisiológico, bioquímico e histológico como indicadores de exposición y/o efecto de xenobióticos a nivel sub-organísmico u organísmico " (Huggett *et al.*,1992)

"cualquier respuesta biológica a un contaminante ambiental por debajo del nivel organísmico, medida en su interior o en sus productos indicando un alejamiento del estado normal, que no puede ser detectado a partir del organismo " *(Van Gestel y Van Brummelen., 1992)*

Que son los Biomarcadores?

Biomarkers at Different Organizational Levels

Organizational Level	Example of Biomarker
Binding to receptor	TCDD binding to Ah receptor
	Nonylphenols binding to estrogen receptor
Biochemical response	Induction of Cytochrome P_{450}IA
	Inhibition of ACh-ase
	Vitellogenin formation
Physiological alteration	Eggshell thinning
	Feminization of embryos
Effect on individual	Behavioral changes
	Scope for growth

(Walker, 2007)

Atributos de los Biomarcadores

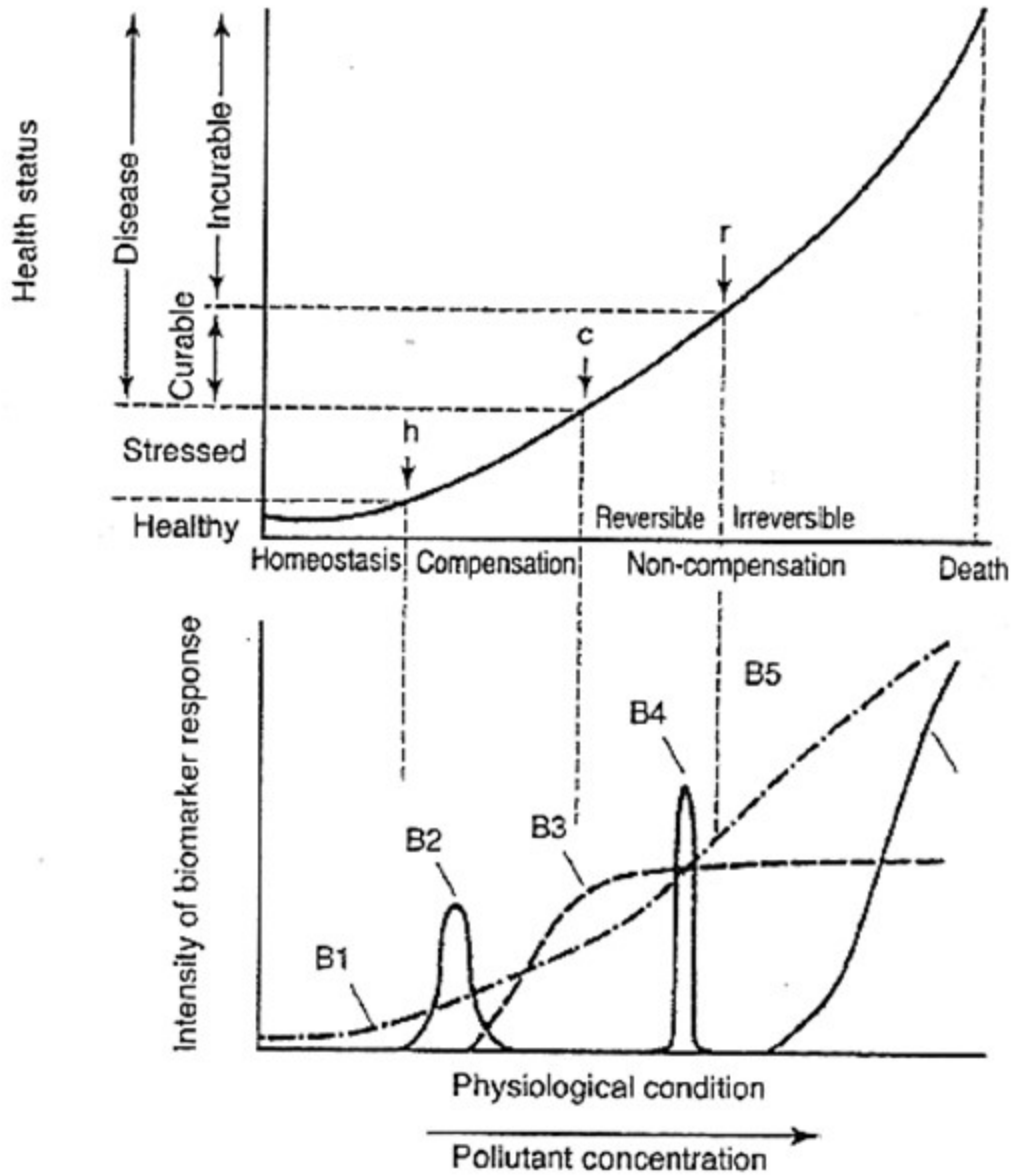
Predicen a corto plazo efectos ecológicos a largo plazo (señales de alerta temprana).

Indican la naturaleza y magnitud de los efectos que causan efectos adversos a nivel ecológico.

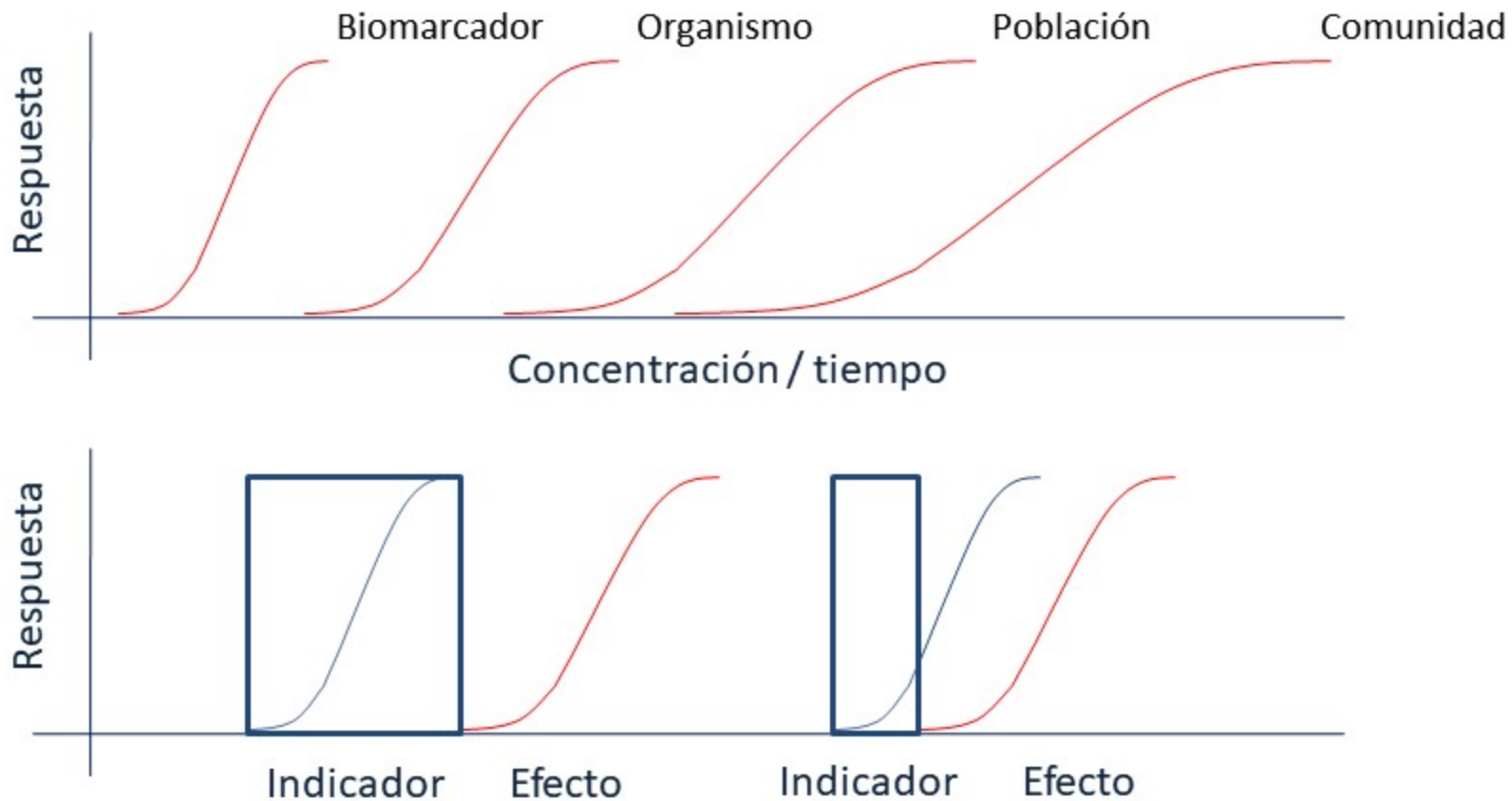
Proveen evidencia de exposición a sustancias que no se bio-acumulan o se metabolizan rápidamente.

Integran la farmacodinamia y las interacciones toxicológicas de mezclas de contaminantes.

Atributos de los Biomarcadores



Atributos de los Biomarcadores



Clasificación de Biomarcadores

- Biomarcadores de exposición: permiten la detección de una sustancia exógena o la de su metabolito o el producto de la interacción entre un agente xenobiótico y alguna molécula blanco que es medida en un compartimiento corporal

- Biomarcadores de efecto: medida de alteraciones bioquímicas, fisiológicas, o de otro tipo en los tejidos o fluidos de un organismos que puede ser asociada a un efecto adverso sobre la salud

- Biomarcadores de susceptibilidad: Indicador de habilidades inherentes o adquiridas de un organismo para responder a la exposición de un xenobiótico específico, incluyendo factores genéticos y cambios en receptores que alteran la susceptibilidad de un organismo a la exposición.

Especificidad de los Biomarcadores

Biomarkers Listed by Decreasing Specificities to Pollutants

Biomarker	Pollutant	Comments and References
ALAD inhibition	Lead	Sufficiently reliable to replace chemical analysis (Wigfield et al., 1986)
Metallothionein induction	Cadmium	More difficult to measure than cadmium levels (Hamer, 1986)
Eggshell thinning	DDT, DDE, dicofol	Degree of eggshell thinning is easily measured (Ratcliffe, 1967)
AChE inhibition	OPs, carbamates	Easier and more reliable than chemical analysis (Fairbrother et al., 1991)
Anticoagulant clotting proteins	Rodenticides	Measurements similar in complexity to chemical analysis (Huckle et al., 1989)
Monooxygenase induction	OCs, PAHs	Dioxin equivalent more easily measured than chemical analysis (Murk et al., 1997)
Porphyrin profiles	Several OCs	Separation by high-performance liquid chromatography well developed (Kennedy and James, 1993)
Retinol profiles	OCs	Demonstrates exposure to specific chemicals (Shugart, 1994); considerable natural variations; ratios more reliable than absolute values (Spear et al., 1986)
DNA and hemoglobin adducts	Largely PAHs	Several tests available; complicated by repair mechanisms
Vitellogenin induction	Estrogenic chemicals	Induction in male fish is sensitive indicator of estrogenic chemicals (Harries et al., 1997)
Other serum enzymes	Metals, OCs, PAHs	Several enzyme systems have been studied (Fairbrother, 1994)
Stress proteins	Metals, OCs	Wide range of stress proteins have been studied (Sanders, 1993)
Immune responses	Metals, OCs, PAHs	Many tests available (Wong et al., 1992)

Especificidad de los Biomarcadores

Biomarkers Listed by Decreasing Specificities of Adverse Effects

Biomarker	Organizational Level	Comments and References
Eggshell thinning	Intact animal—population	Wide species variation in sensitivity; related to reproductive success (Peakall, 1993)
Inhibition of AChE	Organ—intact animal	Degree of inhibition related to mortality and sublethal effects (Grue et al., 1991)
Inhibition of ALAD	Organ—intact animal	Degree of inhibition related to mortality (Scheuhammer, 1989)
Clotting proteins	Intact animal—population	Related to mortality; risk assessed from blood protein levels (Hegdal and Blaskiewicz, 1984)
Induction of monooxygenases	Organ—population	Analysis of dioxin equivalents related to reproductive success; induction of P_{450} enzymes related to specific chemicals (Bosveld and van den Berg, 1994)
Depression of plasma retinol and thyroxine	Organ	Binding to specific protein; relation to adverse effects tenuous (Brouwer and van den Berg, 1986)
DNA integrity	Organ	DNA damage indicates serious harm; relationship to effects often tenuous (Everaarts et al., 1998)
Immune responses	Organ	Proper functioning critical to health, but system has considerable reserve (Richter et al., 1994)
DNA and hemoglobin adducts	Organ	Good monitor of exposure, especially for PAHs; relation to effects is tenuous (Varanasi et al., 1989)
Other enzymes	Organ	Relationship to effects not clear (Fairbrother, 1994)
Porphyrin profiles	Organ	Levels in environmental samples well below those causing adverse effects (Fox et al., 1988)
Induction of vitellogenin	Organ—intact animal	Clear link between induction of vitellogenin and presence of estrogenic chemicals; biological significance is speculative (Arcand-Hoy and Benson, 1998)
Induction of metallothionein	Organ	Protective mechanism, not related to mechanism of toxicity (Hamer, 1986)
Stress proteins	Organ	Difficult to separate effects from nonchemical stresses (Pyza et al., 1997)

Tipos de Biomarcadores

- Biomarcadores del sistema de detoxificación de hidrocarburos policíclicos.
- Biomarcadores de estrés oxidativo
- Biomarcadores de exposición a metales
- Biomarcadores generales de estrés
- Biomarcadores de genotoxicidad

Biomarcadores y Monitoreo Ambiental

- Integración espacial y temporal de contaminantes biodisponibles.
- Identificación de la exposición y el riesgo a contaminantes ambientales
- Determinación de diferencias en las rutas de exposición en organismos con diferentes hábitats.

A Multibiomarker Approach To Environmental Assessment

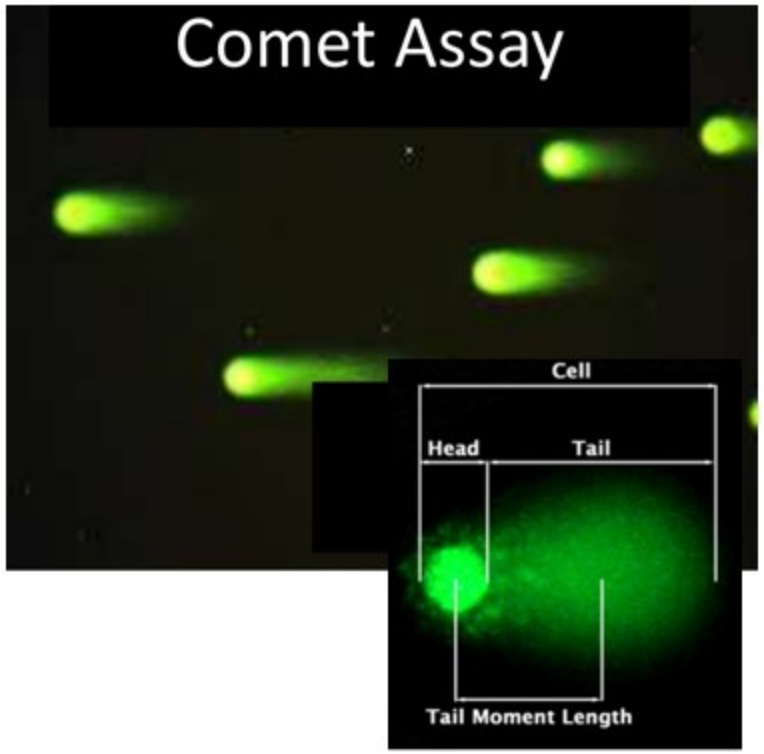
TAMARA S. GALLOWAY,*,† REBECCA J. BROWN,† MARK A. BROWNE,† AWANTHA DISSANAYAKE,† DAVID LOWE,‡ MALCOLM B. JONES,† AND MICHAEL H. DEPLEDGE§

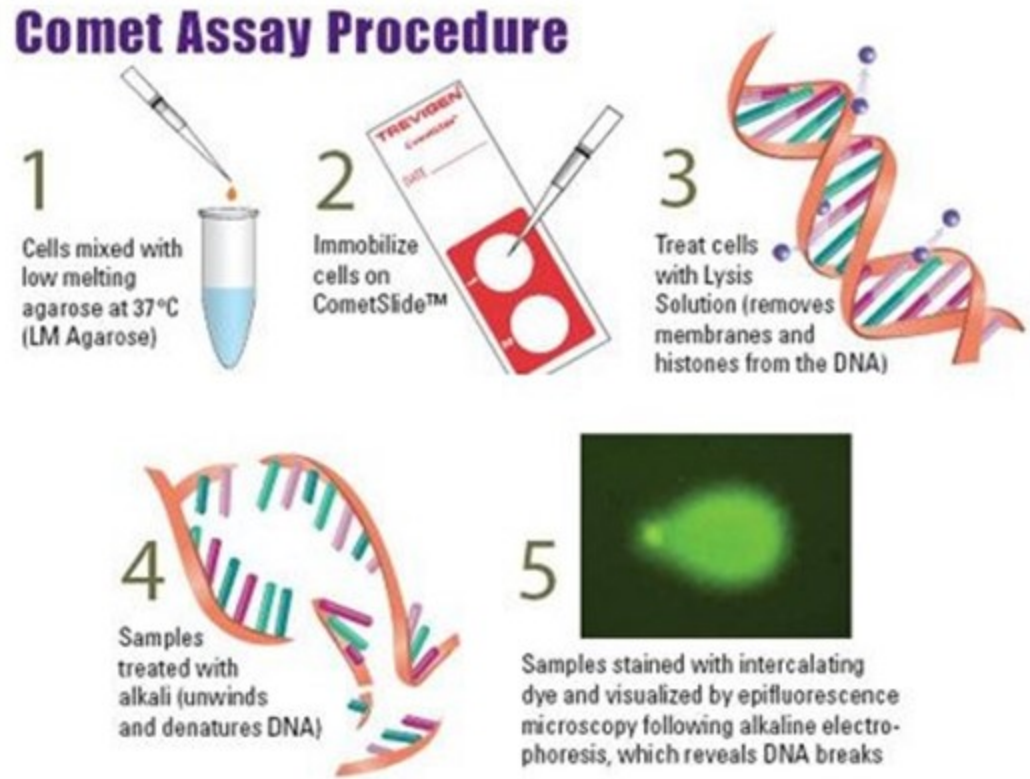
TABLE 1. Biomarker Responses Measured for Each Organism[d]

		organism		
	biomarker	*C. edule* filter-feeder	*L. littorea* grazer	*C. maenas* omnivore
molecular	esterase activity	$p > 0.05$	ND	$p > 0.05$
	metallothionein	$p > 0.05$	ND	**$p < 0.002$[b]**
	total haemolymph protein	$p > 0.05$	ND	**$p < 0.05$[c]**
	PAH metabolites in urine	ND	ND	**$p < 0.006$[b]**
cellular	micronucleus formation	**$p < 0.02$[a]**	ND	$p > 0.05$
	cell viability	**$p < 0.02$[a]**	ND	$p > 0.05$
	lysosomal stability	**$p < 0.2$[a]**	ND	$p > 0.05$
	phagocytosis	$p > 0.05$	ND	$p > 0.05$
physiological	heart rate	$p > 0.05$	ND	$p > 0.05$
	intersex index	ND	**$p < 0.0001$[a]**	ND

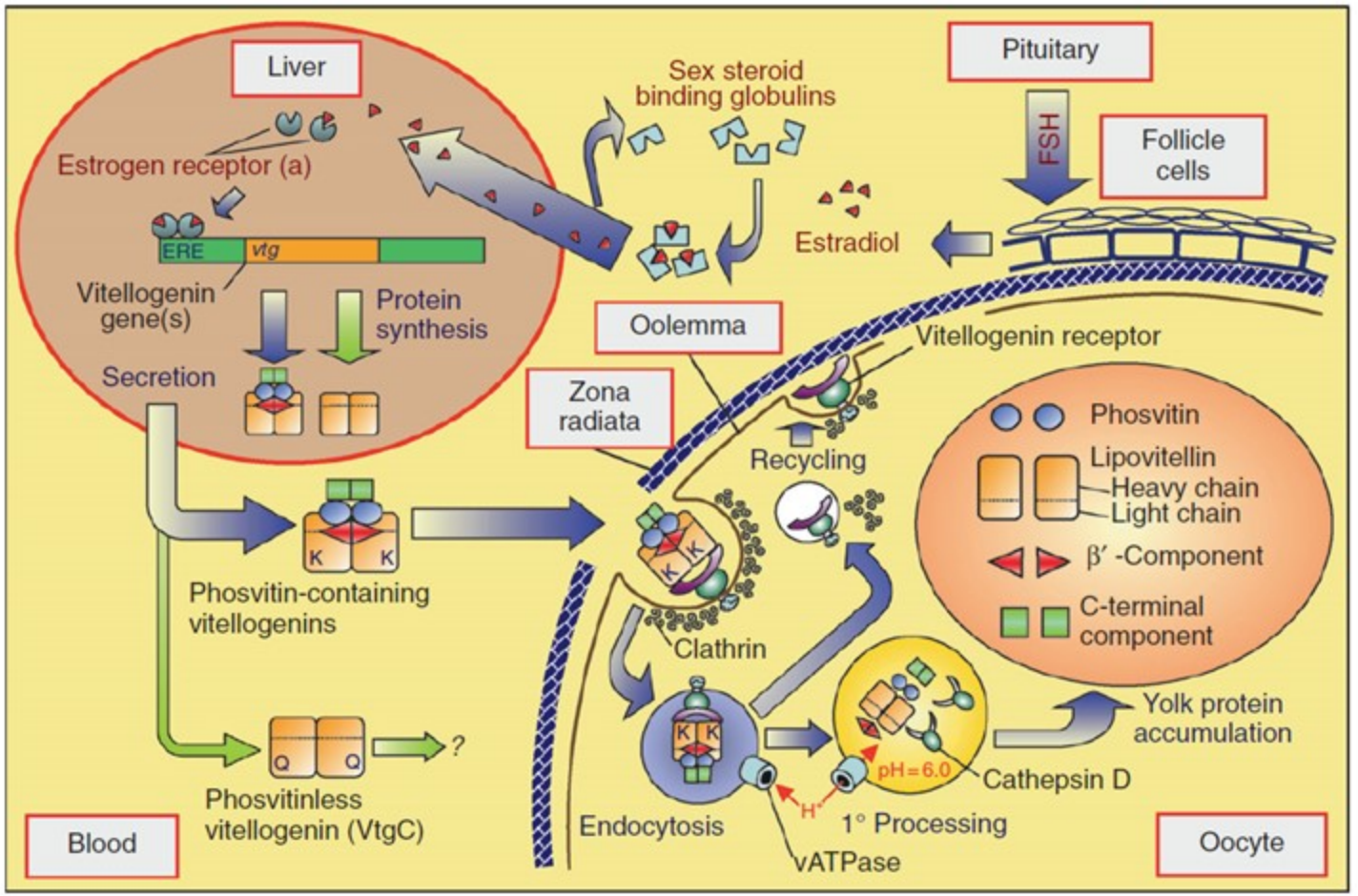
[a] Anova, between Cracknore Hard and remaining sites. [b] Anova, between Esso outfall and remaining sites. [c] Kruskal Wallis, between Esso Outfall and remaining sites. [d] $n = 8$ for each site, except for intersex index, for which $n = 50$. Significant differences between sites are shown in bold. ND = not determined.

Biomarcadores de efecto: genotoxicidad

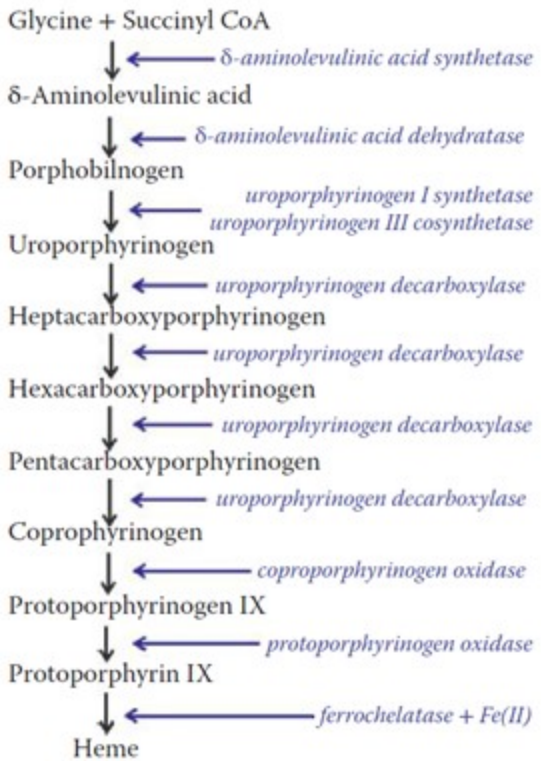




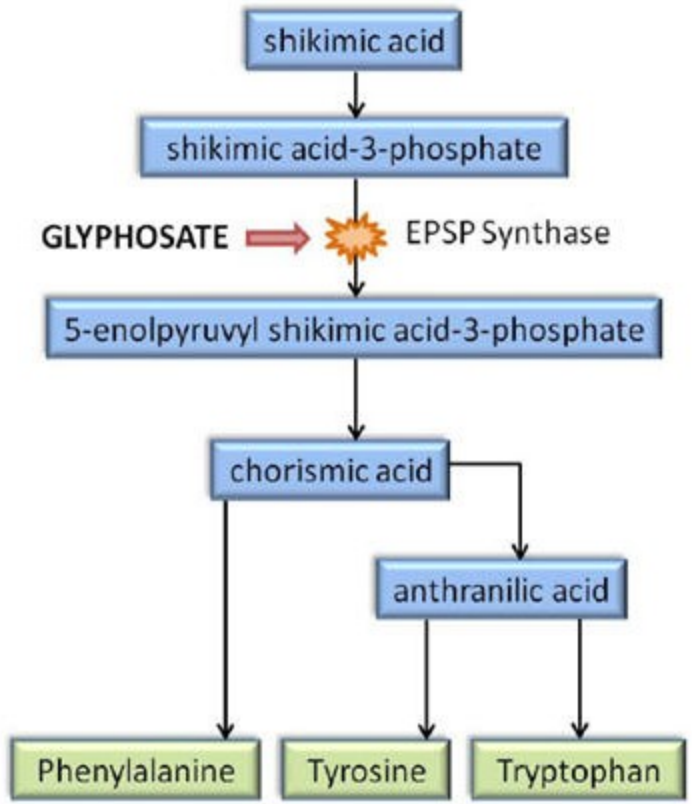
Biomarcadores de exposición:
Mediados por receptores
(P450, VTG, MT, etc.)

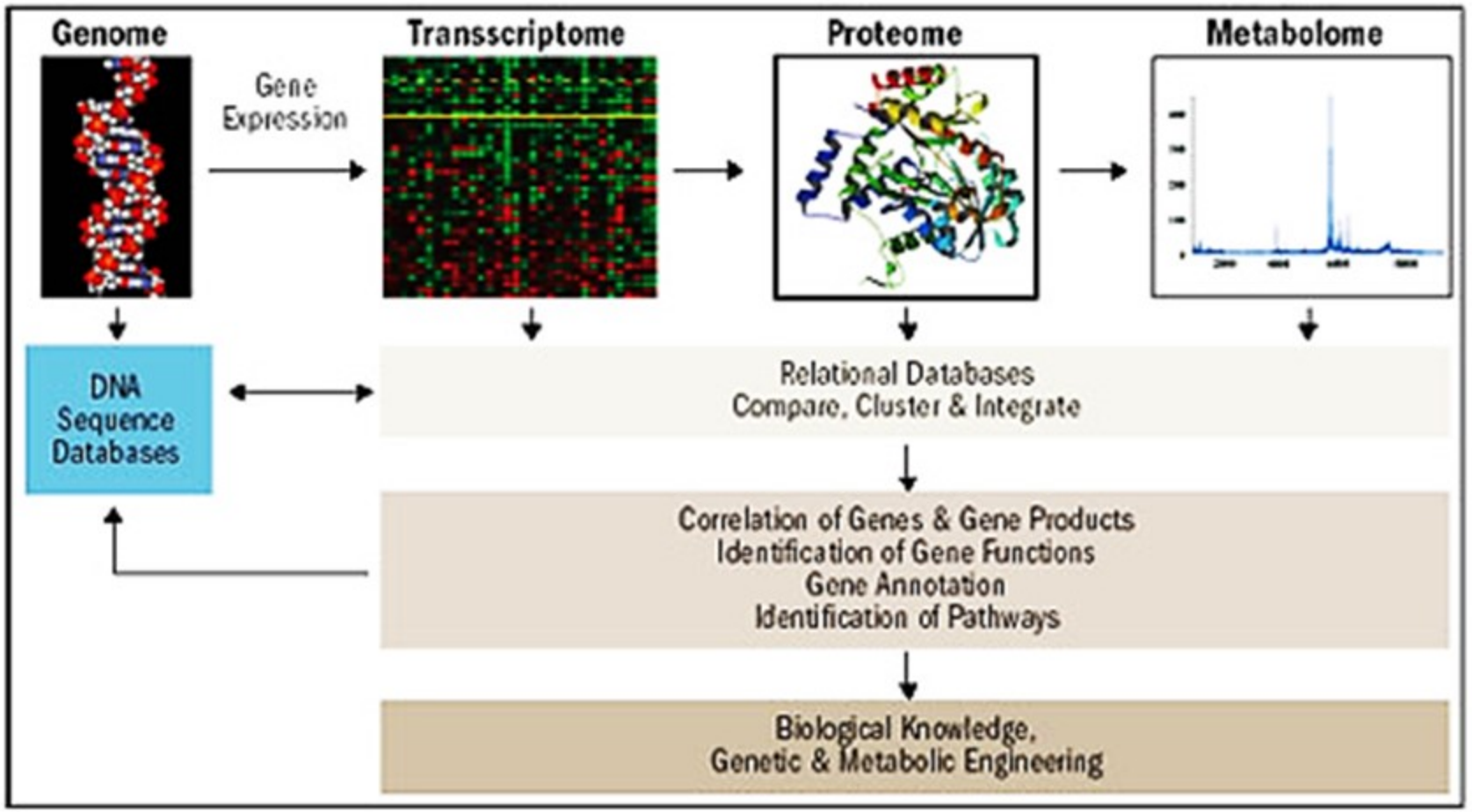


Biomarcadores de exposición: Inhibición enzimática (AchE, ALA-D, Shikimato)



Steps in the synthesis of heme. Enzymes catalyzing each conversion are italicized and placed to the right of the reaction sequence. (Modified from Figure 1 of Woods, J.S., et al. *J. Toxicol. Environ. Health*, 40, 235–246, 1993.)




Genome
Gene Expression
Transscriptome
Proteome
Metabolome
DNA Sequence Databases
Relational Databases
Compare, Cluster & Integrate
Correlation of Genes & Gene Products
Identification of Gene Functions
Gene Annotation
Identification of Pathways
Biological Knowledge,
Genetic & Metabolic Engineering

Biomarcadores de exposición: inducción génica

Aquatic Toxicology 254 (2023) 106366

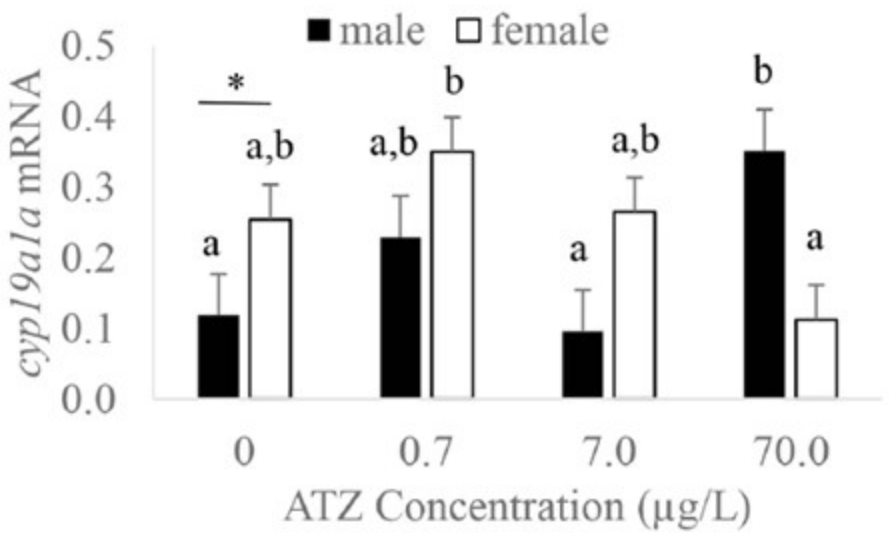
Contents lists available at ScienceDirect

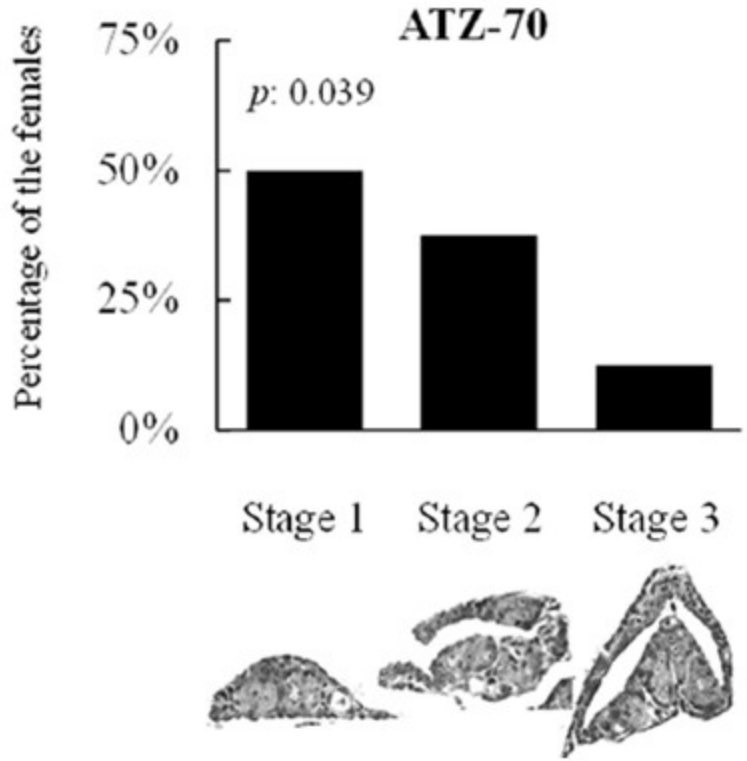
Aquatic Toxicology

journal homepage: www.elsevier.com/locate/aqtox

Atrazine alters early sexual development of the South American silverside, *Odontesthes bonariensis*

Pedro Carriquiriborde [a], Juan Ignacio Fernandino [b,c], Carina G. López [b,c], Eduardo de San Benito [a], Juan Manuel Gutierrez-Villagomez [d], Diego Cristos [e], Vance L. Trudeau [d], Gustavo M. Somoza [b,c,*]





Ecotoxicology and Environmental Safety 76 (2012) 46–54

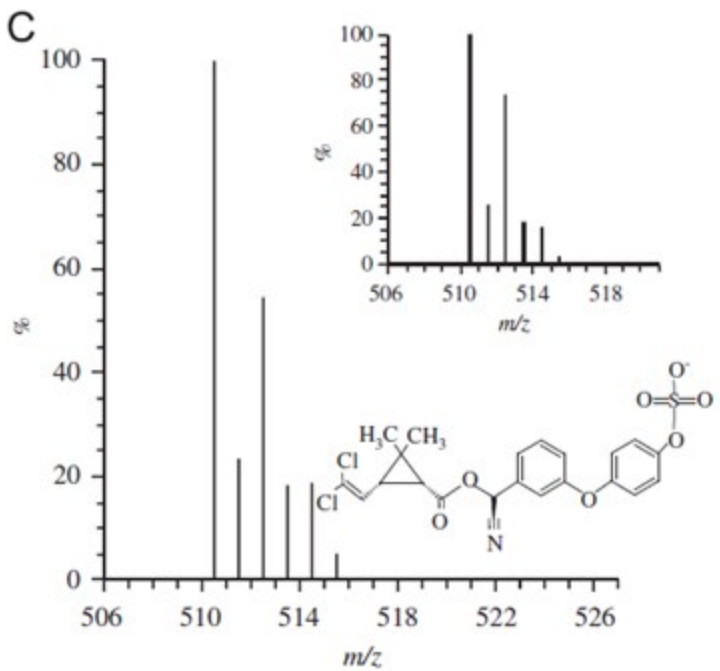
Contents lists available at SciVerse ScienceDirect

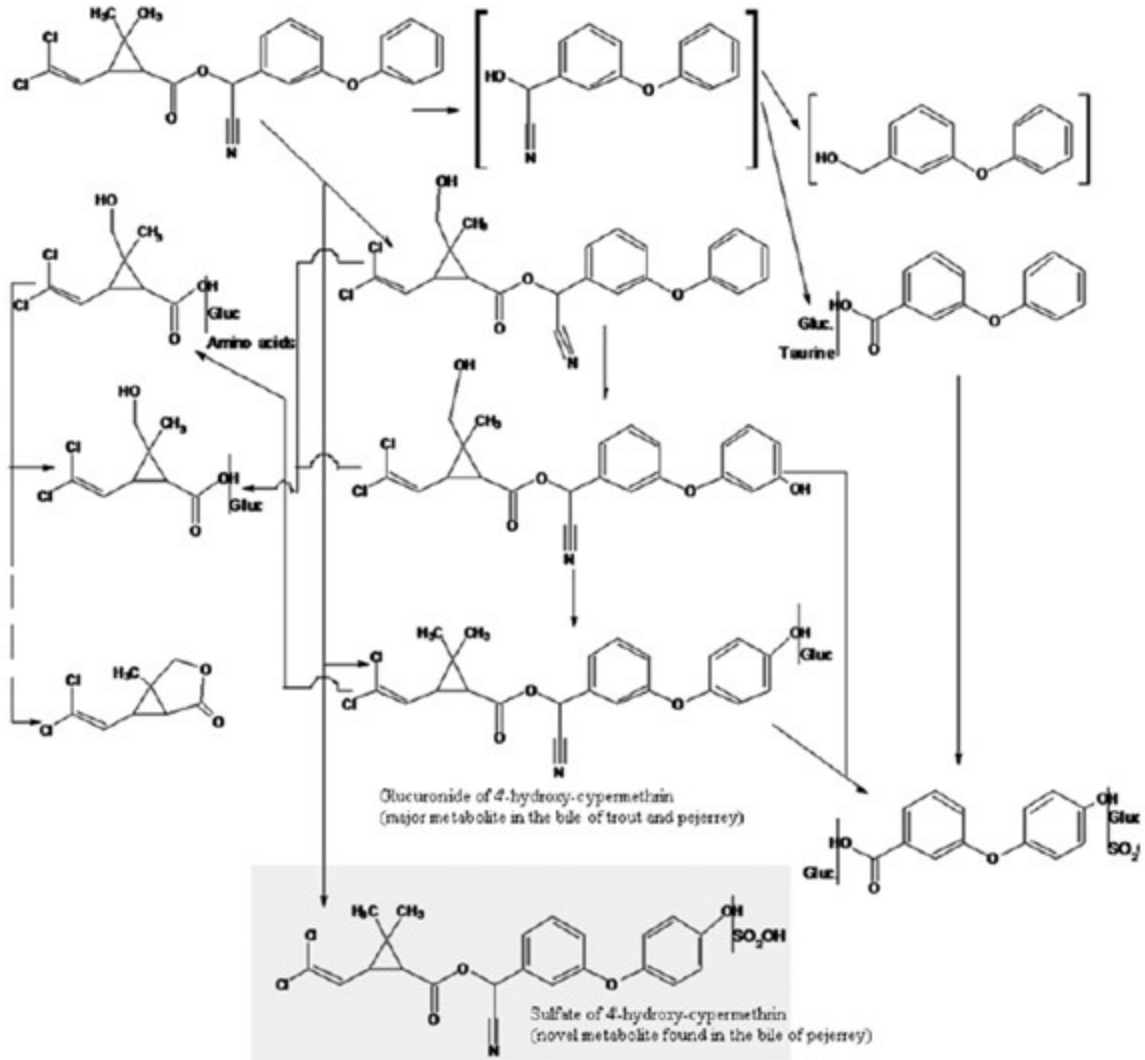
Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

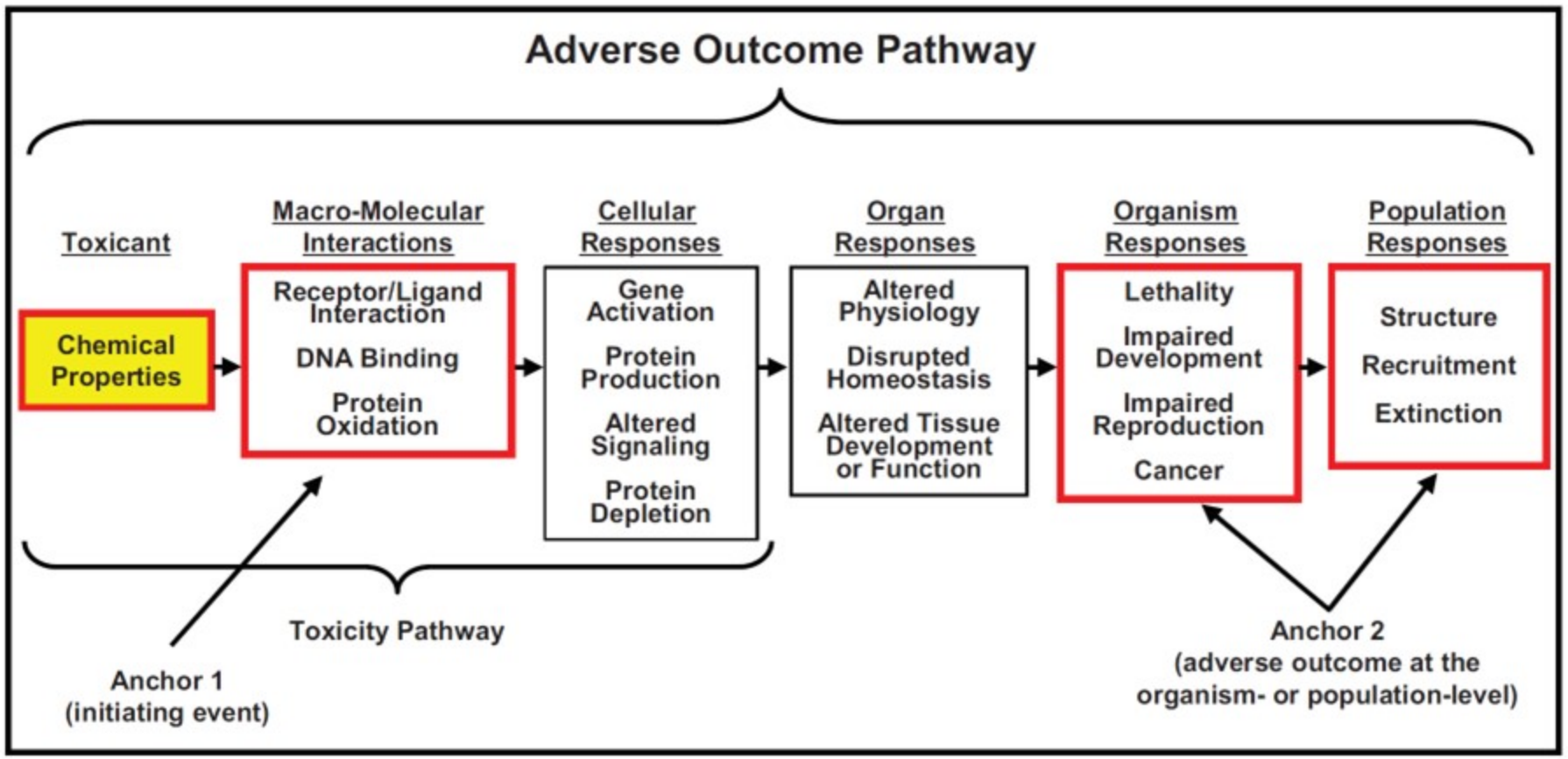
Global metabolic response in the bile of pejerrey (*Odontesthes bonariensis*, Pisces) sublethally exposed to the pyrethroid cypermethrin

Pedro Carriquiriborde[a,*,1], Damián J. Marino[a,b,1], Gabriela Giachero[a], Eduardo A. Castro[b], Alicia E. Ronco[a]

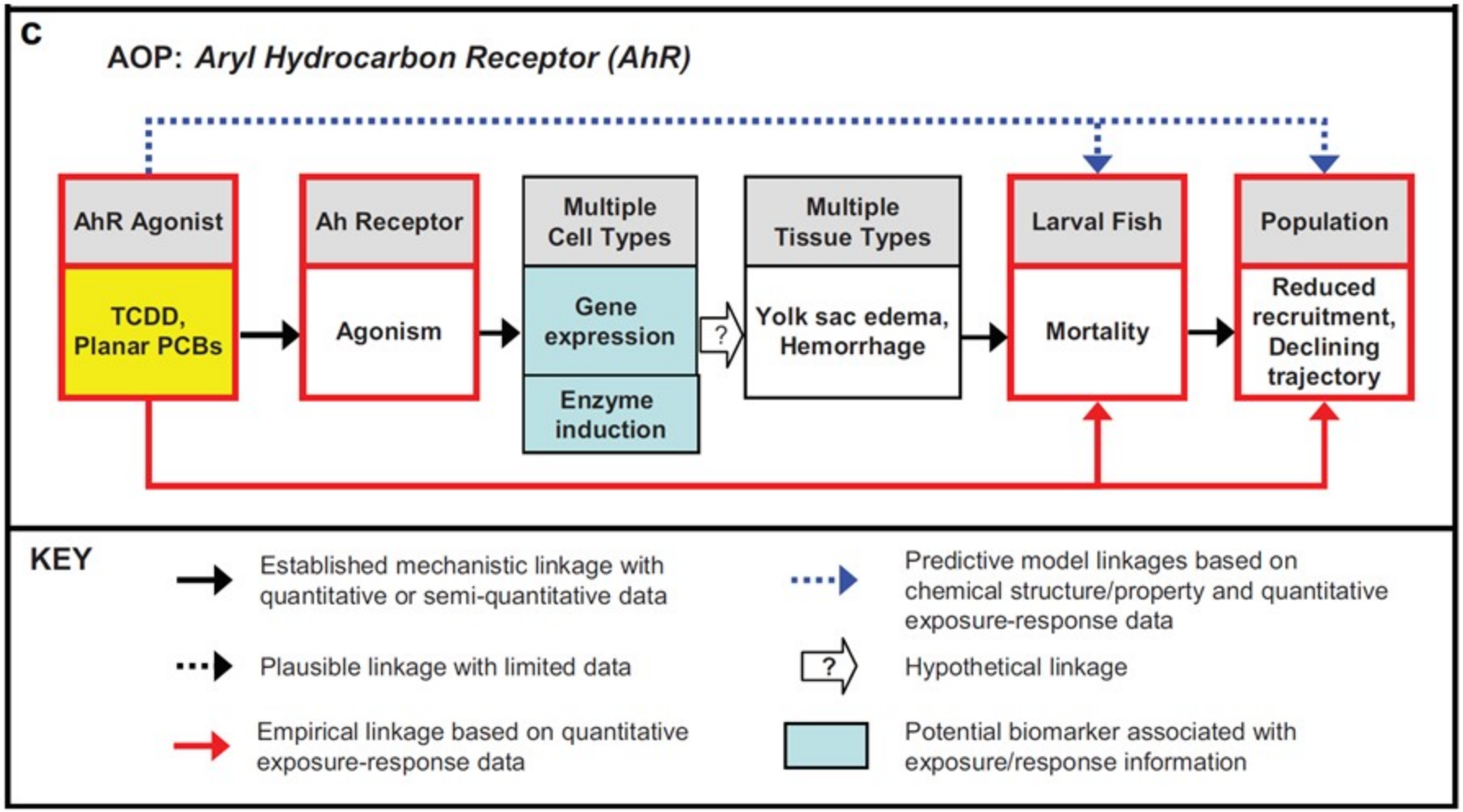




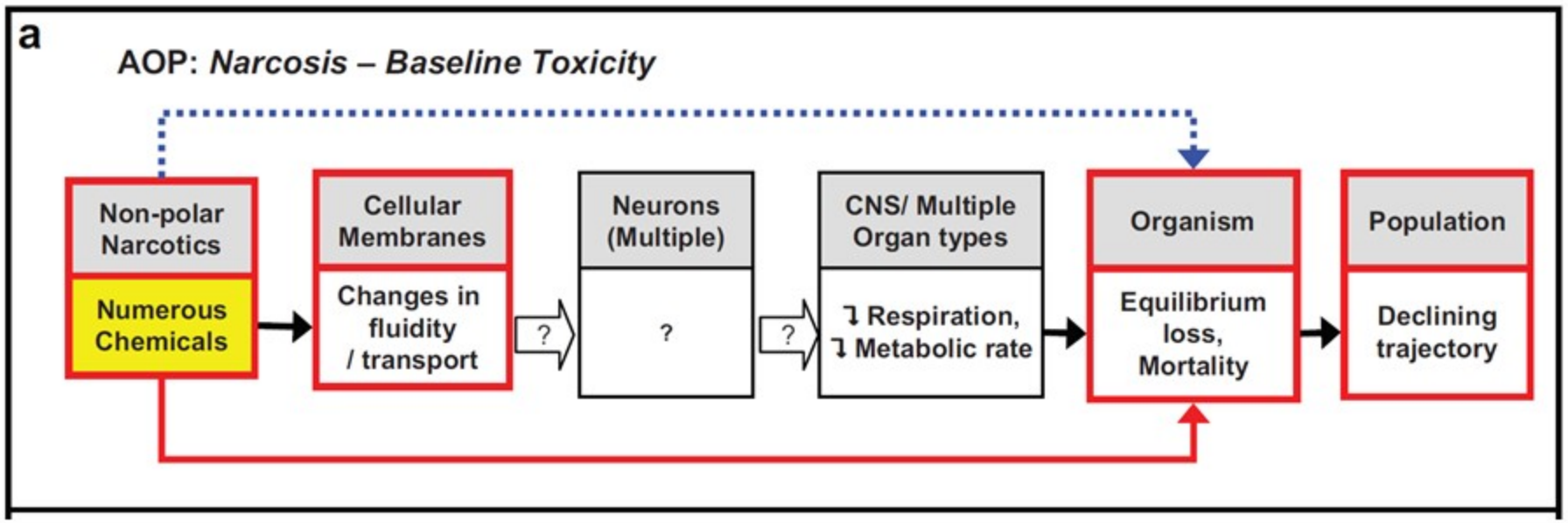
Vías de efectos adversos



Vías de efectos adversos



Vías de efectos adversos



Vías de efectos adversos