Valutazione del rischio chimico

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Valutazione della tossicità per la valutazione del rischio per la salute umana *(RAoC cap.6)*

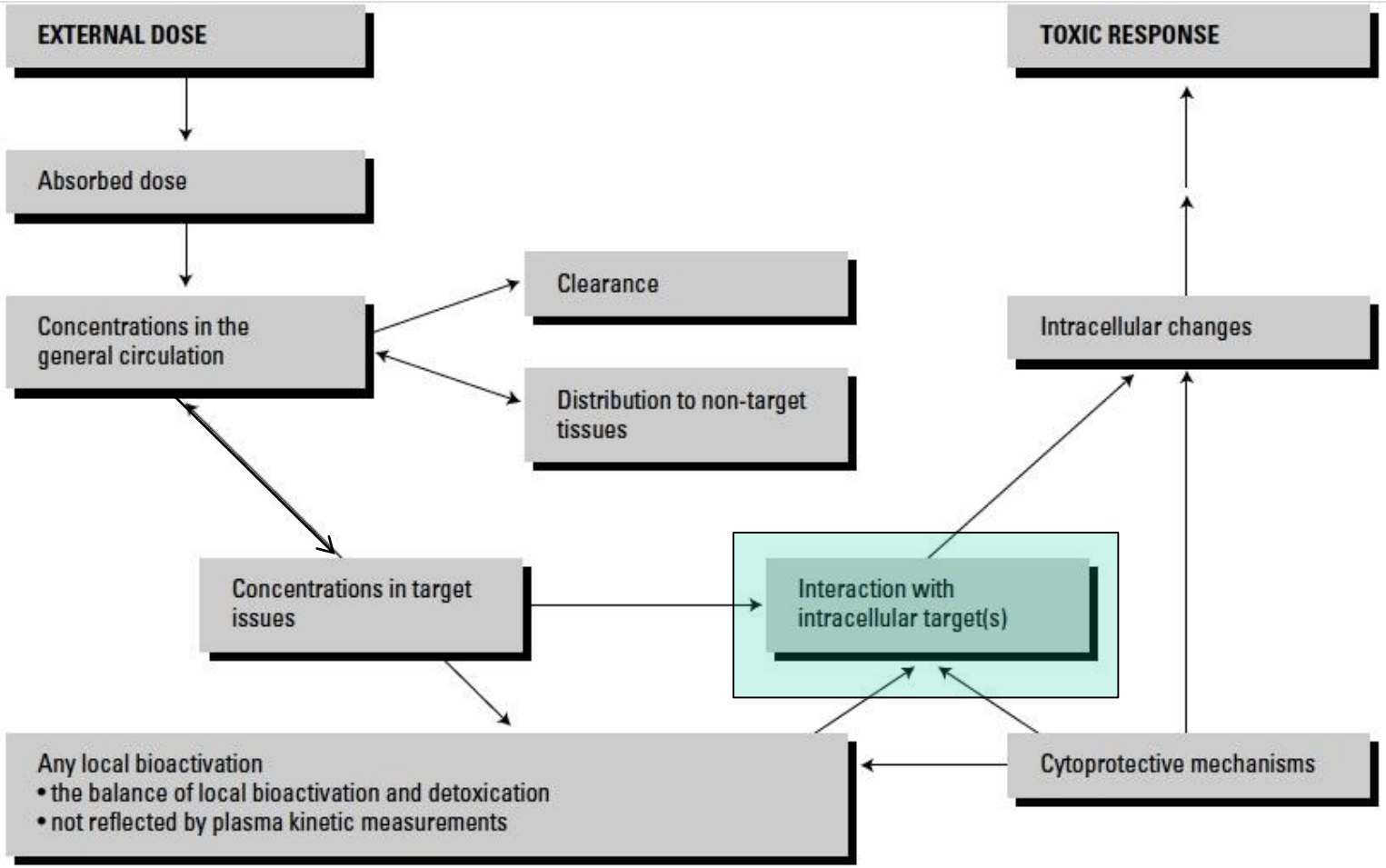


Figure 6.1. Processes leading to the generation of a toxic response [2].
Note:"Concentrations" refers to the relevant active form delivered by the general circulation and may be the parent compound or an active metabolite produced in another tissue and delivered to the target tissue or organ

Tossicologia cinetica: Specie trasportate / metabolizzate

Veleni sistemici, possono attraversar membrane e agire su **recettori**

Quando consideriamo la pericolosità di una ***sostanza*** assumiamo che gli effetti avvengano per ***interazione tra essa ed un sito recettore***. Si ha una *risposta solo se un quantitativo sufficiente della specie o di un suo metabolita attivo raggiunge il recettore*. Ciò evidenzia la rilevanza dell'informazione sui processi di **assorbimento, distribuzione, metabolismo ed escrezione** (ADME), molto studiati in farmacologia, che determinano il destino all'interno del corpo e le dosi interne al sito bersaglio.

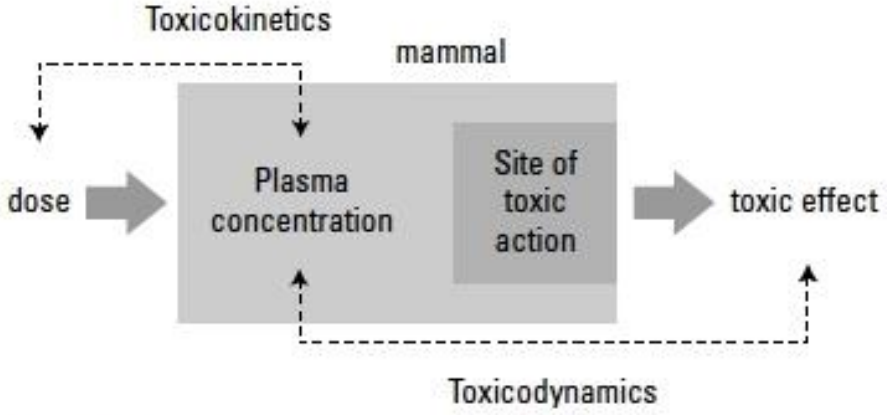


Figure 6.2. Toxicokinetics

Tossicologia – tossificazione e detossificazione

Composto genitore attivo

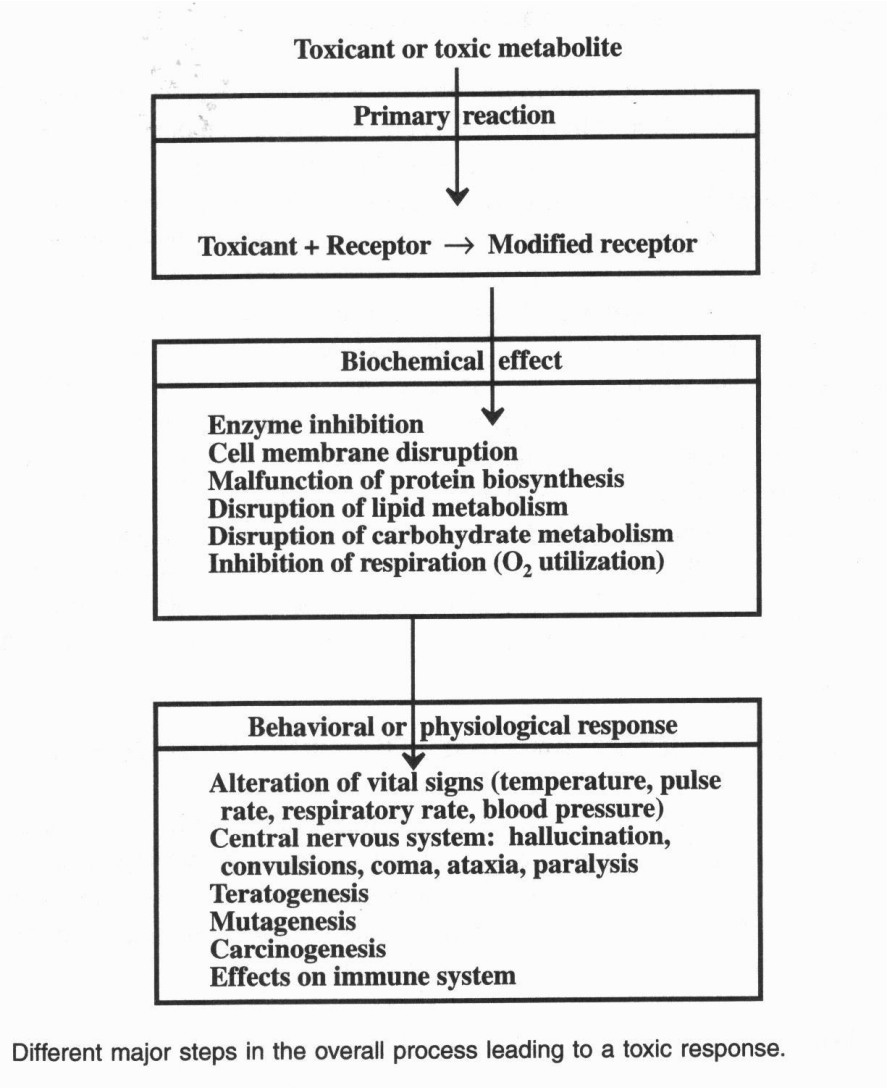
Metabolita attivo.

Effetti additivi / sinergici / di potenziamento /

Effetti antagonisti / “blockers” (competizione per un sito)

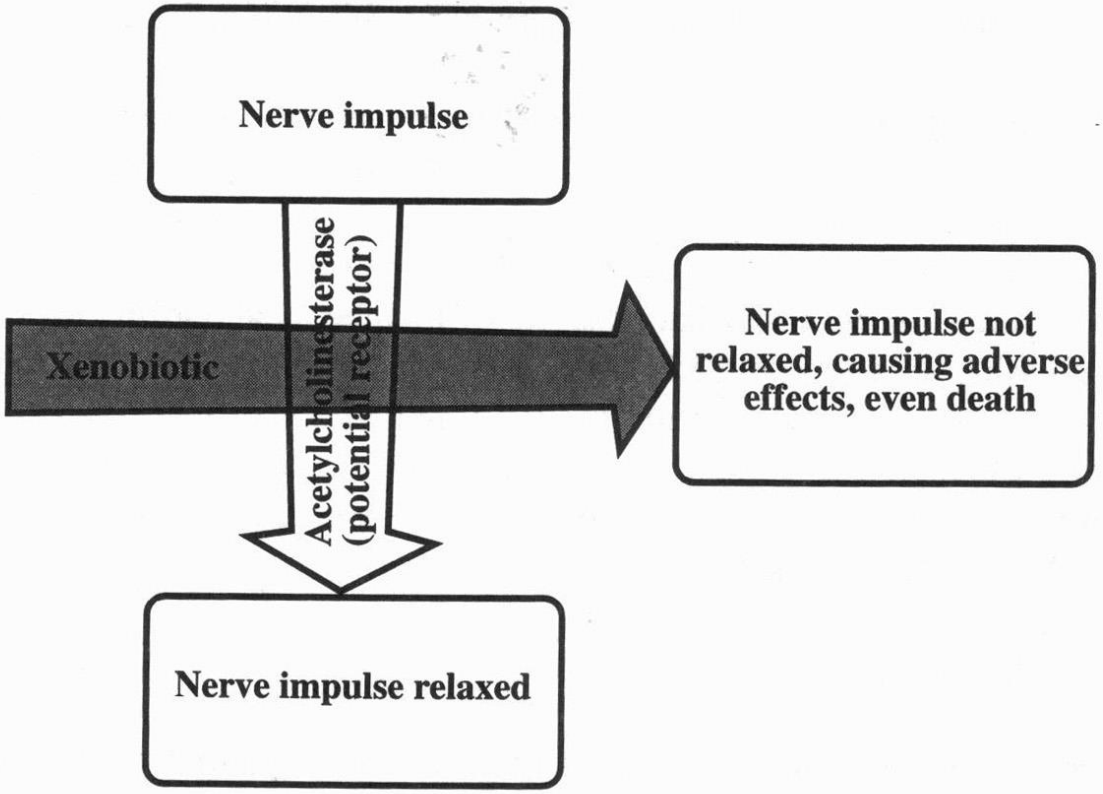
Tossicologia – fasi di tossicità

Dopo la *fase cinetica*, che trasporta la specie tossica al recettore, inizia la ***fase dinamica***



Different major steps in the overall process leading to a toxic response.

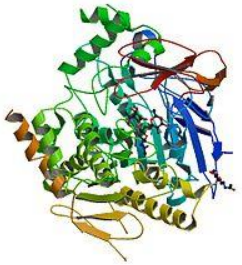
Un esempio – recettori e sostanze tossiche



Example of a toxicant acting on a receptor to cause an adverse effect. When acetylcholinesterase is bound by a xenobiotic substance, the enzyme does not act to stop nerve impulse. This can result in paralysis of the respiratory system and death.

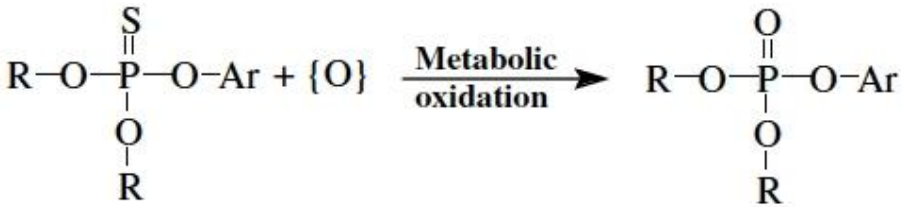
RECETTORI e sostanze tossiche

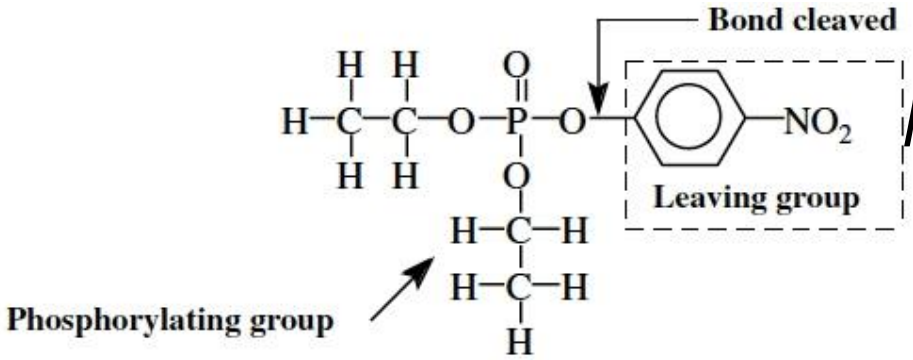
Es. Funzionamento normale: l'acetilcolina è un neurotrasmettitore che deve essere idrolizzato enzimaticamente per evitare eccessiva stimolazione da parte ai recettori nervosi



S. Manahan
Toxicological chemistry and biochemistry, 2003
p.374-375

Parathion -> Paraoxon attivazione





paraoxon

The reaction of this compound with cholinesterase enzyme (E) can be represented by the following reaction:

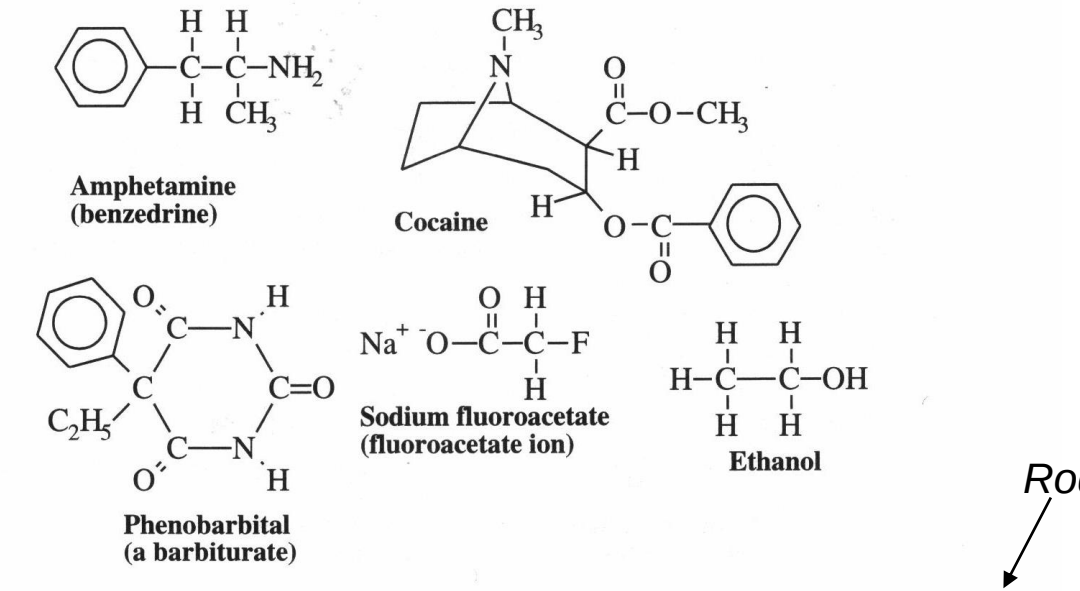
$$E + PL \rightarrow EP + L \xrightarrow[\text{bound enzyme}]{\text{Slow dissociation of covalently}} E + \text{Products} \qquad (18.7.4)$$

Tessuto nervoso e recettori colpiti	Sito colpito	Manifestazioni
Fibre nervose postgangliari parasimpatiche (recettori muscarinici) del SNA	Ghiandole esocrine	Scialorrea, lacrimazione, sudorazione
	Occhi	Miosi (a punta di spillo e non reattiva), difficoltà di accomodazione, irritazione congiuntivale, dacriorrea.
	Tratto gastrointestinale	Nausea, vomito, tensione, gonfiori e dolori addominali, diarrea, tenesmo, incontinenza fecale.
	Tratto respiratorio	Eccessive secrezioni bronchiali, rinorrea, respiro affannoso, edema, tensione al torace, broncospasmo, broncocostrizione, tosse, bradipnea, dispnea.
	Sistema cardiovascolare	Brachicardia, ipotensione
	Vescica	Pollachiuria e incontinenza
Fibre parasimpatiche e simpatiche (recettori nicotinici) del SNA	Sistema cardiovascolare	Tachicardia, pallore, ipertensione

Approfondimento: http://www.federica.unina.it/medicina-veterinaria/tossicologia-veterinaria/avvelenamento-pesticidi-attivita-anticolinesterasica/

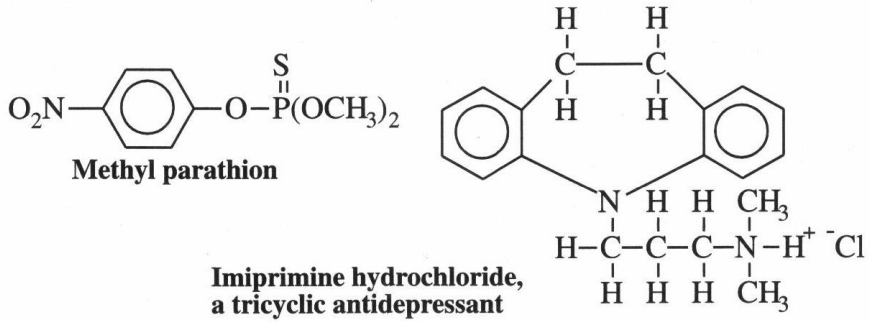
Fine esempio 1 tox

Tossicologia – risposte fisiologiche e comportamentali



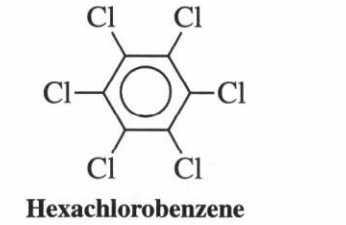
Rodenticida

Examples of toxicants that affect body temperature. Amphetamine, cocaine, and fluoroacetate increase body temperature; phenobarbital and ethanol decrease it.

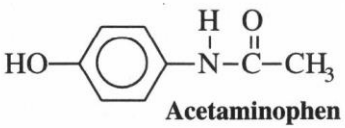


Structures of toxicants that can affect pulse rate. Methyl parathion, a commonly used plant insecticide, can cause bradycardia. Imiprimine hydrochloride, a tricyclic antidepressant, can cause either tachycardia or arrhythmia.

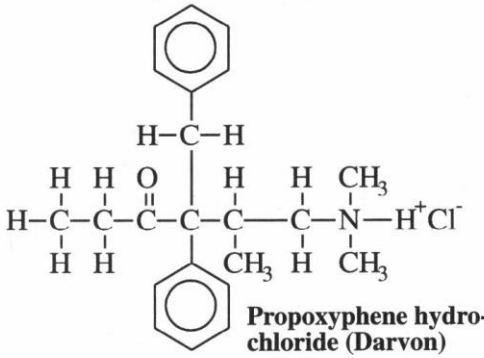
Tossicologia – risposte fisiologiche e comportamentali



Hexachlorobenzene

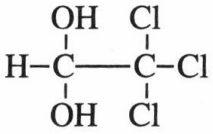


Acetaminophen

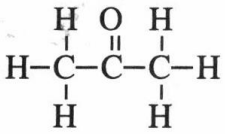


Propoxyphene hydrochloride (Darvon)

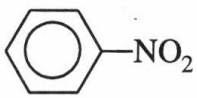
Some compounds that affect respiratory rate. Acetaminophen is one of the simple analgesics, which in therapeutic doses relieves pain without any effect on an individual's consciousness. Propoxyphene hydrochloride is a narcotic analgesic, a class of substances that can cause biochemical changes in the body leading to chemical dependency.



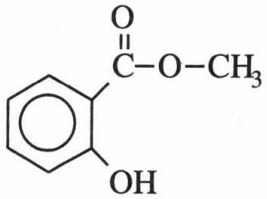
Chloral hydrate (pear odor)



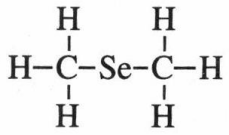
Acetone (acetone odor)



Nitrobenzene (shoe polish)



Methyl salicylate (wintergreen)



Dimethyl selenide (garlic)

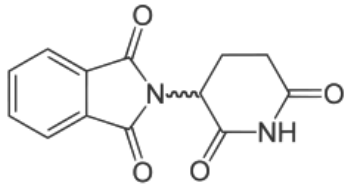
Some toxicants and the odors they produce in exposed subjects.

Effetti ritardati nel tempo

Tossicologia – effetti riproduttivi e sullo sviluppo

Effetti tossici sullo sviluppo

Effetti teratogeni (es. talidomide) (primo trimestre di gravidanza)



Effetti sul sistema riproduttivo

Effetti mutageni (alterazione del DNA)

Studi sulla tossicità

Molti aspetti critici ci si riferisce spesso alla ***"bibbia" gialla del WHO/OMS*** "*Principles and methods for evaluating the toxicity of chemicals: Part I*"; http://www.inchem.org/documents/ehc/ehc/ehc006.htm

Indicazioni sono reperibili anche su "*Guidelines for testing chemicals*" dell'OECD/OCSE

Bada a:

- Proprietà chimiche
- ie d'esposizione
- Selezione e cura degli animali (dieta e condizioni di stabulazione)
- Acquisizione dei dati e presentazione e interpretazione dei risultati
- *Good laboratory practices (US-FDA, USEPA, OECD, EC)*

Incertezze nei test su animali *UN International Program on Chemical Safety* (1978)

Aspetti generali

Test substance
Dose selection
Animal species
Test duration
Diet
Other environmental variables
Parameters studied
Electronic data processing
Presentation of results
Interpretation and evaluation of results
GLP
Requisiti del personale
Benessere degli animali
Dati umani
Incertezza e variabilità

International Program on Chemical Safety. 1978. Principles and methods for evaluating the toxicity of chemicals. Part I. World Health Organization, *Environmental Health Criteria* 6.
http://www.inchem.org/documents/ehc/ehc/ehc006.htm

Test di tossicità acuta:

singola dose o dosi ripetute nelle 24 ore
Esiti rilevati entro 14 giorni dall'esposizione
Richiesto nel REACh (esposizione orale se non sono disponibili dati di e. inalatoria) per sostanze con produzione importazione maggiore di 1 tonnellata/anno; per più di 10 t/y serve test su ulteriore via d'esposizione.
Si verifica in genere letalità

Test acuti locali

Irritazione e corrosione richiesti nel REACh per sostanze con t/y >10
"Irritant substances are non-corrosive substances which cause inflammation as evidenced by erythema and oedema of the skin and corneal opacity, iridal effects and conjunctival redness or swelling for the eye. Corrosive substances may destroy living tissues."
In vivo su conigli / no dose-risposta, no LOEL

Sensibilizzazione richiesto nel REACh per sostanze con t/y >1
Skin sensitization (-> allergic contact dermatitis) is a common form of allergy. Following skin exposure, it develops in 2 phases: *induction (sensitization* - induzione) and *elicitation* (scatenamento).

1) a primary immune response is triggered following a reaction between the chemical allergen and skin protein.
2) if the sensitized individual comes in contact with the same chemical allergen again in a later stage, a more pronounced secondary response is induced

Test di tossicità acuta

Table 5.2. Acute toxicity tests

Conditions	chemical identification of substance, its purity and chemical characteristics
Route	oral, dermal, inhalatory
Experimental animals	rat, (mouse), rabbit, guinea pig, (dog)
Number of animals	5 of each sex per group
Dose levels	control and at least 3 or more if necessary for calculating LD50 or LC50[a]
Examinations	- clinical examination for signs of toxicity or death - gross examination - histopathological examination if indicated
Results	the LD50 or LC50 value for each sex at 95% confidence interval

[a] If a dose of 2000 mg/kg_{bw} does not cause acute toxicity and compound-related mortality, a full study may not be necessary.

Table 5.4. Evaluation and interpretation of results of acute toxicity tests (fixed dose procedure)

Dose	Results	Interpretation
5 mg/kg_{bw}	less than 100% survival	compounds which are *very toxic*
	100% survival; but evident toxicity	compounds which are *toxic*
	100% survival; no evident toxicity	see results at 50 mg/kg
50 mg/kg_{bw}	less than 100% survival	compounds which may be *toxic* or *very toxic*; see results at 5 mg/kg
	100% survival; but evident toxicity	compounds which are *harmful*
	100% survival; no evident toxicity	see results at 500 mg/kg
500 mg/kg_{bw}	less than 100% survival	compounds which may be *toxic* or *harmful*; see results at 50 mg/kg
	100% survival; but evident toxicity	compounds considered as having no significant acute toxicity
	100% survial; no evident toxicity	see results at 2000 mg/kg
2000 mg/kg_{bw}	less than 100% survival	see results at 500 mg/kg
	100% survival; with or without evident toxicity	compounds which do not have significant acute toxicity

Tossicità per dosi ripetute

Più che a dosi elevate a seguito di incidenti gli esseri umani possono essere esposti ripetutamente a basse dosi di contaminanti ambientali.

Esempi di test con somministrazioni ripetute ad animali da esperimento sono la prova sub-acuta di 28 giorni, il test subcronico di 90 giorni e il test cronico per la durata di vita. Il requisito minimo di solito è la prova di 14 o 28 giorni con ratti.

In base al REACh, è richiesto uno studio di tossicità a dose ripetuta (almeno una prova di 28 giorni) per un livello annuale di produzione o di importazione di 10 tonnellate.

Si ottengono informazioni su quelli che sono gli organi bersaglio, relazioni dose/risposta, NOAEL o BDC.
Ratti e cani, usualmente giovani (più sensibili)

Table 5.5. Repeated dose studies (28 and 90 d)

Conditions	chemical identification of substance, its purity and chemical characteristics
Route	oral, dermal, inhalatory
Experimental animals	rat (mouse, dog)
Number of animals	5 to 10 of each sex per group[a]
Dose levels	control and at least 3 dose levels with an increment of 2 to 10 (sometimes satellite groups)
Examinations	- body weight, food consumption and water consumption - clinical examination. haematological parameters: haematocrit, haemoglobulin concentration, erythrocyte counts, total and differential leukocyte count, clotting potential; biochemical parameters: including organ function, parameters, electrolyte balance, carbohydrate metabolism, serum salts (Ca, P, Na, K, Cl), glucose, serum enzymes, urea nitrogen, albumen, serum protein, creatonin, bilirubin (lipids, hormones, methaemoglobin, choline-esterase activity), urine analysis - gross examination: daily observation and extensive examination at autopsy - organ weights - histopathological examination: of all preserved organs and tissues (30 or more) of highest dose and control. If indicated, intermediate and low dose groups
Results	information concerning effects of repeated dose exposure for parameters measured, target organ(s); if possible, mechanism of action and NOAEL

[a] For a range finding test 5 animals per sex per group may be sufficient for experiments with dogs, usually groups of 4 to 5 animals per sex are used.

Table 5.6. Chronic toxicity studies (6 to 24 months)

Conditions	chemical identification of substance, its purity and chemical characteristics
Route	oral, inhalatory
Experimental animals	rat (mouse, dog)
Number of animals	20 (dogs 4 to 5) per sex per group
Dose levels	control and at least 3 dose levels with an increment of 2 to 10 (sometimes satellite groups)
Examinations	- body weight, food consumption and water consumption during the first 13 weeks at weekly intervals and later at 4 week intervals (body weight) or 3 month intervals (food and water consumption) - clinical examination: haematological and biochemical examination and urine analysis (Table 5.5) at onset of study and at 6 month intervals - gross examination: daily observation and extensive examination at autopsy - organ weights - histopathological examination in full of all preserved organs and tissues of highest dose and controls. If indicated, of intermediate and lowest dose
Results	information concerning effects of repeated dose exposure on parameters studied, target organ(s); if possible, mechanism of toxicity and NOAEL

Genotossicità

Genotoxicity refers to potentially harmful effects on genetic material. It ***includes mutagenicity*** which can be defined as the induction of permanent transmissible changes in the amount or structure of the genetic material.
Genotoxicity tests also provide indications of **other DNA damage** through unscheduled DNA synthesis, sister chromatid exchange (*scambio di porzioni omologhe di DNA tra i due cromatidi costituenti un cromosoma*), strandbreaks, adduct formation, mitotic recombination and Numerical chromosome aberrations (aneuploidy - *variazione nel numero dei cromosomi, rispetto a quello che normalmente caratterizza le cellule di un individuo*).

Genotoxicity testing is very useful in **pre-screening for potential genotoxic carcinogenicity**

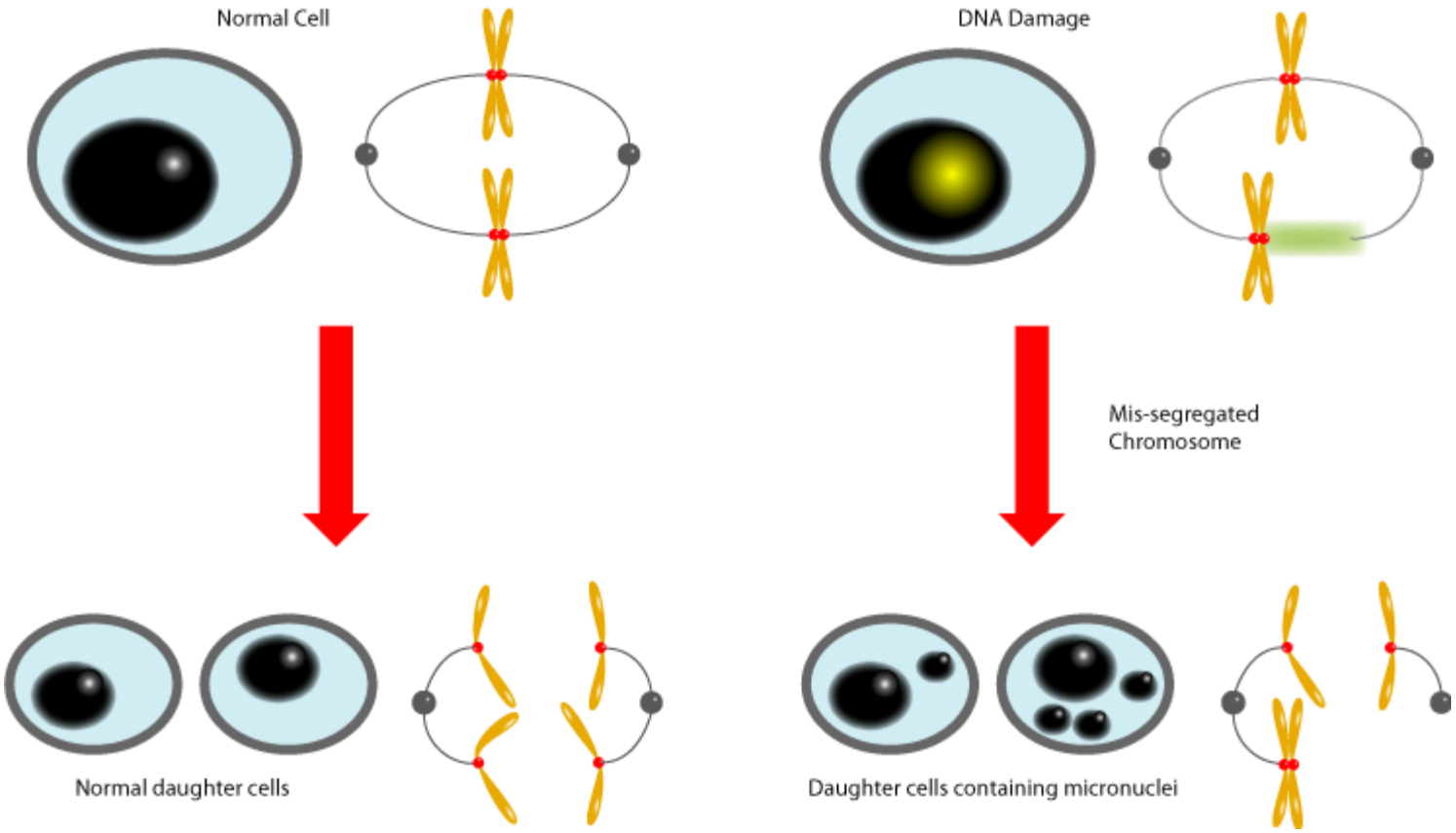
Regolamento REACh: Il requisito di base è un
test di Ames su batteri per le mutazioni per un quantitativo di sostanza annuale di 10 tonnellate.

Il test di Ames, ideato da Bruce Ames nel 1973, è un test genetico per l'analisi della genotossicità di una sostanza.

Si basa sulla *valutazione della capacità di un sospetto mutageno di provocare la reversione di un carattere auxotrofo his- in un ceppo di batteri mutato (Salmonella typhimurium), rendendolo nuovamente capace di sopravvivere in un terreno privo di istidina*.

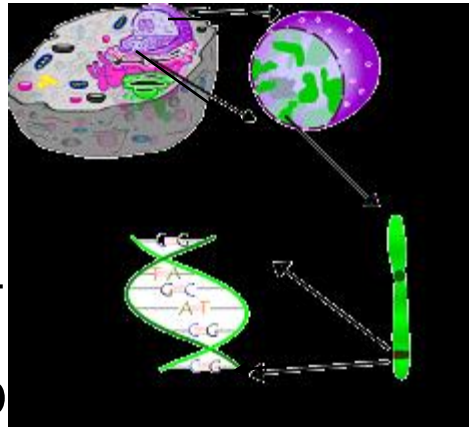
Essendo condotto in cellule batteriche, *il test di Ames non consente di valutare la capacità dei mutageni di alterare la struttura cromosomica del DNA umano.*
Va eseguito *insieme a test su cellule eucariotiche* (test dei micronuclei, test della cometa, quantificazione degli addotti al DNA) e su animali in vivo.
Vi è comunque una buona correlazione fra l'effetto mutageno riscontrato nel test di Ames e la cancerogeneità della sostanza

Test dei micronuclei



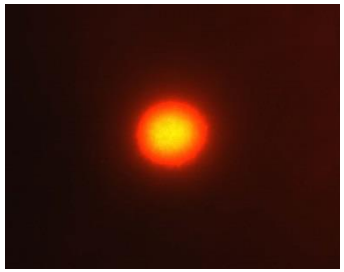
http://old.iss.it/binary/publ/cont/13_27_web.pdf

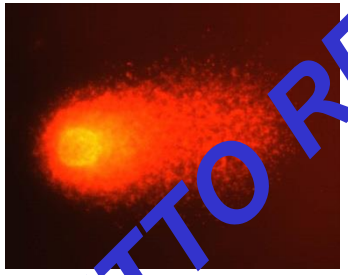
Test della Cometa (SCGE)



PRINCIPIO

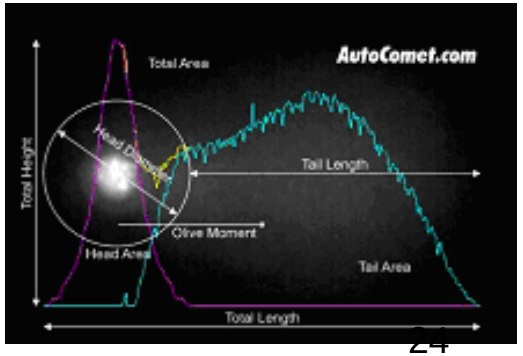
- LE ROTTURE DEL FILAMENTO DEL DNA SI POSSONO EVIDENZIARE TRAMITE L'ELETTROFORESI





EFFETTO REVERSIBILE

- OSSERVAZIONE AL MICROSCOPIO A FLUORESCENZA



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Review

Environmental and occupational biomonitoring using the Comet assay

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ABSTRACT

Biomonitoring of human populations exposed to potential mutagens or carcinogens can provide an early detection system for the initiation of cell disregulation in the development of cancer. In recent years, the Comet assay, also known as a "single cell gel" (SCG) electrophoresis assay, has become an important tool for assessing DNA damage in exposed populations. This is the method of choice for population-based studies of environmental and occupational exposure to air pollutants, metals, pesticides, radiation, and other xenobiotics as we show in this review. To appreciate the role of the Comet assay in the field of biomonitoring, we review data from 122 studies that employed the assay. These studies evaluated environmental versus occupational exposures and the levels of DNA damage in cells of individuals exposed in each case. Our review of the literature reveals the importance of the need to establish standard methodological conditions that affect unwinding and electrophoresis times and tail values (tail length, tail DNA, tail moment), with the goal of being able to compare data collected in different laboratories throughout the world. The Comet assay is susceptible to subtle artifacts of manipulation depending on the type and timing of sampling performed. Therefore, in the reporting of DNA damage detected by the Comet assay, the context of how the DNA damage was created also needs to be reported and considered in the interpretation of Comet assay results. The success of the Comet assay is reflected by its use over the past 20 years in the field of biomonitoring, and by the increasing number of studies that continue to report its use. As the shortcomings of the assay are identified and considered in the interpretation of DNA damage detection, the Comet assay will continue to provide improved reliability as a biomarker in human biomonitoring studies.

Mutagenesis. 2013 May;28(3):315-21. doi: 10.1093/mutage/get005. Epub 2013 Feb 27.

Malondialdehyde-deoxyguanosine and bulky DNA adducts in schoolchildren resident in the proximity of the Sarroch industrial estate on Sardinia Island, Italy.

Peluso M[1], Munnia A, Ceppi M, Giese RW, Catelan D, Rusconi F, Godschalk RW, Biggeri A.
Author information

Abstract

Air quality is a primary environmental concern in highly industrialised areas, with potential health effects in children residing nearby. The Sarroch industrial estate in Cagliari province, Sardinia Island, Italy, hosts the world's largest power plant and the second largest European oil refinery and petrochemical park. This industrial estate produces a complex mixture of air pollutants, including benzene, heavy metals and polycyclic aromatic hydrocarbons. Thus, we conducted a cross-sectional study to evaluate the prevalence of malondialdehyde-deoxyguanosine adducts in the nasal epithelium of 75 representative children, aged 6-14 years, attending primary and secondary schools in Sarroch in comparison with 73 rural controls. Additionally, the levels of bulky DNA adducts were analysed in a subset of 62 study children. DNA damage was measured by (32)P-postlabelling methodologies. The air concentrations of benzene and ethyl benzene were measured in the school gardens of Sarroch and a rural village by diffusive samplers. Outdoor measurements were also performed in other Sarroch areas and in the proximity of the industrial estate. The outdoor levels of benzene and ethyl benzene were significantly higher in the school gardens of Sarroch than in the rural village. Higher concentrations were also found in other Sarroch areas and in the vicinity of the industrial park. The mean levels of malondialdehyde-deoxyguanosine adducts per 10(8) normal nucleotides ± standard error (SE) were 74.6±9.1 and 34.1±4.4 in the children from Sarroch and the rural village, respectively. The mean ratio was 2.53, 95% confidence interval (CI): 1.71-2.89, $P < 0.001$, versus rural controls. Similarly, the levels of bulky DNA adducts per 10(8) normal nucleotides ± SE were 2.9±0.4 and 1.6±0.2 in the schoolchildren from Sarroch and the rural village, respectively. The means ratio was 1.90, 95% CI: 1.25-2.89, $P = 0.003$ versus rural controls. Our study indicates that children residing near the

Table 5.7. Carcinogenicity studies

Conditions	chemical identification of substance, its purity and chemical characteristics
Route	oral, inhalatory
Experimental animals	rat, mouse, (dog), (monkey)
Number of animals	50 per sex per group (sometimes satellite groups); dogs and monkeys usually not more than 7 to 10 per group
Dose levels	control and at least 3 dose groups, for proper quantitative risk assessment more dose groups
Examinations	- body weight, food consumption and water consumption at various intervals (see Table 5.6) - clinical examination at intervals (see Table 5.6) of 10 to 20 animals per sex per group - gross examination: daily observation and extensive gross examination on termination - histopathological examination in full of highest dose and controls where indicated, for other dose levels
Results	information on carcinogenic properties, tumour incidence in relation to dose, latency period, tumour multiplicity, potential for metastasis

Table 5.8. Genotoxicity tests

Gene mutation assays	
Tests with prokaryotes	- *Salmonella typhimurium* reverse mutation assay (OECD Guideline 471)
	- *Escherichia coli* reverse mutation assay (OECD Guideline 472)
Tests with eukaryotes	- *Saccharomyces cerevisiae* gene mutation assay (OECD Guideline 480)
	- *in vitro* mammalian cell gene mutation assay (OECD Guideline 476)
	- *in vivo* sex linked recessive lethal test in *Drosophila melanogaster* (OECD Guideline 477)
Chromosomal damage assays	
In vitro tests	- mammalian cytogenic test (OECD Guideline 473)
	- chromatid exchange assay in mammalian cells (OECD Guideline 479)
In vivo tests	- mammalian bone marrow cytogenetic test for chromosomal analysis (OECD Guideline 475)
	- micronucleus test (OECD Guideline 474)
DNA damage/repair/adduct formation assays	
	- DNA adduct formation 32P-post coupling [43]
	- DNA repair synthesis in mammalian cells *in vitro* (OECD Guideline 482)
	- DNA repair test in primary liver cells [44]
	- DNA repair *in vivo* [44]

Table 5.9. Types of adverse effects detected in reproductive toxicity [46]

Time and targets at which a substance initiates its toxicity	Examples of adverse effects on
Adult toxicity	- libido - behaviour - endocrine function - mating - gamete production - reproductive life span
Maternal toxicity (changing physiology and metabolism during pregnancy and lactation)	- susceptibility - ability to nurse - milk quality/quantity
Developmental toxicity Pre-implantation and implantation	- fertilization - movement of fertilized ova - implantation - survival of ova
Embryonic development	- growth and differentiation - organ development - survival
Placental development	- growth - organ function
Foetal development	- growth and differentiation - organ function - survival
Postnatal development (neonatal, pre-weaning, post-weaning, puberty)	- birth weight - organ function - hormone function - immune function - CNS and peripheral NS function - sexual function - other cellular functions (transplacental carcinogenesis) - survival

Table 5.10. Approach to the development of *in vitro* test methods that might lead to regulatory acceptance [52]

Step	Requirements
Scientific justification	1. Select simple endpoint essential for hazard identification 2. Develop *in vitro* assays for these endpoints 3. Understand the mechanism of the *in vitro* assay and demonstrate similarities to the target event 4. Publish the assay(s) in a high quality peer-reviewed journal
Database development	5. Conduct the *in vitro* assays parallel to the relevant *in vivo* studies 6. Conduct and report all studies fully in accordance with GLP 7. Integrate results of the *in vitro* assays in dossiers submitted to regulatory agencies 8. Propose the *in vitro* assays to the OECD to be considered for test guideline development

MECCANISMI BIOCHIMICI DELLA TOSSICITA’

Quali sono i meccanismi e le reazioni tramite le quali i composti xenobiotici e i loro metaboliti interagiscono con le biomolecole per causare un effetto tossicologico avverso?

Per generare una risposta tossica, le sostanze devono esser spesso molto reattive
-> se introdotte direttamente nell’organismo, reagirebbero prima di raggiungere un bersaglio in dove causare l’effetto avverso.

-> se prodotte metabolicamente, posson trovarsi in un sito in cui interagire facilmente con le biomeolecole, membrane o tessuti per causare la risposta tossica

Si possono identificare 4 categorie di specie tossiche in base alla reattività

1) **Specie elettrofile**: caricate positivamente o con cariche parziali positive -> hanno tendenza a legare atomi o gruppi funzionali ricchi di elettroni (N, O ed S che son abbondanti in acidi nucleici, proteine (tra le quali ci son gli enzimi)). Comuni.

2) **Specie nucleofile**: caricate negativamente o con cariche parziali negative -> hanno tendenza a legare atomi o gruppi funzionali poveri di elettroni. Meno comuni (es. CO metabolico formato da dealogenazione ed ossidazione di alometani -> lega con Fe^{2+} di emoglobina, impedisce trasporto O_2; CN^- prodotto da metabolismo di acrilonitrile -> lega con Fe^{3+} di ferricitocromo ossidasi, impedisce respirazione).

Si possono identificare 4 categorie di specie tossiche in base alla reattività

3) Radicali liberi: specie neutrali o ioniche che hanno elettroni spaiati (es. radical anione superossido $O_2^{\cdot -}$; radicale idrossilico $HO^{\cdot}$, prodotto dalla decomposizione omolitica di H_2O_2. Queste specie reagiscon con molecole più grandi per generare altri radicali liberi. Trasferimento elettronico da citocromo P 450 a CCl_4 produce $Cl_3C^{\cdot}$ (terribile!).

4) Reagenti redox: posson far decorrere reazioni di ossido-riduzione pericolose (es. NO^{3-} → NO^{2-} → ossidazione di Fe^{2+} a Fe^{3+} (metemoglobinemia))

Spesso sono importanti le interazioni tra specie tossiche e recettori

Cos'è un recettore?

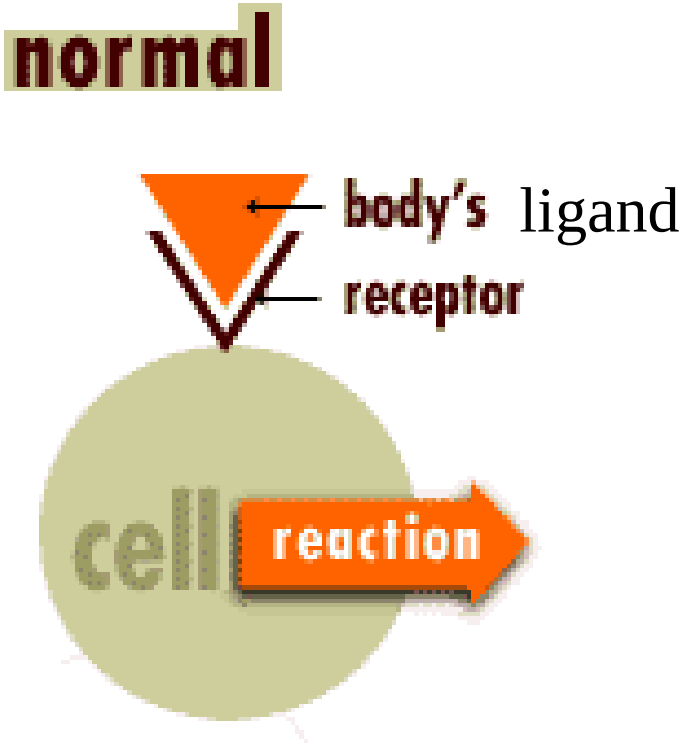
Nel presente contesto per **recettore** si intende un'entità biochimica che interagisce con una specie tossica per produrre un effetto avverso.

In genere i r. sono macromolecole (come proteine, acidi nucleici o fosfolipidi di membrane cellulari) interne alle o sulla superficie delle cellule.

La sostanza che interagisce con un r. è detta **legante**.
I leganti sono di solito piccole molecole (*endogene* - come gli ormoni – o *xenobiotiche* – come molte sostanze tossiche)

La FUNZIONE del r. dipende dalla sua elevata specificità per particolari leganti; ciò implica spesso un adattamento stereochimico tra recettore e legante

(simile a interazione tra enzima e substrato)



Meccanismo “serratura e chiave”

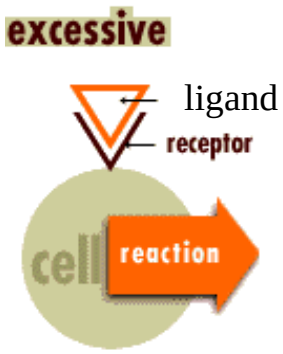
(lock and key)

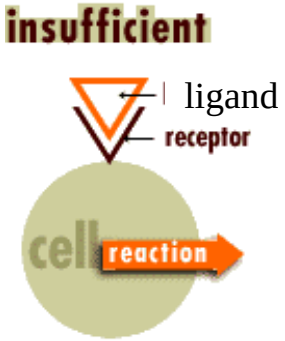
Si noti che reazioni tra r. e tossico sono spesso 100 x più forti di quelle tra enzimi e substrati.

Inoltre mentre gli enzimi alterano un substrato chimicamente (es tramite idrolisi), i tossici non alterano la natura dei recettori se non legandosi ad essi.

In molti casi l'identità del recettore NON è nota (es. insetticidi piretroidi). In tal caso, per il tossico X, ci si riferisce al recettore X.

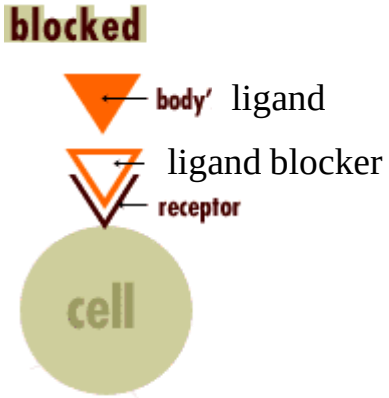
Varie interazioni tra tossici e r. sono studiate in analogia con studi farmacologici (ove si studia l'interazione farmaco-recettore).





Azione diversa in grado (effetti avversi)

Azione antagonista



Si verifica anche se legame di tossico con un sito prossimo a r. ma tale che addotto ostacola stericamente il funzionamento di r.

Il recettore potrebbe anche non avere leganti endogeni

Interferenze con l'azione degli enzimi

Gli enzimi devon funzionare correttamente per far funzionare i processi metabolici essenziali che avvengono nelle cellule.

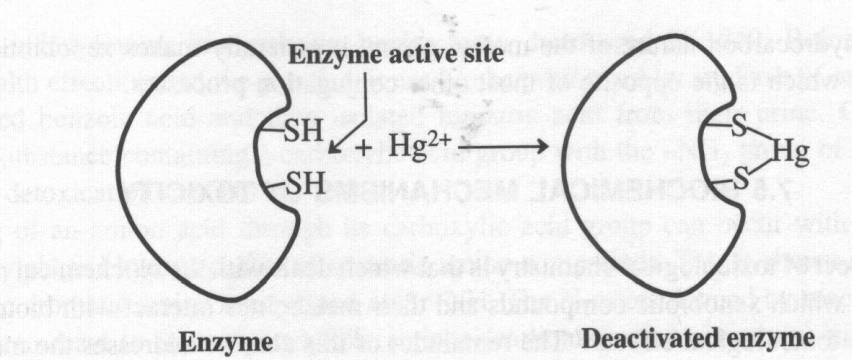
Xenobiotici a volte sono **inibitori di enzimi** che rallentano o bloccano
gli e. dall'effettuare la loro normale funzione di catalizzatori biochimici.

L'**induzione enzimatica** è un processo per cui il corpo è stimolato a sintetizzare enzimi per un particolare scopo.

Alcuni inibitori enzimatici sono endogeni per controllare i processi catalizzati da e..

Esempio di inibizione dovuta a specie tossiche:

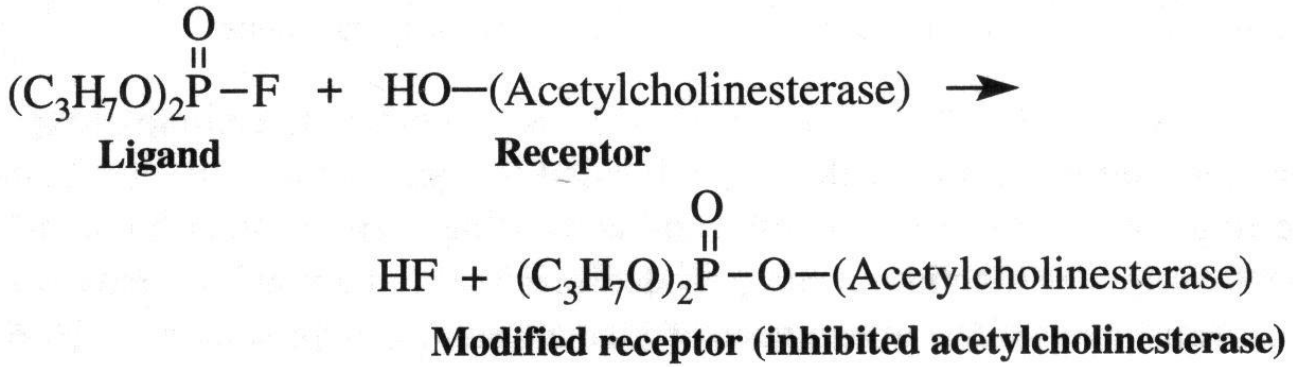
ioni di metalli pesanti Hg^{2+}, Cd^{2+}, Pb^{2+} tendono a legarsi fortemente a gruppi funzionali contenenti zolfo (-SS- , -SH, -S-CH_3) presenti nei siti attivi di e. inibendone il funzionamento.



Binding of a heavy metal to an enzyme active site.

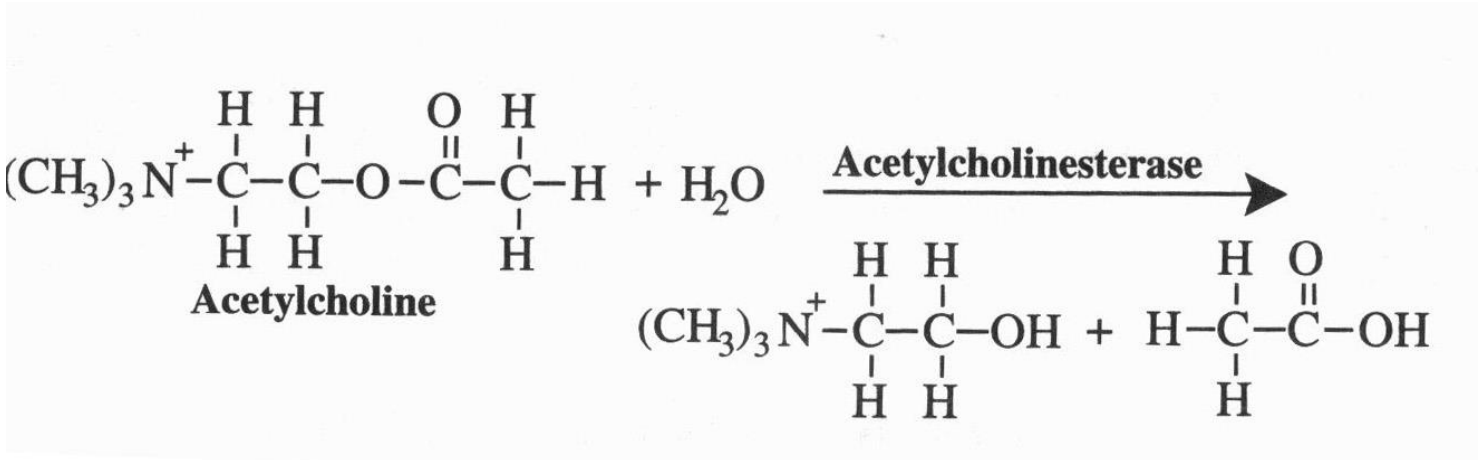
Inibizione di metalloenzimi (e. che contengono un metallo nella loro struttura) avviene spesso per sostituzione del metallo con un m. xenobiotico (es. Cd^{2+} sostituisce Zn^{2+} in ATPasi, alcol deidrogenasi)

Inibizione dovuta a composti organici che formano legami covalenti

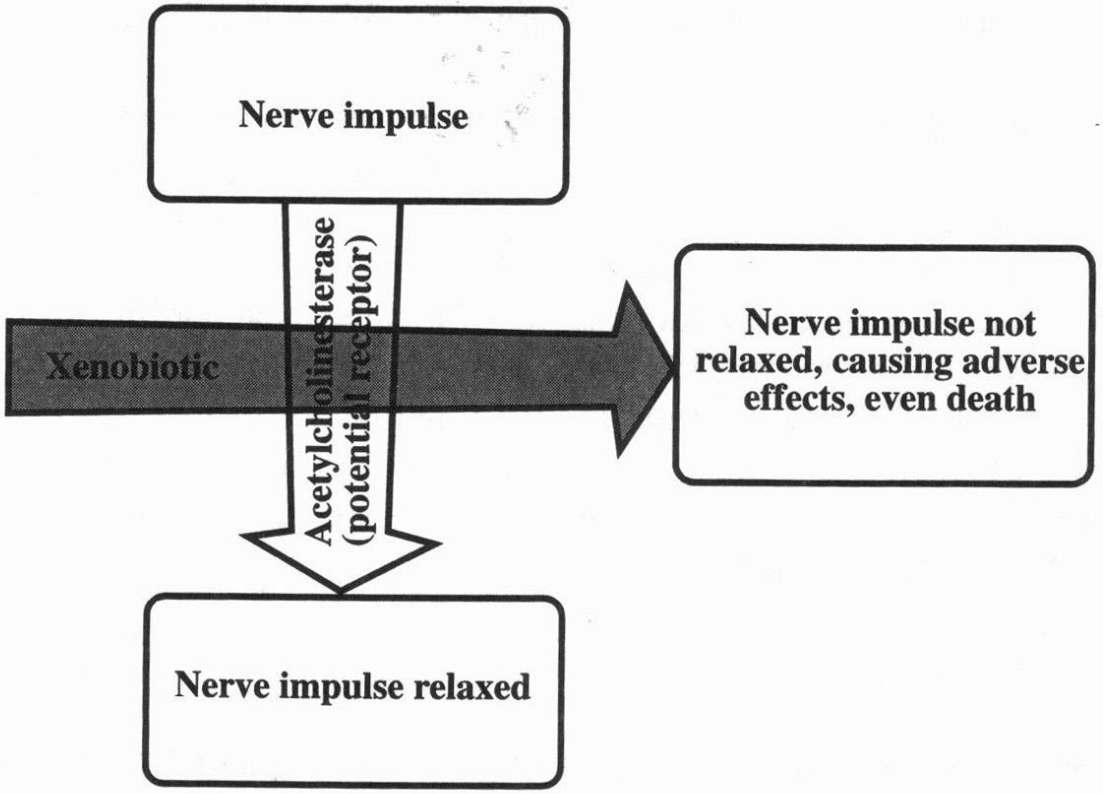


-> Effetti tossici su sistema nervoso
(il legante è un gas nervino - diisopropilfosfofluoridato)

Tossicologia – recettori e sostanze tossiche



Tossicologia – recettori e sostanze tossiche



Example of a toxicant acting on a receptor to cause an adverse effect. When acetylcholinesterase is bound by a xenobiotic substance, the enzyme does not act to stop nerve impulse. This can result in paralysis of the respiratory system and death.

https://www.nap.edu/download/25004

National Academies of Sciences, Engineering, and Medicine. 2018. *Advances in Causal Understanding for Human Health Risk-Based Decision-Making: Proceedings of a Workshop—in Brief*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25004.

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