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PROBIOMA

Contaminantes Agroindustriales

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Universidad de Cartagena
Fundada en 1827

Acreditación Institucional de Alta Calidad
Resolución 2583 del 26 de febrero de 2014. Ministerio de Educación Nacional

Pesticides

US EPA – PESTICIDE

Any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. The term pest means any harmful, destructive, or troublesome animals, plants, or microorganisms.

PESTICIDES – RISKS AND BENEFITS

BENEFITS

- Crop protection
- Food preservation
- Material preservation
- Disease control

RISKS

- Toxic to humans
- Impact on environment and ecosystems

PESTICIDES – CLASSIFICATION BY USE

Chemicals designed to kill, reduce or repel pests

- Insects → **Insecticides**
  - **Insect repellents**
- Weeds → **Herbicides**
- Moulds → **Fungicides**
  - **Wood preservatives**
- Rats, mice, moles (**Topos**) → **Rodenticides**

Fumigants

PESTICIDES – CLASSIFICATION BY USE AND CHEMICAL STRUCTURE

Different chemicals used for different purposes

INSECTICIDES
- Pyrethroids
- Organophosphorus
- Carbamates
- Organochlorine
- Manganese compounds

HERBICIDES
- Bipyridyls
- Chlorophenoxy
- Glyphosate
- Acetanilides
- Triazines

FUNGICIDES
- Thiocarbamates
- Dithiocarbamates
- Cupric salts
- Tiabendazoles
- Triazoles
- Dicarboximides
- Dinitrophenoles
- Organotin compounds
- Miscellaneous

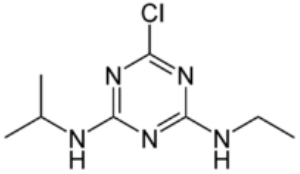
RODENTICIDES
- Warfarines
- Indanodiones

FUMIGANTS
- Aluminium and zinc phosphide
- Methyl bromide
- Ethylene dibromide

$$Zn_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Zn(OH)_2$$

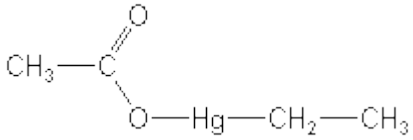
INSECT REPELLENTS
- Diethyltoluamide

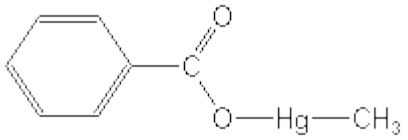
Atrazine, 2-chloro-4-(ethylamino)-6-(isopropylamino)-triazine



Pesticides

Basic Classes of Pesticides





Insecticides

- Organochlorines
- Organophosphates
- Carbamate Esters
- Pyrethroids
- Botanical Insecticides

Herbicides

- Chlorophenoxy compounds
- Bipyridyl derivatives

Rodenticides

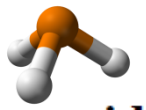
- Zinc Phosphide
- Fluoroacetic acid and derivatives
- α-Napthyl Thiourea (ANTU)
- Anticoagulants

Fungicides

- Hexachlorobenzene
- Organomercurials
- Pentachlorophenol
- Phthalimides
- Dithiocarbamates

Fumigants

- Phosphine



- Ethylene dibromide
- Dibromochloropropane

Pesticides

Table 1 The main groups of pesticides.

Group	Subgroups	Examples
Organochlorines (OCs)		DDT Endrin Aldrin Dieldrin Endosulfan γ-Hexachlorocyclohexane (lindane)
Anticholinesterases	Organophosphates (OPs)	Malathion Fenitrothion Dichlorvos Diazinon
	Carbamates	Carbaryl Aldicarb
Pyrethrins and synthetic pyrethroids		Pyrethrum Permethrin Cypermethrin Flumethrin
Natural compounds, other than pyrethrins		Abamectin Ivermectin Rotenone Nicotine
Substances which interfere with systems specific to insects	Juvenile hormone analogues Chitin synthesis inhibitors Ecdysone agonists	Cyromazine Diflubenzuron Tebufenozide
Miscellaneous synthetic insecticides	Formamidine $GABA_A$ blocker	Amitraz Fipronil

SOME PESTICIDES PERSIST AND BIOCONCENTRATE

- PERSISTENT ORGANIC POLLUTANTS (POPs)

  - Low water solubility
  - Persist in the environment
  - Accumulate in the food-chain
  - Lypophilic
  - Travel long distances
  - Concentrate in marine animals
  - May produce toxic effects

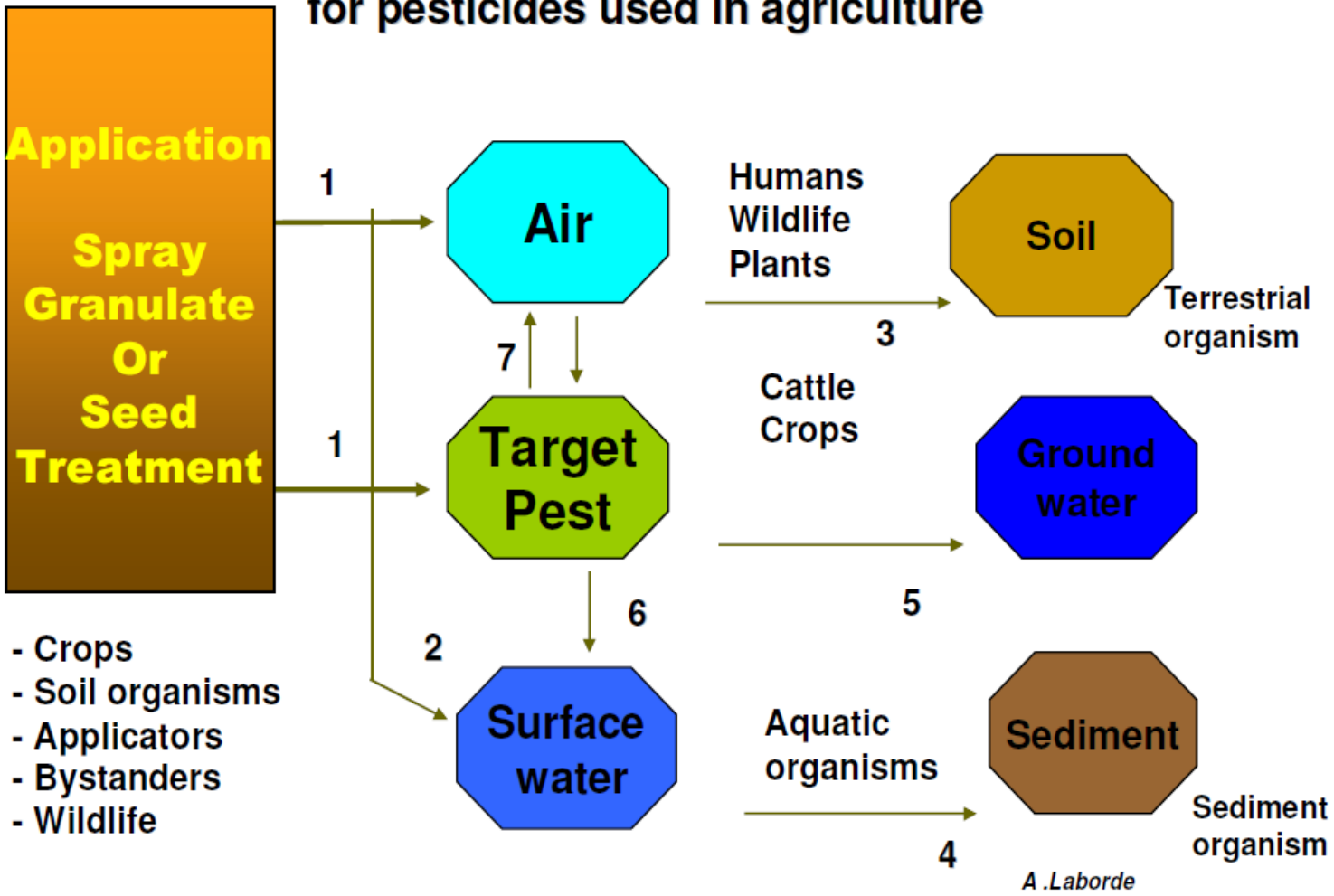
PESTICIDES

Aldrin
Dieldrin
Chlordane
DDT
Endrin
Heptachlor
Mirex
Toxaphene

ORIGIN, TRANSPORT AND FATE

Distribution routes and "receptor" organisms for pesticides used in agriculture

1. Emission
2. Drift **Arrastre**
3. Deposition
4. Sedimentation
5. Leaching
6. Drainage
7. Volatilization



A .Laborde

PESTICIDES IN DIFFERENT MEDIA

Food residues

- Many food products have detectable levels of pesticides
- Guideline levels of pesticides in food (MRL)
- Guidelines to limit the population exposure: acceptable daily intake (ADI)

WHO

The Dirty Dozen

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Apples 1 of 13

ZOOM SHARE THIS SLIDE

According to the EWG report, nearly 98 percent of apples tested positive for pesticides and 92 percent contained two or more.

Celery 2 of 13

ZOOM SHARE THIS SLIDE

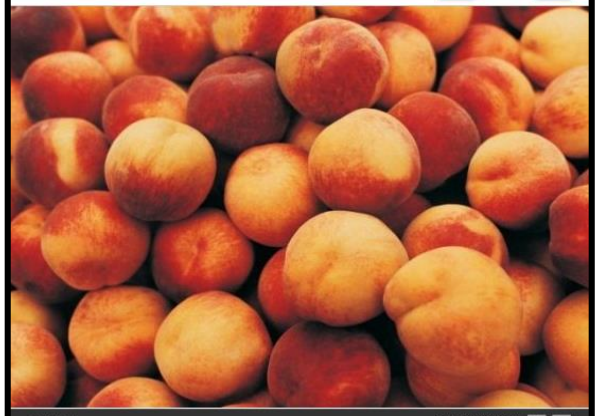
Ranked the "dirtiest" vegetable, more than 95 percent of celery samples tested positive for pesticides, while almost 90 percent contained more than one pesticide.

Strawberries 3 of 13

ZOOM SHARE THIS SLIDE

13 different types of pesticides were found on a single strawberry sample in the analysis.

Peaches 4 of 13



ZOOM SHARE THIS SLIDE

More than 85 percent of peaches contained the residue of more than one pesticide -- "As a category, peaches have been treated with more pesticides than any other produce, registering combinations of up to 57 different chemicals," according to the "Methodology" section of the report.

Nectarines 6 of 13

ZOOM SHARE THIS SLIDE

Every nectarine sample tested positive for pesticides, according to EWG.

Spinach 5 of 13

ZOOM SHARE THIS SLIDE

Spinach is the second vegetable on the list, after celery.

The Dirty Dozen

Imported Grapes

7 of 13

ZOOM SHARE THIS SLIDE

While domestic grapes didn't make the "dirty dozen" list, imported grapes turned up 14 different types of pesticides on a single sample.

Sweet Bell Peppers

8 of 13

ZOOM SHARE THIS SLIDE

Almost 70 percent of sweet bell peppers contained multiple pesticides.

Potatoes

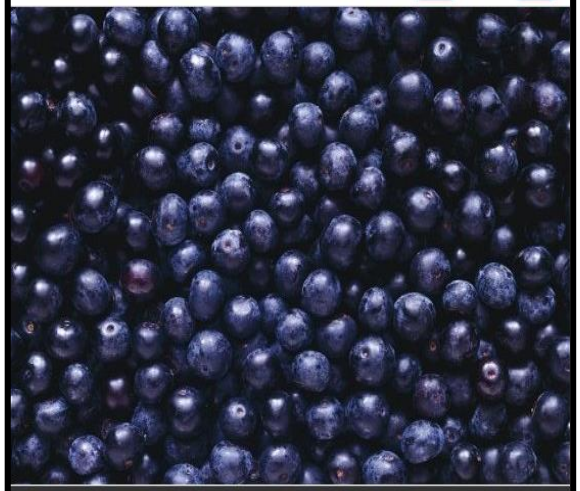
9 of 13

ZOOM SHARE THIS SLIDE

More than 91 percent of potatoes tested positive for pesticides.

Domestic Blueberries

10 of 13



ZOOM SHARE THIS SLIDE

Blueberries are the sixth and final fruit on the dirty dozen list.

Lettuce

11 of 13

ZOOM SHARE THIS SLIDE

Lettuce is among the vegetables most likely to retain pesticides, according to EWG.

Kale/Collard Greens

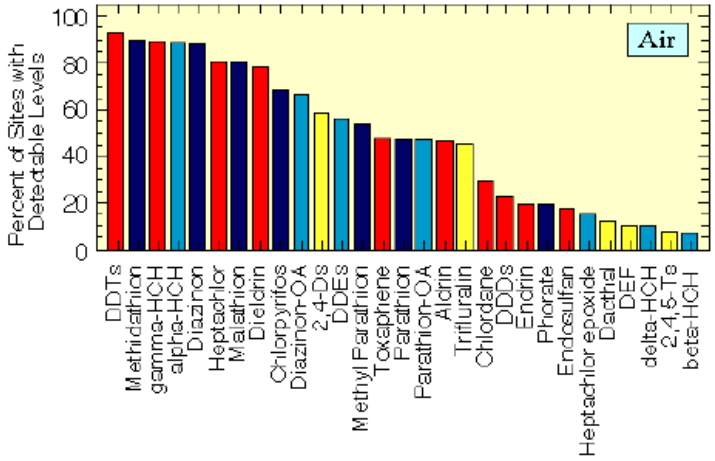
12 of 13

ZOOM SHARE THIS SLIDE

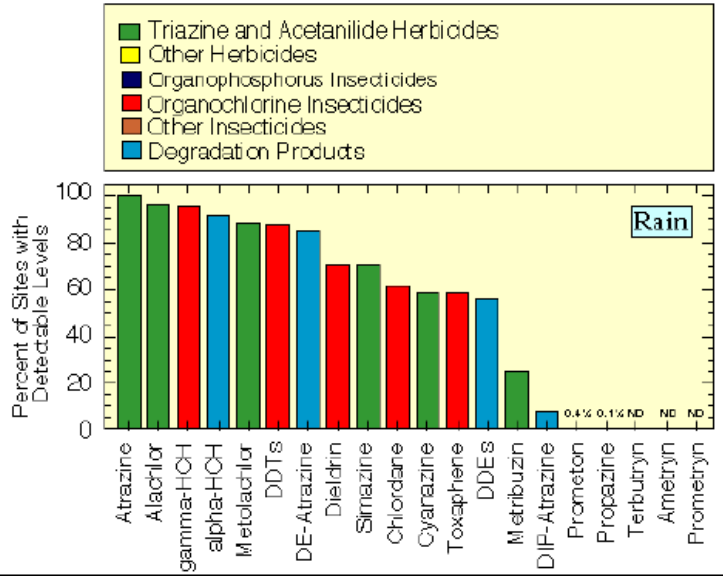
Rounding out the dirty dozen list is kale/collard greens.

PESTICIDES IN THE ATMOSPHERE

AIR



RAIN



USGS

CHILDREN'S EXPOSURE

A cause of concern

- Multiple chemicals
- Multiple sources of exposure
- Multiple routes of exposure
- Multiple effects

WHO

CHILDREN'S ENVIRONMENTAL EXPOSURE

- Pesticides in: homes and schools, playgrounds, parks fields, hospitals and other public places
- Children in: farms, agricultural areas (rural setting)
- Pesticides present in: air, soil, food, water, parents' clothing and shoes, other objects…

SOURCES AND SETTINGS OF EXPOSURE...

HOME, SCHOOL, DAY-CARE, INSTITUTIONS, ...

Indoor and outdoor application

- Mosquito control
- Professional/domestic application

Health uses

- Lice or scabies (Sarna)
- Fleas or ticks on pets

Pesticide residues

- Dust, soil, furniture, carpets, toys, food…
- Playgrounds, playing fields, lawns, gardens
- Wood preservatives in play structures (e.g. PCP: pentachlorophenol)
- Long range transport of POPs (e.g. DDT)

ROUTES OF EXPOSURE

Multiple/simultaneous routes of exposure

- Ingestion
- Inhalation
- Dermal absorption
- Transplacental

- Breastfeeding
- Accidental ingestion
- Residues in food
- Mouthing

- Indoor and outdoor spraying
- Occupational exposure

- Accidental contact
- Occupational exposure
- Residues on surfaces
- Contaminated clothing
- Medical use: scabies, head lice

PERINATAL EXPOSURE

- Mother's intake and body burden is transferred across the placenta
- Breast milk may be contaminated

"The very top of the food chain"

TOXICOKINETICS VARIES FOR DIFFERENT TYPES OF PESTICIDE

Important to consider:

- **Routes of Absorption**
  - Dermal, ocular, ingestion, inhalation, injection
- **Biotransformation**
  - Into inactive or more active metabolites
- **Distribution and storage**
  - Fat soluble pesticides are stored in adipose tissue
  - Other
- **Elimination**
  - Urinary excretion
  - Biliary / faecal excretion
  - Excretion in milk

METABOLIC PATHWAYS

- **Organophosphates metabolize into:**
  - **Oxones**
  - **Specific inactive metabolites (ME)**
  - **Non-specific metabolites: dialkylphosphates (DAPs)**

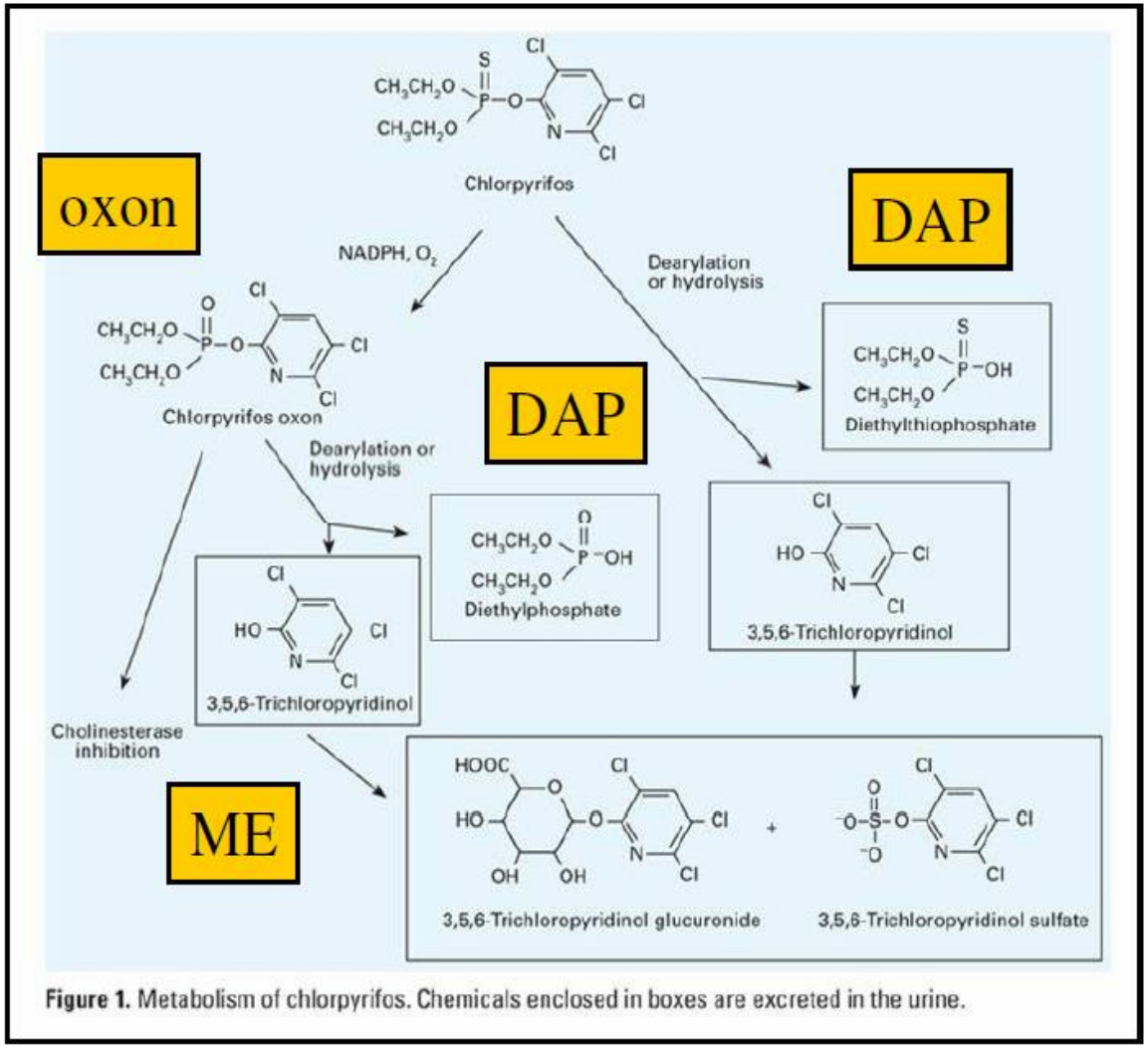


Figure 1. Metabolism of chlorpyrifos. Chemicals enclosed in boxes are excreted in the urine.

Pesticides

Toxicity of Pesticides

Many different pesticides in use with very different modes of action and levels of toxicity

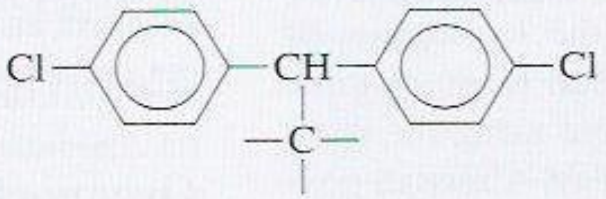
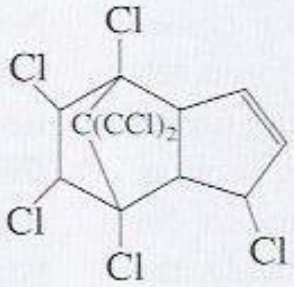
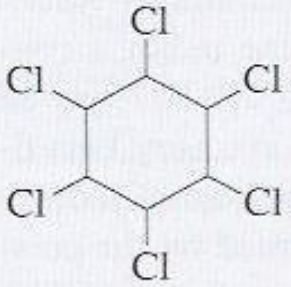
The WHO Recommended Classification of Pesticides by Hazard

CLASS		LD_{50} FOR THE RAT (mg/kg BODY WEIGHT)			
		ORAL		DERMAL	
		SOLIDS	LIQUIDS	SOLIDS	LIQUIDS
Ia	Extremely hazardous	≤5	≤20	≤10	≤40
Ib	Highly hazardous	5–50	20–200	10–100	40–400
II	Moderately hazardous	50–500	200–2000	100–1000	400–4000
III	Slightly hazardous	>500	>2000	>1000	>4000
III+	Unlikely to present hazard in normal use	>2000	>3000	—	—

Pesticides

Organochlorine insecticides

Table 22-5
Structural Classification of Organochlorine Insecticides

Dichlorodiphenylethanes		DDT, DDD Dicofol Perthane Methoxychlor Methlochlor
Cyclodienes		Aldrin, Dieldrin Heptachlor Chlordane Endosulfan
Chlorinated benzenes Cyclohexanes	 	HCB, HCH Lindane (α-BHC)

Organochlorine insecticides

- **DDT**
  - **First commercially produced insecticide** (1940's)
  - Banned in the US in the 1970's but is still manufactured and exported (1 ton/day)
- Cyclodienes
  - **Most toxic (CNS) and persistent pesticides known.**
- HCH and Cl-benzene
  - Mixtures of isomers
  - Medicinal use (lice shampoo) (lindane)

• $T_{1/2}$ = 7-30 y	• Non-selective
• Bioaccumulates	• Endocrine disrupter
• Persistent	• Reproductive toxins
• Lipophilic	• Neurotoxic (Lindane)

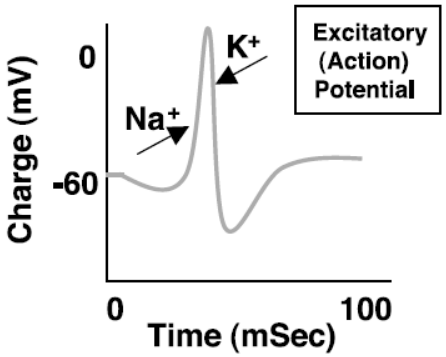
Observed effects

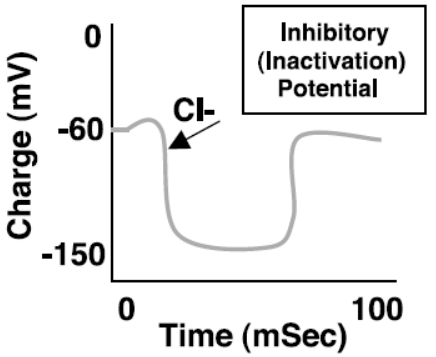
- DDT
  - Enzyme induction
  - Competes with estradiol for receptor.
- Cyclodienes
  - Reproductive toxicity (reduced fertility, loss of pups, teratogenic)
  - CNS toxicity
- HCH and Cl-benzene
  - CNS toxicity
  - Increased hepatocellular tumors (mice).

Pesticides

Organochlorine insecticides

Mechanisms of action





A

- **DDT**
  - Peripheral sensory neurons
  - prolonged negative afterpotential in neurons.
  - K^+ transport, inactivate Na^+ channel closure, inhibit Na^+ /K^+ and Ca^{2+} /Mg^{2+} ATPases, inhibit calmodulin-transport of Ca^{2+} .

- **Cyclodienes**
  - CNS localized
  - $GABA_A$ receptor/channel antagonists, inhibit Cl^--uptake and Na^+ /K^+ and Ca^{2+} /Mg^{2+} ATPases,

- **HCH and Cl-benzene**
  - Suggested similar to cyclodienes.

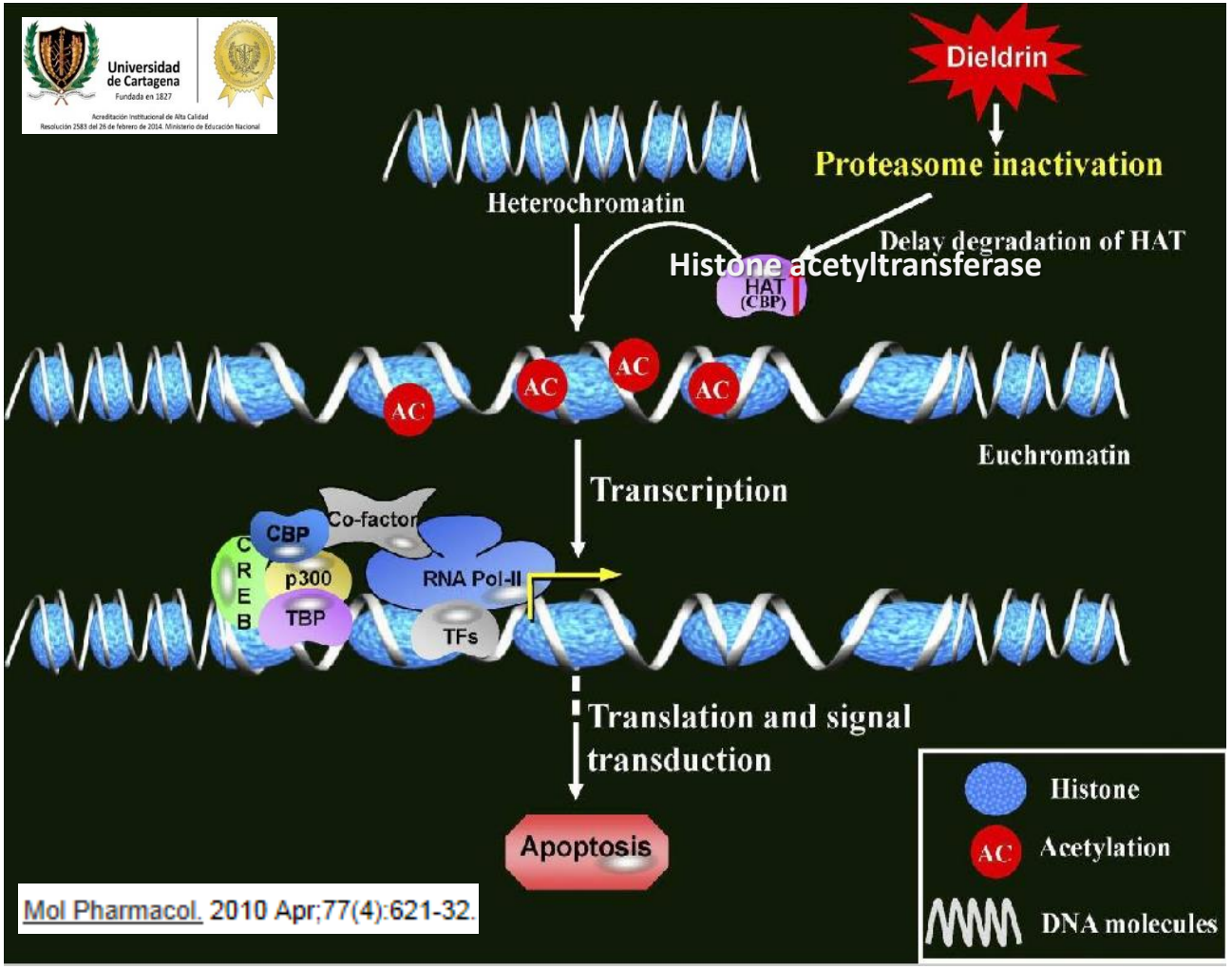
Organochlorine insecticides

DDT-induced Prolonged Repolarization

- DDT affects the permeability of the nerve cell membrane to K+ ions reducing K+ transport across the membrane.
- DDT alters the Na+ channels, they open normally but are closed (inactivated) slowly.
- DDT inhibits neuronal ATPase activity particularly Na/K ATPase and Ca ATPase which play a role in repolarization of the neuron.

All of these factors reduce the rate at which repolarization occurs and increase the sensitivity of the neurons to small stimuli that would not elicit a response in a fully repolarized neuron.

In dopaminergic neuronal cells, dieldrin induced a time-dependent increase in the acetylation of core histones H3 and H4. Histone acetylation occurred within 10 min of exposure indicating acetylation is an early event in dieldrin neurotoxicity. The hyperacetylation was attributed to dieldrin-induced proteasomal dysfunction, resulting in accumulation of a key histone acetyltransferase (HAT), cAMP response element-binding protein.



Schematic representation of mechanisms underlying dieldrin-induced hyperacetylation. Exposure to neurotoxic insult dieldrin inhibits proteasome dysfunction, resulting in accumulation of a major HAT CBP. Increased CBP results in greater acetylation of nuclear histones in the chromatin, which ultimately results in alterations of gene expression associated with the neurodegenerative process, including oxidative damage and apoptosis in dopaminergic neurons.

Cholinesterase inhibitors

- **Organophosphates (OP) and Carbamates**
  - Strong Acute neurotoxicity - AChE inhibition (cholinergic effects).
  - Nervous system toxins - nerve gas (sarin).

Pesticides

OP-Carbamate insecticides

1st OP: TEPP (tetraethylpyrophosphate), followed by parathion
1st carbamic: 1930

WWII chemical warfare
1988 Iraq- against Kurds
1994 Japan
1995 Tokyo subway

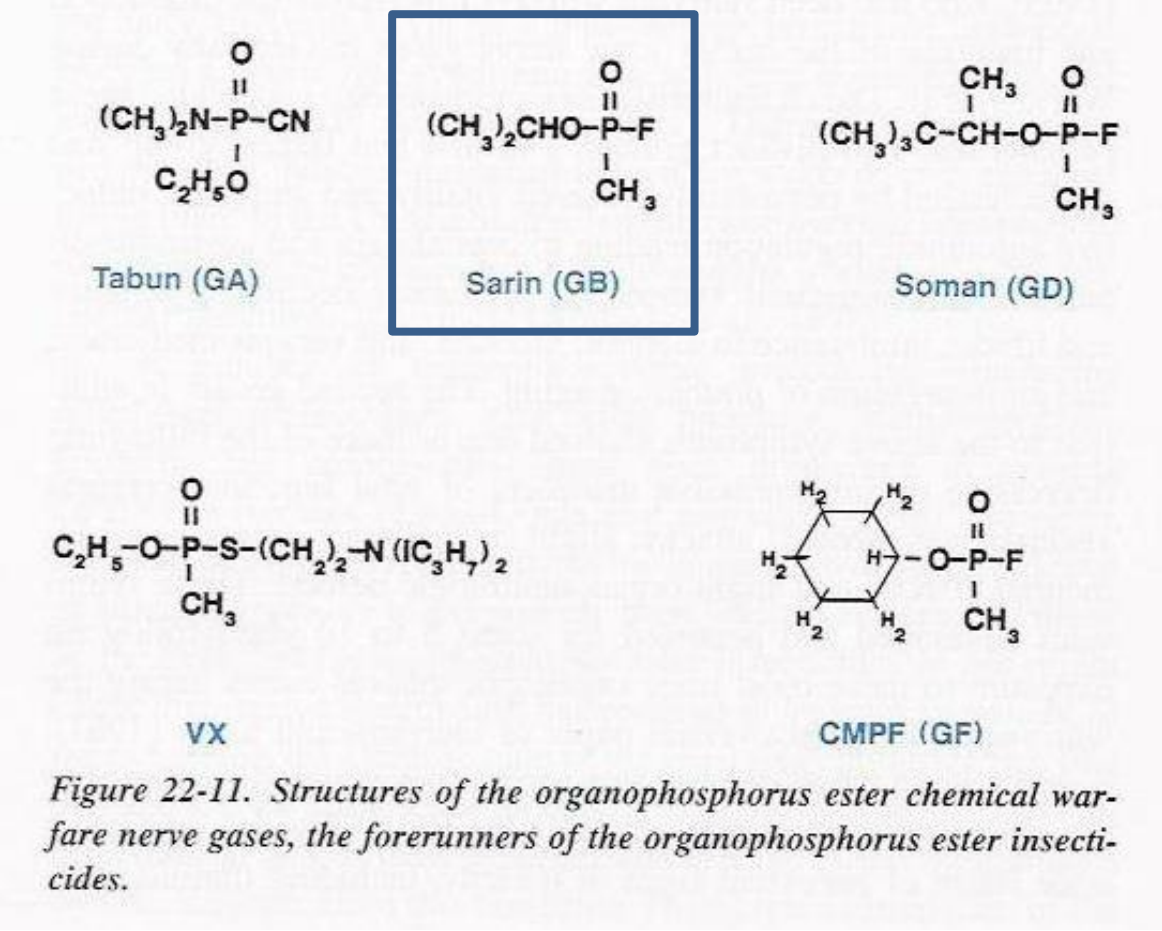
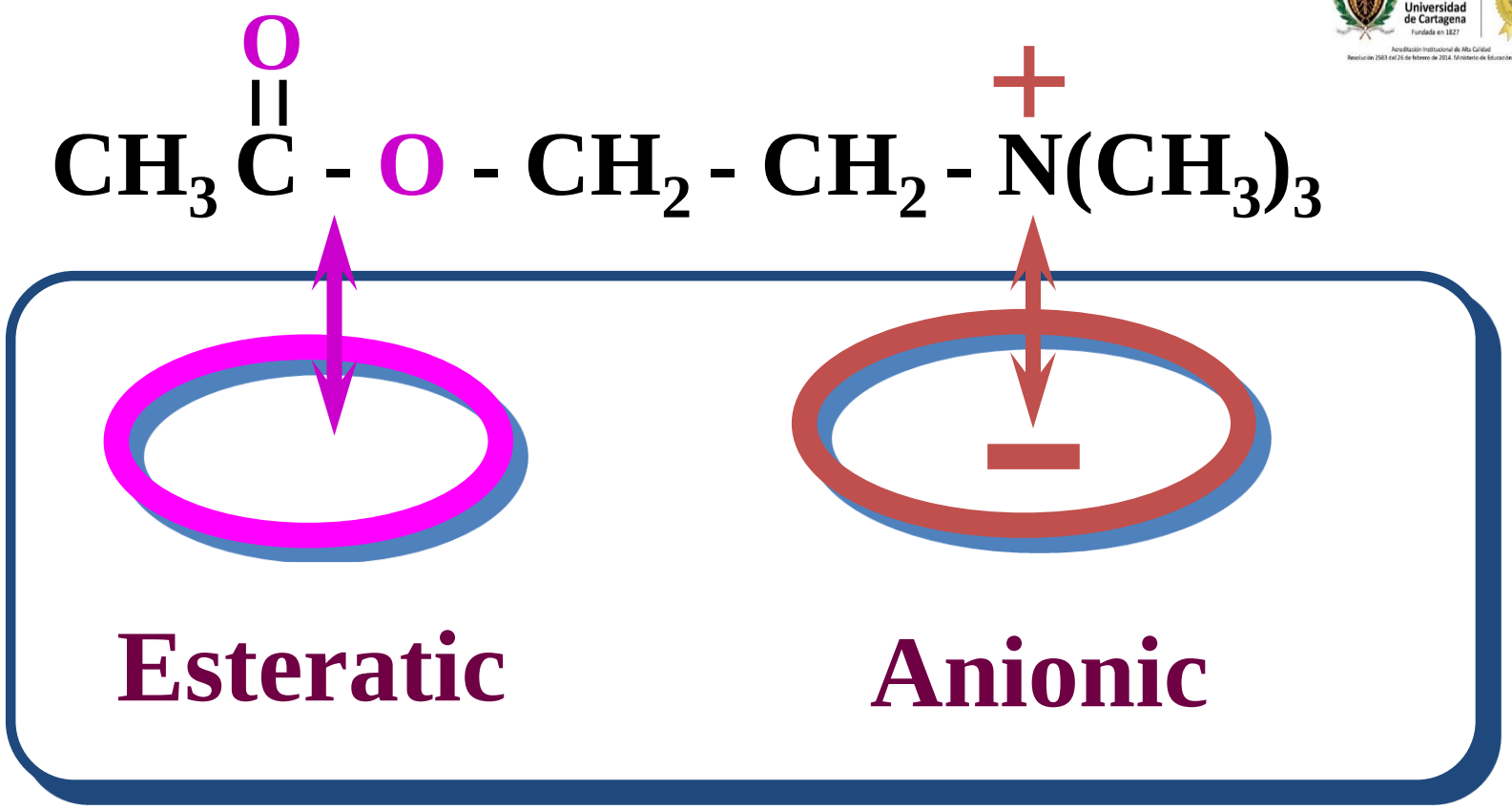


Figure 22-11. Structures of the organophosphorus ester chemical warfare nerve gases, the forerunners of the organophosphorus ester insecticides.

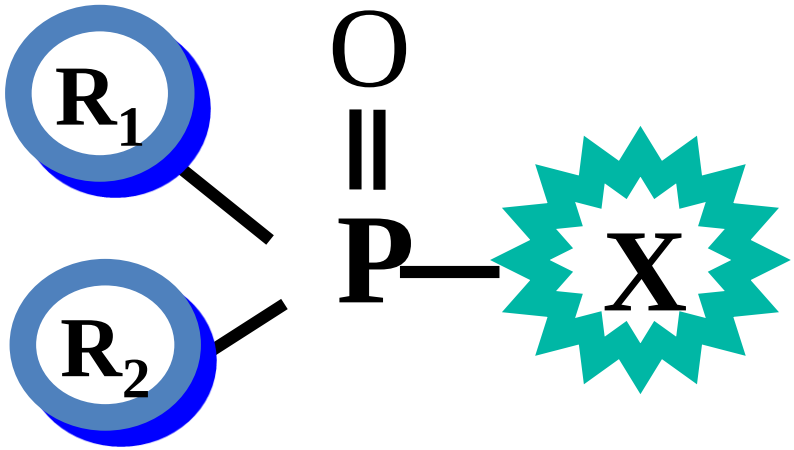
Cholinesterase

Pesticides



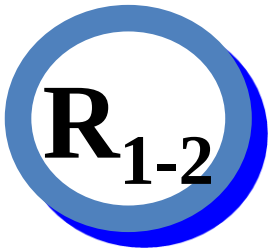
$$CH_3C(=O)-O^- + HO-CH_2-CH_2-N^+(CH_3)_3$$

Organophosphates

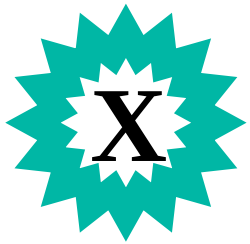


Parathion

Malathion

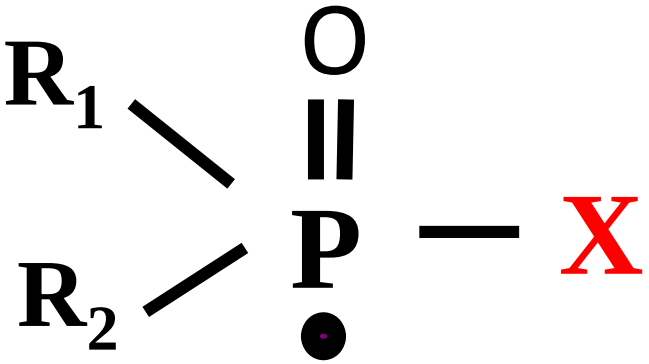


= aliphatic



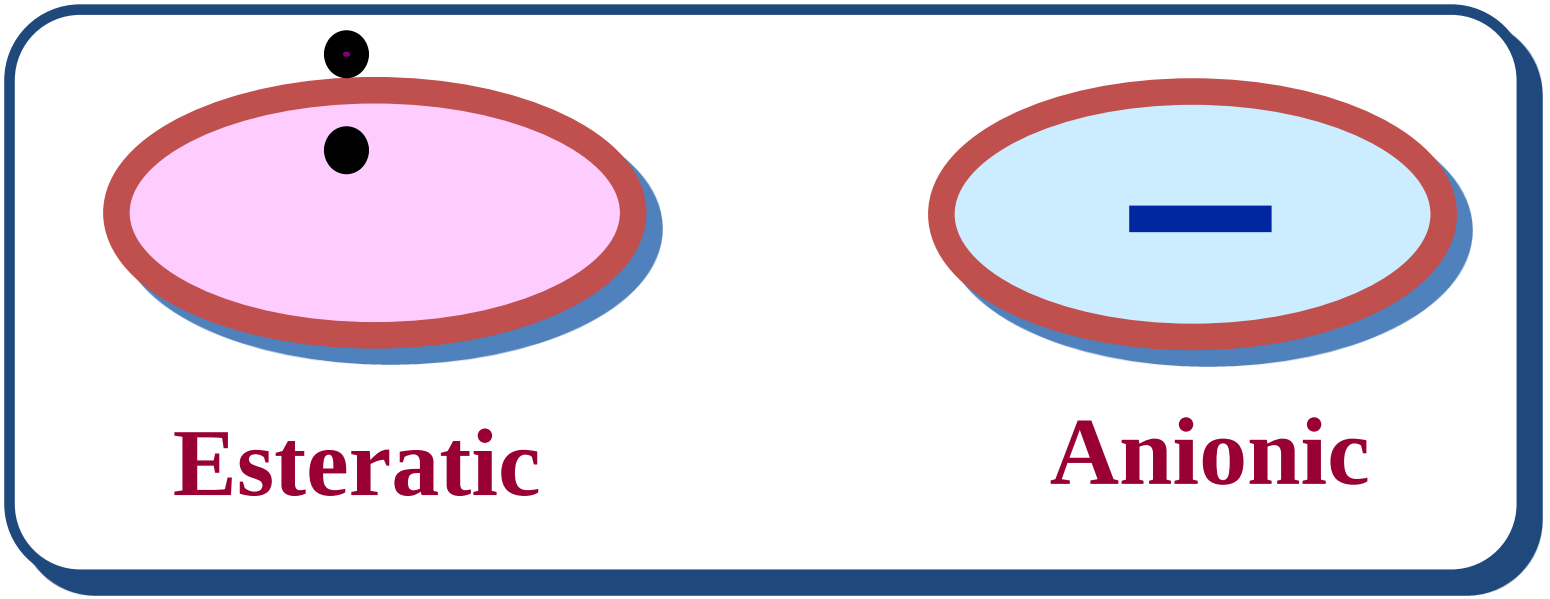
= e^- withdrawing

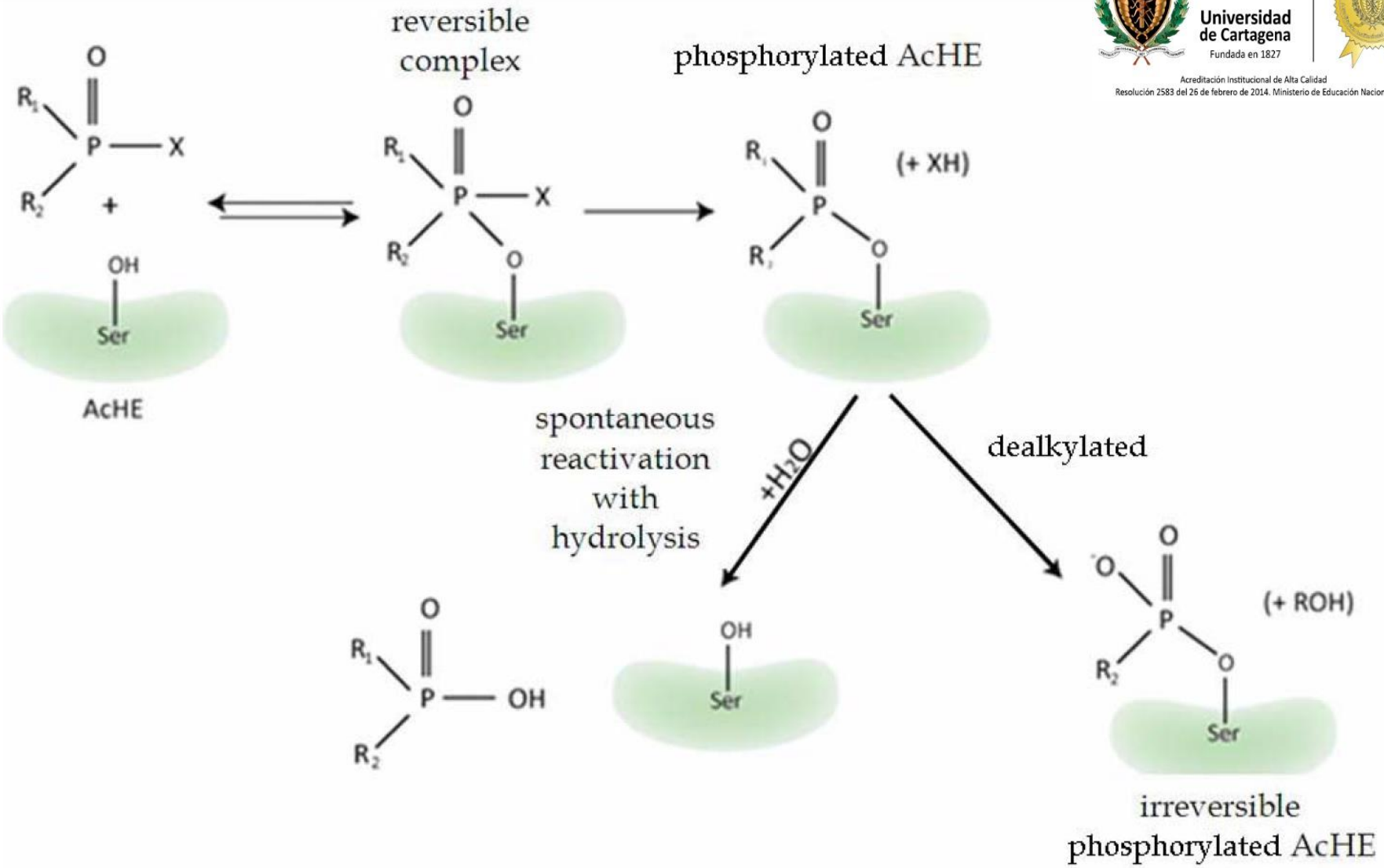
Organophosphates



Strong Covalent Bond,
Inactivates Enzyme
(stable >100h)

Aging of complex





The binding of OP to the active site of AcHE (adapted from Hreljac, 2009)

Chem Biol Interact. 2010 September 6; 187(1-3): 344–348.
Published online 2010 March 6. doi: 10.1016/j.cbi.2010.03.002

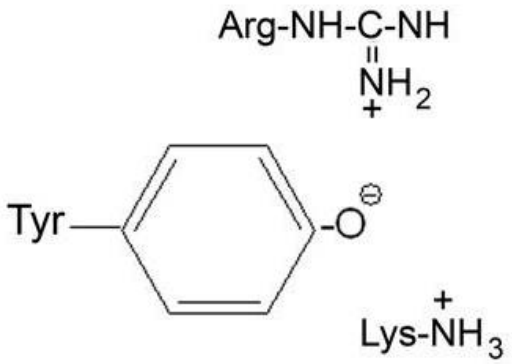
Review of tyrosine and lysine as new motifs for organophosphate binding to proteins that have no active site serine

Oksana Lockridge and Lawrence M. Schopfer

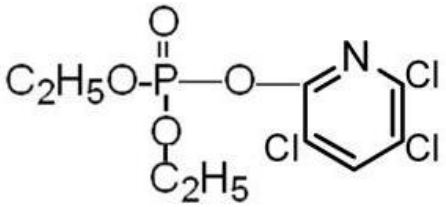
Abstract

Other Sections ▾

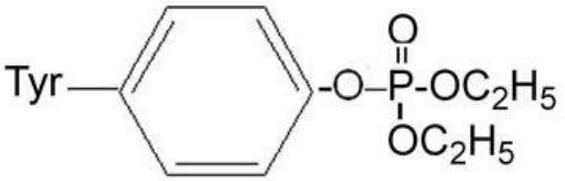
The accepted target for organophosphorus agent (OP) binding to enzymes is the active site serine in the consensus sequence Gly × Ser × Gly. New motifs have been identified by using mass spectrometry to fragment OP-labeled peptides. It has been found that OP can make covalent bonds with tyrosine and lysine in proteins that have no active site serine. The OP-tyrosine bond is stable, and does not undergo the decay seen with OP-serine.



Tyrosine ion stabilized by Arg and Lys



Chlorpyrifos oxon



Diethoxyphosphorylated tyrosine

Reaction of tyrosinate anion with chlorpyrifos oxon to yield diethoxyphosphorylated tyrosine. The anion of tyrosine is stabilized by interaction with positively charged arginine and lysine side chains. The tyrosine anion reacts with chlorpyrifos oxon to make a covalent bond with diethoxyphosphate while displacing 3,5,6-trichloro-2-pyridinol.

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Review of tyrosine and lysine as new motifs for organophosphate binding to proteins that have no active site serine

Oksana Lockridge and Lawrence M. Schopfer

Proteins labeled by OP on tyrosine.

protein	accession number	OP-labeled tyrosine	reference
human albumin	gi 28592	NALLVRY$_{411}$TKKVPQ	[25,27]
bovine albumin	gi 30794280	NALIVRY$_{410}$TRKVPQ	[45]
guinea pig albumin	gi 33518896	NALAVRY$_{411}$TQKAPQ	[29]
mouse albumin	gi 3647327	NAILVRY$_{411}$TQKAPQ	present report
mouse albumin	gi 3647327	YEKLGEY$_{401}$GFQNAI	present report
bovine tubulin alpha	gi 73586894	EVRTGTY$_{83}$RQLFHP	[36]
bovine tubulin beta	gi 75773583	EATGGKY$_{59}$VPRAVL	[36]
bovine tubulin beta	gi 75773583	SRGSQQY$_{281}$RALTVP	[36]
bovine tubulin beta	gi 75773583	SKIREEY$_{159}$PDRIMN	[36]
mouse tubulin beta	gi 21746161	LERINVY$_{50}$Y$_{51}$NEATGN	[41]
human transferrin	gi 136191	RKPVDEY$_{257}$KDCHLA	[46]
human transferrin	gi 136191	RKPVEEY$_{593}$ANCHLA	[46]
human kinesin 3C motor domain	gi 160286524	YLVRASY$_{157}$LEIYQE	[47]
mouse transferrin	gi 21363012	RKPVDQY$_{257}$EDCY$_{261}$LARIPS	[46]
mouse transferrin	gi 21363012	RMDYRLY$_{333}$LGHNY$_{338}$VTAIRN	[46]
mouse transferrin	gi 21363012	GIFPKGY$_{448}$Y$_{449}$AVAVVK	[46]
mouse transferrin	gi 21363012	QGCAPGY$_{510}$EKNSTL	[46]
mouse transferrin	gi 21363012	PNNKEEY$_{534}$NGY$_{537}$TGAFRC	[46]
mouse ATP synthase	gi 20455479	QKILQDY$_{431}$KSLQDI	[47]
papain	gi 129614	NEGALLY$_{256}$SIANQP	[13]

Pesticides

The following effects of organophosphorus agents have been demonstrated in animals

The inactivation of the cholinesterases occurs in the blood and in a wide range of nerve, neuromuscular (skeletal, smooth and cardiac) and glandular tissues where these enzymes have a role in cell-to-cell communication and the hydrolysis of xenobiotics. These enzymes have possibly as yet unidentified roles such as cell development and growth.

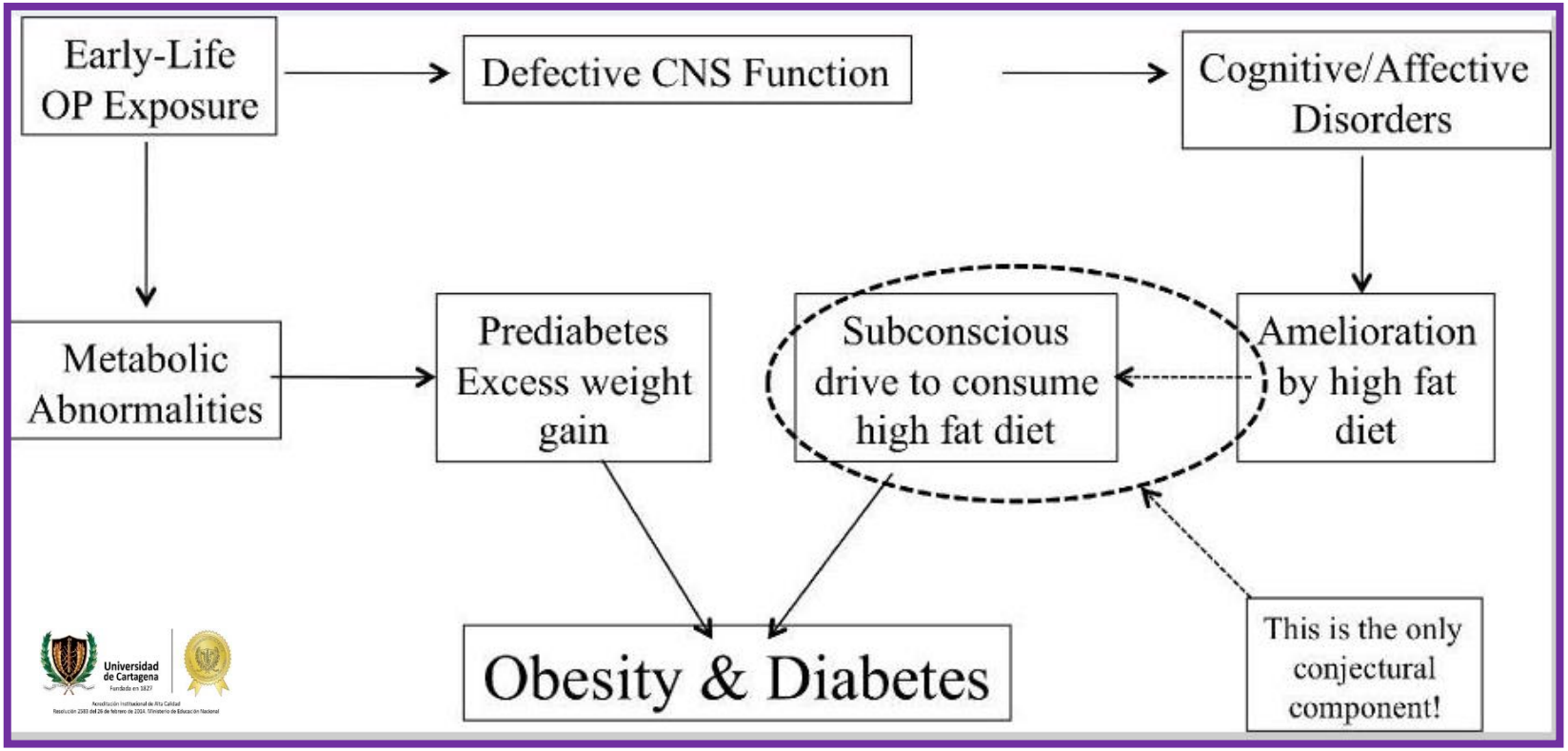
The inhibition of AChE leads to the accumulation of acetylcholine, the neurotransmitter at all ganglia in the autonomic nervous system and at many synapses in the brain, skeletal neuromuscular junctions, at some post-ganglionic nerve endings of the sympathetic nervous system and adrenal medulla.

1. Inactivation by phosphorylation of other beta esterases.
2. Altering the release of neurotransmitters, e.g. γ-aminobutyric acid (GABA) and glutamate.
3. Increasing the number of GABA and dopamine receptors.
4. Acting as agonists at M2/M4 muscarinic receptors.
5. Inhibition of mitochondrial enzymes, respiration and ATP generation.
6. Induction of mast cell degranulation, probably causing the release of histamine or histamine-like compounds.
7. Inhibition of nitric oxide.
8. Interference with surfactant in the lung.
9. Inhibition of phospholipase A_2.
10. Interference with humoral and cellular immunity, e.g. the function of T lymphocytes.

Pesticides

The inactivation of AChE by alkyl phosphorylation of a serine hydroxyl group at the esteratic site of this enzyme leads to accumulation of acetylcholine at the following locations.

1. Muscarinic sites, which causes an increase in secretions (bronchorrhoea, salivation, tearing and sweating), bronchoconstriction (tightness in the chest and wheezing), bradycardia, vomiting and an increase in gastrointestinal motility (abdominal tightness, cramps and diarrhoea). Organophosphates cause the diagnostic miosis in the eye, which results in blurring of vision.
2. Nicotinic sites (e.g. neuromuscular junctions), which causes muscle fasciculations and a flaccid paralysis in severe exposures.
3. Within the central nervous system, which causes headache, insomnia, giddiness, confusion, drowsiness and, in severe exposures, slurred speech, convulsions, coma and respiratory depression.



Early-life exposure to OP pesticides contribute to later dietary choice, obesity and diabetes.

OP exposure during a critical developmental window altered the trajectory of hepatic adenylyl cyclase/cyclic AMP signaling, culminating in hyperresponsiveness to gluconeogenic stimuli. Animals developed metabolic dysfunction resembling prediabetes. When the OP-exposed animals consumed a high fat diet in adulthood, metabolic defects were exacerbated and animals gained excess weight compared to unexposed rats on the same diet. At the same time, the high fat diet ameliorated many of the central synaptic defects caused by organophosphate exposure, pointing to nonpharmacologic therapeutic interventions to offset neurodevelopmental abnormalities, as well as toward fostering dietary choices favoring high fat intake. Common insecticides may contribute to the increased worldwide incidence of obesity and diabetes.

Reprod Toxicol. 2011 Apr;31(3):297-301.

Pesticides

OP-Carbamate insecticides

Organophosphates are slower to release from AchE – "also aging effect"

Carbamates are faster: reversible

Phase I metabolic activation .

Multiple metabolic reactions.

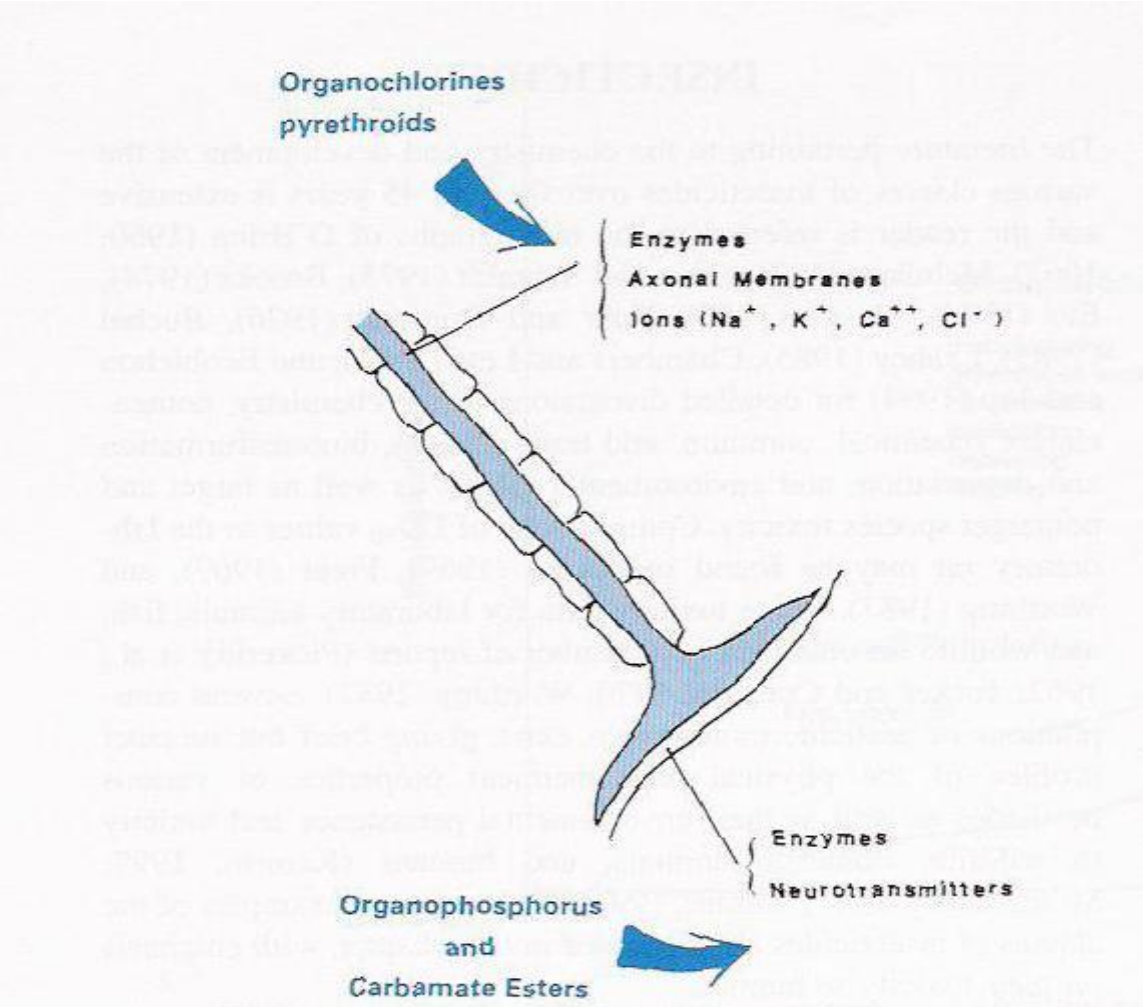


Figure 22-5. Potential sites of action of classes of insecticides on the axon and terminal portions of the nerve.

Pesticides

OP-Carbamate insecticides

Neurobehavioral, muscular and cognitive effects

Delayed Neuropathy (OPIDN) - ginger jake.

Organophosphate-induced delayed neuropathy

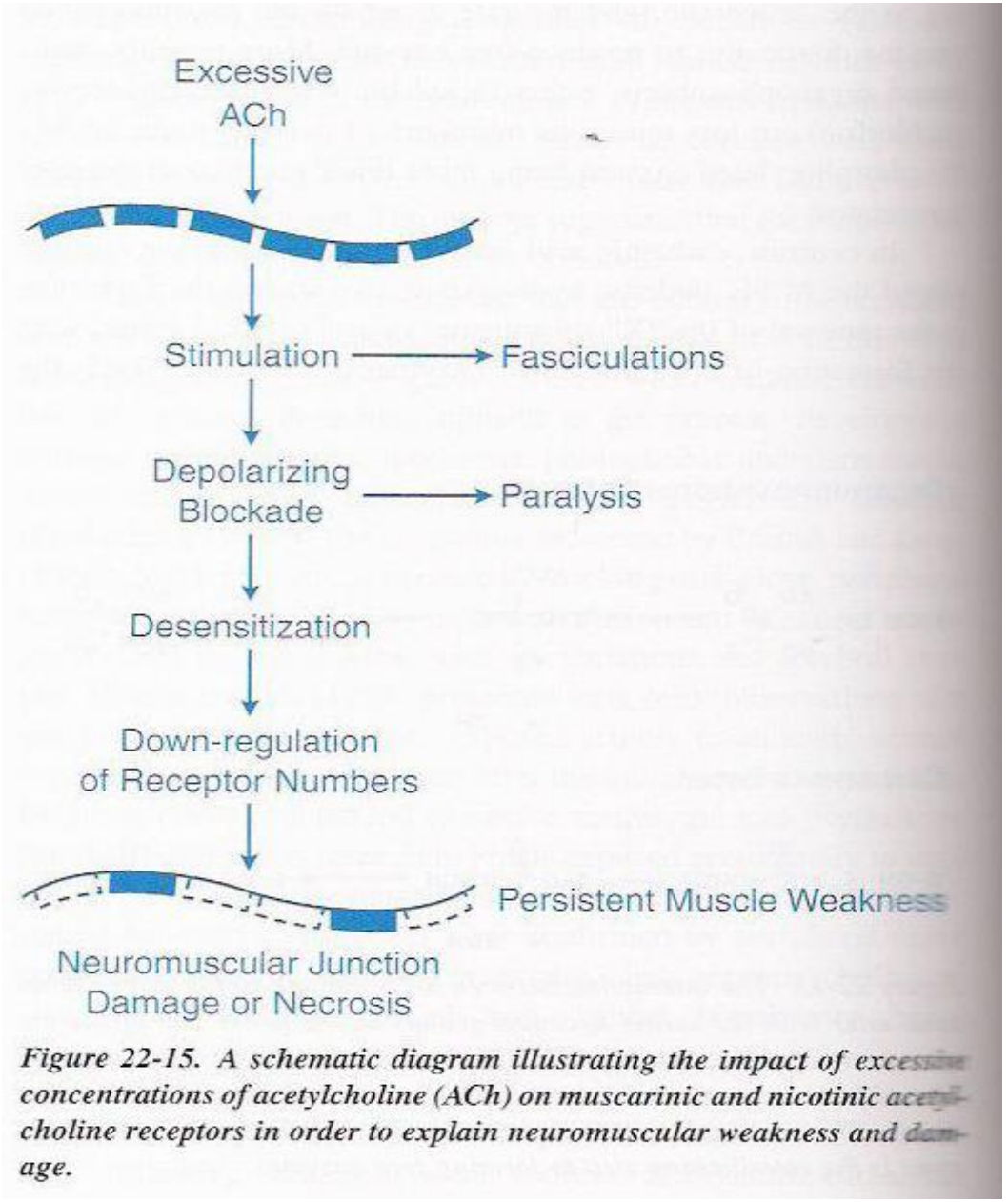


Figure 22-15. A schematic diagram illustrating the impact of excessive concentrations of acetylcholine (ACh) on muscarinic and nicotinic acetylcholine receptors in order to explain neuromuscular weakness and damage.

Pesticides

Pyrethroids

Newer (1980)

Extensive agricultural use.
Indoor use.
Pet flee control.
Household plants.

Modify Na^+ channel kinetics.
Abnormal repetitive discharges.

Type A shorter action than type B

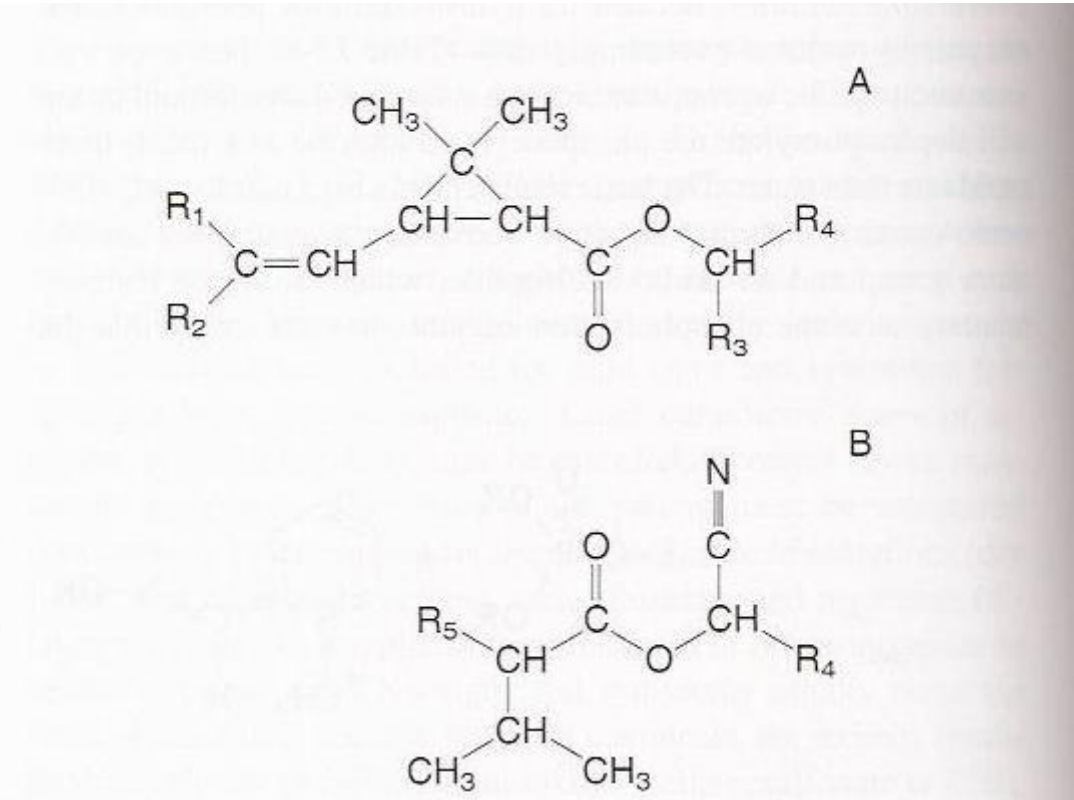
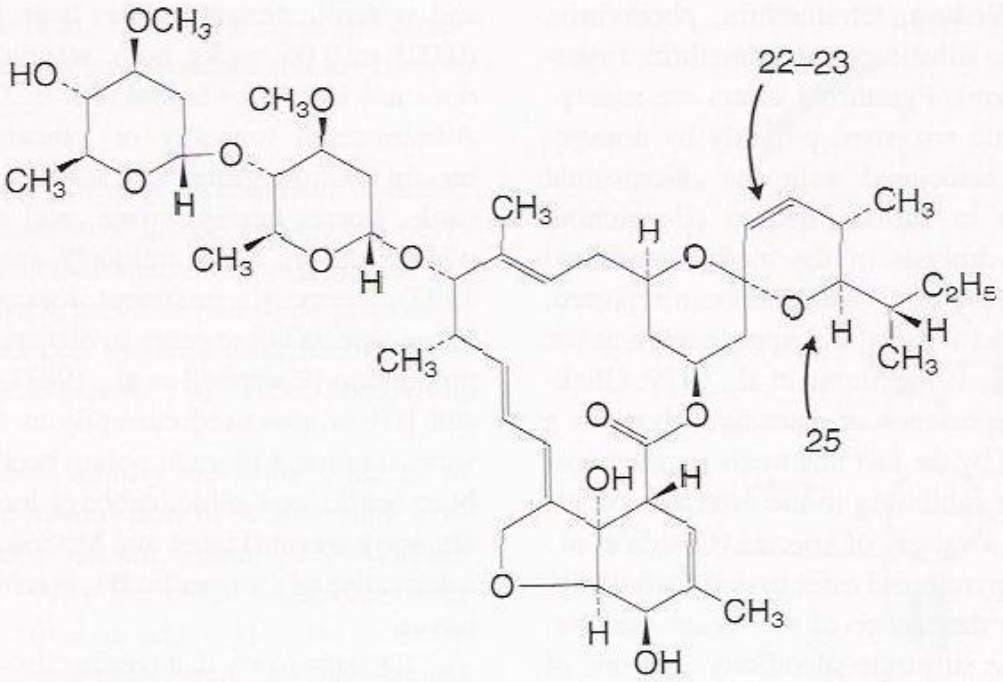


Figure 22-18. The basic structures of the synthetic pyrethroid ester insecticides showing (A) the intact cyclopropane ring in type I esters, with R_1 and R_2 (methyl, bromine, chlorine, etc.), R_3 (hydrogens or cyano) and R_4 (3-phenoxybenzoate, other) substituents; and (B) the "open" structure of type II esters with R_4 (3-phenoxybenzoate, other) and R_5 (substituted phenyl substituents).

Pesticides

Avermectins

Streptomyces avermitilis



Ivermectin binds with high affinity to **glutamate-gated chloride channels** which occur in invertebrate nerve and muscle cells, causing an increase in the permeability of the cell membrane to chloride ions with **hyperpolarization** of the nerve or muscle cell.

Hyperpolarization results in paralysis and death of the parasite either directly or by causing the worms to starve.

Common Name	Structural Positions		
	22–23		25
Avermectin Bla	As above		As above
Avermectin Blb Abamectin	As above		—$CH(CH_3)_2$
Ivermectin	—CH_2—CH_2—	80% 20%	As above —$CH(CH_3)_2$

Figure 22-20. A structural representation of the macrocyclic lactone avermectin (B1a), abamectin (B1b), and the semisynthetic insecticide ivermectin showing the structural differences at positions 22 to 23 and 25 of the ring.

Herbicides

Phenoxyherbicides

- Introduced in 1946
- 2,4-Dichloro- and 2,4,5-Trichloro phenoxy acetic acids.
- Defoliants (Vietnam war) – Forestry.
- Nerve toxicity, peripheral neuropathy.
- Controversy about NHL and HL.
- Contaminants may be responsible for toxicity.

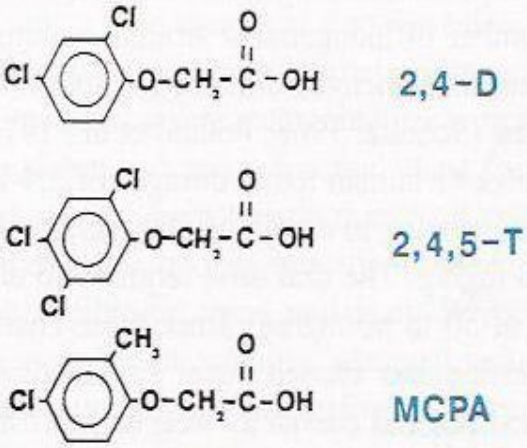
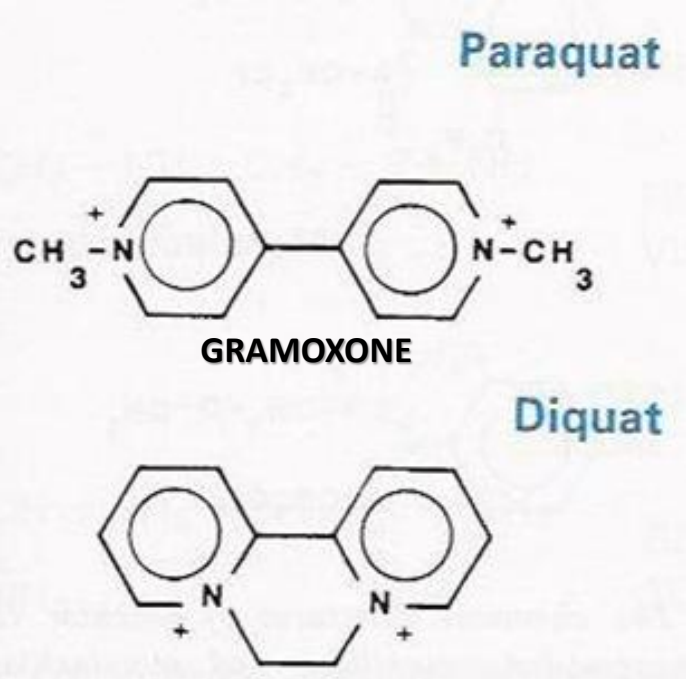


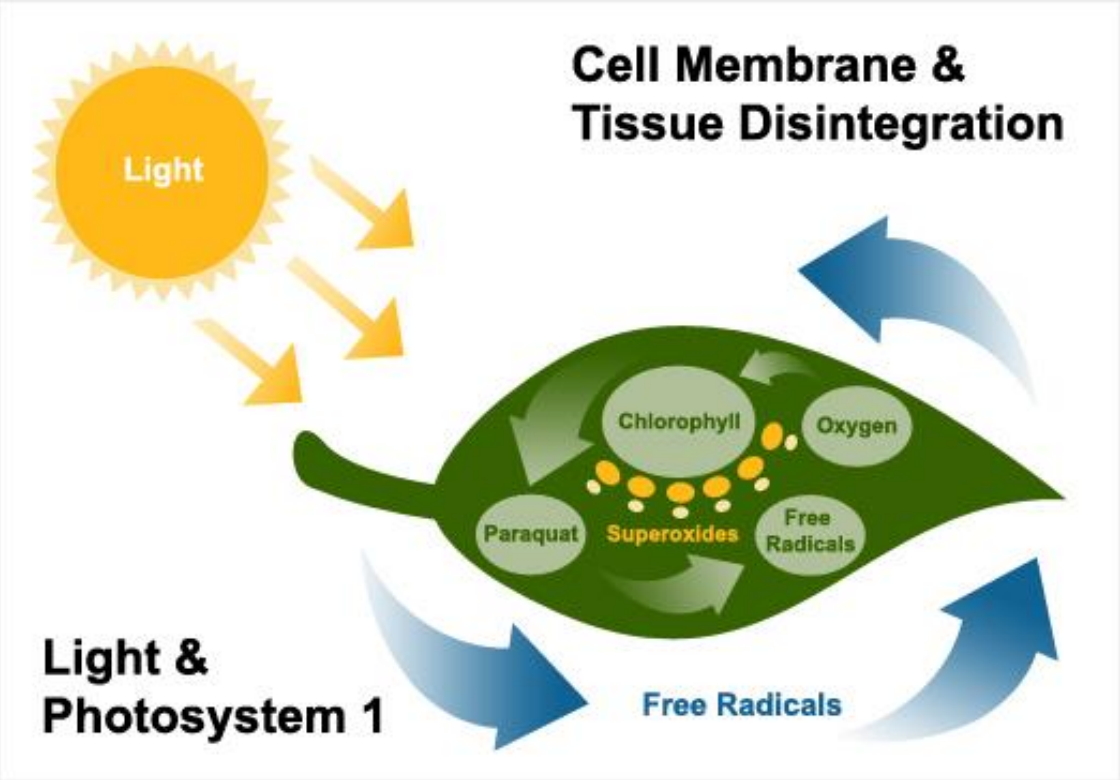
Figure 22-22. The molecular structure of the three most common chlorophenoxyacetic acid herbicides: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 4-chloro-o-toloxyacetic acid (MCPA). Ester and amine salt derivatives are also marketed.

Pesticides

Herbicides

Dipyridyl derivatives





"Startling human toxicity"

Banned in many countries but still in use in 130 others

Lung is the most susceptible target organ

Highly polar- poor GI absorption (5-10%)

LD50=22-262 mg/kg

LD50=100-400 mg/kg

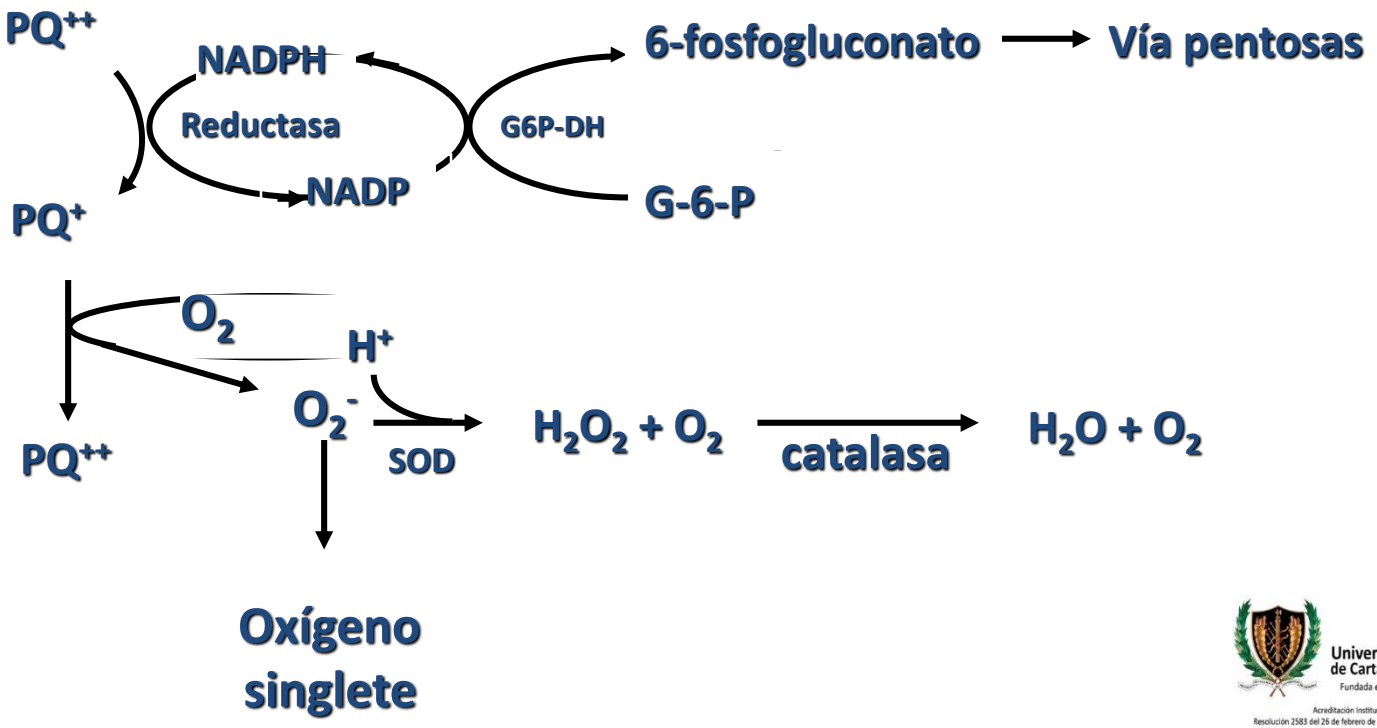
Pesticides

Herbicides

Dipyridyl derivatives

MECANISMO DE ACCIÓN

☞ **Generación de Radicales Superóxido:**



Pesticides

Herbicides

Phosphomonomethyl aminoacids

- Non-selective systemic herbicides.
- Free acids or salts - ocular and mucus membrane irritants.
- Class E carcinogens (EPA)
- Solvent may be the toxic compound (POEA)

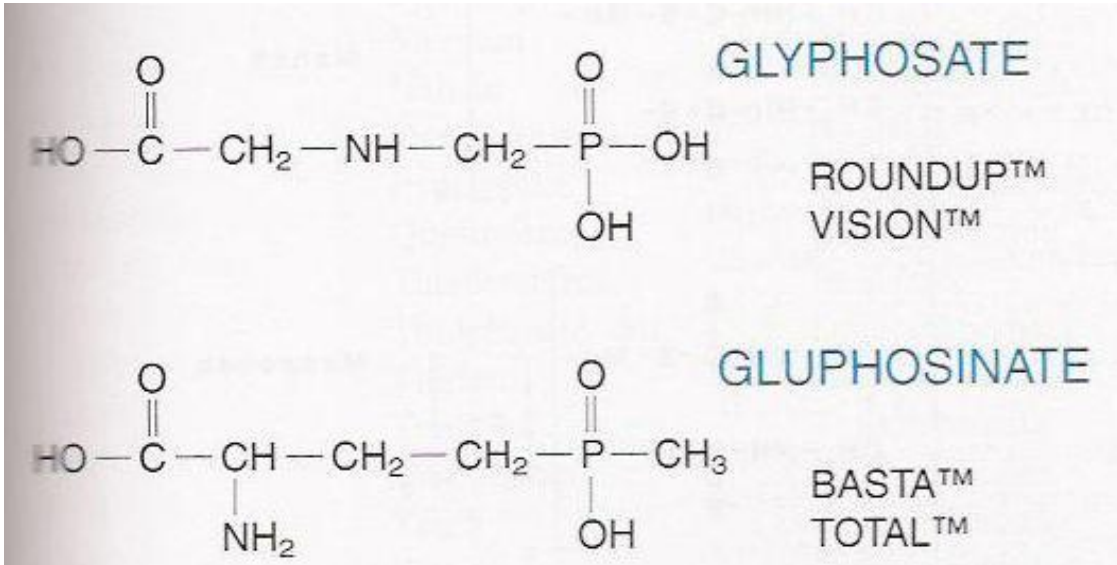


Figure 22-25. The chemical structures of glyphosate (N-phosphonomethyl glycine) and glufosinate (N-phosphonomethyl homoalanine).

Pesticides

Fungicides

- Lipophilic, accumulate
- 90% are carcinogenic in animal models.
- Contaminants are dioxins and furans.

- Hexachlorobenzene (banned)
- Pentachlorophenol (banned).

- Phthalimides.

- Dithiocarbamates

TBZ inhibits mitochondrial, helminth-specific enzyme, fumarate reductase

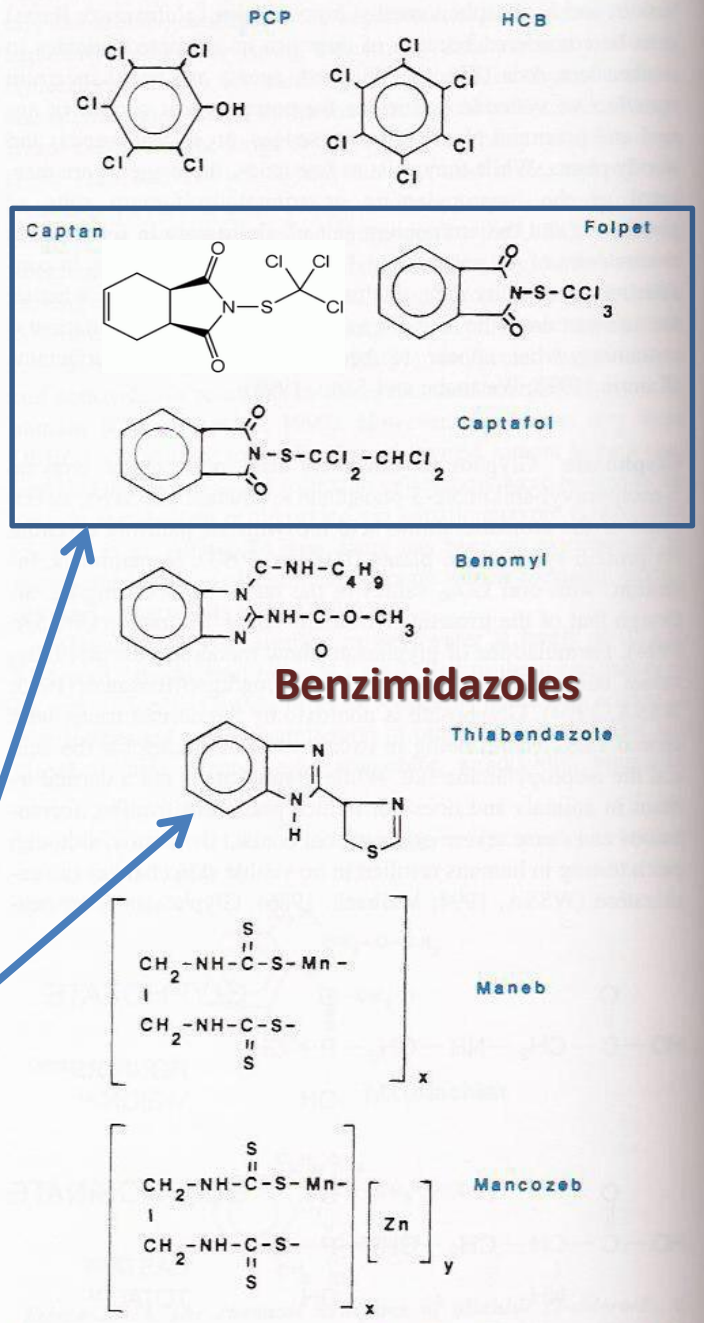


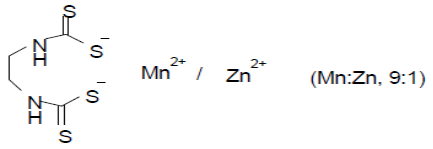
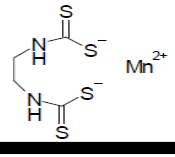
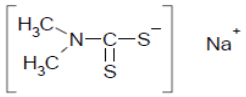
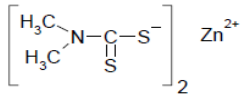
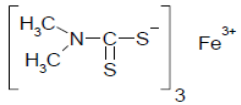
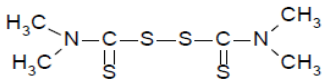
Figure 22-26. Chemical structures of fungicides representative of various chemical classifications.

Pesticides

Fungicides

Dithiocarbamates

Structures of the Dithiocarbamates in the Candidate Group

Chemical	Structure	CAS No.
EBDC's[1]		
Mancozeb		8018-01-7
Maneb		12427-38-2
DMDTC's[1]		
Na-Dimethyl-dithiocarbamate		128-04-1
Ziram		137-30-4
Ferbam		14484-64-1
Thiram		137-26-8

EBDC's = Ethylene-(bis)-dthiocarbamates.
DMDTC's = Dimethyldithiocarbamates.

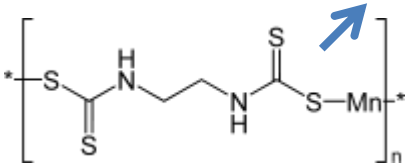
Pesticides

Fungicides

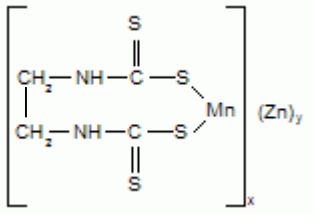
Universidad de Cartagena
Fundada en 1827
Acreditación Institucional de Alta Calidad
Resolución 2583 del 26 de febrero de 2014. Ministerio de Educación Nacional

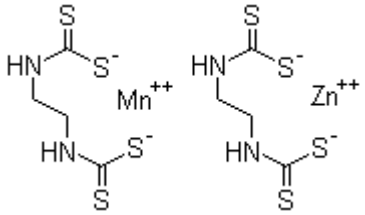
Dithiocarbamates.

Used to create an animal model of Parkinson's disease

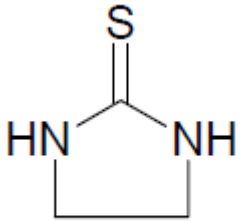


- Ferbam, ziram, maneb, **mancozeb** (metal-based names)
- Some reported as teratogenic.





- Degradation to ethylene thiourea (ETU): a known mutagen, carcinogen, teratogen and antithyroid compound.
- Some neurotoxicity at high doses.
- May cross into CNS if bound to divalent metals.



ETU

Pesticides

Fungicides

Dithiocarbamates.

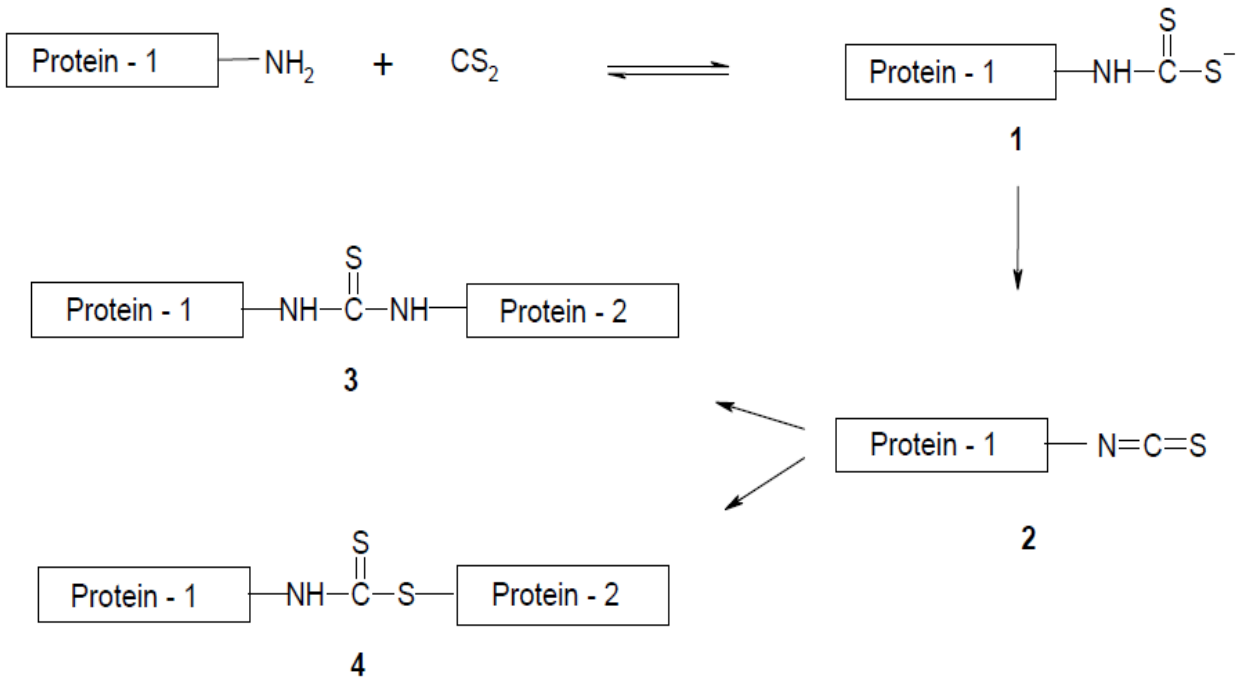
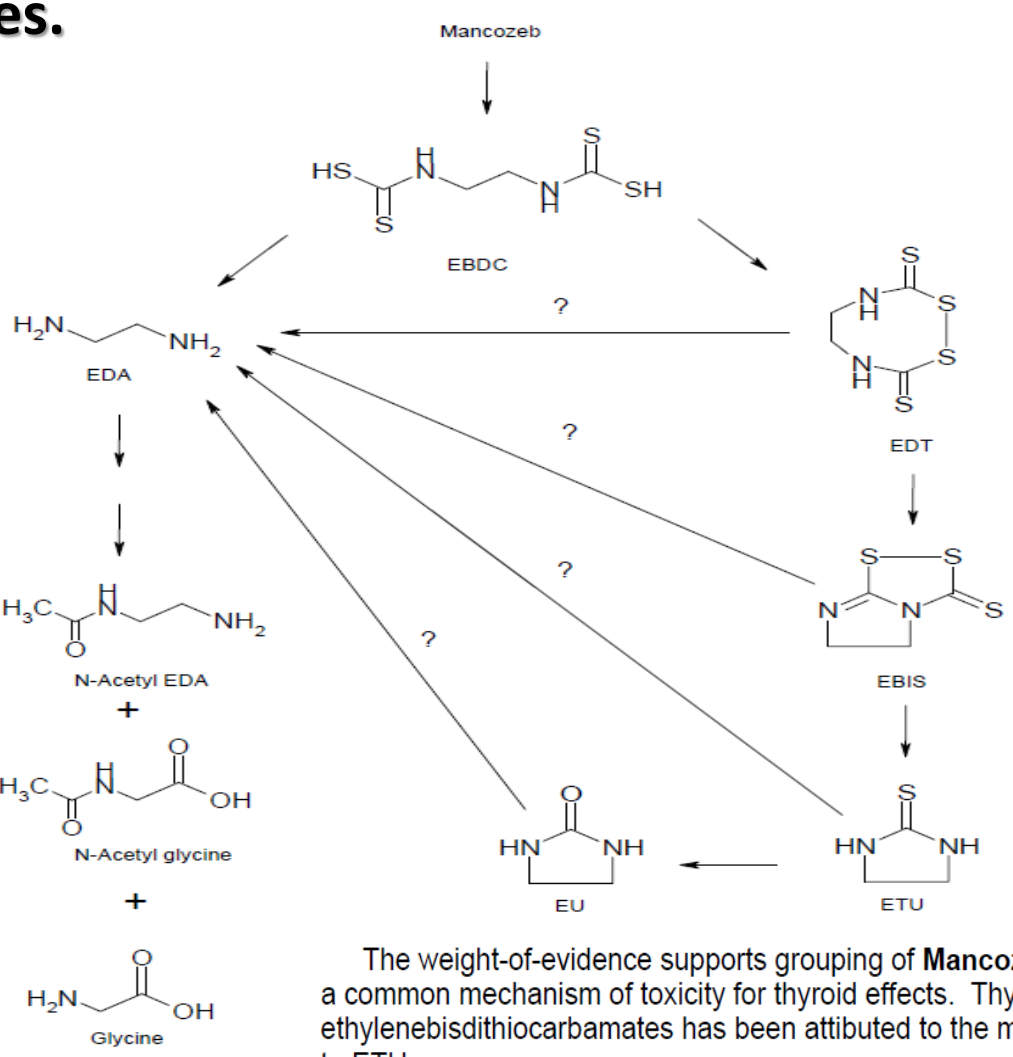


Figure 3. Proposed reaction sequence in CS_2 mediated cross-linking of proteins. Lysyl amino groups of proteins (e.g. protein 1) react with CS_2 to yield the dithiocarbamate 1, part of which is converted yo isothiocyanate 2. Conceptually, nucleophilic attack by amino or thiol groups in another protein (e.g. protein 2) may take place yielding the thiourea 3 or the N,S-dialkyl dithiocarbamate ester 4.

Pesticides

Fungicides

Dithiocarbamates.



The weight-of-evidence supports grouping of **Mancozeb, Maneb, and Metiram,** by a common mechanism of toxicity for thyroid effects. Thyroid toxicity induced by the ethylenebisdithiocarbamates has been attibuted to the metabolism of these chemicals to ETU.

Biotransformation of Mancozeb. Adapted from Accession Nos. 262834 and 262835. EBDC: Ethylenebisdithiocarbamic acid; EDA: Ethylenediamine; ETU: Ethylenethiourea; EU: Ethyleneurea. Conversion of Mancozeb to EBDC and then to EDA or EDT are known chemical, nonenzymatic conversions. For reactions with a " ? ", it is not known to what extent do these reactions take place.

Pesticides

Summary of effects of treatment of rats or mice with dithiocarbamate

Chemical	Neuropathology	Thyroid	CNS - developmental	Cholinesterase inhibition
mancozeb	+	+	+	not measured
maneb	+	+	+	-
metiram	+	-	no study	not measured
Na-dimethyldithio-carbamate	-	-	-	-
ziram	+	+	-	+
thiram	+	±	+	not measured
ferbam	-	+	+	no study
metam sodium	+	-	-	+

Pesticides

Mancozeb

The widely used fungicide mancozeb has been shown to cause hypothyroxinemia and other adverse effects on the thyroid hormone system in adult experimental animals. In humans, hypothyroxinemia early in pregnancy is associated with adverse effects on the developing nervous system and can lead to impaired cognitive function and motor development in children.

Mancozeb exposure did reduce T(4) levels in dams and may therefore still be a potential contributor to thyroid disruption in humans and in result adversely affects the developing brain.

Low thyroid hormone levels (hypothyroxinemia). There is a dose–response relationship in the lower range of the thyroid hormone distribution with verbal and nonverbal delays in early childhood. This means that the lower the T4 level, the worse the delay.

Thyroid peroxidase or thyroperoxidase (TPO) is an enzyme expressed mainly in the thyroid that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of thyroxine (T_4) or triiodothyronine (T_3), thyroid hormones.

Mancozeb must be considered a multipotent carcinogenic agent.

Fumigants

- Very volatile - inhalation exposure
- Non-selective, highly reactive and cytotoxic.
  - Acrylonitrile
  - Carbon disulfide
  - Carbon tetrachloride
  - Ethylene dibromide (gastric carcinomas, sterility)
  - Ethylene oxide (carcinogen, developmental tox.)
  - Phosphine (PH_3) released from aluminum phosphide (AlP) in moist conditions (grain storage)

ACUTE PESTICIDE-RELATED ILLNESS

- Dermal and ocular irritation (or allergic response)
- Upper and lower respiratory tract irritation
- Allergic responses / asthma (fungicides)
- Gastrointestinal symptoms
- Neurological symptoms
- Specific syndromes
  - Cholinergic crisis (organophosphorus pesticides)
  - Bleeding (warfarin-based rodenticides)
  - Caustic lesions and pulmonary fibrosis (herbicide, paraquat)

Paraquat lesions courtesy of Dr. J Pronczuk

ACUTE POISONING BY "ACCIDENTAL" INGESTION

- Storage of leftover pesticide in a medicine or soft drink bottle
- Confusion with pharmaceutical
- Pesticide container reused for storing drinks or food
- Pesticide container present in the child's environment

Bottles containing pharmaceuticals and the pesticide chlorpyriphos
Laborde, CIAT, Montevideo

LOW-LEVEL CHRONIC EXPOSURE

Growing body of epidemiologic and animal data and research studies suggests a link between long-term exposure and:

- Abnormal growth and development
- Impaired neurobehavioral development / functions
- Cancer
- Increased susceptibility to infections

PRECONCEPTIONAL PRENATAL EXPOSURE

Pesticide exposure before or during pregnancy has been associated with increased risk of:

- Infertility
- Perinatal death
- Spontaneous abortion
- Premature birth
- Fetal growth retardation
- Congenital malformations
- Early childhood cancer

WHO

Exposure during brain growth has subtle and permanent effects on:

- Brain structure and function
- Neuronal and axonal differentiation
- Serotoninergic system
- Synaptogenesis
- Programming of synaptic function

PESTICIDES AND CHILDHOOD CANCER

Some studies have found an association between postnatal pesticide exposure and an increased risk of paediatric cancer

- **Brain tumours**
- **Acute lymphocytic leukaemia**
- **Non-Hodgkin lymphoma**

ENDOCRINE DISRUPTION

- Low doses of certain pesticides may mimic or block hormones or trigger inappropriate hormone activity
- Endocrine disruption may alter development and reproduction and induce birth defects
- Endocrine disruption has been linked to:
  - Infertility
  - Low sperm count
  - Early puberty
  - Hormone-dependent cancers (testicular, breast, prostate)
  - Altered sex ratio

PESTICIDES IN CHILDREN'S COMPLEX ENVIRONMENT

PESTICIDES
Agriculture
Veterinary
"Cosmetic"
Human health
Public health

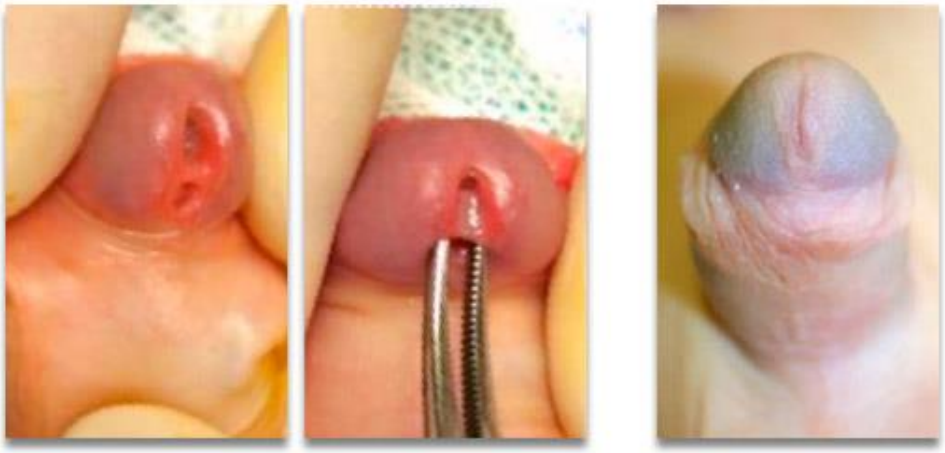
Air, water, food, soil and objects

Home
School
Playground
Farms
Fields

Eating and drinking contaminated food and beverages
Playing in contaminated areas
Reaching unsafely stored pesticides
House and farm help/child labour

SUSCEPTIBILITIES
Paraoxonase (PON)
Critical windows
Age
Nutritional status
Poverty

- **Acute effects**
- **Poisoning**
- **Neurotoxicity**
- **Impaired development**
- **Endocrine disruption**
- **Cancer?**



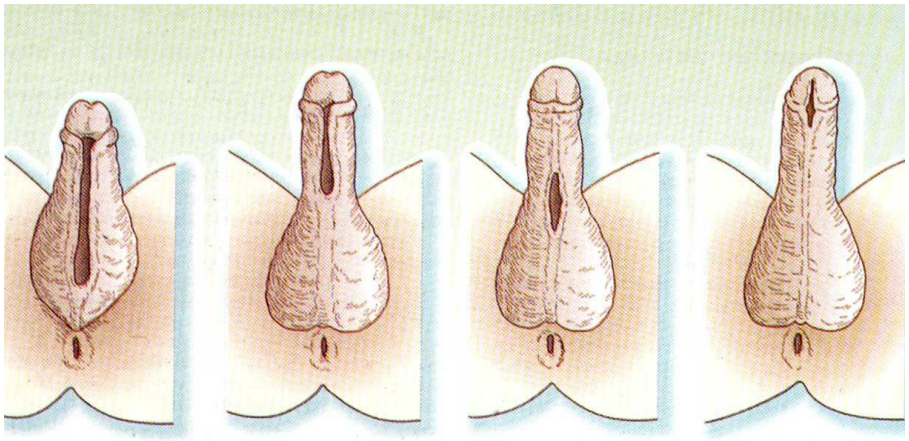


Figura 15-36 Variaciones en el grado de hipospadias.

Hipospadias

OBSOLETE PESTICIDES

Obsolete pesticides are pesticides that can no longer be used for their intended purpose or any other purpose.

They may include:

- Pesticides in liquid, powder or dust, granule, emulsion form.
- Empty and contaminated pesticide containers
- Heavily contaminated soil
- Buried pesticides

Causes of obsolete pesticides:

- Use prohibited for health/environmental reasons
- Product deteriorated as result of improper or prolonged storage
- Product not suitable for intended use and cannot be used for other purposes, nor can it easily be modified to become usable.

Agradecimientos

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PROBIOMA

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GRACIAS

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