Pesticide Toxicity

by Noor Mansour

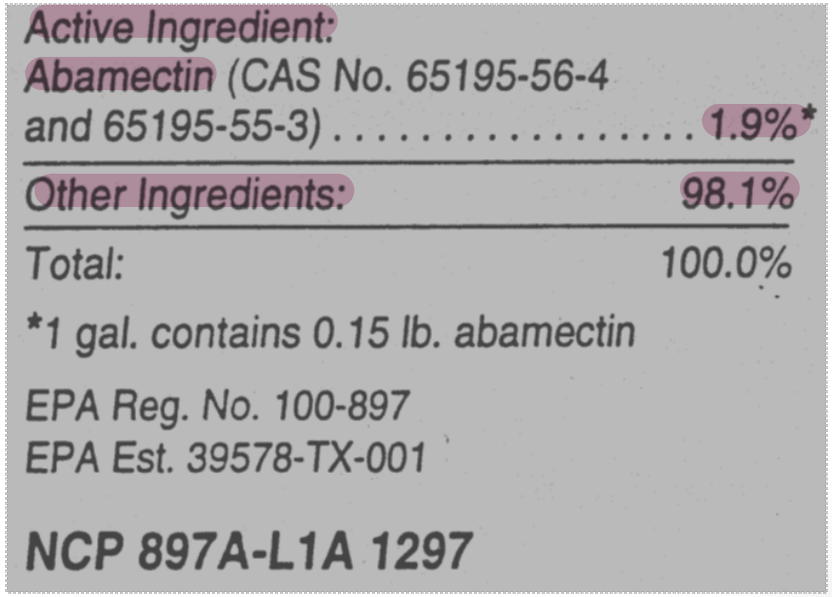
Definition of Pesticide

- ✓ Pest = unwanted creature or living,
- ✓ Cide = killing or elimination.
- ✓ Any substance or mixture of substances deliberately added to the environment and intended for **preventing, destroying, repelling, or mitigating pests**
- ✓ Pesticides may be more specifically identified as **insecticides** (insects), **herbicides** (weeds), **fungicides** (fungi and molds), **rodenticides** (rodents), **acaricides** (mites), **molluscides** (snails and other mollusks), **miticides** (mites), **larvicides** (larvae), and **pediculocides** (lice)

Use of pesticides

- Pesticides are often, if not always, used as **multi-agent formulations**, in which the **active ingredient is present together with other ingredients** to allow mixing, dilution, application, and stability…."**inert" or "other**" (**e.g., formaldehyde, sulfuric acid, benzene, toluene, other organic solvents**)

مواد مساعدة



Active Ingredient:
Abamectin (CAS No. 65195-56-4 and 65195-55-3) 1.9%*

Other Ingredients: 98.1%

Total: 100.0%

*1 gal. contains 0.15 lb. abamectin

EPA Reg. No. 100-897
EPA Est. 39578-TX-001

NCP 897A-L1A 1297

"Others"

مش مبيدات حشرية بس هذا لايعني انها غير سامة

- "Others": Though they do not have pesticidal action, such **inert ingredients** may not always be devoid of toxicity, thus, an ongoing task of manufacturers and regulatory agencies is to assure that inert ingredients do not pose any unreasonable risk of adverse health effects

* لازم يتأكدوا انه inert ingredients ما يعملوا adverse effects

US Pesticide Use

استخدام المبيدات الحشرية في امريكا

- 4.5 billion pounds chemicals per year
  - 890 active ingredients, 30,000 formulations
  - Uses
    - **75% agricultural** زراعة
    - **25% home, garden** منازل وحدائق

Exposure

- Exposure to pesticides can occur via the **oral** or **dermal** routes or by **inhalation**
- **High oral doses,** leading to severe poisoning and death, are achieved as a result of pesticide ingestion for suicidal intent, or of accidental ingestion, commonly due to storage of pesticides in improper containers
- **Chronic low doses,** on the other hand, are consumed by the general population as pesticide residues in **food** or as contaminants in **drinking water**

Exposure

- **Workers** involved in the production, transport, mixing and loading, and application of pesticides, as well as in harvesting of pesticide-sprayed crops, are at the highest risk for pesticide exposure
- **Dermal exposure during normal handling or application of pesticides**, or in case of accidental spillings, occurs in body areas not covered by protective clothing, such as the face or the hands, or by inhalation
- Furthermore, pesticides deposited on **clothing may penetrate the skin** and/or potentially expose others, if clothes are not changed and washed on termination of exposure

Human Poisoning

يعني هي مش selective بس للآفة او الحشرات
هي كمان بتأثر على الانسان

- Pesticides are **not always selective** for their intended target species…..adverse health effects can occur in non-target species, including humans

- Several million poisonings and a couple hundred thousand of deaths….World Health Organization **(WHO) classified pesticides by hazard**, where acute oral or dermal toxicities in rats were considered

صنفوا السمية حسب اثرها
على الفئران.

Table 22–1 WHO-recommended classification of pesticides by hazard (2009).

* الأرقام موجوده بس افهموا التصنيف

WHO Class الجرعة إلي بتقتل 50% من الفئران		LD50 for the rat (mg/kg body weight) ←	
		Oral	Dermal
Ia	Extremely hazardous خطورة شديدة جدا	< 5	< 50
Ib	Highly hazardous	5–50	50–200
II	Moderately hazardous	50–2000	200–2000
III	Slightly hazardous خطورة بسيطة	Over 2000	Over 2000
U	Unlikely to present acute hazard	5000 or higher	

* على قلت LD_{50} ← زادت الخطورة

Diagnosis of Pesticide Toxicity

كيف بشخصوا المصاب بتسمم المبيدات الحشرية؟

- **Exposure history (most important)**
  - Occupational and environmental history
  - Duration, dose, route of potential exposure
  - information about the patient's job, home use of chemicals, and proximity of residence to industrial sites, including agriculture
- **Symptom review**
  - Important to remember that symptoms may be caused by "**inert" ingredients** and therefore may not be typical of the active pesticidal ingredient in a **formulation**
- **Physical exam and lab findings**

بشغل — مدة التعرض — الجرعة — oral, inhalation, Dermal — باخذ معلومات عن الشغل والريف — اذا بستخدم مواد كيميائية بالبيت — اذا ساكن قريب من مصنع او مزرعة

Active مش inert ingredient ممكن الاعراض بسبب

الفحص السريري ، التحاليل المخبرية

بتوقع مش مطلوب خلص احفظه سكيب ☺

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

Ballantyne et al (ed.) *General and Applied Toxicology*, 1999

* كل الأنواع بتشتغل على CNS .

Insecticides

- All of the chemical insecticides in use today are **neurotoxicants**, and act by poisoning the nervous systems of the target organisms

- **Cholinesterase Inhibitors**
  - Carbamates
  - Organophosphates

- **Pyrethrins & Pyrethroids**

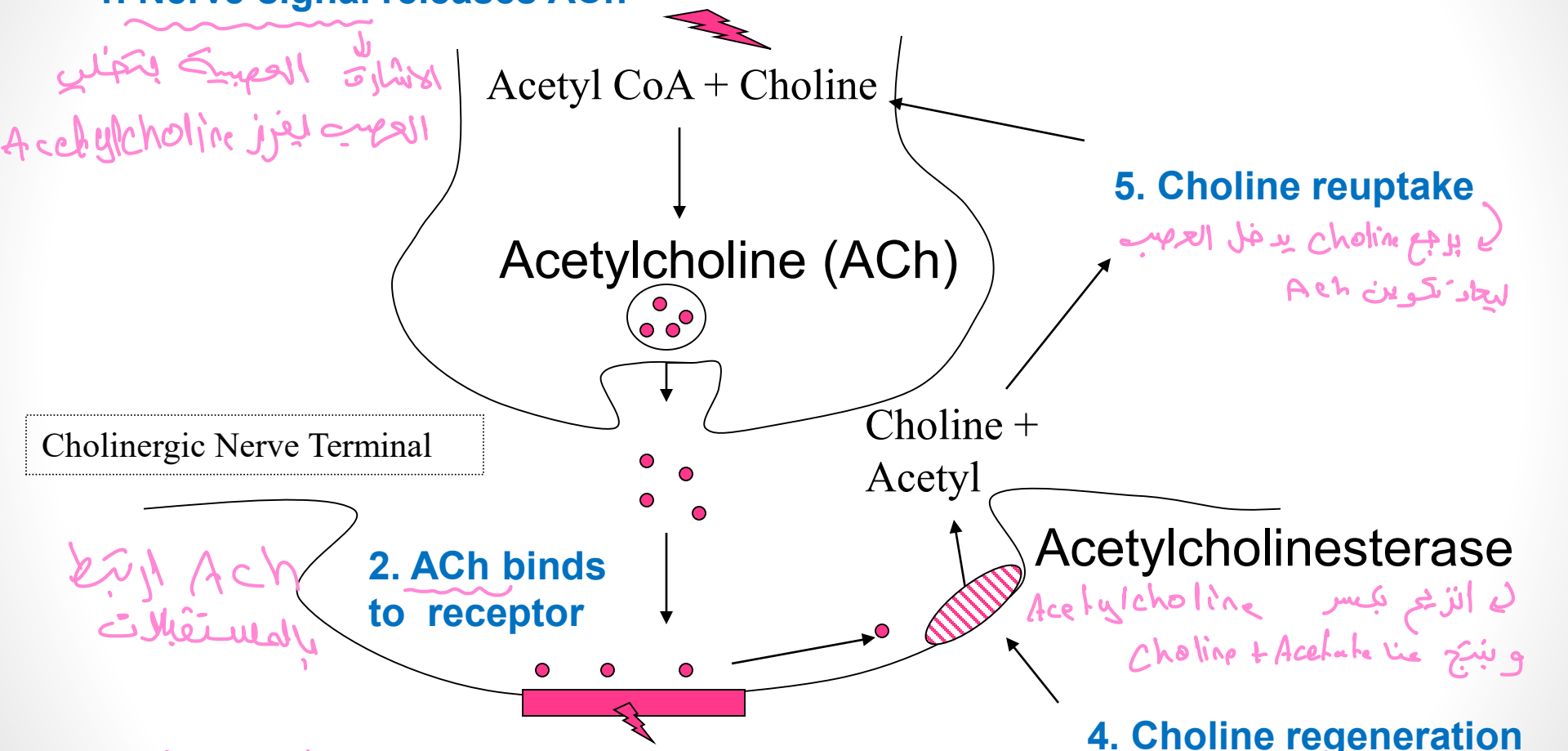
- **Organochlorines**

Cholinesterase Normal Function

* بالوضع الطبيعي

1. Nerve signal releases ACh

الاشارة العصبية بتخلي العصب يفرز Acetylcholine



5. Choline reuptake

يرجع choline يدخل العصب ليعاد تكوين Ach

الـ Ach ارتبط بالمستقبلات

2. ACh binds to receptor

Acetylcholinesterase

انزيم يكسر Acetylcholine وينتج عنه Choline + Acetate

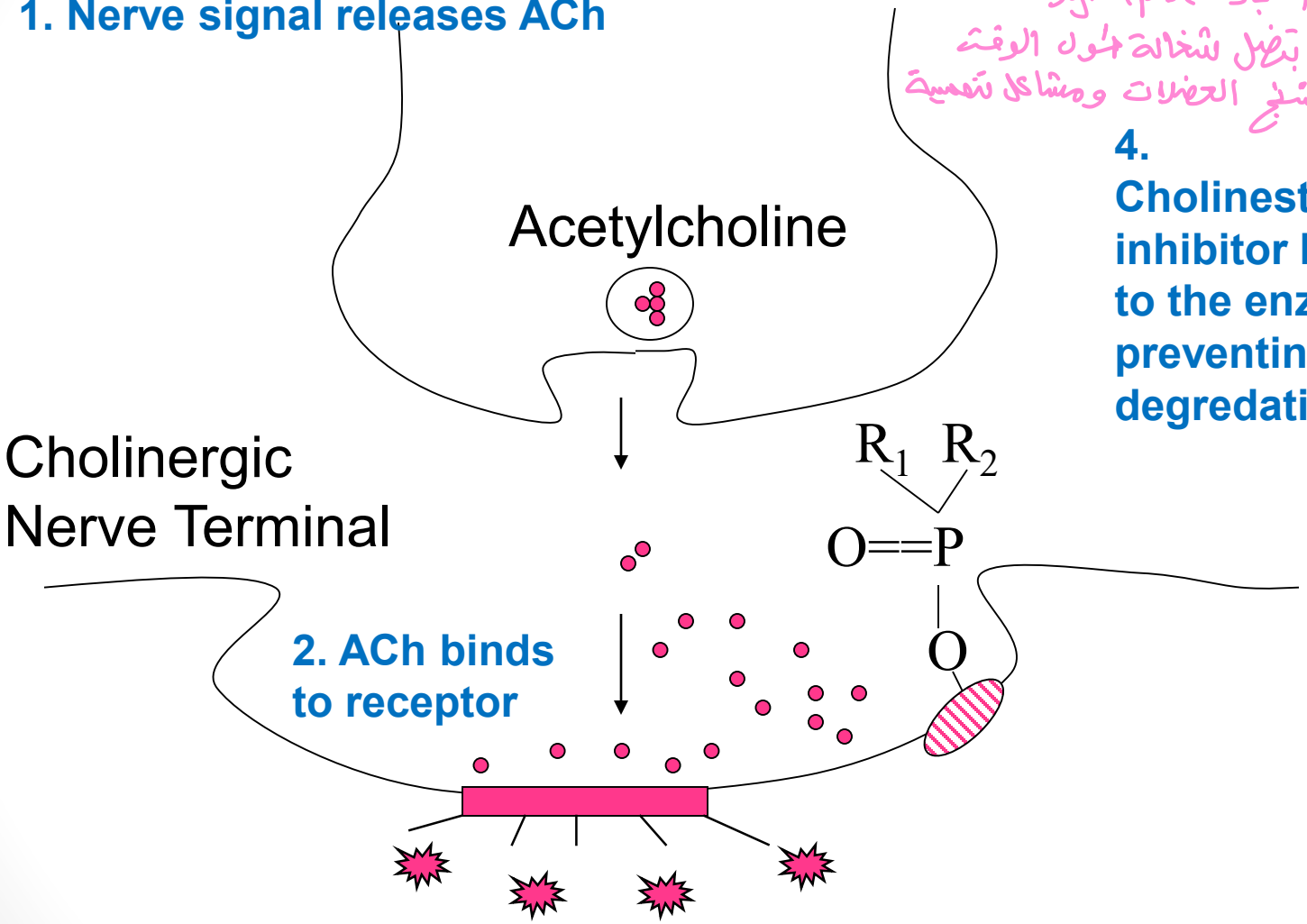
4. Choline regeneration by acetylcholinesterase

العضو يتحفز بسبب Ach

3. End organ activates in presence of acetylcholine

Inhibition of Cholinesterase

1. Nerve signal releases ACh



4. Cholinesterase inhibitor binds to the enzyme, preventing Ach degredation

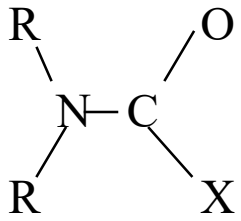
3. Activity of end organ does not cease

Cholinesterase Blood Tests

- Two cholinesterase enzymes
  - RBC, NMJ and neural synapses
    - "true"/ acetylcholinesterase
  - Plasma
    - "pseudo"/ butyrylcholinesterase

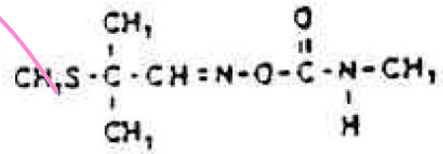
Insecticides: Cholinesterase Inhibitors

- **N-methyl Carbamates** (carbamic acid)
  - **Carbaryl, Carbofuran, Aldicarb**



Generic structure for N—methyl carbamates

- Dermal **skin penetration** by carbamates is **increased by organic solvents and emulsifiers** present in most formulations
- Carbamates inhibit AChE **reversibly**……susceptible to a variety of enzyme-catalyzed biotransformation reactions, (oxidation and hydrolysis)

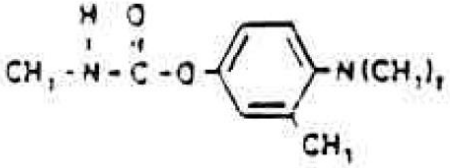


Aldicarb
(Temik)

Propanal, 2-methyl-2-(methylthio)-,
O-[(methylamino) carbonyl] oxime

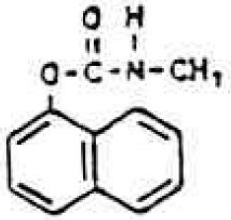
Bendiocarb
(Ficam)

1,3-Benzodioxol-4-ol, 2,2-dimethyl-,
methylcarbamate



Aminocarb
(Matacil)

Phenol, 4-(dimethylamino)-3-methyl-,
methylcarbamate



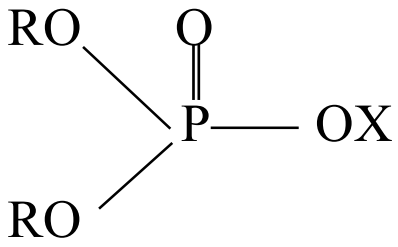
Carbaryl
(Sevin)

1-Naphthalenol, methylcarbamate

Names and chemical structures of some carbamate insecticides.

Insecticides: Cholinesterase Inhibitors

- **Organophosphates (OPs)**
  - **Chlorpyrifos, Diazinon, Malathion**



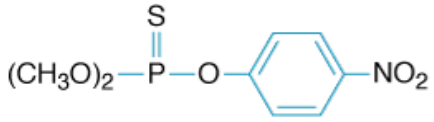
Generic structure for organophosphates

- Compounds that contain a **sulfur** bound to the **phosphorus**, **metabolic bioactivation is necessary** for their biological activity to be manifest…..only compounds with a **P=O** moiety are effective inhibitors of AChE

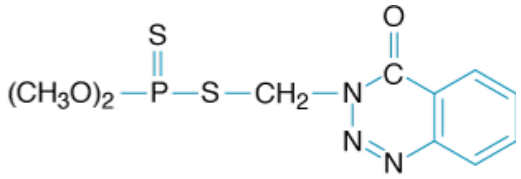
P=S

Sarin مثل

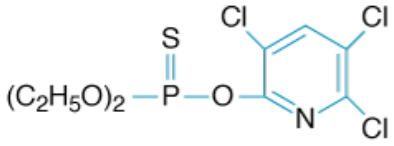
metabolic bioactivation يحتاج



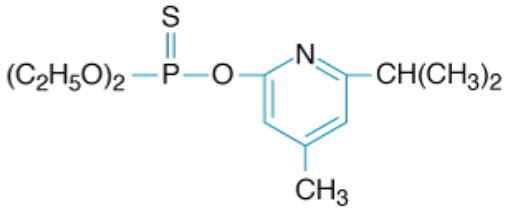
Methylparathion



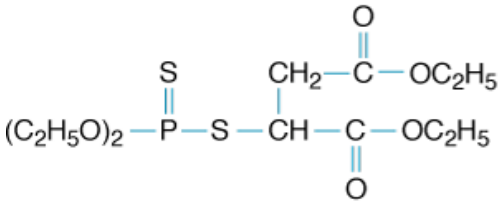
Azinphosmethyl (Guthion)



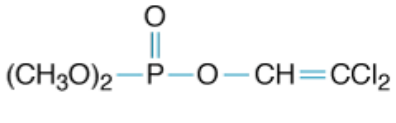
Chlorpyrifos



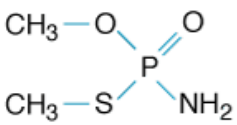
Diazinon



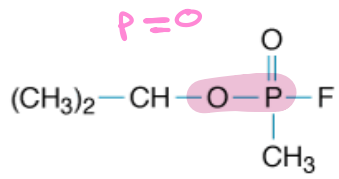
Malathion



Dichlorvos



Metamidophos



Sarin

- Structures of some organophosphorus insecticides and of the nerve agent sarin
- Most commonly used compounds are organophosphorothioates (i.e., have a P=S bond), but **some, including sarin, have a P=O bond and do not require metabolic activation**

Insecticides: organophosphate

- Phosphorylated AChE is hydrolyzed slowly, and the rate of "**spontaneous reactivation**" depends **on the chemical nature of the R substituents**

- When there is a loss of one of the two alkyl (R) groups, the enzyme-inhibitor complex has "**aged**" and reactivation of phosphorylated AChE does not occur

- The enzyme is considered to be **irreversibly inhibited, and synthesis of the new enzyme** is required to restore activity, a process that may take days

Table 22–4 Signs and symptoms of acute poisoning with anticholinesterase compounds.

Site and Receptor Affected	Manifestations
Exocrine glands (M)	Increased salivation, lacrimation, perspiration
Eyes (M)	Miosis
Gastrointestinal tract (M)	Abdominal cramps, vomiting, diarrhea
Respiratory tract (M)	Increased bronchial secretion, bronchoconstriction
Bladder (M)	Urinary frequency, incontinence
Cardiovascular system (M)	Bradycardia, hypotension
Skeletal muscles (N)	Muscle fasciculations, twitching, cramps, generalized weakness, flaccid paralysis
Central nervous system (M, N)	Dizziness, lethargy, fatigue, headache, mental confusion, depression of respiratory centers, convulsions, coma

M: muscurinic receptor
N: nicotininc receptor

Commonly-used Acronyms for Cholinesterase Inhibition Syndromes

DUMBLES

- Salivation
- Lacrimation
- Urination
- Diarrhea

- Defecation + Diarrhea
- Urination
- Miosis
- Bronchospasm
- Excessive salivation
- Lacrimation
- Salivation sweating

Treatment of Pesticide Intoxication

Decontamination (ABCD)

- Procedures aimed at decontamination and/or at minimizing absorption **depend on the route of exposure.**

نزع الملابس

- **Dermal exposure**: contaminated clothing should be removed, and the **skin washed with soap.** Scrub under fingernails

غسل الملابس بالصابون

الفحم النشط

غسيل المعدة

- **Ingestion**: administer **activated charcoal or gastric lavage in case of large ingestions, caution**: possibility of seizures or rapidly changing mental status

Specific Management for AChl Poisoning

- **Respiratory distress**: maintain **ABC;** Oxygen, bronchodilators if indicated
- **Atropine** (i.v), (**muscarinic receptor** antagonist), prevents the action of accumulating acetylcholine on these receptors
- Administration of **pralidoxime** (2-PAM) early after exposure can **help prevent AChE aging**
- **Diazepam** may be used to relieve **anxiety in mild cases, and control convulsions in the more severe cases**

Treatment: Atropine

- Reverses DUMBELS syndrome
- Give **atropine in escalating doses** until **clinical improvement is evident**. Begin with 2–5 mg IV initially
- Double the dose administered every 5 minutes until respiratory secretions have cleared.
- ***Note:*** Atropine will reverse **muscarinic** but not nicotinic effects

pralidoxime

2-PAM Treatment Regimen

loading dose → continuous infusion

- **Loading dose** (30–50 mg/kg, total of 1–2 g in adults) over 30 minutes
- followed by **a continuous infusion** of 8–20 mg/kg/h
- Most effective if **started early,** before aging
- but may still be effective if given **later,** particularly after exposure to **highly lipid-soluble compounds** released into the blood from fat stores over days to weeks
- Continue **pralidoxime for 24 hours after the patient becomes asymptomatic, or at least as long as atropine infusion is required**

Insecticides
① Pyrethrins & Pyrethroids

- Pyrethrins
  - **Natural** insecticides developed from extracts of the flower head of *Chrysanthemum cinerariaefolium*

زهرة الأقحوان

- Pyrethroids
  - **Synthetic** derivatives
  - Used with piperonyl butoxide to

Prolong their activity

زهرة الأقحوان

Pyrethroid Insecticides

- Pyrethroids now account **for >25% of the global insecticide market.**

  - ✓ High insecticidal potency
  - ✓ Relatively low mammalian toxicity (not well absorbed from skin and GIT),
  - ✓ low tendency to induce insect resistance.

- **used widely as insecticides in :**

  - ✓ in the house and in **agriculture**,
  - ✓ in medicine topically for Tx of **scabies and head lice**
  - ✓ in tropical countries as soaks to prevent **mosquito bites**

Pyrethrins & Pyrethroids

Mechanism of Toxicity

- They are **axonic poisons** and cause paralysis of an organism

بخلي قنوات الصوديوم مفتوحة لفترة

- The chemical causes paralysis by **keeping the sodium channels open** in the neuronal membranes of an organism

- Pyrethroids are rapidly **metabolized** through both phase I and phase II reactions (**hydrolysis and oxidation as well as conjugation)**

phase I

phase II

phase I

Pyrethroids Toxicity

- **Dermal contact** with pyrethroids is **paresthesia** (from a direct effect on cutaneous nerve endings)
- Symptoms include **continuous tingling & tickling** or, when more severe, **burning**
- **Ingestion** of large doses resulting in **seizures, coma, or respiratory arrest**.
- Chronic studies indicate that at high dose levels, they cause **slight liver enlargement** accompanied by some histopathologic changes
- Little evidence of teratogenicity and mutagenicity

Pyrethroid Toxicity Treatment

- Symptomatic relief
- Decontamination
- Topical application of vitamin E?? (in part due to sequestration of lipophilic pyrethroid into the vitamin E)
- administer activated charcoal orally
- **Enhanced elimination.** …no role…rapidly metabolized

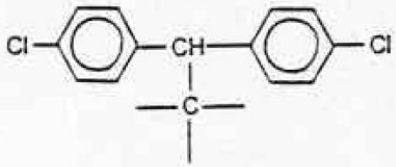
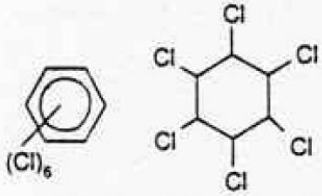
الخطيرين

(3) # Insecticides: **Organochlorines**

* مهم تحفظ الأسماء ولأي مجموعة تابعين

- Chlorinated ethane derivatives (DDT) (prototype)
- Cyclodienes (Chlordane, aldrin, dieldrin, heptachlor, endrin, toxaphene)
- Hexachlorocyclohexane (Lindane)

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 (*a*-BHC)

DDT and Its Analogs

- **DDT** effective against agricultural pests, and insects that transmit serious diseases (malaria & yellow fever)
- DDT has a **moderate oral acute toxicity** and its **dermal absorption is very limited**
- The earliest symptom DDT poisoning is **pyresthesia** of the mouth and lower part of the face
- **High doses** also causes **motor unrest, increased frequency of spontaneous movements, followed by the development of tremors, and eventually convulsions**

DDT and Its Analogs

- Both in insects and in mammals, DDT **interferes with the sodium channels in the axonal membrane** by a mechanism similar to that of pyrethroids
- An important target for chronic DDT exposure is the liver……**cause hepatic cell hypertrophy and necrosis**
- **Potent inducers of cytochrome P450s**
- Both **DDE** and **DDD** (**breakdown product),** are **carcinogenic** in rodents, causing primarily an increase in **hepatic tumors**

Hexachlorocyclohexanes and Cyclodienes

- These two families of **organochlorine insecticides** comprise a large number of compounds that share a similar mechanism of neurotoxic action
- **Lindane** and **cyclodienes** have moderate to high acute oral toxicity….readily absorbed through the skin
- The primary target for their toxicity is the **CNS**….. **binds to the chloride channel, blocking its opening** and **antagonizing GABA action**
- Tremor is absent, but **convulsions** are a prominent aspect of poisoning

Other Insecticides

Rotenoids At least six rotenoid esters (rotenone)

- Isolated from *Derris* root
- Toxicity due to its ability to inhibit, at nanomolar conc the **mitochondrial respiratory chain**
- Toxicity varies greatly in different species. يختلف السمية بين الانواع
- Low acute toxicity in humans, but causes allergic reactions.
- **Poisoning symptoms**: increased respiratory and cardiac rates, muscular depression, followed by respiratory depression

* مشاكل بالتنفس

Derris root

The main targets and classes of insecticides

بوضح اماكن تأثير insecticides على العشبك العصبي.