Pesticides

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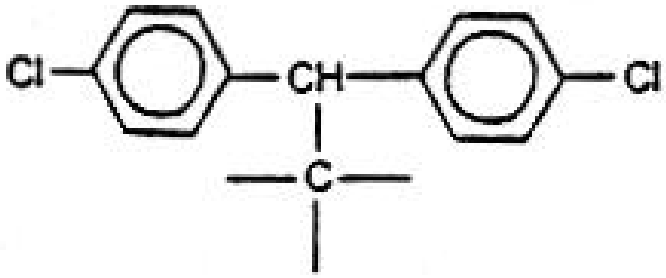
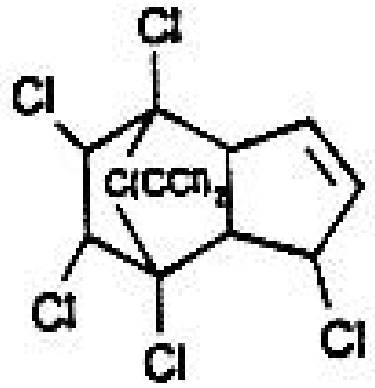
Program in Toxicology
NURS 678 - Applied Toxicology
February 27, 2002



Dichlorodiphenylethanes



Cyclodienes

Pesticides are chemicals that are used to kill pests:

Insecticides target harmful or destructive insects
Herbicides target weeds
Fungicides target fungi
Rodenticides target rodents
Acaricides target acarose (mites)

Chemical structures differ within categories as well as between categories. Thus toxicity to humans can vary widely within each group.

Pesticide Use: An Old Practice

1000 BC	**Chinese used sulfur as a fumigant**
1800s	**Europeans used sulfur as a fungicide to control powdery mildew on fruit**
2001	**Sulfur still used in California today**

16th century	**Japanese mixed poor quality whale oil with vinegar to spray on rice paddies to prevent development of insect larvae by weakening the cuticle**
17th century	**Water extracts of tobacco leaves were sprayed on plants to kill insects**
	Nux vomica, the seed of *Strychnos nuxmomica* (strychnine) used to kill rodents

Pesticide Use: An Old Practice

19th century

Insecticides isolated from plants included rotenone from the root of *Derris eliptica* and pyrethrum extracted from flowers of chrysanthemums

Arsenic trioxide used as a weed killer, esp. dandelions

Copper arsenite (Paris Green) used for control of Colorado beetle

Bordeaux mixture (copper sulfate, lime and water) used to combat vine downy mildew

Pesticide Use: An Old Practice

20th century	**Sulfuric acid (10%) used to destroy dicotyledonous weeds without harming monocotyledonous cereal grains and other cultivated plants with waxy coat on leaves**
1920s	**Public concern because some treated fruits and vegetables were found to contain pesticide residues**
Post WWII	**Pesticide development and use increased dramatically in agriculture and public health.**
	Widespread use of pesticides for insect control to prevent transmission of diseases such as typhus, river blindness and malaria
	Need to make risk/benefit decisions

Toxicity of Pesticides

Must remember that pesticides are inherently toxic.

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

Table 22–13
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	—	—

SOURCE: From Copplestone, 1988.

WHO (1990) estimated 3 million cases of acute, severe poisonings annually, with 220,000 deaths.

In U.S. - 80,000 cases/year. Primarily agricultural workers

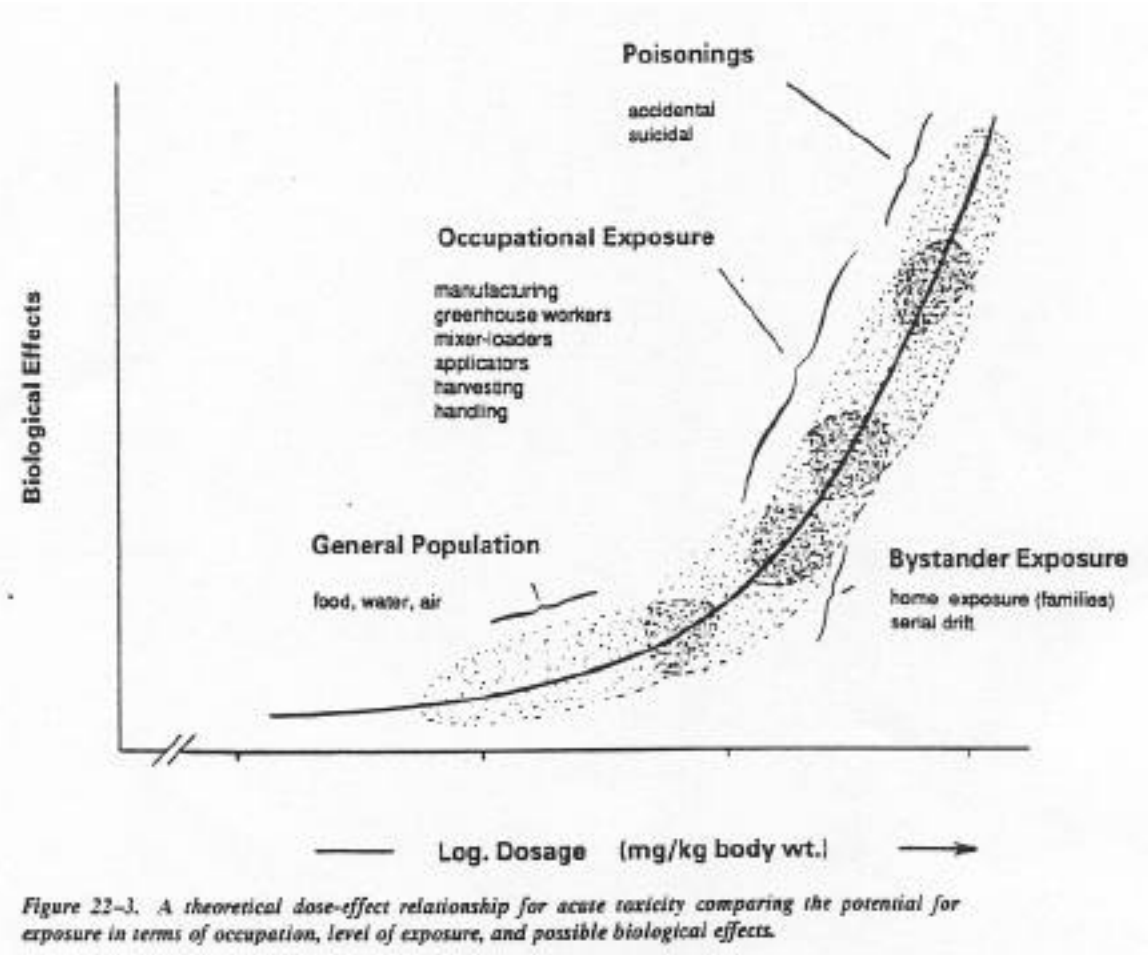


Figure 22–3. A theoretical dose-effect relationship for acute toxicity comparing the potential for exposure in terms of occupation, level of exposure, and possible biological effects.

Basic Classes of Pesticides

Insecticides

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

Herbicides

- **Chlorophenoxy compounds**
- **Bipyridyl derivatives**

Rodenticides

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

Fungicides

- **Hexachlorobenzene**
- **Organomercurials**
- **Pentachlorophenol**
- **Phthalimides**
- **Dithiocarbamates**

Fumigants

- **Phosphine**
- **Ethylene dibromide**
- **Dibromochloropropane**

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

Insecticides

Insecticides act by poisoning the nervous system of target organisms - including man if dose is sufficiently high!

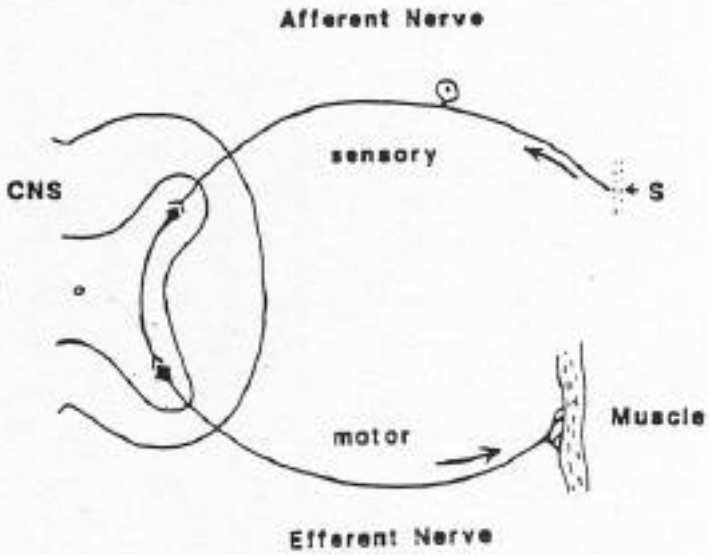


Figure 22–5. A simple, intact reflex arc involving a peripheral, afferent (sensory) neuron, interneurons in the CNS, and a peripheral, efferent (motor) neuron that innervates a muscle.

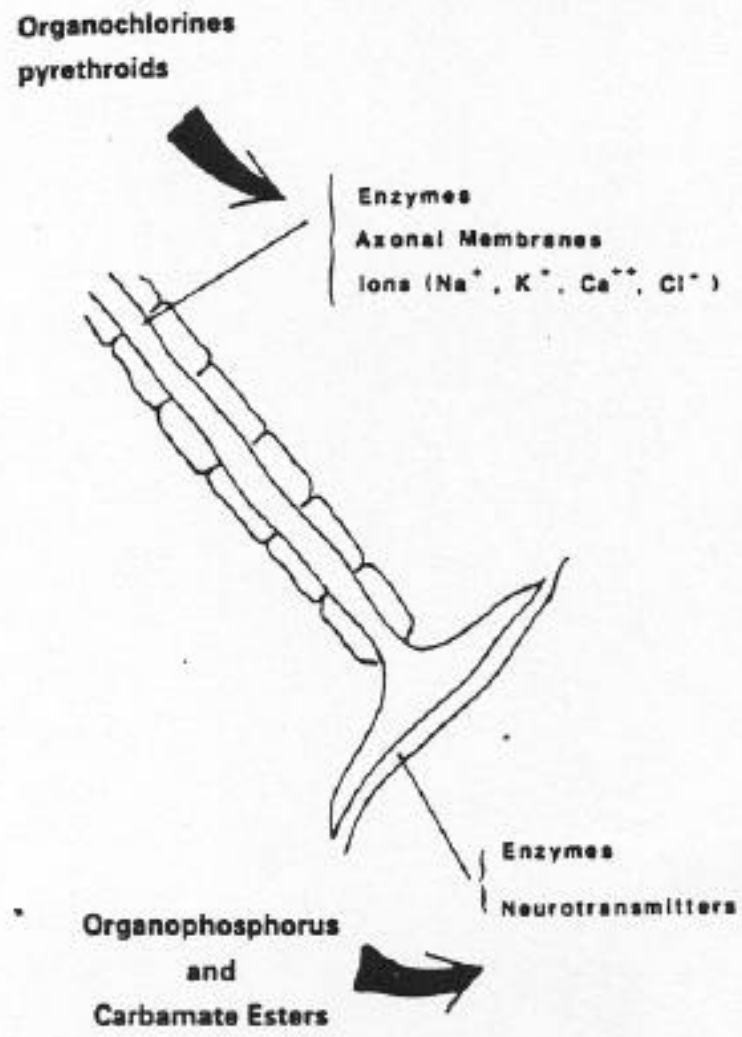
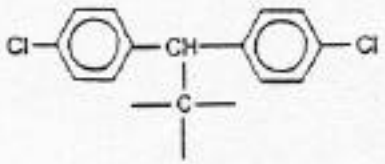
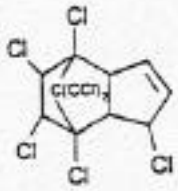
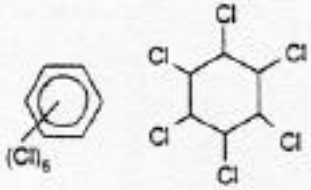


Figure 22–4. Potential sites of action of classes of insecticides on the axon and the terminal portions of the nerve.

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 Toxicity

Acute:

- **DDT produces tremors and incoordination at low doses and convulsions at higher doses through effects on Na channels**

- **HCH and cyclodienes produce convulsions as first sign of intoxication, and fever, through a central nervous system effect - possibly through disturbances in GABA-mediated inhibitory transmission.**

Chronic:

- **Apathy, headache, emotional lability, depression, confusion and irritability**

Carcinogenicity:

- **OCs have been weakly linked with non-Hodgkin's lymphoma**

Organochlorine: DDT

DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl)ethane

- **First synthesized in 1874**
- **Used to kill moths and carpet beetles in 1939**
- **Used on humans to control typhus epidemic by killing lice in Italy in winter of 1943-1944**
- **Used extensively from 1940s to 1960s in:**
  agriculture and forestry
  building and structural protection from termites
  disease prevention in humans

Organochlorine: DDT

Mammalian Toxicity:

- **DDT is a Class II pesticide: Oral LD_{50} is 250 mg/kg**
- **As little as 10 mg/kg will produce signs of poisoning in man**
- **DDT causes repetitive discharge of axonal action potentials in response to a single stimulus**

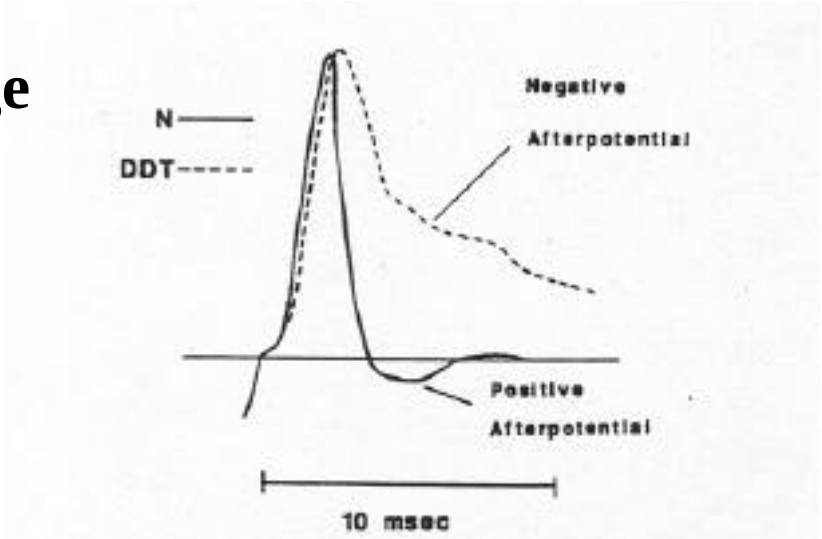


Figure 22–6. A schematic diagram of an oscilloscope recording of the depolarization and repolarization of a normal neuron (—— and one from a DDT-treated animal (- - - -), showing the prolongation of the negative afterpotential (NAP).

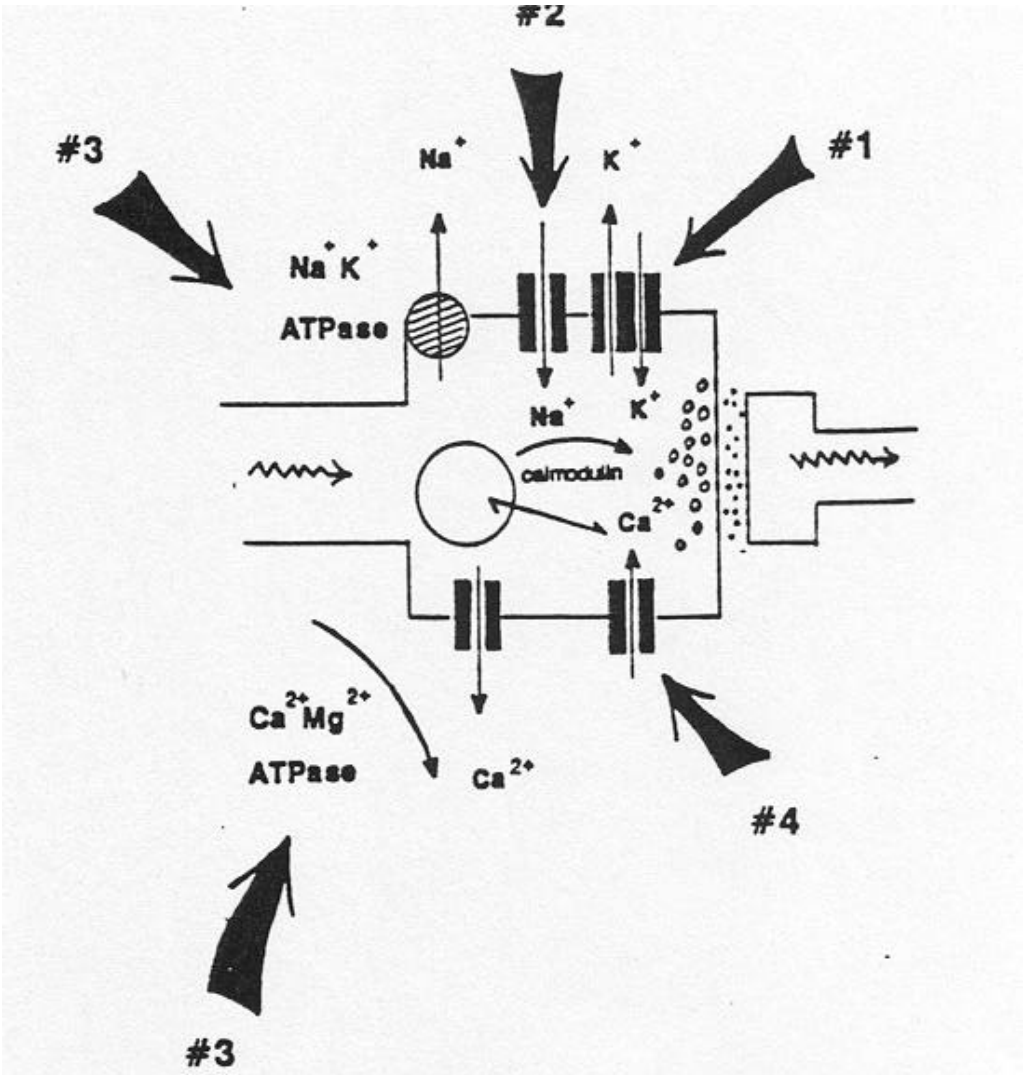


Figure 22–7. Proposed sites of action of DDT on (1) reducing p tassium transport through pores; (2) inactivating sodium chann closure; (3) inhibiting sodium-potassium and calcium-magnesiu ATPases; and (4) calmodulin-calcium binding with release of neur transmitter.

TABLE 79–1. CATEGORIES OF ORGANOCHLORINE PESTICIDES AND TOXIC POTENTIAL

	ACUTE ORAL TOXICITY
DDT and analogs	
DDT	Low to moderate
Methoxychlor	Low
Benzene hexachloride	
Gamma-hexachlorobenzene (Lindane)	Moderate
Cyclodienes and related compounds	
Aldrin	High
Chlordane	Moderate
Chlordecone (Kepone)	Moderate
Dieldrin	High
Endosulfan (Thiodan)	High
Endrin	High
Heptachlor	Moderate
Isobenzan	High
Mirex (Dechlorane)	Low
Toxaphene and related compounds	
Toxaphene	Moderate

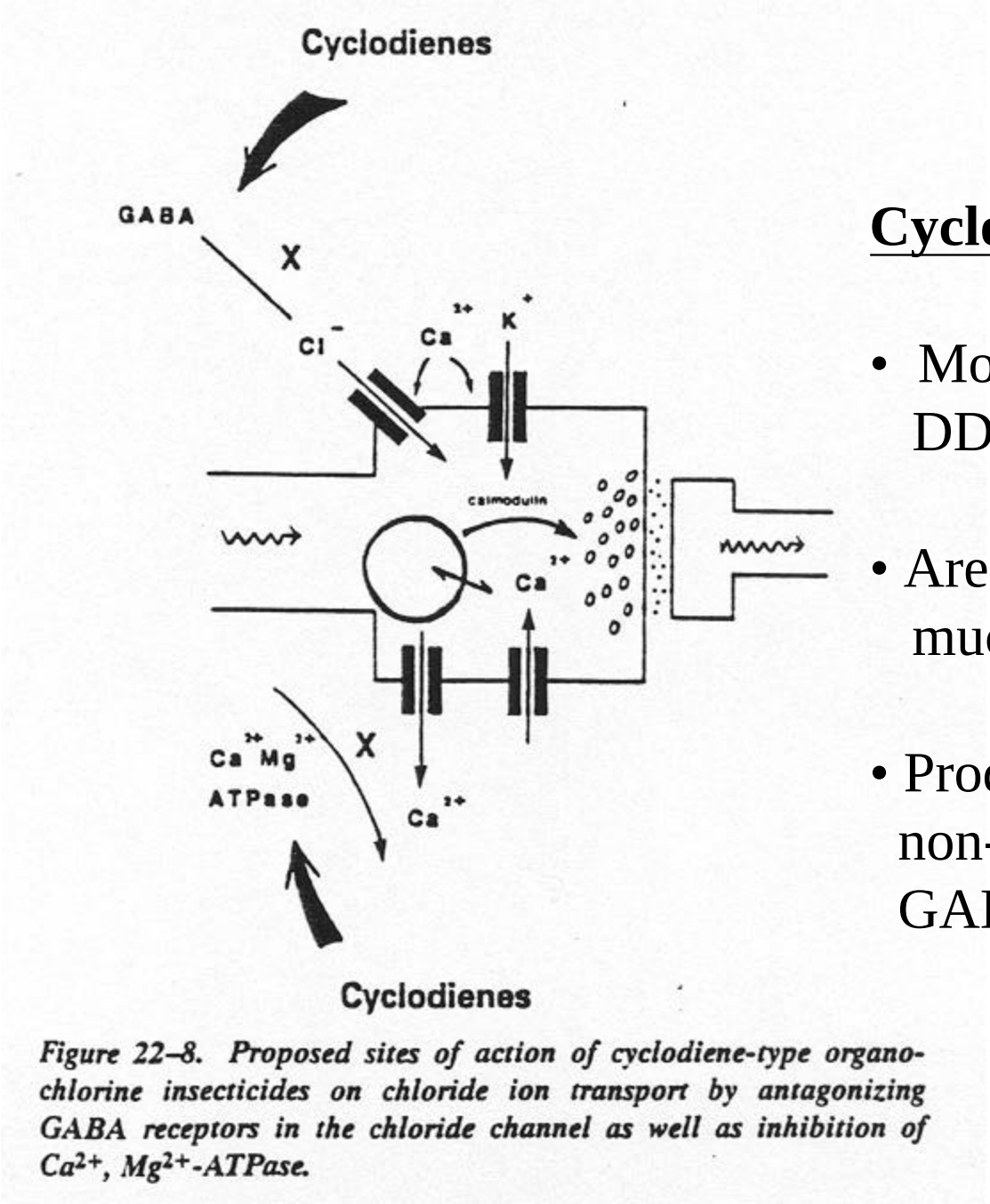


Figure 22–8. Proposed sites of action of cyclodiene-type organochlorine insecticides on chloride ion transport by antagonizing GABA receptors in the chloride channel as well as inhibition of Ca^{2+}, Mg^{2+}-ATPase.

Cyclodienes and BHC (Lindane)

- More toxic to mammals than DDT
- Are absorbed through skin to a much greater extent than DDT
- Produce convulsions by acting as non-competitive antagonist of GABA receptors in CNS

Kepone (Chlordecone)

Occupational exposure occurred from mishandling in plant in Hopewell, VA in 1975

76 of 148 workers developed a neurological syndrome called “Kepone shakes”

Latency of onset - 30 days

Persistent for months after cessation of exposure

Pathology: Damage to Swann cells which caused abnormal myelination

Major target organs: CNS, liver, adrenals, testes

Environmental Problems with Organochlorine Pesticides

Chemical Properties: **low volatility**
chemical stability
lipid solubility
slow biotransformation and degradation

Good qualities for pesticides = Bad environmentally

Persistent, Bioconcentrate, Biomagnify

Environmental Problems with Organochlorine Pesticides

Ecological Effects: Interference with reproductive success of organisms high on the food chain, especially fish eating birds (osprey, pelicans, falcons and eagles)

Ortho and para isomers of DDT have estrogenic effects: compete with estradiol for binding to estrogen receptors in uterine cytosol

Estrogenic and enzyme inducing properties of DDT cause changes in steroid metabolism. Alters ability of birds to mobilize Ca to produce strong egg shells

Environmental Problems with Organochlorine Pesticides

Organochlorine pesticides now banned in North America and Europe, but still used in developing countries because:

- **inexpensive to manufacture**
- **highly effective**
- **relatively safe to humans**

Risk/benefit weighted in favor of control of insects for better food production and disease control

Acetylcholinesterase Inhibitors: Organophosphates and Carbamates

Ecological toxicity ⇩

Human toxicity ⇧

Degrade relatively rapidly in the environment, **but** Class I toxicity rating in humans.

Many fatal poisonings in 1950s as parathion replaced DDT due to improper training of pesticide applicators

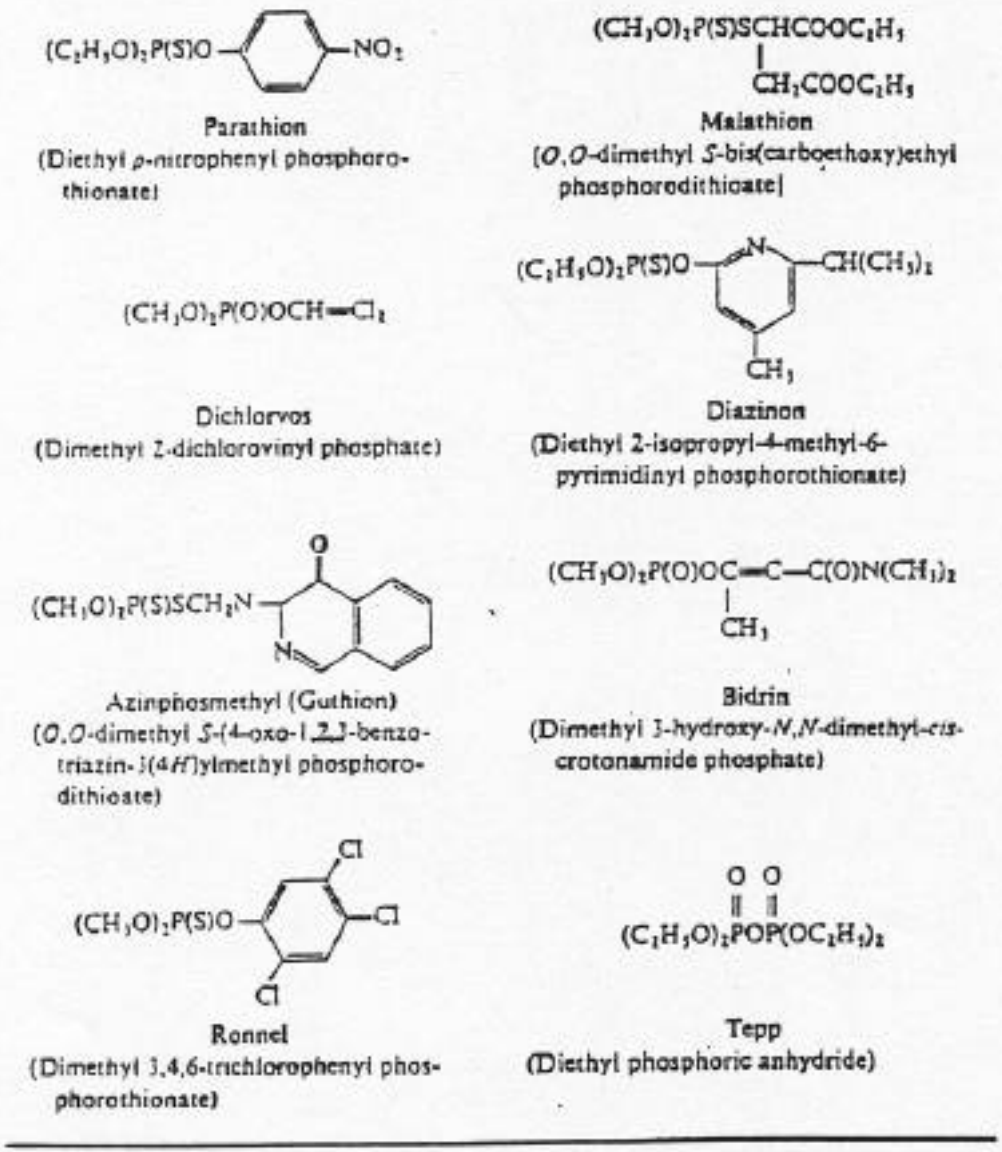
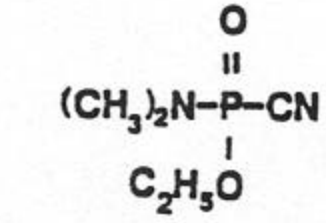
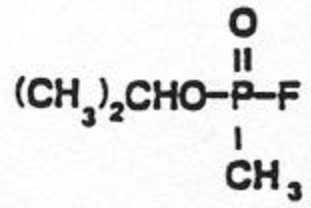


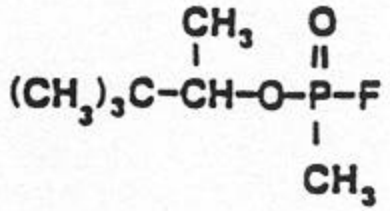
Fig. 2. Names and chemical stuctures of some common organophosphorus insecticides.



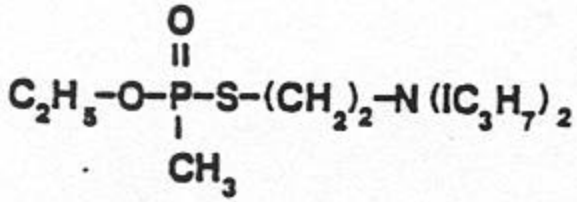
Tabun (GA)



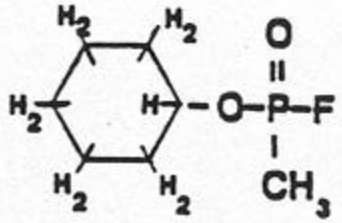
Sarin (GB)



Soman (GD)



VX

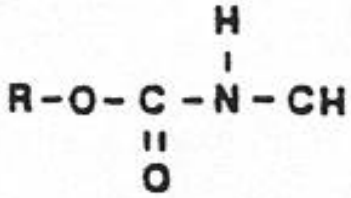


CMPF (GF)

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

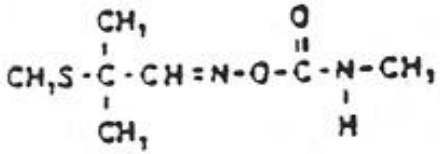
Organophosphorus Esters

Carbamate Esters



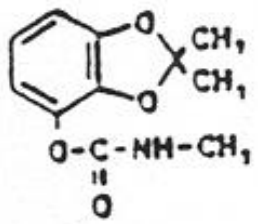
X, Y	alkyl, alkoxy, amido	Z	aryl, alkyl, alkoxy	R	aryl, alkyl

Figure 22–10. The basic backbone structures of the two types of anticholinesterase class insecticides, the organophosphorus and the carbamate esters.



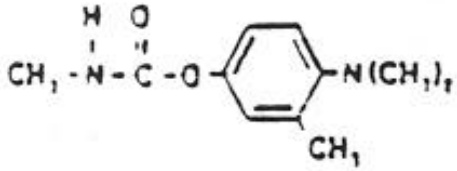
Aldicarb
(Temik)

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



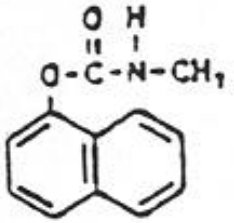
Bendiocarb
(Ficam)

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



Aminocarb
(Matacil)

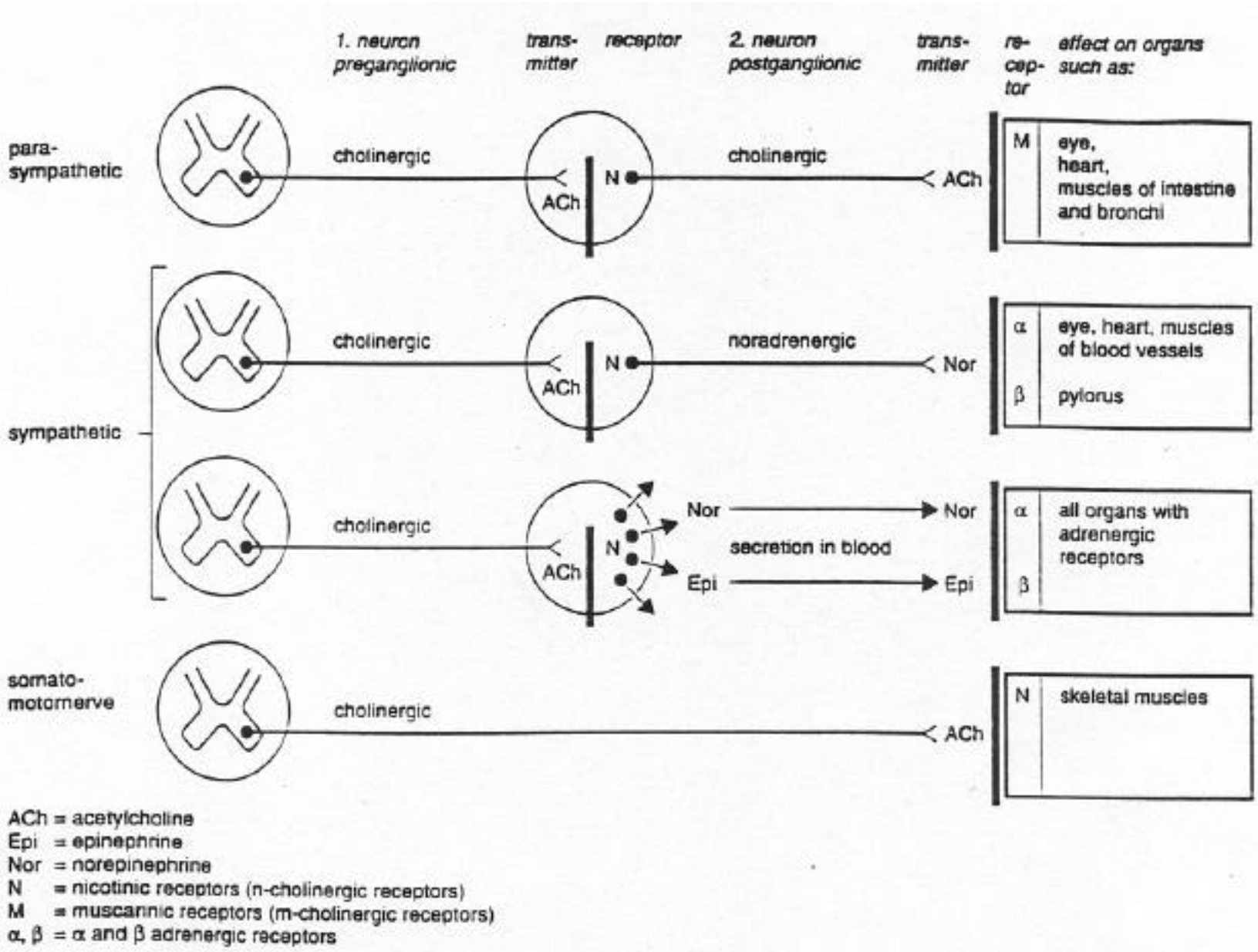
Phenol, 4-(dimethylamino)-3-methyl-,
methylcarbamate



Carbaryl
(Sevin)

1-Naphthalenol, methylcarbamate

Names and chemical structures of some carbamate insecticides.



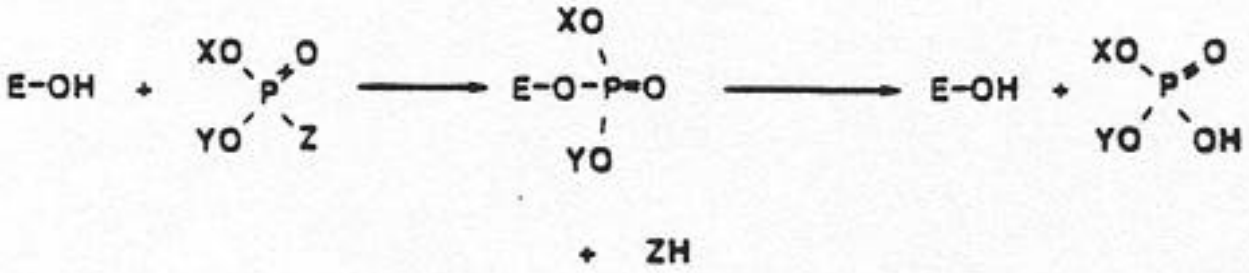
ACh = acetylcholine
Epi = epinephrine
Nor = norepinephrine
N = nicotinic receptors (n-cholinergic receptors)
M = muscarinic receptors (m-cholinergic receptors)
α, β = α and β adrenergic receptors

Signs and Symptoms of Anticholinesterase Insecticide Poisoning

NERVOUS TISSUE AND RECEPTORS AFFECTED	SITE AFFECTED	MANIFESTATIONS
Parasympatheic autonomic (muscarinic receptors) postganglionic nerve fibers	Exocrine glands	Increased salivation, lacrimation, perspiration
	Eyes	Miosis (pinpoint and nonreactive), ptosis, blurring of vision, conjunctival injection, "bloody tears"
	Gastrointestinal tract	Nausea, vomiting, abdominal tightness, swelling and carmps, diarrhea, tenesmus, fecal incontinence
	Respiratory tract	Excessive bronchial secretions, rhinorrhea, wheezing, edema, tightness in chest, bronchospasms, broncho-constriction, cough, bradypnea, dyspnea
	Cardiovascular system	Bradycardia, decrease in blood pressure
	Bladder	Urinary frequency and incontinence
Parasympathetic and sympathetic autonomic fibers (nicotinic receptors)	Cardiovascular system	Tachycardia, pallor, increase in blood pressure
Somatic motor nerve fibers (nicotine receptors)	Skeletal muscles	Muscle fasciculations (eyelids, fine facial muscles), cramps, diminished tendon reflexes, generalized muscle weakness in peripheral and respiratory muscles, paralysis, flaccid or rigid tone
		Restlessness, generalized motor activity, reaction to acoustic stimuli, tremulousness, emotional lability, ataxia
Brain (acetylcholine receptors)	Central nervous system	Drowsiness, lethargy, fatigue, mental confusion, inability to concentrate, headache, pressure in head, generalized weakness
		Coma with absence of reflexes, tremors, Cheyne-Stokes respiration, dyspnea, convulsions, depression of respiratory centers, cyanosis

SOURCE: From Ecobichon and Joy, 1982.

Organophosphorus Ester



Carbamate Ester

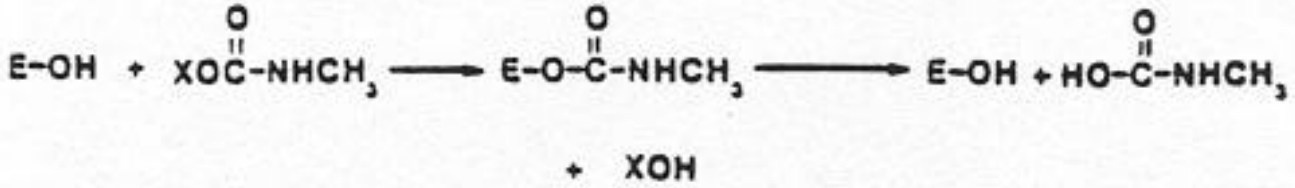
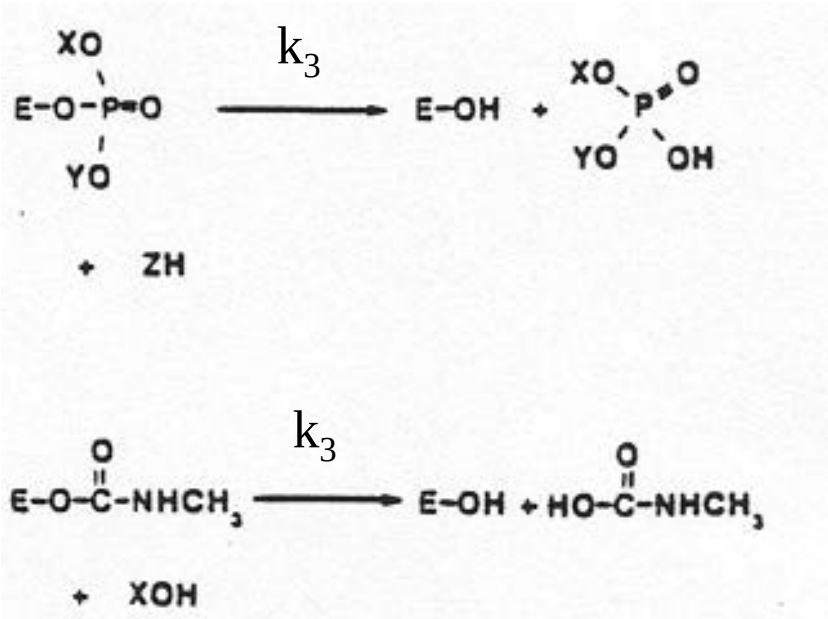


Figure 22–13. The interaction between an organophosphorus or carbamate ester with the serine hydroxyl group in the active site of the enzyme acetylcholinesterase (E-OH).

The intermediate, unstable complexes formed before the release of the "leaving" groups (ZH and XOH) are not shown. The dephosphorylation or decarbamoylation of the inhibited enzyme is the rate-limiting step to forming free enzyme.

Reversible versus Non-reversible Effects



Rate at which pesticide molecule leaves the enzyme active site is proportional to it toxicity.

k_3

k_3 = sec for acetylcholine

= 30 min for carbamates

= 17 hr for organophosphate

"Aging" of the enzyme/pesticide complex is also possible with organophosphates. With time a covalent bond is formed, making the inhibition of the enzyme activity permanent

Treatment of Acetylcholinesterse Insecticide Poisoning

Table 22–9
Classification and Treatment of Organophosphorus Insecticide Poisoning Based on Plasma Pseudocholinesterase Activity Measurements

ASSIFICATION OF POISONING	ENZYME ACTIVITY (% OF NORMAL)	TREATMENT	
		ATROPINE	PRALIDOXIME
Mild	20–50	1.0 mg SC	1.0 g IV over 20 to 30 min
Moderate	10–20	1.0 mg IV every 20 to 30 min until sweating and salivation disappear and slight flush and mydriasis appear	
Severe	10	5.0 mg IV every 20 to 30 min until sweating and salivation disappear and slight flush and mydriasis appear	1.0 g IV as above. If no improvement, administer another 1.0 g IV. If no improvement, start IV infusion at 0.5 g/h

RCE: From Ecobichon et al., 1977.

Treatment with atropine counteracts muscarinic effects

Pralidoxime given in the case of organophosphates to prevent aging of the enzyme/pesticide complex

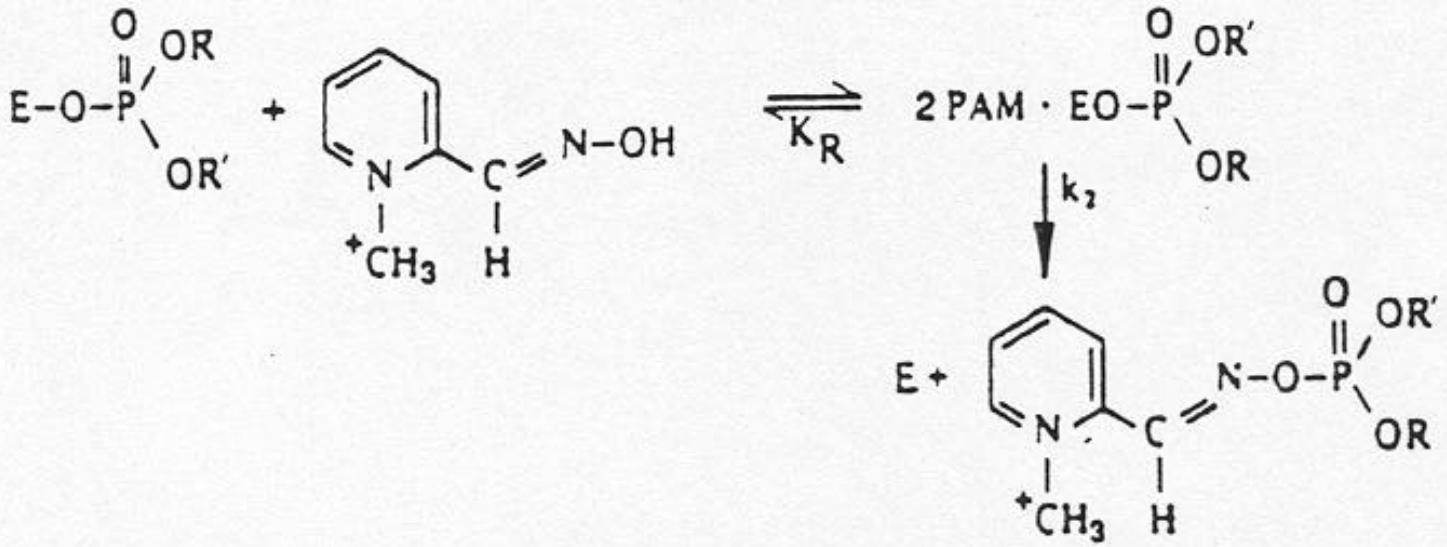


Figure 22–18. The pralidoxime-catalyzed reactivation of an organophosphate-inhibited molecule of AChE, showing the release of active enzyme and the formation of an oxime-phosphate complex.

Pyrethroid Insecticides

Synthetic pyrethroids available in the 1980s rapidly accounted for 30% of the worldwide market due to lower toxicity

Replaced natural pyrethroid preparations which often caused allergic reactions such as contact dermatitis or asthma

Pyrethroids fall into two categories based on their acute toxicity:

- **Type I Peripheral and CNS effects**
- **Type II Primarily CNS effects**

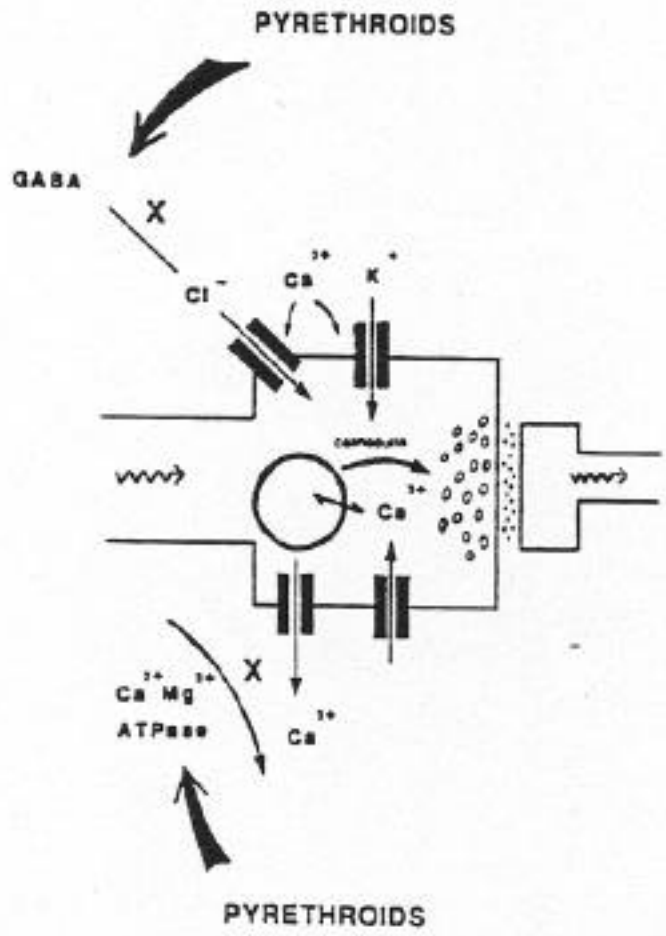
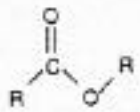
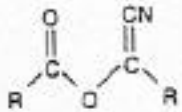


Figure 22–20. Proposed cellular mechanisms by which pyrethroid esters interfere with neuronal function.

These are (1) by inhibition of Ca^{2+}, Mg^{2+}-ATPase, thereby interfering with calcium removal from the ending; (2) questionable binding to GABA receptors in the chloride channel; (3) inhibition of calmodulin that binds calcium ions, thereby increasing the levels of free calcium in the nerve ending to act on neurotransmitter release.

Table 22–10
Classification of Pyrethroid Ester Insecticides on the Basis of Chemical Structure and Observed Biological Activity

	STRUCTURE	SIGNS AND SYMPTOMS		CHEMICALS
		COCKROACH	RAT	
Type I syndrome ("T" syndrome)		Restlessness Incoordination Prostration Paralysis	Hyperexcitation Sparring Aggressiveness Enhanced startle response Whole body tremor Prostration	Pyrethrin I Allethrin Tetramethrin Kadethrin Resmethrin Phenothrin Permethrin
Type II syndrome ("CS" syndrome)		Hyperactivity Incoordination Convulsions	Burrowing Dermal tingling Clonic seizures Sinuous writhing Profuse salivation	Cypermethrin Fenpropanthrin Deltamethrin Cyphenothrin Fenvalerate Fluvalinate

Pyrethroid Insecticides

Human toxicity:

- **Cutaneous paresthesia observed in workers spraying -cyano type pyrethroid. Stinging or burning sensation on skin, progressing to tingling and numbness lasting 12-18 hr**

- **Occupational exposure has result in dizziness in addition burning skin. At higher doses, can develop convulsions and loss of consciousness. Seizures can last up to 2 to 3 weeks.**

Metabolism of Pyrethroid Insecticides:

- **Low toxicity in large part due to rapid metabolism**
- **Hydrolytic enzymes (non-specific carboxyl esterases) deactivate pyrethroid compounds**
- **Toxicity to insects is often increased by addition of piperonyl butoxide, a monooxygenase inhibitor. This enhances potency 10 to 300 fold.**

Botanical Insecticides

Nicotine

Bold as Black Leaf 40
Extremely toxic: Oral LD_{50} is 50-60 mg/kg
Is readily absorbed through skin
`
Mimics the action of acetylcholine

Retinoids

Isolated from derris root
Toxicity varies greatly in different species
Very toxic to fish - Used to paralyze fish for capture and consumption
Blocks nerve conduction by inhibiting electron transport in mitochondria
Low acute toxicity in humans, but causes allergic reactions

Herbicides

- **Generally low toxicity to mammals.**
- **Mechanisms of action toward plants primarily involve phyto-processes.**
- **Can be dermal irritants since often strong acids, amines, esters and phenols.**
- **Can cause contact dermatitis in sub-populations of sensitive people.**

Herbicides

Chlorophenoxy Compounds: Mimic the action of auxins, plant hormones that stimulate growth

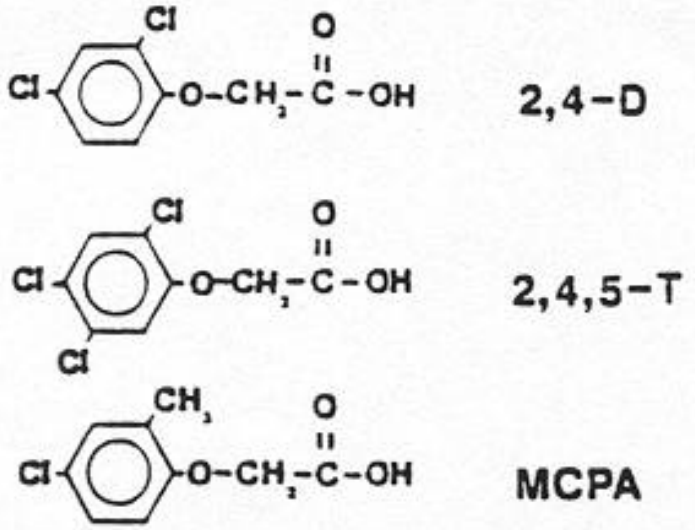


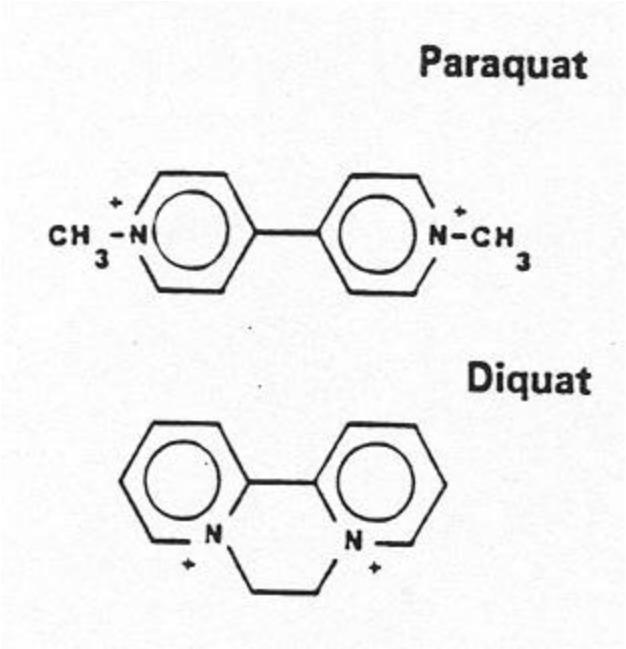
Figure 22–21. The molecular structure of the three most common chlorophenoxyacetic acid herbicides: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; and MCPA, 4-chloro-o-toloxyacetic acid.

Herbicides

Bipyridyl Derivatives

Paraquat is a very potent, specific pulmonary toxicant

Diquat is much less toxic



Differential toxicity based on uptake:

Paraquat is preferentially accumulated by Type I and Type II alveolar cells by a diamine/polyamine transport system. Diquat is not.

In alveolar cells, paraquat under goes NADPH-dependent one-electron reduction to form a free radical

Exposure causes intra-alveolar hemorrhage, congestion and pulmonary fibrosis

Fungicides

Acute toxicity generally very low in mammals:

LD_{50} range from 800-10,000 mg/kg

However, most (>90%) fungicides test positive in mutagenicity assays, raising concerns about carcinogenicity

Fungicides

Most cases of human poisonings have resulted from consumption of feed grain.

Hexachlorobenzene: Caused "black sore" syndrome in Turkey

Dermal blistering and epidemolysis, infection with pigmented scars and photosensitivity.

Rats show evidence of immunosuppression and dose-dependent increase in hepatic and thyroid tumors. Also perinatal exposure caused enlarged kidneys, hepatomegaly and possible immune system effects

Fungicides

Organomercurials: Used to treat seed grain

Peripheral and central nervous system effects seen in two cases:

Iraq - people consumed seed grain

New Mexico - people consumed meat from hogs fed treated grain

Fungicides

Phthalimides:

Low acute toxicity, but similar in structure to thalidomide

Captan is a weak initiator of benign squamous cell papillomas

Dithiocarbamates:

Low acute toxicity, but teratogenic and causes tumors in animals.

Suggestion that exposure can cause Parkinson-type syndrome. Possible breakdown to carbon disulfide which is a known neurotoxicant

Fumigants

Fumigants are highly reactive, non-specific toxicants, so potential for human toxicity is high

Phosphine:

Aluminum phosphide (AP) releases phosphine (PH_3) when in contact with moisture. Accidental exposure causes pulmonary irritation, nausea, headache, jaundice and fatigue.

Ethylene Dibromide/Dibromochloropropane (DBCP):

Causes pulmonary edema and inflammation at > 200 ppm
Repeated exposures causes hepatic and renal damage
Chronic exposure causes malignant gastric squamous cell carcinomas in mice and sterility in humans at 5 ppm