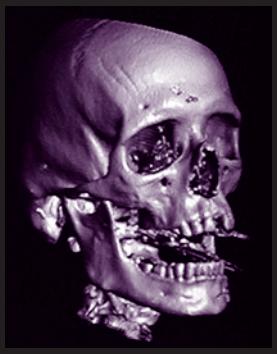

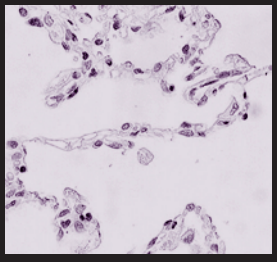

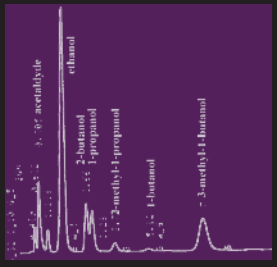

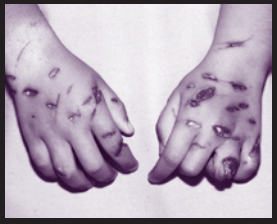

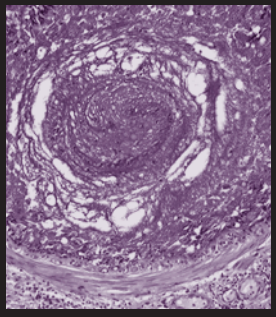

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10

Agrochemical Poisoning

Anil Aggrawal, MBBS, MD

CONTENTS

SUMMARY

A general increase in the use of chemicals in agriculture has brought about a concomitant increase in the incidence of agrochemical poisoning. Organophosphates are the most common agrochemical poisons followed closely by herbicides. Many agricultural poisons, such as parathion and paraquat are now mixed with a coloring agent such as indigocarmine to prevent their use criminally. In addition, paraquat is fortified with a "stenching" agent. Organochlorines have an entirely different mechanism of action. Whereas organophosphates have an anticholinesterase activity, organochlorines act on nerve cells interfering with the transmission of impulses through them. A

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kerosene-like smell also emanates from death due to organochlorines. The diagnosis lies in the chemical identification of organochlorines in the stomach contents or viscera. Organochlorines also resist putrefaction and can be detected long after death. Paraquat has been involved in suicidal, accidental, and homicidal poisonings. It is mildly corrosive and ulceration around lips and mouth is common in this poisoning. However, the hallmark of paraquat poisoning, especially when the victim has survived a few days, are the profound changes in lungs. Other agrochemicals such as algicides, aphicides, herbicide safeneres, fertilizers, and so on, are less commonly encountered. Governments in most countries have passed legislations to prevent accidental poisonings with these agents. The US government passed the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) in 1962 and the Indian government passed The Insecticides Act in 1968. Among other things, these acts require manufacturers to use signal words on the labels of insecticides, so the public is warned of their toxicity and accompanying danger.

Key Words: Agrochemical poisoning; rodenticides; insecticides; organophosphates; carbamates; organochlorines; fungicides.

1. INTRODUCTION

Early humans are believed to have started agriculture around 9000 BCE. As the knowledge of chemistry grew, so did the use of chemicals in agriculture. Today, chemicals are used in agriculture for three main purposes: to increase farm production (fertilizers and related chemicals), to kill pests (pesticides), and to preserve farm products (preservatives). Unfortunately, all three classes of chemicals can cause serious poisoning in humans, mainly through improper labeling, storage, or use.

Most poisonings with agrochemicals occur in predominantly agricultural economies where a lack of hygiene, information, or adequate control creates unsafe and dangerous working conditions. Cases of such poisonings also occur in small factories where pesticides are manufactured or formulated with little respect for safety requirements.

Accidental poisonings may also take place at home when pesticides are mistaken for soft drinks or food products, and often the victims are curious children who can easily reach pesticides if they are not kept safely away from them. Then, there are the intentional poisonings, where compounds, such as phosphorus, arsenic, paraquat, organophosphates, and strychnine, are used as agents for suicidal or even homicidal purposes. This may happen because these chemicals are easily available, relatively cheap, and almost certainly cause death.

Poisoning occurring as a result of improper use of chemicals used in agriculture has been termed "agrochemical poisoning." Agrochemical poisoning can be classified as shown in Table 1.

Agrochemical poisoning remains one of the major causes of morbidity and mortality around the world today *(1–14)*, and a review of this relatively untouched subject seems to be justified.

Experience has shown that above the wide range of chemicals a vast majority of poisonings occur because of pesticides only. The 2002 annual report of the American Association of Poison Control Center's (AAPCC) Toxic Exposure Surveillance System listed a total of 2,380,028 human exposures to poisons occurring in the United States during the year 2002 alone *(15)*. Out of these, there were 96,112 exposures to pesticides (4% of all exposures) and 10,632 exposures to fertilizers (0.5% of all exposures); a total of 18 fatalities caused by pesticides and one caused by fertilizers were reported. The break-up for 2002 pesticide exposure is shown in Table 2, and the 18 fatalities caused by pesticides are given in Table 3. Two categories in which deaths were not reported at all were fungicides and repellants. Most deaths (n = 7) were to the result of insecticides. Herbicides and rodenticides accounted for five deaths each, and one death was caused by fumigants.

A comparison of poisoning data for the years 1998 to 2002 *(16–19)* indicates that, although the absolute number of pesticide exposure has been increasing, it is more or less stable at around 4% of all exposures to poisons; fatalities owing to pesticide poisoning amount to 1.5 to 2% of all fatalities resulting from poisons (Table 4).

In the following sections, those agrochemical poisons that are important from a medicolegal and pathological point of view will be discussed.

2. Insecticides

2.1. Organophosphorus Insecticides

2.1.1. Short History

Organophosphorus insecticides are derivatives of phosphoric acid (H_3PO_4) or phosphonic acid (H_3PO_3) in which all H atoms have been replaced by organic moieties (Figs. 1–3). L represents the so-called "leaving moiety" and is the most reactive and most variable substituent. It is called so because this moiety "leaves" the organophosphate molecule after it is attached to the esteratic site of the acetylcholinesterase (AChE, also known as true cholinesterase type 1 ChE). R_1 and R_2 are less reactive moieties. Most commonly they are

Table 1
Classification of Agrochemical Poisons

1. Chemicals/plants used as fertilizers
   - (i) Nitrites and nitrates (methemoglobinemia).
   - (ii) Ammonium sulfate (hyperammonemia).
   - (iii) Anhydrous ammonia.
   - (iv) Fertilizers containing urea.
   - (v) Poisonous plants (used as green manure, e.g., *Ricinus communis*).
2. Chemicals used to kill pests (pesticides)
   - (i) Acaricides (used to kills mites and ticks, also known as miticides, e.g., avermectins, azobenzene, benzoximate, bromopropylate, dofenapyn, nikkomycins, tetranactin).
   - (ii) Algicides used to control growth of algae in lakes, canals, and water stored for agricultural purposes (e.g., cybutryne, hydrated lime [component of Bordeaux mixture]).
   - (iii) Aphicides (used to kill aphids, e.g., triazamate, dimethoate, and mevinphos).
   - (iv) Avicides (used to kill birds harmful to agriculture, e.g., 4-aminopyridine, 3-chloro-*p*-toluidine hydrochloride).
   - (v) Bactericides (e.g., bronopol, nitrapyrin, oxolinic acid, oxytetracycline).
   - (vi) Fumigants (gas or vapor intended to destroy insects, fungi, bacteria, or rodents, used to disinfect interiors of buildings, as well as soil, before planting, e.g., carbon disulfide, sulfuryl fluoride, methyl bromide).
   - (vii) Fungicides (e.g., sodium azide, various compounds of copper and mercury, thiocarbamates, Captan, Captafol).
   - (viii) Herbicide safeners (e.g., benoxacor, cloquintocet, cyometrinil, dichlormid, dicyclonon). These compounds basically protect crops from herbicide injury by increasing the activity of herbicide detoxification enzymes, such as glutathione-*S*-transferases and cytochrome P-450.
   - (ix) Herbicides/weed killers (e.g, paraquat, diquat, 2-4 Dichlorophenoxyacetic acid, Mecoprop).
   - (x) Insecticides (e.g., organophosphorus compounds, organochlorine compounds, carbamates).
   - (xi) Microbial pesticides (those pesticides whose active ingredient is a bacterium, virus, fungus, or some other microorganism or product of such an organism, e.g., *Bti* which is made from the bacterium *Bacillus thuringiensis* var. *israelensis* and used to control mosquito and black fly larvae, *Bacillus sphaericus* and *Laegenidium giganteum*, a fungal parasite of mosquitoes).
   - (xii) Molluscicides (used to kill molluscs, such as snails and slugs, e.g., metaldehyde).
   - (xiii) Nematicides (used to kill nematodes that feed on plant roots, e.g., 1,3-dichloropropene, 1,2-dibromoethane, ethylene dibromide, diamidafos, fosthiazate, isamidofos).

Table 1
(Continued)

(xiv) Ovicides (used to kill eggs of insects and mites).
(xv) Pesticide synergists (e.g., piperonyl butoxide, *N*-octyl bicycloheptene dicarbozimide, piprotal, propyl isome, sesamex, sesamolin).
(xvi) Rodenticides (used to kill rodent pests, e.g., Strychnine, Vacor, ANTU, Cholecalciferol, anticoagulants and Red Squill).
(xvii) Virucides (e.g., ribavirin, imanin).
(xviii) Miscellaneous chemical classes including contaminants and adjuvants of some pesticides which are toxic on their own (e.g., dioxins, present as contaminants of some herbicides produce toxicity of their own).

3. Chemicals used to disturb the feeding/growth/mating behavior etc. of pests, or used for other miscellaneous agricultural purposes
(i) Bird repellents (e.g., anthraquinone, chloralose, copper oxychloride).
(ii) Chemosterilants (e.g., 1,2-dibromo-3-chloropropane, apholate, bisazir, busulfan, dimatif, tepa).
(iii) Desiccants (chemicals which promote drying of living tissues such as unwanted plant tops or insects).
(iv) Defoliants (chemicals which cause leaves or foliage to drop from a plant, usually to facilitate harvest).
(v) Feeding deterrents or antifeedants (chemicals having tastes and odors that inhibit feeding behavior, e.g., pymetrozine, azadirachtin A).
(vi) Insect attractants (substances that attract or lure an insect to a trap, e.g. brevicomin, codlelure, cue-lure, dominicalure, siglure).
(vii) Insect growth regulators (chemicals which disrupt the action of insect hormones controlling molting, maturity from pupal stage to adult, or other life processes, e.g., hexaflumuron, teflubenzuron and pyriproxyfen).
(viii) Insect repellents (e.g., butopyronoxyl, dibutyl phthalate, diethyltoluamide).
(ix) Mammal repellents (e.g., copper naphthenate, trimethacarb, zinc naphthenate, ziram).
(x) Mating disrupters (e.g., disparlure, gossyplure, grandlure).
(xi) Plant activators (a new class of compounds that protect plants by activating their defense mechanisms, e.g., acibenzolar, probenazole).
(xii) Plant growth regulators (substances [excluding fertilizers or other plant nutrients] that alter the expected growth, flowering, or reproduction rate of plants through hormonal rather than physical action).

4. Chemicals used for preservation of grains
(i) Aluminum phosphide.
(ii) Nitric oxide.

Table 2
2002 Pesticide Exposures

Category of pesticide	Pesticide	Number of exposures	Total exposures by category
1. Fungicides (nonmedicinal)	Carbamate	181	1498
	Copper compound	25	
	Mercurial	2	
	Nonmercurial	60	
	Phthalimide	125	
	Wood preservative	480	
	Other/unknown	625	
2. Fumigants	Aluminum phosphide	97	680
	Metam sodium	10	
	Methyl bromide	4	
	Sulfuryl fluoride	458	
	Other	43	
	Unknown	68	
3. Herbicides (including algicides, defoliants, desiccants, plant growth regulators)	Carbamate	42	9562
	2,4-D or 2,4,5-T	455	
	Chlorophenoxy	1717	
	Diquat	355	
	Glyphosate	4472	
	Paraquat	75	
	Triazine	352	
	Urea	93	
	Other	1623	
	Unknown	378	
4. Insecticides (including insect growth regulators, molluscicides, nematicides)	Arsenic pesticide	422	50,911
	Borate/boric acid	3818	
	Carbamate only	3022	
	Carbamate with other insecticide	723	
	Chlorinated hydrocarbon only	1522	
	Chlorinated hydrocarbon with other insecticide	242	
	Insect growth regulator	160	
	Metaldehyde	199	
	Nicotine	15	
	Organophosphate	8031	
	Organophosphate/carbamate	189	
	Organophosphate/chlorinated hydrocarbon	42	

Table 2
(Continued)

Category of pesticide	Pesticide	Number of exposures	Total exposures by category
	Organophosphate/other insecticide	1338	
	Organophosphate/carbamate/ chlorinated hydrocarbon	22	
	Piperonyl butoxide only	30	
	Piperonyl butoxide/pyrethrin	1123	
	Pyrethrins only	877	
	Pyrethrin	4967	
	Pyrethroid	12,475	
	Rotenone	84	
	Veterinary insecticide	151	
	Other	7611	
	Unknown	3848	
5. Repellants	Bird, dog, deer, or other mammal repellant	205	12,954
	Insect repellant with DEET	5321	
	Insect repellant without DEET	1196	
	Insect repellant unknown	2183	
	Naphthalene	1883	
	Paradichlorobenzene	123	
	Other moth repellant	40	
	Unknown moth repellant	2003	
6. Rodenticides	ANTU	1	20,507
	Anticoagulant: warfarin type	462	
	Anticoagulant: long-acting superwarfarin		17,100
	Bromethalin	389	
	Cholecalciferol	27	
	Cyanide	2	
	Monofluoroacetate	2	
	Strychnine	124	
	Vacor	3	
	Zinc Phosphide	146	
	Other	791	
	Unknown	1460	
Total			**96,112**

2,4-D, 2-4 dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; DEET, *N*,*N*-diethyl-meta-toluamide; ANTU, α-naphthyl-thiourea.

Modified according to ref. *15*.

Table 3
Deaths Due to Pesticides

Category	Subcategory	Deaths	Total deaths by subcategory
1. **Fungicides**	-	0	0
2. **Fumigants**	Sulfuryl fluoride	1	1
3. **Herbicides**	Paraquat	2	5
	Chlorophenoxy	1	
	Glyphosate	1	
	Other	1	
4. **Insecticides**	Organophosphates	5	7
	Other	2	
5. **Repellants**	-	0	0
6. **Rodenticides**	Superwarfarin anticoagulants	3	5
	Strychnine	1	
	Other	1	
Total		**18**	**18**

According to ref. *15*.

alkoxy groups, but may be alkyl, aryl, alkylamino, or alkylthio. X can be an oxygen or sulfur atom. The extreme variability of L, R_1, R_2, and X gives rise to virtually hundreds of organophosphates; these can generally be divided into five broad categories *(20)* depending on the characteristics of these groups. Figure

Table 4
Comparison of Pesticide Poisoning Data From 1998 to 2002

Year	Total poisonings reported	Pesticide poisonings	Percentage of total poisonings reported	Total fatalities reported due to all poisons	Total fatalities due to pesticides	Percentage of total fatalities reported
1998	2,241,082	86,289	3.8%	775	16	2.06%
1999	2,201,156	78,853	3.6%	873	15	1.72%
2000	2,168,248	86,880	4.0%	920	17	1.85%
2001	2,267,979	90,010	4.0%	1074	17	1.58%
2002	2,380,028	96,112	4.0%	1153	18	1.56%

Data taken from refs. *16–19*.

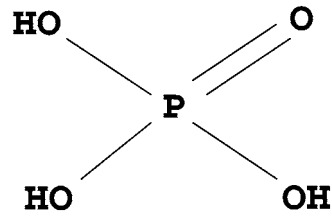


Fig. 1. Phosphoric acid (H_3PO_4).

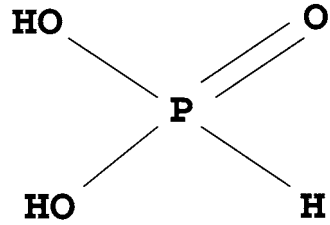


Fig. 2. Phosphonic acid (H_3PO_3).

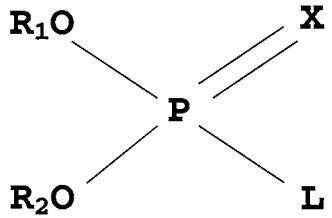


Fig. 3. General structure of organophosphorus insecticides.

4 shows five different categories of organophosphates depending on variations of different side chains.

Available as dusts, granules, or liquids, organophosphorus insecticides are among the most popular and widely used insecticides throughout the world. They began to be synthesized first around 1820 with the esterification of alcohols to phosphoric acid. The earliest synthesis of an organophosphate, tetraethyl pyrophosphate, was reported by Phillipe de Clermont at a meeting of the French Academy of Sciences in 1854 *(21)*. Many different organophosphorus compounds were synthesized in the early 1900s, but their toxicity was first recognized

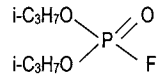
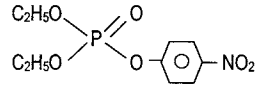
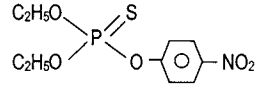
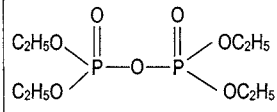
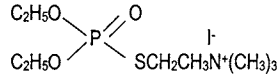
GROUP	DEFINING PROPERTY	REPRESENTATIVE MOLECULE	
A	L = Cyanide, Halogen or Thiocyanate		Diisopropyl fluorophosphate (DFP)
B	L = Alkylthio, Arylthio, Alkoxy or Aryloxy Group		Paraoxon (MINTACOL)
C	Thionophosphorous or Thio-thionophosphorous comporids X=S		Parathion
D	Pyrophosphates and similar compounds		Tetraethyl Pyrophosphate (TEPP)
E	L = Quaternary ammonium group		Diethoxyphosphinyl thiocholine Iodide (ECHOTHIOPHATE)

Fig. 4. Five different categories of organophosphates depending on variations of different side chains.

by Lange in 1932. Lange stated that inhalation of the vapor of dimethyl or diethyl phosphofluoridate produced a choking sensation and dimness of vision.

As nations started looking for lethal gases with the start of World War II in 1939, interest in these compounds was rekindled. By 1940, Schrader in Germany and Saunders in England and their study groups had synthesized a number of highly toxic organophosphates for possible use in warfare. Most notable among these were soman, sarin, and tabun.

Currently, about 50 organophosphorus compounds are in use as insecticides worldwide. Of these, parathion is the most effective for insecticidal use. Tetraethyl pyrophosphate enjoys two distinctions among organophosphates: it was the first organophosphate to be synthesized in 1854 and is the

most dangerous organophosphorus insecticide by either oral or dermal route of application.

2.1.2. Signs and Symptoms

Organophosphorus insecticides are basically AChE inhibitors allowing the accumulation of excess acetylcholine at various nicotinic and muscarinic receptors throughout the body including the central nervous system (CNS). This essentially results in acetylcholine toxicity. The main symptoms can be remembered by either of the two acronyms SLUDGE (salivation, lacrimation, urination, defecation, gastrointestinal distress, emesis) or DUMBELS (diarrhea, urination, miosis, bronchospasm and bradycardia, emesis, lacrimation, salivation). Rarely, there is chromolachryorrhoea (shedding of red or bloody tears) *(22)* because of a disturbance in porphyrin metabolism and its accumulation in lacrimal glands. LD_{50} (lethal dose; the amount of a material, given all at once, which causes the death of 50% of a group of test animals) of these compounds varies from 1 to 50 mg/kg (extreme toxicity) to more than 5000 mg/kg (slight toxicity). Compounds that are extremely toxic are chlorfenvinphos, diazinon, and methyl parathion, whereas those that are slightly toxic are malathion, acephate, and trichlorphon *(23)*. Most patients who have ingested a fatal dose will die within 24 hours of ingestion. Organophosphorus toxicity has recently been reviewed extensively by Rousseau and co-workers *(24)*.

2.1.3. Postmortem Findings

2.1.3.1. External Findings

Signs of asphyxia are commonly found in fatal intoxications with organophosphorus insecticides. There is congestion of the face and cyanosis of the lips, nose, fingers, and acral parts of the extremities. One of the most remarkable findings is the characteristic odor emanating from the corpse: it has been described as garlic- or kerosene-like and is due to the fact that organophosphates are dissolved on a kerosene base. There is often frothy, bloody staining at the mouth and nostrils, and the pupils may be constricted.

A coloring agent, indigocarmine, is added to parathion (E605®) to prevent its accidental ingestion or criminal use as a poison. This gives rise to a bluish-greenish discoloration of the lips and oral mucosa. The addition of indigocarmine, however, is not a general practice worldwide. For instance, in India and several other Asian countries, this practice is not followed. An interesting sign to be observed (albeit only in somewhat less modern mortuaries) is the death of bluebottles and others insects and flies dying immediately after they alight on an opened cadaver at autopsy *(25)*.

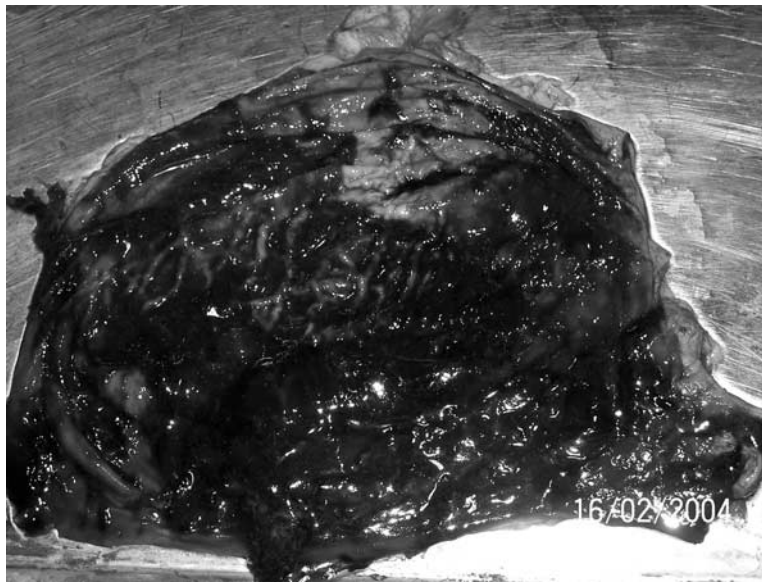


Fig. 5. Congested and hemorrhagic stomach mucosa in a case of fatal organophosphorus poisoning. (Courtsey of Dr. Avneesh Gupta and Dr. Puneet Setia, Maulana Azad Medical College, New Delhi, India.)

2.1.3.2. Internal Findings

The gastric mucosa is congested and may appear hemorrhagic (Fig. 5) and the stomach contents often contain an oily, greenish scum. The mucosa of the respiratory tract is congested and the airway passages contain frothy hemorrhagic exudate. The lungs show congestion, hemorrhagic pulmonary edema, and subpleural petechiae. The brain is swollen and there is generalized visceral congestion.

2.1.3.3. Histopathology

Parathion (E605) has been studied most extensively for histopathological lesions and these are considered to be representative of other organophosphorus insecticides, too *(26)*. In the kidneys, there is epithelial necrosis in the straight sections of the renal tubules. In the epithelia of the remaining renal cortical sections, there is pronounced plasma granulation, nuclear wall hyperchromatosis, and clumping and reduction in the chromatin and marginal nucleoli. Epithelia in loops of Henle and collecting tubules appear swollen.

The liver is more resistant to the effects of organophosphates, partly because of its ability to manufacture serum cholinesterase on its own. Hepa-

tocytes show opaque swelling and glycogen depletion; there are destructive changes in the liver cell strands, detached hepatocytes, and perivascular edema.

Myocardium, medulla oblongata, and vagal nuclei of the brain show fine, maculate perivascular hemorrhages. Limaye has described a type of toxic myocarditis that he had observed in 76 autopsy cases *(27)*. Kiss and Fazekas described focal myocardial damage with pericapillary hemorrhage, micronecrosis, and patchy fibrosis in victims of organophophorus poisoning *(28)*. Pimentel and da Costa *(29)* have described the following myocardial ultrastructural changes in fatal poisonings with organophosphorus:

1. Areas of partial or extensive lysis of myofibrils.
2. Mitochondria exhibiting decreased electron density, swollen forms and fragmentation or lysis of cristae.
3. Nuclei showing irregularity in shape and various degrees of disorganization of chromatin.
4. Z-line abnormalities of various degrees.

Multiple circumscribed necroses are found in the skeletal musculature. The oolemma is damaged and sometimes even necrotic. The glomus caroticum shows an increase in the number of dark-cell nuclei, perhaps as a consequence of increased nuclear metabolism owing to augmented demand.

2.1.3.4. Postmortem Biochemistry

AchE and butyrylcholinesterase (BChE, also known as pseudocholinesterase or type 2 ChE) levels are depressed in deaths owing to organophosphorus insecticides. The measurement of their levels can assist in the determination of the cause of death *(30)*. AChE is found mostly in red blood cells, motor endplates, and gray matter, whereas BchE is found mostly in plasma, white matter, liver, heart, and pancreas. The physiological function of BChE is unknown *(31)*, but it is established that BchE hydrolyzes suxamethonium (succinylcholine), and for this reason it is of interest to anesthesiologists as well. Postulated functions of BChE include its role in transmission of slow nerve impulses, lipid metabolism, choline homeostasis, permeability of membranes, protection of the fetus from toxic compounds, and degradation of acetylcholine and in tumorneogenesis *(32)*.

The plasma cholinesterase (pseudocholinesterase) is more sensitive and levels fall more rapidly than those of the red blood-cell cholinesterase. Red blood-cell cholinesterase levels are more satisfactory for the diagnosis of organophosphorus poisoning because they represent the true cholinesterase levels.

Sample collection and storage (time and temperature) are critical to the catalytic stability of ChE and thus influence the quality and interpretation of results of the toxicological analysis. Fluids and tissues that should be collected at autopsy are blood, cerebrospinal fluid (CSF), semen, muscle, brain, liver, heart, and pancreas. The recommended procedures for collection and storage of biological fluids are as follows:

1. Blood must be collected in heparinized tubes.
2. The samples must be collected and stored in glass rather than plastic containers to avoid contamination by leachates from plastic.
3. Sample contamination with acid or alkali must be avoided.
4. Samples must be immediately refrigerated because ChE catalytic activity is temperature dependent.
5. Fluid and cellular components of blood, CSF, and semen have to be separated.
6. Determine enzyme activity as soon as possible. If enzyme activity is not determined immediately, samples can be stored for several days at 4°C. If tissues are intended to be stored for longer periods, the storage temperature should be –20°C or below.
7. Tissue should be homogenized at pH 7.6 to 8.0 using a sonicator or nonmetallic homogenizer and then should be stored as indicated above.

ChE activity in blood, serum, and tissues can be measured by a number of methods. One of the most popular is the pH method by Michael *(33)*, whereby a change in pH is measured when ChE acts on acetylcholine. The principle is that cholinesterase hydrolyzes acetylcholine, thus producing acetic acid, which in turn decreases the pH of the reaction mixture. Electrometric determination of the change in pH from 8.1 for a definite period of time (e.g., 1 hour) at a specific temperature (e.g., 25°C) represents the enzyme activity. Normal values of ChE activity as measured by this method (in ΔpH/hour/0.02 mL red blood cells or plasma at 25°C, mean ± standard deviation) are given in Table 5 *(34)*.

In deaths owing to organophosphorus insecticides, the values will be much lower. A 25% or greater depression of the red blood-cell ChE level is a true indicator of poisoning. Death occurs when levels have decreased by more than 90%.

2.1.4. Toxicological Analysis

Blood and urine should be preserved for toxicological analysis of ChE levels. Samples from lung, liver, kidney, skeletal muscle, brain, and spinal cord, as well as gastric contents, must similarly be preserved for toxicological analysis of cholinesterase levels *(35)* according to the precautions detailed in Steps

Table 5
Normal Red Blood Cell and Plasma Cholinesterase Activity in Men and Women

	Men	Women
RBC ChE	0.766 ± 0.081	0.750 ± 0.082
Plasma ChE	0.953 ± 0.157	0.817 ± 0.187

RBC, red blood cell; ChE, cholinesterase.

1–7 in Section 2.1.2.4. Paranitrophenol is a metabolite of many organophosphates. It is excreted in urine and its presence in urine is characteristic of organophosphorus poisoning.

2.1.5. Organophosphates and Putrefaction

Organophosphates usually resist putrefaction and can be detected in the viscera for quite some time after death. Wehr *(36)* studied five exhumations where the decedents were suspected having been poisoned with parathion. He could detect the degradation products of parathion (aminoparathion and *p*-nitrophenol) up to 7 years after burial, but after 13 years, neither parathion nor any of its degradation products were detectable. Pohlmann and Schwerd found evidence of parathion in a corpse exhumed after 21 months *(37)*.

More recently, Karger and co-workers *(38)* described a case where they detected paraoxon, the main conversion product of parathion, from the abdominal cavity of a 9-month-old boy, 8 months after his death. His mother had poisoned him with parathion; her deed was detected when, several months later, her second child—a 3-year-old girl—also suffered the same fate and parathion was detected in her blood.

2.2. Carbamates

Carbamates (Fig. 6) are derivatives of carbamic acid. Their structure is similar to that of organophosphates (Fig. 7). The first recognized anti-ChE was in fact a carbamate, physostigmine (also called eserine), obtained in pure form in 1864 by Jobst and Hesse from the Calabar bean *(39)*. Some common carbamates used as insecticides today are aldicarb, carbaryl, γ-benzene hexachloride, triallate, propoxur, methomyl, carbofuran, and carbendazim. Like organophosphates, carbamates are inhibitors of AChE, but instead of phosphorylating, they carbamoylate the serine moiety at the active site. This is a reversible type of binding, and therefore, their toxicity is less severe and of

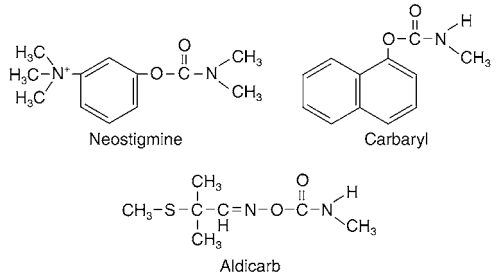


Fig. 6. Some representative carbamates.

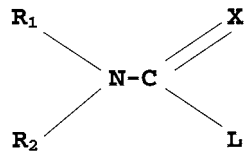


Fig. 7. General structure of carbamates. Note the similarity of the structure with that of organophosphates.

lesser duration *(40)*. Because they do not penetrate the CNS to any great extent, the CNS toxicity of carbamates is relatively low. Signs and symptoms are the same as those seen in poisoning with organophosphates/organophosphorus insecticides but they are milder in nature. Convulsions are not seen in carbamate poisoning.

Postmortem findings in carbamate poisonings are mostly similar to those found in organophosphates. A bluish discoloration of the mucosa of the mouth and stomach is not seen because the blue green dye indigocarmine is usually not mixed with carbamates. Determination of cholinesterase levels is not of much help because these are restored very rapidly in carbamate poisoning.

2.3. Organochlorines

Organochlorine pesticides are nonselective insecticides. They are cyclic in nature, have molecular weights between 300 and 550 D, are CNS stimulants, and have limited volatility. They are poorly soluble in water but readily soluble in organic solvents and fats, which is the way how they accumulate in the human body. They are very stable, both in the environment and in the body tissues, and can be demonstrated in the bodies of most people born since 1940.

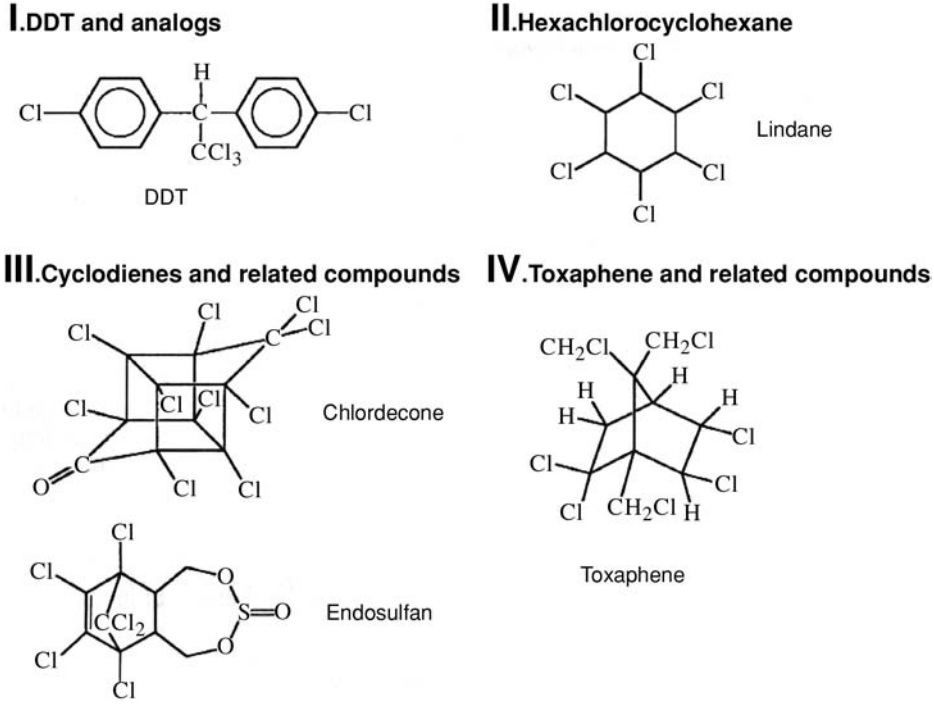


Fig. 8. Four general categories of organochlorine pesticides.

Based on their chemical structures, organochlorines can be divided into four categories (Fig. 8) *(41)*: (a) dichlorodiphenyltrichloroethane (DDT) and related analogs, such as methoxychlor, (b) hexachlorocyclohexane or lindane, (c) cyclodienes and related compounds (e.g., aldrin, dieldrin, endrin, endosulfan, chlordane, chlordecone, heptachlor, mirex, isobenzan), and (d) toxaphene and related compounds.

2.3.1. Short History

The best known organochlorine, DDT, was synthesized by the German chemist Othmar Zeidler in 1874, but he failed to realize its value as an insecticide. It was the Swiss Paul Hermann Müller (1899–1965) who recognized its potential as an effective insecticide. In 1939, DDT was tested successfully against the Colorado potato-beetle by the Swiss government. The United States Department of Agriculture used it successfully in 1943. In January 1944, DDT was used to quash an outbreak of typhus carried by lice in Naples, Italy; this was the first time a winter typhus epidemic could be stopped.

So revolutionary was his work that Müller was awarded with the Nobel Prize in Medicine in 1948. It is ironic that just 24 years later, in 1972, DDT was banned in the United States. It is perhaps a unique example in the history of science that a Nobel Prize-winning work was banned within such a short period of time. The main driving force behind this ban was the ecologists' concerns about the persistence of DDT in the environment and its resulting harm to the habitat—humans are equally affected by persistent DDT in the environment. It was Rachel Carson's (1907–1964) book *Silent Spring*, published in 1962, which brought the problem to everyone's notice.

Endrin, one of the cyclodienes, is chiefly used against insect pests of cotton, paddy, sugarcane, and tobacco. It is active against a wide variety of insect pests, and hence is commonly known as *plant penicillin*. It has been banned in most Western countries, but unfortunately continues to be used in several agrarian economies.

2.3.2. Signs and Symptoms

The mechanism of action of organochlorines is entirely different from that of organophosphates and carbamates. Organochlorines act on axonal membranes affecting the sodium channels and sodium conductance across the neuronal membranes. Organochlorines also alter the metabolism of acetylcholine, noradrenaline, and serotonin. Lindane and cyclodienes appear to inhibit the γ-aminobutyric acid-mediated chloride channels in the CNS.

Therefore, not very surprisingly, the main symptoms induced by poisoning with organochlorines are CNS-related and include vertigo, confusion, weakness, agitation, hyperesthesia or paresthesia of the mouth and face, myoclonus, rapid and dysrhythmic eye movements, and mydriasis (in contrast to organophosphates and carbamates, where miosis is found). Other symptoms include nausea, vomiting, fever, aspiration pneumonitis, and renal failure.

The fatal dose of DDT and lindane is 15 to 30 g, whereas that of aldrin, dieldrin, and endrin is 2 to 6 g *(42)*.

2.3.3. Postmortem Findings

2.3.3.1. External

The conjunctivae are congested and the pupils are dilated. There may be a kerosene-like smell emanating from the mouth and nostrils. This is because most organochlorines are poorly soluble in water and are dispensed as solutions in organic solvents that may have a kerosene-like smell. Fine white froth, which may or may not appear hemorrhagic, can be seen around the mouth and nostrils; this is a general effect of pulmonary edema coupled with respiratory distress and therefore, signs of cyanosis are seen on the face, ears, nail beds, etc.

2.3.3.2. Internal Findings and Histopathology

The mucosa of the respiratory tract appears congested and the respiratory passages contain frothy mucus which may or may not be tinged with blood. Subpleural and subpericardial petechial hemorrhages are common. The lungs appear large and bulky, showing pulmonary edema. The mucosa of the esophagus, stomach, and bowel is congested owing to the irritating effect of organochlorines on the gastrointestinal tract. The stomach contents smell kerosene-like. The visceral organs are congested. Hepatic necrosis may be found on cut sections of the liver.

In animals killed by DDT, vacuolization around large nerve cells of the CNS, fatty change of the myocardium, and renal tubular degeneration can be detected histologically *(43)*.

2.3.4. Toxicological Analysis

Feces, urine, and subcuatenous adipose tissue (placed in a glass-stoppered vial or a vial with a teflon-lined cap *[43]*) should be collected for toxicological analysis. Samples must be frozen before onward transmission to the toxicology laboratoy.

2.4. Nicotine

Nicotine salts, such as nicotine sulfate, were very popular pesticides in the 1920s and 1930s. These compounds generally contained 40% nicotine (Fig. 9). Now, because most countries have banned nicotine-based insecticides, less than 1% of home garden insecticides are nicotine-based. These are usually available in powder form. Main among these is Black Leaf-40 (manufactured by Black Leaf Products Company, Elgin, IL).

When nicotine-based insecticides come in contact with moist skin, fatal doses of nicotine may be absorbed through the skin *(44)*. Apart from occupational exposure to nicotine spray, other methods of fatal exposure include careless storage and inadvertent mixing with foodstuffs, fruits, and vegetables. These insecticides have also been used successfully with suicidal or homicidal intention.

2.4.1. Postmortem Findings

Brownish froth around the mouth and nostrils is a frequent finding in nicotine poisoning. There is a characteristic odor of stale tobacco emanating from the gastric contents. The esophageal and gastric mucosa is intensely congested, showing a brownish discoloration. Liver and kidneys show considerable acute congestion *(23)*.

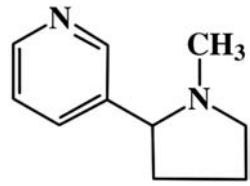


Fig. 9. Nicotine.

2.4.2. Histopathology

The liver shows plaque-like granulations in the cytoplasm of centrilobular and intermediary hepatocytes. Intrapulmonary hemorrhages and pulmonary edema are typical and there often is detachment of the alveolar epithelium. In the kidneys, there is necrosis and detachment of the epithelia in the straight and convoluted renal tubules. A variety of arterial wall lesions, including lacerations of the elastic interna, are seen that have been connected with extreme fluctuations in blood pressure from the effects of nicotine *(26)*.

3. Herbicides or Weed Killers

3.1. Short History and General Remarks

An estimated 10% of all plant species are weeds, with a total of some 30,000 species. Chemicals, such as common salt, have been used for centuries for weed control. The era of chemical weed control is generally recognized as starting in 1896. Bonnet in France found that the Bordeaux mixture, already being used on vines to control powdery mildew, also provided control of specific weeds. By the 1930s, farmers were still using simple chemicals for this purpose; for example, copper sulfate (Blue Vitriol), which was first used for weed control in 1821, was still in use at this time. In the early 20th century, scientists in Europe started using the salts of heavy metals to control weeds but when this was attempted in the United States, the low humidity in the Western states prevented these chemicals from being absorbed by the weeds. Other chemicals were tried, but most of them had drawbacks. For instance, carbon bisulfide used to control thistles and bindweeds smelled like rotten eggs and was, therefore, quite understandably unpopular. Most chemical weed killers of those times (such as sodium arsenate, arsenic trioxide, and sulfuric acid) were highly toxic to humans and had to be used in large quantities (several kilograms per hectare), which was another serious drawback.

The first synthetic organic chemical for selective weed control was introduced in 1932. Its chemical name was 2-methyl-4, 6-dinitrophenol, and it could control some broadleaf weeds and grasses in large seeded crops, such as beans.

More modern herbicides are now available. These have to be sprinkled in very low doses (grams per hectare) in order to kill weeds and the crop is spared.

Herbicides are categorized as *selective* when they are used to kill weeds without harming the crop and as *nonselective* when the purpose is to kill all vegetation. Killing of all vegetation is generally not intended in an agricultural setting. It is required more often in places such as recreational areas, railroad embankments, irrigation canals, fence lines, industrial sites, roadsides, and ditches.

Both selective and nonselective herbicides can be applied to weed foliage or to soil containing weed seeds and seedlings depending on the mode of action. The term *true selectivity* refers to the capacity of an herbicide, when applied at the proper dosage and time, to be active only against certain species of plants but not against others. Selectivity can also be achieved by placement, such as when a nonselective herbicide is applied in such a way that it reaches only the weeds but not the crop.

Herbicides can also be classified as *contact* or *translocated*. Contact herbicides kill the plant parts to which the chemical is applied. Translocated herbicides are absorbed either by the roots or the above-ground parts of plants and are then circulated within the plant system to distant parts.

Timing of herbicide application regarding the stage of crop or weed development forms another basis of classification. A *preplanting* herbicide is sprinkled on the farm before the planting of the crop. A *preemergence* herbicide is sprinkled after planting but before emergence of the crop or weeds. Finally, a *postemergence* herbicide is used after the emergence of the crop or weed.

Herbicides can be applied to weeds in a number of ways. A *band application* treats a continuous strip, such as along or in a crop row. *Broadcast application* covers the entire area, including the crop. *Spot treatments* are confined to small areas of weeds. *Directed sprays* are applied to selected weeds or to the soil to avoid contact with the crop. In the more recent *over-the-top-application*, herbicides are applied "over the top" of the crop and weeds shortly after germination. The crops in these instances are naturally tolerant to the specific herbicide or have been genetically engineered to be tolerant to the herbicide used.

From a toxicological point of view, the following herbicides are the most important.

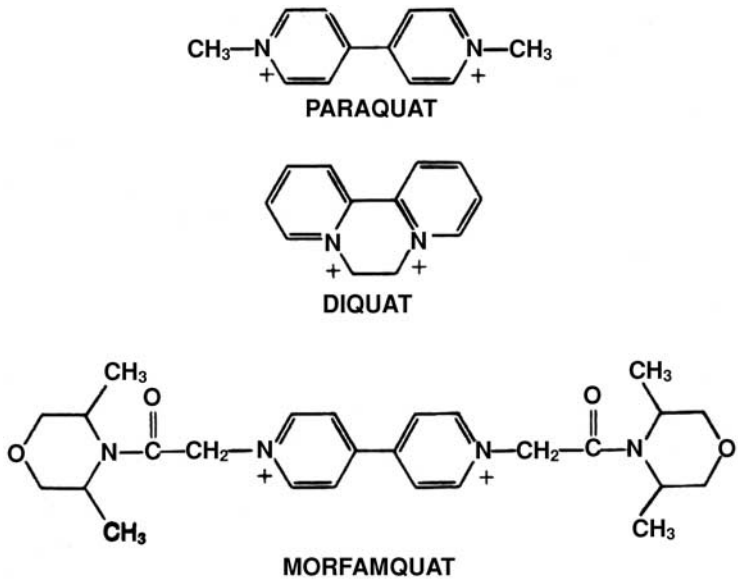


Fig. 10. The three most common dipyridyl weed killers: paraquat, diquat, and morfamquat.

3.2. Dipyridyl Weed Killers

Dipyridyl weed killers include paraquat, piquat, and morfamquat (Fig. 10). Paraquat is the most important of these three.

3.2.1. Paraquat

Paraquat (1,1′dimethyl-4-4′bipyridylium dichloride) is an important agricultural chemical from a toxicological viewpoint. Out of the 18 deaths caused by pesticides reported by the 2002 AAPCC annual report *(15)*, two were the result of paraquat poisoning.

Paraquat was first synthesized in 1882, but its herbicide activity was discovered very late. Its use as an herbicide was first reported in 1958, and paraquat was introduced commercially as a nonselective herbicide in 1962. The introduction of paraquat caused an agricultural revolution because it has some unique properties. It can be sprayed from the ground level or the air and is totally denatured when it comes in contact with the earth. Thus, it cannot harm the seeds or young plants that will be placed in the same ground a short time later. Indeed, the crop can be planted within days, if not hours, after herbicidal treatment with paraquat. An additional advantage is that plowing is unnecessary

in many cases with much less soil erosion. Paraquat is therefore of immense value in an economic sense *(45)*. In countries like Sri Lanka, its use has resulted in three crops, instead of two, per year being taken off the same field *(46)*.

Paraquat is highly soluble in water and is marketed most commonly as a concentrate containing 200 g paraquat dichloride per liter (20% wt/vol); this is an odorless brown liquid. A "stenching" agent (a pyridine derivative) is added to prevent accidental or criminal poisoning; a bluish-greenish dye is also added for the same reason, and an emetic may be added as well. Paraquat is sometimes sold in combination as a mixture with diquat and other herbicides. The liquid concentrate is known as Gramoxone (not to be confused with Gammexane, which is the trade name for lindane); a weaker, granulated preparation for horticultural use, known as Weedol, is also available (5% wt/vol). The solution may be decanted in soda bottles and left unlabelled. Because it looks like a cola drink, accidental ingestion may occur. It may be mistaken for vinegar as well; one patient is reported to have sprinkled it on his french fries.

Wesseling and co-workers *(47)* reported that paraquat is the pesticide most frequently associated with injuries among banana workers in Costa Rica; the injuries involve mostly the skin and eyes.

Although most fatalities caused by paraquat occur from ingestion, absorption through the skin can also cause fatalities. Wohlfahrt *(48)* reviewed paraquat poisoning in Papua New Guinea from 1969 to 1981 and found that out of 35 fatalities caused by paraquat, six were the result of transdermal absorption.

3.2.2. Diquat

Diquat (1,1′-ethylene-2,2′-dipyridylium dibromide) is less commonly used than paraquat. It has the same indications and mode of action as paraquat. Diquat is, however, used additionally for the control of aquatic weeds. Jones and Vale *(49)* compiled all cases of diquat poisoning published between the years 1968 and 1999 and found that only 30 cases were reported in detail in the literature, of which 13 (43%) were fatal. Conning et al. showed that out of the three dipyridyl weed killers, it was only diquat that produced bilateral cataracts *(50)*.

Diquat was introduced in 1957 as a fast-knockdown, contact herbicide and plant desiccant. Diquat-only formulations manufactured by Syngenta (formerly Imperial Chemical Industries) or its subsidiaries do not contain the dye, "stenching" agent, or emetic added to paraquat *(41)*.

3.2.3. Signs and Symptoms in Poisoning With Dipyridyl Weed Killers

The symptoms include intense pain in the mouth and pharynx, with inflammation and even ulceration of the oral mucosa. Esophageal ulceration

may lead to perforation with all its attendant risks. Renal and hepatic failure develop within 2 to 4 days. The most important effect is on the lungs (*pneumotropism*), where massive, irreversible pulmonary fibrosis is seen. Pulmonary fibrosis is thought to be the result of an increase in the pulmonary concentrations of prolyl hydroxylase, an enzyme which promotes collagen formation. Paraquat is one of the few poisons that may produce necrosis of the adrenal glands, possibly leading to hypotension. The fatal dose is 1 to 2 g (about a mouthful of Gramoxone). Subcutaneous injection of just 1 mL of Gramoxone has shown to be fatal *(51)*, with death occuring after 1 to 2 weeks as a result of respiratory failure caused by pulmonary fibrosis; greater doses can kill a human within 24 hours.

3.2.4. Mechanism of Toxicity of Dipyridyl Weed Killers

Why does paraquat show such remarkable pneumotropism? It has been postulated that inside the pneumocytes, the paraquat dication PQ^{2+} accepts one electron from reduced nicotinamide adenine dinucleotide and becomes the monocation $PQ^{+\cdot}$ (pyridinyl-free radical) (Fig. 11). The monocation $PQ^{+\cdot}$ is unable to cause any injury on its own, but in the presence of molecular oxygen (O_2) in the lungs, it is oxidized once again to its dication form (PQ^{2+}). In this process, it passes on its electron to the molecular oxygen (O_2), which, in turn, becomes the superoxide anion radical ($O_2^{\cdot-}$). This process, known as *redox cycling*, is sustained by oxygen in the lungs. The superoxide anion radical $O_2^{\cdot-}$ (reactive oxygen species) generated as a result of this cycle is responsible for cell death. This also explains why oxygen enhances the toxicity of paraquat and should never be administered during paraquat intoxication; by administering oxygen, one is supplying the "raw material" for the formation of the damaging superoxide radical.

Formation of free radicals is implicated in injuries caused by at least two other poisons—myocardial injury caused by doxorubicin and liver injury by carbon tetrachloride.

The related bipyridylium compounds, such as diquat and morfamquat, do not affect the lung as seriously, but rather cause liver damage *(52)*.

3.2.5. Postmortem Findings and Histopathology in Poisoning With Dipyridyl Weed Killers

There is ulceration around lips and mouth, although it is not as bad as is seen after ingestion of inorganic acids, such as nitric or sulfuric acids. The oral and esophageal mucosa is reddened and desquamated. A unique feature of paraquat ingestion is the formation of pseudomembranes in the pharynx resembling to that seen in diphtheria *(53)*.

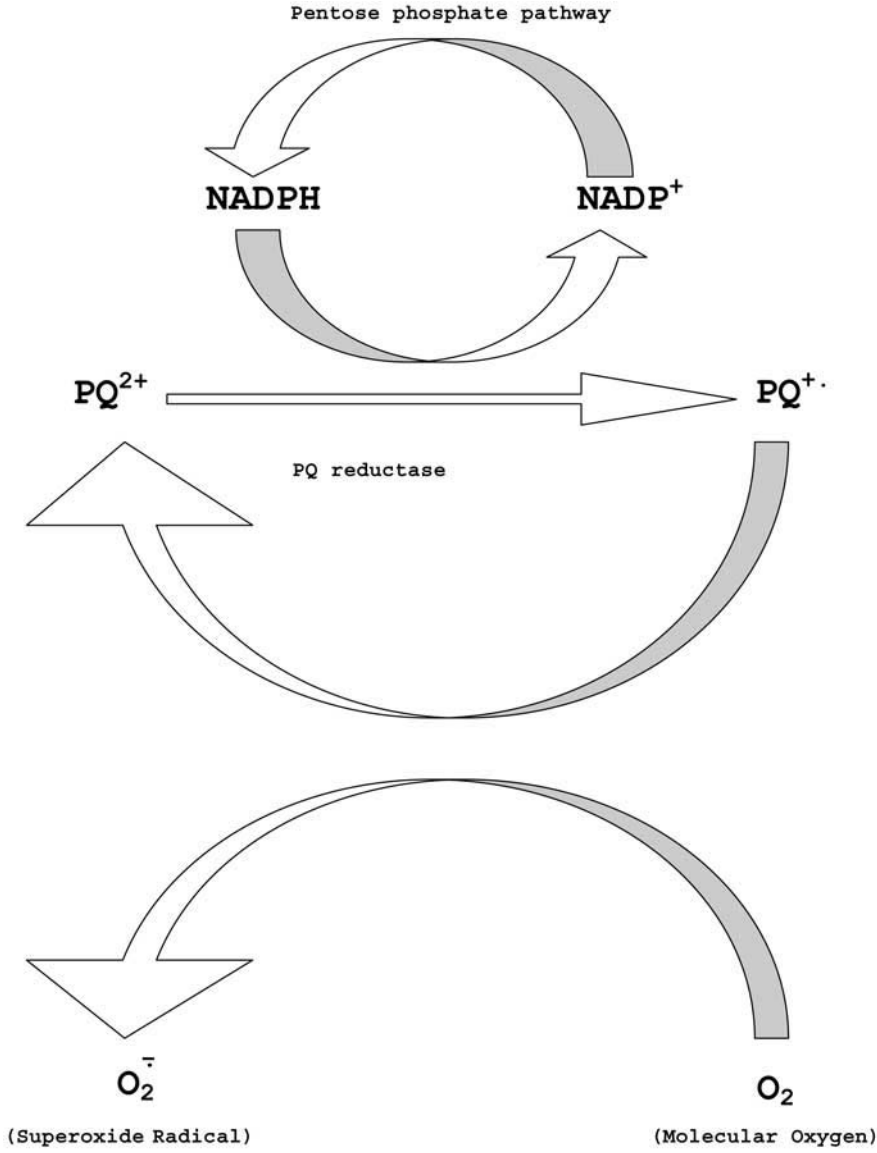


Fig. 11. Mechanism of paraquat toxicity.

Patchy hemorrhages in the stomach mucosa are a frequent finding. The liver is pale, showing fatty changes. The kidneys may exhibit pallor of the cortex. The most striking findings are found in the lungs. Both type 1 and type 2 alveolar epithelial cells accumulate paraquat and are thereby destroyed. This destruction is followed by inflammatory cell infiltration and hemorrhages; fibroblast proliferation then leads to fibrosis and impaired gas exchange. The lungs are congested, appear stiffened, and retain their shape during evisceration. Each lung is typically approx 1000 g or more in weight. Teare *(46)* reported a case of paraquat poisoning (a 44-year-old man dying of suicidal ingestion of paraquat after 17 days of illness), with the left lung weighing 1980 g and the right lung weighing 1920 g. Blood-stained pleural effusions and fibrinous pleurisy are other typical autopsy findings. Cut surfaces of the lungs reveal edema and fibrosis. Subendocardial hemorrhages may accompany the aforementioned pathological findings. The pathological features of paraquat poisoning have been reviewed in detail by Vadnay and Haraszti *(54)*.

At the beginning of the toxic process, severe degenerative changes appear in the pneumonocytes with fatty infiltration, desquamation, necrosis, and detachment *(26)*. Later, there is splintering of the basement membranes, fragmentation, aneurysma formation, and multiple ruptures. Fibrinous edematous fluid is seen in the interstitium and within alveoli and hyaline membranes can be observed. There is a large-scale dissolution of the pulmonary structure. There may be active proliferation of the bronchial epithelium, forming small adenomata within the pulmonary parenchyma. Marked proliferation of fibroblasts with an increase in macrophages in the alveoli (these two mechanisms obliterate the alveolar spaces) can be seen. Acute tubular necrosis is a frequent finding in the kidneys. Extensive renal cortical necrosis is also seen at times. In the liver, centrilobular hepatic necrosis, cholestasis, and giant mitochondria with paracrystalline inclusion bodies can be detected *(26)*. In the myocardium, there is edematous disaggregation of the sarcoplasm and sporadic fragmentation of the myofibrils.

3.2.6. Toxicological Analysis

Paraquat-type herbicides in aqueous solutions have traditionally been determined by colorimetric methods. These involve measurement of the complex formed with some chemical (α-dipicrylamine hexanitrodiphenylmethane). Plasma paraquat levels can be assayed by spectroscopy, high-performance liquid chromatography *(55)* or radioimmunoassays; levels greater than 0.2 µg/mL confirm death by paraquat intoxication. Urine paraquat levels can be deter-

mined using spectrophotometry, too; levels greater than 10 µg/mL confirm death by paraquat intoxication *(23)*. Berry and Grove introduced an ion exchange and colorimetric method in 1971 for the determination of paraquat in urine *(56)*.

Diquat (Reglone) is selectively concentrated in the kidneys and causes marked renal tubular damage. In a case of fatal diquat poisoning, McCarthy et al. found esophagitis, tracheitis, gastritis, and ileitis *(57)*. Autopsy findings and toxicokinetic data in diquat poisoning have been described in detail by Hantson et al. *(58)*.

3.2.7. Morfamquat

Morfamquat is used far less commonly than the other two bipyridyls, paraquat and diquat. Conning et al. have shown that rats that fed on morfamquat developed renal damage *(50)*.

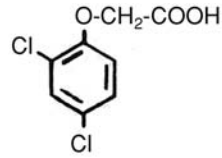
3.3. Chlorophenoxy Herbicides

Chlorophenoxy herbicides (Fig. 12) are growth regulators or auxins. They cause abnormal plant growth, thereby ultimately destroying the plant. Chlorophenoxy herbicides are commonly used for control of broadleaf weeds in cereal crops and pastures *(59)*. 2-4 Dichlorophenoxyacetic acid (2,4-D; Trimec) has been and continues to be one of the most useful herbicides developed; it is frequently applied to lawns to control broadleaf weeds and is often found in fertilizer products along with other phenoxy herbicides, such as dicamba, mecoprop, and (4-chloro-2-methylphenoxy)acetic acid.

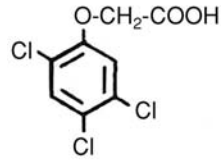
2,4-D is easily absorbed through the skin and lungs *(60)*. On ingestion, 2,4-D causes peripheral neuropathy, muscle weakness, Cheyne-Stokes respirations, hyperthermia, acidemia, and coma *(23)*. The patient is hypotonic, hyporeflexive, hypotensive, and comatose *(61)*, and nasogastric aspirate may be guaiac-positive *(62)*.

2,4-D earned a notorious reputation during the Vietnam war as an ingredient of Agent Orange sprinkled by United States troops over Vietnam (*see* Subheading 9.4). Suicidal ingestions of 2,4-D are occasionally reported *(61,62)*.

Postmortem findings in deaths caused by chlorophenoxy herbicides are nonspecific. The gastrointestinal mucosa may be intensely congested and/or hemorrhagic. All internal organs are usually congested. Confirmatory tests of suspected poisonings with chlorophenoxy herbicides are the demonstration of these herbicides in plasma and urine,which can be detected by radioimmunoassay *(63)* and gas liquid chromatography *(64)*.



2, 4-D



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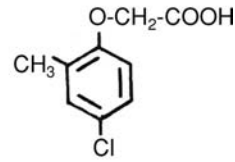

MCPA

Fig. 12. The three most common clorophenoxy herbicides: 2-4 dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, and (4-chloro-2-methylphenoxy)acetic acid.

3.4. Phenolic Weed Killers

This category comprises mainly dinitrophenol (DNP), dinitro-orthocresol (DNOC), and pentachlorophenol *(65)*. These substances are used in agriculture mainly as selective weed killers for cereal crops. The effects of DNP in stimulating metabolism have been known since 1885, and DNP was used at one time for "slimming." DNP (Fig. 13) is a potent "uncoupler" of oxidative phosphorylation, causing the energy obtained from the oxidation of nicotinamide adenine dinucleotide and reduction of O_2 to be released as heat.

It has been demonstrated that these compounds are dangerous to humans and thus, they are no longer used for medicinal purposes. The principal risk of poisoning is in the agricultural use of concentrated solutions for spraying crops

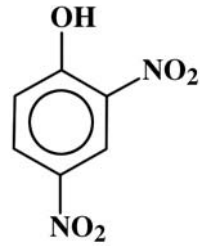

Fig. 13. Dinitrophenol.

(as weed killers). Dinitrophenol (DNP) is also used in agriculture for the control of mites and aphids *(66)*.

Absorption occurs by inhalation and thus, breathing apparatus are a must for those who are exposed to this poison. Absorption also occurs by ingestion and through the skin. Excretion of DNP is extremely slow, so the poison accumulates in the body gradually. The symptoms are fatigue, insomnia, restlessness, excessive sweating, weight loss, and thirst. Clinical signs include tachycardia, increase in the rate and depth of respiration, rise in temperature (up to 41°C and higher) and some yellow discoloration of the sclera. In severe cases, body temperature may keep rising and just before death, it may reach 44°C. When death occurs, the onset of rigor mortis is rapid.

3.5. Chlorate Compounds

Sodium chlorate is a nonselective herbicide. It acts as a soil sterilant at rates of 200 lbs/acre. It is also used as a foliar spray at 5 lbs/acre as a cotton defoliant. It was once avidly advocated as a weed killer, not only because it is effective, but also because it was considered safe. This fallacy was so prevalent that containers of sodium chlorate used to be marked as "nonpoisonous." However, chlorates cause methemoglobinemia. Severe hemolysis is a constant clinical feature in sodium chlorate poisoning, with presence of Heinz bodies in the red blood cells. Acute renal failure and anuria sets in later. Anuria occurs because of (a) a direct damaging action of chlorates on the renal tubular epithelium, and (b) mechanical obstruction of the renal tubules by the hemoglobin set free by hemolysis. The fatal dose of sodium chlorate is 20 to 35 g with death occuring within 4 to 5 days.

3.5.1. Circumstances of Poisoning With Sodium Chlorate

Poisoning with sodium chlorate can occur accidentally, suicidally, or even homicidally. Accidental poisoning is probably the most common. A 48-year-old

gardner was severely poisoned in a curious way. He was using a concentrated solution of sodium chlorate in an atomizer while a strong wind was blowing. Consequently, spray was blown onto his face and he inhaled and ingested some of the solution. Symptoms of poisoning started the same evening. He was saved with some heroic effort on the part of the doctors, yet he could only return to full-time work after about 1 year *(67)*.

3.5.2. Postmortem Findings

The skin has a distinctive chocolate-brown color. Blood smears may show evidence of hemolysis and Heinz bodies. The kidneys are enlarged and their principal change is a brown streaking of the cortex; microscopical examination reveals acute renal tubular degeneration with blockage of tubules by broken red blood cells and brown pigment granules (released hemoglobin owing to hemolysis).

3.6. Glyphosate

Glyphosate is an important agricultural chemical from the toxicological viewpoint. Out of the 18 deaths caused by pesticides reported by the 2002 AAPCC annual report *(15)*, one was caused by glyphosate. Glyphosate is a broad-spectrum, nonselective, systemic herbicide used for control of annual and perennial plants including grasses, sedges, broad-leaved weeds, and woody plants. It can be used on non-cropland as well as on a great variety of crops. Although glyphosate itself is relatively harmless, its chemical formulations (e.g., Roundup®, Rodeo®, Touchdown®, Gallup®, Landmaster®, Pondmaster®, Ranger®) have been used successfully for committing suicide. This is because glyphosate invariably is formulated in a surfactant (polyethoxylated tallow amine), which is quite toxic *(68,69)*.

Glyphosate is generally distributed as water-soluble concentrates and powders. Mild poisoning results only in gastrointestinal symptoms, such as vomiting, abdominal pain, diarrhea, and nausea, which usually resolve within a day or two. Severe poisoning results in intestinal hemorrhage and ulceration, acid base disturbances, renal failure, hypotension, cardiac arrest, pulmonary dysfunction, convulsions, coma, and death.

Postmortem findings are nonspecific. Glyphosate and the concomitant surfactant are demonstrated by toxicological analysis in the gastric contents and other visceral organs. Glyphosate levels of 1 mg/mL or more can be detected postmortem in blood, liver, and urine in less than a minute by using ^{31}P nuclear magnetic resonance *(70)*.

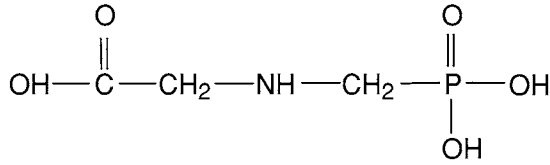

Fig. 14. Glyphosate.

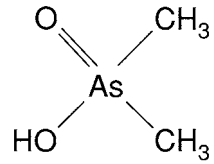

Fig. 15. Cacodylic acid.

3.7. Arsenical Herbicides

Among the several arsenical herbicides available are cacodylic acid, calcium hydrogen methylarsonate, disodium methylarsonate, hexaflurate (AsF_6K), methylarsonic acid, monoammonium methylarsonate, monosodium methylarsonate, potassium arsenite, and sodium arsenite.

Cacodylic acid (Fig. 15) is also known as dimethylarsinic acid. Cacodylic acid is a white crystalline substance, readily soluble in water and alcohol, and is still used as an herbicide. When it unites with metals and organic substances, it forms salts known as cacodylates. Cacodylic acid contains 54.3% of arsenic.

4. Fungicides

Fungicides, or antimycotics, are toxic substances used to kill or inhibit the growth of fungi that cause economic damage to crop or ornamental plants. Most fungicides are applied as sprays or dusts. Seed fungicides are applied as a protective covering before germination. Systemic fungicides, or chemotherapeutants, are applied to plants, where they become distributed throughout the tissue and act to eradicate existing disease or to protect against possible disease.

Bordeaux mixture ($CuSO_43Cu[OH]_23CaSO_4$) was one of the earliest fungicides to be used *(71)*. Bordeaux mixture is a liquid composed of hydrated (slaked) lime, copper sulfate, and water. It was accidentally discovered in 1882

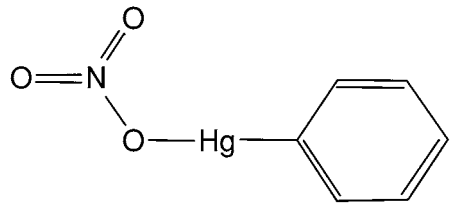

Fig. 16. Phenylmercury nitrate.

in the Modoc region of France, where farmers, tired of schoolboys pilfering their grapes, sprayed their grapevines with a poisonous-looking mixture of lime and copper sulphate; it was a desperate idea meant just to deter schoolboys from stealing their grapes. However, in 1882, PMA Millardet from the University of Bordeaux observed that the very same mixture effectively controlled the downy mildew of grapes as well.

Burgundy mixture is a mixture of copper sulfate and disodium carbonate. Both bordeaux mixture and burgundy mixture are still widely used to treat orchard trees. Copper compounds and sulfur have been used on plants separately and together. Synthetic organic compounds are now more widely used because they give protection and control over many types of fungi.

Cadmium chloride and cadmium succinate are used to control turfgrass diseases. Mercury(II)chloride, or corrosive sublimate, is used as a dip to treat bulbs and tubers.

Mercury salts used as fungicides include mercurous chloride, mercuric chloride, mercuric oxide, phenylmercury nitrate (Fig. 16), tolylmercury acetate, and ethylmercury bromide.

Organophosphorus fungicides include ampropylfos, ditalimfos, edifenphos, and fosetyl (Fig. 17). Carbamate fungicides include benthiavalicarb, furophanate, iprovalicarb, and propamocarb (Fig. 18); the toxicity of organophosphates and carbamates has been dealt with earlier.

Among the most important inorganic fungicides are potassium azide, potassium thiocyanate, sodium azide, and sulfur. Other substances occasionally used to kill fungi include chloropicrin, methyl bromide, and formaldehyde. Many antifungal substances occur naturally in plant tissues. Creosote, obtained from wood tar or coal tar, is used to prevent dry rot in wood.

The most important fungicides—from the toxicological viewpoint—aside from organophosphorus and carbamates, are sodium azide and compounds of copper and mercury. Copper compounds are also especially important because they are used in agriculture as insecticides and algicides.

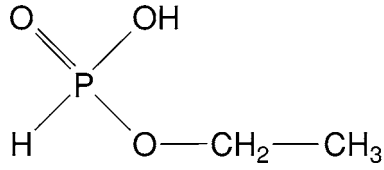

Fig. 17. Fosetyl, an organophosphate fungicide.

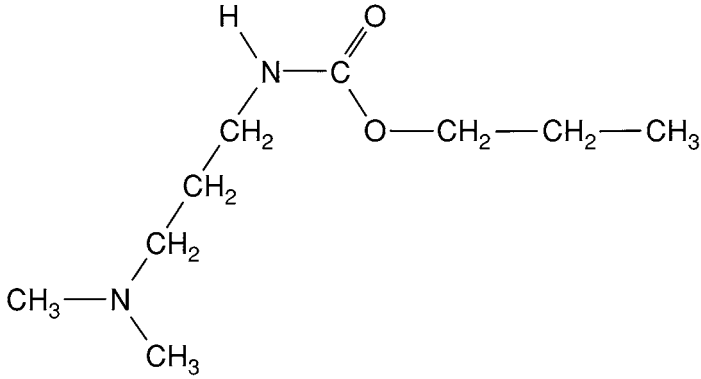

Fig. 18. Propamocarb, a carbamate fungicide.

Somerville discussed the metabolism of several fungicides including maneb, mancozeb, zineb, captan, chlorothalonil, benomyl, triadimefon, triadimenol, and cymoxanil *(72)*.

4.1. Sodium Azide

Sodium azide is important because it is a potential intentional or accidental poison. Aside from being used in agriculture, sodium azide is also used widely in hospitals where it is used as a component chemical in the fluid used to dilute blood samples. Sodium azide, like DNP, is an "uncoupler" of oxidative phosphorylation; it also inhibits the enzymes catalase and cytochrome oxidase.

Ingestion of sodium azide results in nausea, vomiting, diarrhoea, hypotension, and CNS symptoms, such as headache, hyporeflexia, seizures, and coma. Postmortem findings include edema of the brain and lungs. Edema of the myocardium with myocardial necrosis has also been reported *(73)*.

4.2. Copper

Salts of copper, although mostly used as fungicides, are used for a large number of other purposes in agriculture as well. Copper acetate, copper carbonate, cupric 8-quinolinoxide, copper silicate, and copper zinc chromate are used as fungicidal agents only; copper arsenate is used as insecticide and copper sulfate as algicide, fungicide, herbicide, and molluscicide; copper acetoarsenite is employed as insecticide and molluscicide; copper hydroxide is used as bactericide and fungicide; copper naphthenate is used as fungicide and mammal repellent; copper oleate as fungicide and insecticide; and copper oxychloride as bird repellent and fungicide.

Chronic exposure to Bordeaux mixture in vineyard sprayers causes the so-called "vineyard sprayer's lung." Observed mainly in Portugal, the disorder includes pulmonary fibrosis *(74)* and may lead to lung cancer *(75,76)*. Bordeaux mixture is the only other significant pesticide aside from paraquat that induces significant pulmonary fibrosis with organophosphates coming in a distant third *(77)*. The radiological picture in vineyard sprayer's lung resembles that of silicosis with micronodular features in the early stages of the disease *(76)*. Only in later stages does a picture of massive fibrosis emerge with continuing development of respiratory insufficiency.

Plamenac et al. *(78)* examined the sputum of rural workers engaged for years in spraying of vines. Sputum specimens were tested for copper by rubeanic acid. Macrophages containing copper granules in their cytoplasm were found in 64% of the workers engaged in vine spraying compared with none in a control group. Other abnormalities, such as eosinophils, respiratory spirals, respiratory cell atypia, and squamous metaplasia, were also found in the sputum. Atypical squamous metaplasia was observed in 29% of vineyard workers who were also smokers *(78)*. Eckert et al. *(79)* exposed mice to copper sulfate aerosol for a longer period of time and were able to replicate these changes in the animals' lungs. The authors concluded that the changes seen in vineyard sprayer's lung are a result of copper sulfate toxicity.

Pimentel and Menezes studied the liver of vineyard sprayers by percutaneous biopsy and also at autopsy *(80)*. They found histiocytic and noncaseating granulomas containing inclusions of copper as identified by histochemical techniques. They also found that the affected individuals were prone to liver fibrosis, cirrhosis, angiosarcoma, and portal hypertension *(81)*.

Copper sulfate is a popular suicidal poison in India *(82)* and copper sulfate was once a very popular homicidal poison *(83)*. Although no reports of suicide and homicide with Bordeaux mixture exist, this is certainly possible. Quite possibly such cases did, and still do, occur but have never been reported.

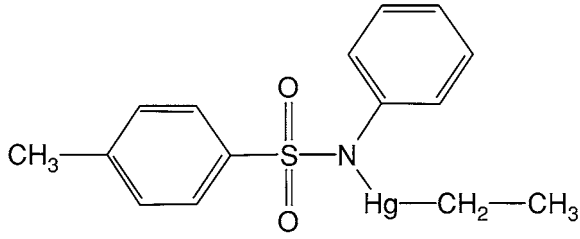

Fig. 19. *N*-ethylmercury-*p*-toluenesulphonanilide.

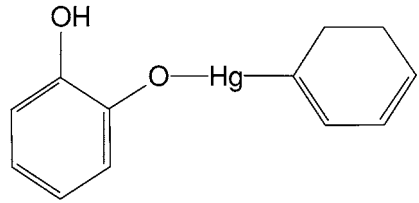

Fig. 20. Phenylmercury derivative of pyrocatechol.

4.3. Mercury

Mercury is widely used as a fungicide in agriculture. Both inorganic and organic salts are used. Inorganic mercury fungicides being used as fungicides include mercuric chloride, mercuric oxide, and mercurous chloride. Organomercury fungicides include (3-ethoxypropyl)mercury bromide, ethylmercury acetate, ethylmercury bromide, ethylmercury chloride, ethylmercury 2,3-dihydroxypropyl mercaptide, ethylmercury phosphate, *N*-(ethylmercury)-*p*-toluenesulphonanilide (Fig. 19), hydrargaphen, 2-methoxyethylmercury chloride, methylmercury benzoate, methylmercury dicyandiamide, methylmercury pentachlorophenoxide, 8-phenylmercurioxyquinoline, phenylmercuriurea, phenylmercury acetate, phenylmercury chloride, phenylmercury derivative of pyrocatechol (Fig. 20), phenylmercury nitrate, phenylmercury salicylate, thiomersal (Fig. 21), and tolylmercury acetate.

The ingestion of wheat and barley seed treated with methyl mercury fungicides for sowing by a largely illiterate population in Iraq led to a major poisoning with mercury in 1971 to 1972 with a high fatality rate *(84)*. The seed—about 95,000 tons of it—was intended for spring planting; there had been ample warning that the seed was unfit for consumption, but this warning was disregarded. There was a latent period of several weeks after which pares-

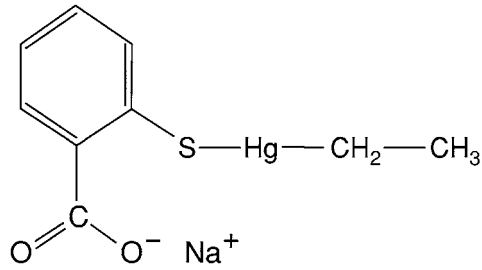

Fig. 21. Phenylmercury derivative of thiomersal.

thesias began to appear in several victims. Paresthesias involved lips, nose, and distal extremities. More serious cases progressed to ataxia, hyperreflexia, hearing disturbances, movement disorders, salivation, dementia, dysarthria, visual field constriction, and blindness. In the most severe cases, individuals remained in a mute rigid posture altered only by spontaneous crying, primitive reflexive movements, or feeding efforts. There were 6520 victims with 500 deaths *(85–88)*. Seven children remained permanently incapacitated both physically and mentally. This was the second major mercury disaster after the Minamata Bay disaster in Japan occurring between 1953 and 1960, when about 1200 people were poisoned and 46 died *(89)*.

Phenylmercury acetate has been found to be embryotoxic and teratogenic *(90)*.

4.3.1. Postmortem Findings in Mercury Poisoning

In deaths caused by acute mercury poisoning, the mucosa of the mouth, throat, esophagus and stomach is greyish in color showing superficial hemorrhagic erosions; a softened appearance of the stomach wall is characteristic. In cases where the patient survived a few days, the large bowel may show ulcerations. The kidneys appear pale and swollen owing to edema of the renal cortex. Microscopically, the kidneys usually demonstrate necrosis of the renal tubules *(23)*.

Sperhake et al. *(91)* reported the case of a 40-year-old chemist who died of mercury poisoning. An autopsy carried out 30 hours postmortem revealed unspecific signs of intoxication including severe edema of the lungs and brain, dilatation of the bowel, and marked congestion of the parenchymatous organs. The stomach contained 30 mL of a reddish fluid. Between the gastric folds, the mucosa appeared highly preserved with a brownish discoloration, but streak-like erosions in the exposed parts. The mucosal surface of the oral cavity and esophagus also appeared brownish and discolored. Histologically, the pre-

served areas of the gastric mucosa were totally unaffected by autolysis with an intact epithelial layer, whereas the eroded areas showed loss of mucosal lining with infiltrates of polymorphonuclear granulocytes and lymphocytes. Mercury was detected in the epithelial layer of the gastric mucosa *in situ* using 1,5-diphenylcarbazone staining (0.2% in 96% ethanol). Tubular necrosis was present in the kidneys.

4.4. Miscellaneous Fungicides

A case of chronic arsenic poisoning in a 75-year-old man has been described; the man used a sodium arsenite-based fungicide for cultivating his vine yard *(92)*.

5. Fumigants

5.1. Methyl Bromide

Methyl bromide (CH_3Br), also known as bromomethane, monobromomethane, embafume, or iscobrome, is mainly used as a gas soil fumigant against insects, termites, rodents, weeds, nematodes, and soil-borne diseases *(93,94)*. It has been used to fumigate agricultural commodities, mills, grain elevators, ships, furniture, clothes, and greenhouses. Its main advantages are its effective penetrating power and absence of danger of fire or explosion hazards.

Methyl bromide acts rapidly, controlling insects in less than 48 hours in space fumigations, and it has a wide spectrum of activity, controlling not only insects but also nematodes and plant-pathogenic microbes *(95)*. About 70% of methyl bromide produced in the United States goes into pesticidal formulations. Pure methyl bromide is a colorless gas that is heavier than air. Odorless and tasteless in low concentrations, it has a musty, acrid smell in high concentrations. Occupational exposure to methyl bromide also occurs frequently. It is estimated that about 75,000 American workers are occupationally exposed to this gas annually. Its toxicity is severe and, despite safeguards, cases of acute and chronic intoxication occur, mainly in the fruit and tobacco industries.

The maximum allowable concentration of methyl bromide is 15 ppm. Concentrations of 70 ppm or less are considered safe. Death has been reported to occur at 8000 ppm *(96)*.

Methyl bromide can enter homes through open sewage connections, thus causing fatalities. Lagard et al. *(97)* reported an interesting case of methyl bromide poisoning where methyl bromide caused toxicity in this manner. The sewage pipes serving two houses (one house was fumigated and in the other the

poisoning occurred) had been sucked empty only 1 to 2 hours prior to the start of fumigation.

Because it depletes ozone into the atmosphere *(95)*, methyl bromide has been banned in several industrialized countries, except for exceptional quarantine purposes. Phosphine, sulfuryl fluoride (*see* Subheading 5.2.), and carbonyl sulfide are considered viable alternatives.

5.1.1. Postmortem Findings and Histopathology

The mucosa of trachea and bronchi is congested and shows petechial hemorrhages. The lungs show subpleural hemorrhages and pulmonary edema. Bilateral bronchopneumonia may also be present.

The brain is edematous with necrosis of cortical cells, especially in the frontal and parietal lobes. Multiple perivascular hemorrhages may be detected throughout the brain and small subarachnoid hemorrhages may be seen in some cases.

Circumscribed hemorrhages may also be present in stomach, duodenum, myocardium, spleen, and retina. The kidneys are acutely congested and show tubular necrosis on the micromorphological level; the proximal tubules are most commonly affected. In severe cases, the loops of Henle and the distal tubules are also affected. The liver is also congested, but liver cell necrosis is not a common feature *(96)*. Methyl bromide can be detected and quantitatively determined in various biological samples by headspace gas chromatography *(98)*.

5.2. Sulfuryl Fluoride

Sulfuryl fluoride (F_2O_2S) is an important agricultural fumigant. According to the 2002 annual report of the AAPCC *(15)*, the only death that occurred as a result of fumigants was caused by sulfuryl fluoride (Fig. 22). It is an inorganic gas fumigant used in structures, vehicles, and wood products for control of drywood termites, wood-infesting beetles, and certain other insects and rodents. It is also used as a gas fumigant for postharvest use in dry fruits, tree nuts, and cereal grains. It is available under the trade name Vikane™ gas fumigant.

Because methyl bromide has now been graded as an ozone-depleting substance and is being gradually phased out, sulfuryl fluoride is taking its place. Because sulfuryl fluoride is an inorganic material, as opposed to the organic methyl bromide, it does not bind onto items being protected and therefore, less quantities of gas are required for the same insecticidal effect.

Sulfuryl fluoride is a colorless and odorless gas. It does not cause tears or immediately noticeable eye irritation and lacks any other warning property. Chloropicrin is added to products containing sulfuryl fluoride to serve as a

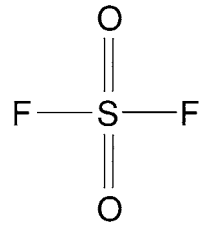

Fig. 22. Sulfuryl fluoride.

warning indicator; chloropicrin is a gas that causes eye and respiratory irritation and vomiting.

Sulfuryl fluoride acts as a CNS depressant. Symptoms of poisoning include itching, numbness, depression, slowed gait, slurred speech, nausea, vomiting, stomach pain, drunkenness, twitching, and seizures. Inhalation of high concentrations may cause respiratory tract irritation and respiratory failure. Skin contact with sulfuryl fluoride normally poses no hazard, but contact with liquid sulfuryl fluoride can cause pain and frostbite-like lesions owing to rapid vaporization. Occupational sulfuryl fluoride exposure may be associated with subclinical effects on the CNS, including effects on olfactory and some cognitive functions *(99)*. The oral LD_{50} for sulfuryl fluoride in rats and guinea pigs is 100 mg/kg.

Scheuerman has reported two cases of suicide by sulfuryl fluoride *(100)*. According to Scheuerman, toxicological analysis should include a plasma and urine fluoride level because the toxic effects of sulfuryl fluoride are probably related to this ion. Concentrations of fluoride in his cases were 20 and 50.42 mg/L, respectively. However, all values have to be interpreted in the light of all information available (kind and length of exposure, symptoms, autopsy findings, etc.) in a given case.

6. Agrochemical Poisoning Associated With Grain Preservation

6.1. Aluminum Phosphide

Aluminum phosphide (AlP) is an ideal grain preservative for a number of reasons. It is highly toxic to almost all stages of insects with remarkable penetration power. AlP dissolves well in water, oil, and fat. It is considered an ideal seed fumigant since the seeds' viability is not affected and is practically free from residual toxic hazards—provided the seeds have less than 20% water content. AlP is minimally absorbed and easily desorbed from the treated commod-

ity, such as wheat grains. It is inflammable at the prescribed dosage and devoid of tainting on fumigated stock. It has a distinct odor, which has been described as a fishy odor. Because of this and also because of delays in evolving, phoshine provides considerable safety in handling this fumigant. Safety in handling is due to both these reasons. Because it has an odor, it is difficult for handlers to accidently ingest it. Because the tablet generates the predetermined weight of gas, it is very convenient to administer the exact dose. Cost of fumigation is low and its effects on the fumigated stock last longer. AlP is easy to transport and handle. Unfortunately, no specific antidote to AlP is known.

AlP is used very extensively throughout agrarian economies like India. On exposure to moisture it releases the poisonous phosphine, which percolates through the grain: $AlP+H_20$ _ $Al(OH)_3+PH_3$.

As long as the grain is stored in airtight godowns, the liberated phosphine remains in the environment, repelling all pests. When the grain is to be used, it is brought out and aerated. This releases phosphine, leaving behind virtually no or only nontoxic residues.

AlP is generally available as tablets (Alphos®, Celphos®, Fumigran®), which are dark brown or grayish in color, 3 g in weight, and measuring 20 mm in diameter and 5 mm in thickness. They come in an aluminum container containing ten tablets. AlP is also available as 0.6-g pellets. The tablets are composed of pure AlP (the active ingredient) and ammonium carbamate/carbonate (the inert ingredient). The ratio of the active and inert ingredient is generally about 56:44. On contact with moisture, each 3-g tablet evolves about 1 g of phosphine along with carbon dioxide and ammonia, which prevents self-ignition of phosphine gas. This is why it is also called a "protective gas." Carbon dioxide and ammonia are liberated by combination of water with other inert ingredients in the tablets. The main function of the inert ingredients is to produce these gases, so phosphine may not ignite easily. The phosphine gas, once liberated, spreads quickly and kills insects and rodents almost in all stages of their development. After complete decomposition of the tablet, AlP is left behind as a harmless and nontoxic grayish white residue, which is less than 25% of the original tablet weight.

AlP is the leading cause of accidental and suicidal deaths in India *(101–105)*. It has been implicated in several homicides including dowry deaths (deaths of newlywed brides occurring in relation to dowry and covered under Section 304 B of the Indian Penal Code).

6.1.1. Postmortem Findings

The mortality rate for poisoning with AlP is almost 50% *(106)*. There is an intense garlic-like odor emanating from the mouth and after opening of the stomach at autopsy. All internal organs are congested and show petechial hem-

orrhages. Pericarditis may be present *(107)*. The stomach contents are hemorrhagic and the mucosa shows detachment. Residues of AlP may be demonstrable in the stomach contents, but rarely can AlP itself be detected because it readily reacts with acid and water within the stomach.

Misra et al. *(108)* described eight cases of AlP poisoning after ingestion of AlP tablets for attempting suicide; the mean age of the patients was 23 years (age range 14–25 years). Six of the patients died; the mean hospital stay was 19 hours (range 4–72 hours). An autopsy was carried out in two patients, revealing pulmonary edema, congestion of the gastrointestinal mucosa, and petechial hemorrhages on the surface of liver and brain.

Anger and co-workers *(109)* reported the case of a 39-year-old man who committed suicide by ingestion of AlP. Autopsy revealed signs of asphyxia with marked visceral congestion. The authors also toxicologically analyzed peripheral blood, urine, liver, kidney, adrenal, brain, and cardiac blood. Phosphine gas was absent in peripheral blood and urine but present in the brain (94 mL/g), the liver (24 mL/g), and the kidneys (41 mL/g). High levels of phosphorus were found in the blood (76.3 mg/L) and liver (8.22 mg/g). Aluminum concentrations were highly elevated in peripheral blood (1.54 mg/L), brain (36 µg/g), and liver (75 µg/g) compared with the reference values.

6.1.2. Histopathology

Histopathological findings in AlP poisoning have been described in detail by Chugh et al. *(106)*. Various viscera show congestion, edema, and inflammatory cell infiltration. In the myocardium, there are patchy areas of necrosis, whereas the liver shows fatty changes and the lung parenchyma displays gray/red hepatization. The adrenal cortex shows complete lipid depletion, hemorrhage, and necrosis. Chugh et al. assumed that the changes in the adrenal cortex could be both a sequel of shock and/or a cellular toxic effect of phosphine. In 20 out of the 30 patients studied by Chugh and associates, there was a significant rise in the plasma cortisol level (>1048 nmol/L). In the remaining 10 patients, the adrenal cortex was critically involved and the cortisol level failed to rise beyond normal levels (<690 nmol/L).

Pillay *(23)* noted that in AlP poisoning the heart shows features of toxic myocarditis, necrosis may be seen histologically in both liver and kidneys, and the lungs may demonstrate evidence of adult respiratory distress syndrome (ARDS). ARDS has also been reported by Chugh et al. *(110)*. The dose of the intoxicant in Chugh's cases varied from two g) to three tablets (corresponding to 6 and 9 g, respectively). All patients were in shock at admission and developed ARDS within 6 hours after ingestion of AlP. According to these authors, the exhalation of phosphine (which they detected by a positive silver nitrate paper test) was the possible noxious triggering factor in developing ARDS.

In Misra at al.'s series *(108)*, histopathological changes included pulmonary edema, desquamation of the lining epithelium of the bronchioles, vacuolar degeneration of hepatocytes, dilatation and engorgement of hepatic central veins and sinusoids, as well as hepatocytes showing nuclear fragmentation.

In Anger's single case *(109)*, microscopic examination revealed congestion of inner organs and pulmonary lesions that were attributed to asphyxia.

6.2. Silo Filler's Disease

Silo filler's disease is another disorder associated with agrochemical poisoning during preservation. Corn used for silage is usually grown under conditions of heavy sunlight and drought and its nitrate content is usually very high. When this silage is stored in a silo, the nitrates are fermented into nitrites, which in turn combine with organic acids to form nitrous acid. Nitrous acid decomposes into water and a mixture of nitrogen oxides. These are nitric oxide (NO), nitrogen dioxide, and dinitrogen tetroxide. The decomposition starts within approx 4 hours of putting the crops into the silo and continues for about 10 days. When entering these silos (which virtually turn into a kind of gas chamber), farm workers may suffer acute poisoning from these gases, and many such deaths have occurred. This type of death in a silo was first described in 1914, but at that time it was wrongly attributed to asphyxia *(111)*.

6.2.1. Pathophysiology

NOs, being relatively poor soluble in water, can reach the terminal bronchioles and even alveoli. Within the lungs, the NOs react with water to form nitrous and nitric acids, which cause extensive lung damage, resulting in chemical pneumonitis and profuse pulmonary edema. NOs trigger histamine release, which causes bronchoconstriction resulting in increased airway resistance.

6.2.2. Postmortem Findings

Douglas and colleagues *(112)* examined 17 patients of silo filler's disease between 1955 and 1987. All exposures had occurred in conventional top-unloading silos. Acute lung injury occurred in 11 patients, one of whom died. In the fatal case, autopsy findings included early diffuse alveolar damage with hyaline membranes, hemorrhagic pulmonary edema, and acute edema of the airway walls.

7. Fertilizers

Poisoning with and fatalities owing to fertilizers are rarely encountered but do occur. The 2002 annual report of the AAPCC Toxic Exposure Surveillance System reported one death caused by fertilizers *(15)* (Table 6).

Table 6
Exposures to Various Different Categories of Fertilizers and One Fatal Case

Fertilizer	Number of toxic exposures	Deaths
Household plant food	3533	0
Outdoor fertilizer	4554	0
Plant hormone	90	0
Other	1858	0
Unknown	597	1
Total	**10,632**	**1**

Data taken from ref. 15.

Used as a fertilizer, anhydrous ammonia is a respiratory irritant, which, in high doses, causes pulmonary edema (113). Exposure most often occurs during transfer operations. Ammonia reacts with water to form the strong alkali ammonium hydroxide, which causes severe tracheobronchial and pulmonary inflammation with bronchiolitis obliterans. Normally, the peculiar odor of ammonia warns the potential victim. During World War II, in London, a brewery cellar having ammonia-carrying condenser pipes was temporarily converted into a bomb shelter. During a bombing, a bomb fragment pierced one such pipe resulting in a mortality rate of the affected individuals as high as 63% (114).

Saito et al. (115) described the case of a 70-year-old male who presumably consumed water contaminated with a nitrate fertilizer. On admission to hospital, the man showed drowsiness, deep cyanosis, and dyspnea; the patient died 7 hours later. At autopsy, no particular morphological changes were noted except for the blood being a chocolate-brown color. Postmortem toxicology of the blood revealed a methemoglobin concentration of 78% and the concentrations of nitrate and nitrite were 1.50 and 0.76 µg/mL, respectively. In deaths caused by nitrate fertilizers, methemoglobinemia and the presence of appreciable quantities of nitrites and nitrates may be demonstrated in cardiac blood and gastric contents (stored at –80°C until toxicological analysis) (115). Capillary gas chromatography-mass spectrometry and capillary gas chromatography with a nitrogen–phosphorus detector can be used to detect nitrates and nitrites in blood.

Sato and colleagues (116) described the case of an 85-year-old woman who supposedly consumed agricultural fertilizer containing ammonium sulfate. She was found lying dead on the ground outside her house. A thorough autopsy could not determine the cause of her death. A beer can was found next to her, and when it was examined, it was found to contain ammonium sulfate. Subsequently, ammonium and sulfate ions were detected in her serum samples and

gastric contents. The cause of her death was determined as poisoning by ammonium sulfate. In order to further confirm that this death was indeed a result of an ammonium sulfate fertilizer, the authors administered a total dose of 1500 mg/kg of ammonium sulfate to three rabbits. The animals developed mydriasis, irregular respiratory rhythms, and local and general convulsions until they came into respiratory failure with cardiac arrest. Electroencephalogram showed slow, suppressive waves and a high-amplitude with a slow wave pattern that is generally observed clinically in hyperammonemia in humans and animals. There was a remarkable increase in the concentration of ammonium ions and inorganic sulfate ions in the animals' serum and blood gas analysis showed severe metabolic acidosis. The authors suggested that when the cause of death can not be clearly determined and the previous history is suggestive of ammonium sulfate intake, measurement of ammonium ions, inorganic ions, and electrolytes in blood, as well as in stomach contents, are a prerequisite for the diagnosis.

Villar and co-workers reported poisoning and death in animals who drank fertilizer-contaminated water *(117)*. The water had been hauled in tanks previously contaminated with a nitrogen-based fertilizer.

In Udaipur, India, chronic fluorotic lesions in cattle and buffalo have been described following consumption of fodder and water contaminated by the fumes and dusts emitting from superphosphate fertilizer plants *(118)*. Similar lesions have been reported from Australia where the main source of fluoride appeared to have been gypsum that was included in a feed supplement and also ingested from fertilizer dumps on paddocks *(119)*. Gypsum fertilizers have caused several deaths in animals *(120)*. Similar morbidity and mortality may be seen in humans who drink contaminated water either intentionally or out of ignorance as well. The latter situation is quite possible among the uneducated farmers of agrarian economies.

Adrian *(121)* drew attention to a very unique situation of poisoning related to fertilizers. In several countries, sewage sludges are used on farms as fertilizers because they do contain these materials. However the sewage—not surprisingly—also contains industrial wastes, such as chromium, lead, zinc, cadmium, and mercury. When this sewage is used as fertilizing material, plants tend to concentrate these heavy metals, especially chromium. Ingestion of such farm produce may lead to heavy metal poisoning. Several other cases of fertilizer poisoning, especially among animals, have been reported, too *(122–129)*.

In several countries, poisonous plants, such as castor, are used as green manure which can cause poisoning of both humans and animals. Soto-Blanco and colleagues from the University of Sao Paulo, Brazil, described a case of canine poisoning where castor bean (*Ricinus communis*) cake was used as a fertilizer *(130)*. The authors stressed that these cakes may be accidentally ingested

by humans as well, and recommended that cake production should include heat treatment to denature the poisonous proteins.

8. *Miscellaneous*

Nematicides can cause poisoning in banana plantations. Wesseling and co-workers, studying pesticide-related illness and injuries among banana workers in Costa Rica, reported that workers at highest risk per time unit of exposure were nematicide applicators *(47)*.

Slugs are major pests of oilseed rape that are poorly controlled by conventional bait pellets. Therefore, compounds, such as metaldehyde and methiocarb, are used as seed dressings to control slugs *(131)*. Metaldehyde is a popular molluscicide that can cause fatal poisoning; the 2002 AAPCC annual report *(15)* mentions as many as 199 cases of exposure to this agent. Kiyota *(132)* reported the case of a 55-year-old mentally retarded man suffering from pica, who ingested about 2.7 g of metaldehyde. Despite medical treatment, he developed acute lung injury and died after 33 days; he was found to have ascites and splenomegaly. High-performance liquid chromatography revealed 80.6 µg/mL metaldehyde in the serum. Jones et al. *(133)* developed a method to detect metaldehyde in samples of stomach contents by gas chromatography-ion trap mass spectrometry for forensic toxicology investigations. A suicide attempt using metaldehyde was reported by Hancock and co-workers *(134)*. A case of homicide using metaldehyde has been described by Ludin *(135)*. Detailed overviews of metaldehyde toxicity have been provided earlier by Booze and Oehme *(136)* and Longstreth and Pierson *(137)*.

Avermectins used as acaricides (avermectin acaricides), insecticides (avermectin insecticides), and nematicides have been used for suicidal poisoning. Chung and co-workers *(138)* from Taiwan studied the clinical spectrum of avermectin poisoning reported to a Poison Center from September 1993 to December 1997. Eighteen patients with abamectin (Agri-Mek; 2% wt/wt abamectin) exposure and one with ivermectin (Ivomec; 1% wt/vol ivermectin) ingestion were identified (14 males, 5 females; age range 15–83 years). Fourteen out of the 18 patients had been exposed as a result of attempted suicide; one patient died 18 days later as a result of multiple organ failure.

Algicides have not been reported to cause fatal poisoning in humans; minor ailments owing to algicide exposure include, e.g., contact dermatitis *(139)*.

Aphicides are known to persist in crops *(140)*; their toxicity in house sparrows has been described in detail by Tarrant and co-workers *(141)*.

Bird repellants are trigeminally mediated avian irritants *(142)*. Toxic effects to humans have apparently not been reported so far.

Chemosterilants are chemicals that aim at destroying the fertility of pests. 1,2-dibromo-3-chloropropane is used to induce infertility in rats *(143)*. The chemosterilant bisazir is extremely hazardous. Ciereszko and co-workers *(144)* have recommended that special safety measures are necessary when handling this chemical. However, toxic effects to humans have not been reported in the medical literature so far.

Antifeedants are chemicals having tastes and odors that inhibit feeding behavior. Several chemicals, such as silphinene sesquiterpenes *(145)*, 1,3,4-oxadiazoles *(146)*, and ryanoid diterpenes *(147)*, are used as antifeedants; again, toxic effects to humans have not been reported so far.

Herbicide safeners are compounds protecting crops from herbicide injury by increasing the activity of herbicide detoxification enzymes such as glutathione-*S*-transferases *(148–150)* and cytochrome P-450s. Several herbicide safeners are used in agriculture such as benoxacor *(151)* and dichloroacetamide *(152,153)*; there toxicity in humans has not been reported so far.

Insect attractants attract or lure an insect to a trap. Several of them are available, such as Boll Weevil Attract and Control Tubes® (Plato Industries, Houston, TX) *(154)*, imidacloprid *(155)*, and GF-120 fruit fly bait *(156)*. Their toxicity has been studied in detail by Beroza et al. *(157)*.

The secondary effects of conventional insecticides on the environment, vertebrates, and beneficial organisms have caused a move to the use of more target-specific chemicals, such as insect growth regulators (IGRs) *(158)*. IGRs are chemicals disrupting the action of insect hormones controlling molting, maturity from pupal stage to adult, or other insect life processes. Several IGRs are known, such as halofenozide *(159)*, *S*-methoprene *(160,161)*, buprofezin *(162)*, tebufenozide *(163)*, the chitin synthesis inhibitors teflubenzuron, diflubenzuron *(164)*, and hexaflumuron, as well as the juvenile hormone mimic pyriproxyfen *(165)*. Halofenozide (RH-0345) is a novel nonsteroidal ecdysteroid agonist that induces a precocious and incomplete molt in several insect orders *(158)*. The antifeedant 1,3,4-oxadiazoles also show a considerable amount of IGR activity *(146)*. The toxicity of these antifeedants to animals has been studied by Wright *(166)*.

Pesticide synergists are chemicals that, although they do not possess inherent pesticidal activity, they nonetheless promote or enhance the effectiveness of other pesticides when used combined (synergism). Synergists usually increase the toxicity of a pesticide so that a smaller amount is needed to bring about the desired effect. This may reduce the cost of application. An example of a synergist is piperonyl butoxide, often used with pyrethrin, pyrethroid insecticides, rotenone, and carbamate-containing pesticides. Piperonyl butoxide is a liver toxicant and a possible human carcinogen *(167,168)*; it also inhibits T-cell activation and function *(169)*.

Avicide 4-aminopyridine (4-AP) is a rapidly fatal nervous system toxin. It dramatically enhances transmission at the neuromuscular junction and other synapses. 4-AP has been employed clinically in the treatment of prolonged paralysis caused by antibiotics and muscle relaxants and in the Eaton-Lambert syndrome. Spyker et al. *(170)* reported on three men who were poisoned with 4-AP. Bischoff et al. *(171)* more recently again stressed the fact that 4-AP can cause poisoning in humans and may cause seizures.

3-Chloro-*p*-toluidine hydrochloride (CPTH) is an aniline derivative registered as a selective, low-volume-use (<45 kg/yr) avicide. Rice baits are treated with CPTH to cause poisoning in birds harmful to crops *(172)*. CPTH may be mutagenic. Stankowski et al. *(173)* conducted three in vitro mutagenicity tests of CPTH according to methods recommended by the United States Environmental Protection Agency, e.g., the Ames/Salmonella assay, the Chinese hamster ovary (CHO)/hypoxanthine-guanine phosphoribosyl-transferase mammalian cell forward gene mutation assay, and the CHO chromosome aberration assay. They found that CPTH did not display mutagenic activity using the Ames/Salmonella or CHO/hypoxanthine-guanine phosphoribosyl-transferase assays. However, CPTH induced statistically significant, concentration-dependent, metabolically activated increases in the proportion of aberrant cells. The authors concluded that the results were suggestive of minimal mutagenicity effects associated with exposure to CPTH *(173)*. Stahl and co-workers draw attention to the consumption of CPTH treated rice baits by nontargeted bird species, such as pigeon (*Columbia livia*) and house sparrow (*Passer domesticus*). CPTH can persist in the breast muscle tissues of both targeted and nontargeted birds which may be a potential secondary hazard to scavengers and predators *(174)*. Toxicity of CPTH both in humans and animals has been discussed by several other authors as well *(175–179)*.

If a particular agrochemical poison has been banned in a country, it is not necessarily that poisoning with this agent will not be seen in that particular country. For example, in Japan, production of Azomite emulsion (an acaricide) has been stopped since 1973. However, Moriya et al. in 1991 *(180)* described a recent Azomite-related fatality. Poisoning with Azomite was confirmed when aramite and azoxybenzene, two effective components of Azomite emulsion, were detected in the patient's serum when qualitatively analyzed with gas chromatography-mass spectrometry. The authors concluded that even if an agrochemical poison is banned, the pathologist must still keep the possibility of its ingestion in mind.

Many times, it is not the active agricultural chemical that is responsible for poisoning but impurities (such as dioxin), surfactants (e.g., polyethoxylated tallow amine used with glyphosate) and adjuvants used along with the chemical. These adjuvants, or "inert" ingredients, could be solvents, stabilizers,

preservatives, sticking or spreading agents, or defoamers *(181)* and may constitute petrochemical solvents, such as acetone, fuel oil, toluene, and other benzene-like chemicals. These could sometimes be *more* toxic than the active ingredient. Rubbiani drew attention to several of these adjuvants and clinical syndromes produced by them *(182)*. According to Harry *(4)*, toxicity is often due to solvents or surfactants included in the composition of a formula used as an agricultural chemical. When the obligatory declaration on the label about identity and concentration of some of these substances is not provided by the actual legislation in a particular country, the problem becomes more acute. It is also often difficult to determine if the cause of the poisoning is the actual agricultural chemical itself or its adjuvants.

Metabolites are breakdown products that form when a pesticide is exposed to air, water, soil, sunlight, or living organisms and often the metabolite is more hazardous than the parent compound.

9. Medicolegal Aspects of Agrochemical Poisoning

An estimated three million cases of agrochemical poisoning are reported from around the world every year, making it one of most serious toxicological problems of the present times. An overwhelming majority of these—more than 90%—are reported from developing countries, such as India, presumably because these are predominantly agrarian economies. In the United Kingdom, pesticides are responsible for only about 1% of deaths *(183)*, whereas in United States, as seen in Table 3, the figure varies between 1 and 2%. The equivalent figures in India have been reported to be as high as 70% *(23)*. Figure 23 shows some common pesticides used in India.

9.1. Accidental Poisoning

Accidental poisoning may occur in a number of ways. Accidental poisoning can occur if the insecticide is stored inadvertently with foodstuffs *(184)*. One of the most shocking cases of mass agrochemical poisonings occurred in the Indian state of Kerala in 1958 (known popularly as the "Kerala food poisoning case of 1958") when bags of foodstuffs, such as wheat and sugar, were inadvertently stored together with those of Folidol (parathion) in the same cabin on a ship *(23)*. The insecticide leaked and contaminated the foodstuffs; more than 1000 people were accidentally poisoned when they consumed these contaminated foodstuffs. Out of these, more than 100 people died.

Mixing of pesticides with foodstuffs may be intentional, albeit entirely because of ignorance and without any criminal intent. Such a case came to notice in the late 1970s in Lakhmipur in Kheri district, in the Indian state of

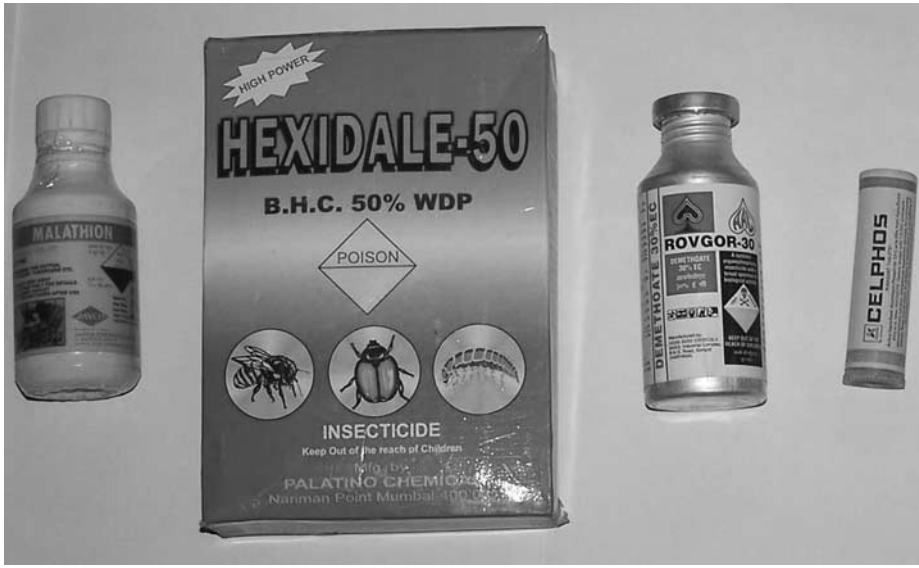

Fig. 23. A smorgasbord of pesticides used in India. (Courtsey of Dr. Avneesh Gupta and Dr. Puneet Setia, Maulana Azad Medical College, New Delhi, India.)

Uttar Pradesh. Farmers in this state were found to be preserving food grains with benzene hexachloride. A severe convulsive epidemic broke out among several hundred people because of this ignorance and more than 250 people died.

In 1997, improper use and application of benzene hexachloride in the town Sunser in the Indian state of Madhya Pradesh resulted in many people falling ill. Fortunately, no human died, but there were reports of several bird casualties.

In March 1999, a case of agricultural poisoning from India was reported where an entire family was poisoned owing to leakage of pesticides into cereal (sorghum/jowar) stored in the same room *(185)*.

The Indian state of Kerala is a major cashew growing region. There have been attempts at aerial spraying of this cash crop with endosulphan. Because these areas are close to local residential areas, deleterious effects occurring in humans have caused a major controversy in recent times *(23)*.

Pillay *(40)* suggests that accidental poisoning due to pesticides can occur in four different scenarios: (a) occupational exposure among agriculturists and those engaged in the task of pesticide spraying, (b) contamination of foodstuffs on account of negligence, (c) inadvertent ingestion by children, and (d) reusing

pesticide containers for storing food or drink (the latter is very common among third-world countries).

Instances of fatalities among agricultural workers due to accidental exposures have been reported from time to time *(186)*. Accidental poisoning owing to some pesticides, such as paraquat, occurs in a number of scenarios, e.g., when the mouthpiece of fumigation equipment is sucked by the operator while cleaning and it is suddenly cleared of obstruction, confusion under the influence of alcohol, consumption of contaminated water or foods, accidental ingestion by children, and accidental cutaneous exposure or oral topical application for toothaches by ignorant persons *(187)*.

Robert G. Book of Bloemfontein, South Africa, reported a unique case of accidental poisoning with paraquat: a young woman tried to "achieve a high" by spiking her Coca-Cola with paraquat. She died after a few days of hospitalization. At the time of her admission she had told the doctor that her husband had maliciously put paraquat in her drink a few days before; however, only 2 days later she changed her version as just mentioned *(188)*. It is noteworthy that in India it is very common for married women at the time of their death to shield their murderous husbands by making such statements. Whether the woman's first or second statement was correct is anybody's guess.

According to Harry *(4)*, accidental pesticide intoxications are mainly caused by ingestions of diluted fertilizers, low-concentration antivitamin K rodenticides, ant-killing products, or granules of molluscicides containing 5% metaldehyde, whereas voluntary intoxications are mostly by chloralose, strychnine, organophosphorus or organochlorine insecticides, concentrated antivitamin K products, and herbicides, such as paraquat, chlorophenoxy compounds, glyphosate, and chlorates.

9.2. Suicidal Poisoning

Suicidal poisoning with agrochemicals, especially organophosphates and AlP, is very common in countries like India. One of the main reasons is the easy availability of these agrochemicals. Many companies now add an emetic to dangerous agrochemicals, such as paraquat and AlP. Addition of a "stenching" agent to paraquat has apparently not deterred suicidals from consuming this poison.

9.3. Homicidal Poisoning

9.3.1. Organophosphorus and Organochlorines

Homicidal poisoning with organophosphorus compounds is possible and from time to time, one gets to hear or read about cases of a homicide commit-

ted with these substances. Svraka and colleagues have described four cases of homicide with organophosphorus compounds *(189)*.

However, homicidal poisonings with organophosphorus compounds are rare because of the unpleasant taste of most agrochemicals, especially of organochlorines, such as endrin, but they have been mixed with alcohol, especially Toddy (a strong liquor that is very popular in India), which masks its smell and has been used with organophosphorus compounds for homicidal purposes in this way.

Homicidal poisoning with parathion is much easier *(190–193)*. To prevent this, a coloring agent, such as indigocarmine, is added to parathion. This is, however, not a universal practice. In India for instance, addition of indigocarmine to parathion is not practiced.

9.3.2. Paraquat

The commonly used herbicide paraquat is odorless and gives rise to symptoms mimicking viral pneumonitis. These two properties—classically hailed as the properties of an ideal homicidal poison—make it very attractive as a homicidal poison. Paraquat is supposed to have a burning taste, but this can be masked in hot liquids or spicy foods *(194)*. Several homicide cases with paraquat undoubtedly must have gone unnoticed.

Teare and Teare and Brown *(46,195)* described five cases of paraquat poisoning, of which, two were homicidal in nature. The first is a well-documented case (*Reg vs Kenyon and Roberts*) in which a 22-year-old man, Keith William Kenyon, was killed by his wife Jennifer Kenyon and her friend, David Roberts, a consultant on the effects of agricultural chemicals. She purchased Gramoxone along with her friend Olive Hemming (who turned out to be the chief prosecution witness) from a farm shop, and most likely administered it to her husband in repeated small doses. Kenyon was taken ill on November 18, 1973 and died 13 days later, on December 1. During his illness, he displayed all the classical symptoms and signs of paraquat poisoning. Postmortem examination confirmed death by paraquat intoxication. Mrs. Kenyon was convicted of murder, whereas David Roberts was acquitted because of lack of evidence against him *(195)*. The second case occurred only 1 month later. After Christmas 1973, on the Falkland Islands, four local agricultural workers had been having a Boxing Day party when some Gramoxone was slipped for some unknown reason into one of their beers. The man died after displaying typical symptoms of paraquat poisoning. Autopsy confirmed poisoning by paraquat. Criminal charges against the other three laborers were contemplated, but eventually it was decided to drop them.

Paul *(196)* described the case of a 28-year-old woman who killed her husband by mixing paraquat in his steak-and-kidney pie twice. When he developed

a sore throat and was prescribed medicine for treatment, she mixed paraquat in the medicine as well. The husband died on June 27, 1981 after suffering a 24-day illness. The cause of death was attributed to cardiac arrest in combination with renal failure and bilateral pneumonia and it was only by a curious chain of circumstances that paraquat was detected in the young man's tissues preserved in the mortuary in a bucket, 8 months after the man's death. His wife and her paramour were found guilty and sentenced.

Stephens and Moormeister from the Medical Examiner's Office of San Francisco, CA, reported four cases of homicidal poisoning by paraquat *(194)*. Of these, the first three murders were perpetrated by one man against members of his immediate family, and the fourth case was equivocal—it could either have been suicide or homicide. The first three murders were committed by a man who had been married five times. His first three wives were alive and healthy. When the fourth wife threatened to divorce him, she found herself ill and died 24 days after the onset of her illness (19 days after hospitalization). Eight years later, when his fifth wife threatened divorce, she suffered the same fate, and a few months later, his 79-year-old mother also died. All three showed typical symptoms of paraquat poisoning. The postmortem findings seemed to suggest natural disease of the lungs. Although a suggestion of paraquat poisoning was made in all three cases, the concerned pathologist was reluctant to sign death certificates as paraquat poisoning. Toxicological analysis in the second and third cases revealed the presence of paraquat in the victims' tissues and this resulted in conviction of the murderer. It was found that the defendant worked as a mechanic on a large agricultural ranch and had easy access to paraquat; his thumb print was found on one of the opened paraquat containers, although he had earlier denied having to do anything with those containers. The fourth case involved a 27-year-old man, a registered herbicide and pesticide user, who had marital difficulties with his aggressive, "shrew-like" wife who also stood to benefit from a large insurance policy upon his death. While in hospital, the victim denied suicidal ingestion; he died 21 days after the start of his illness. No testing of toxic effects from the compounds he worked with was ever performed, nor was any consideration given to this possibility. The case did not result in court charges for anyone. Stephens and Moormeister concluded that the reason why such cases will often go unnoticed is because of the reluctance on the part of both clinicians and forensic pathologists to even think in the direction of paraquat poisoning when they see such a clear and typical picture of "viral pneumonia." In their opinion, the clinician should suspect paraquat ingestion in all cases in which there is progressive pulmonary involvement with no features of viral infection *(194)*. The pathologist conducting the postmortem would do well to go through the clinical history, if available, in detail to rule out

the possibility of paraquat poisoning. In all doubtful cases, a full toxicological analysis should be done and the tissues should be particularly analyzed for paraquat.

Daisley and Simmons from the University of the West Indies in Trinidad reported two cases of homicide by paraquat poisoning *(197)*. Both cases occurred in children and the common clinical presentations were gastrointestinal ulceration and acute respiratory distress with pneumomediastinitis. At autopsy, the most prominent finding was bullous lung emphysema. The authors stress that pathologists should be aware of this finding because they feel that if this autopsy finding is seen combined with the typical clinical presentation mentioned in Sections 3.2.1. and 3.2.3., it is almost diagnostic of acute paraquat poisoning. Da Costa et al. have dealt with the medicolegal aspects related to paraquat poisoning in detail *(198)*.

9.3.3. Sodium Chlorate

Another weed killer that has been used commonly for homicidal purposes is sodium chlorate. In *Reg vs Hargreaves*, Hampshire (Winchester) Assizes, April 1962, a 54-year-old woman was charged with the murder of a 78-year-old man whom she had known for the last 50 years as an uncle. In August 1960, he made his last will, written out by the accused in her favor. On January 10, 1961 the accused bought the weed killer sodium chlorate apparently for a friend who was a gardener. On January 19, 1961, the old man died and the postmortem examination showed signs of death from sodium chlorate poisoning. The victim had consumed beer and the remaining beer in the mug contained some 65 mg of sodium chlorate. The jury found the woman guilty of manslaughter and sentenced her to 18 months of imprisonment *(199)*.

9.4. Agent Orange

One of the biggest and most well-known medicolegal controversies in connection with herbicides has been that of Agent Orange. Agent Orange is the name given to a mixture of herbicides that United States military forces sprayed in Vietnam from 1962 to 1971 during the Vietnam War for the dual purpose of destroying crops that might feed the enemy and defoliating forest areas that might conceal Viet Cong and North Vietnamese forces.

The defoliant consisted of approximately equal amounts of the unpurified butyl esters of 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Agent Orange also contained small, variable proportions of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin—commonly known as dioxin—which is a byproduct of the manufacture of 2,4,5-T and is toxic even in minute quantities; dioxin is considered one of the most toxic compounds synthesized by humans.

Agent Orange was delivered in 55-gallon drums with an orange stripe to distinguish the drums visually from those containing other chemical agents (hence the name). About 50 million liters of Agent Orange were sprayed over Vietnam from low-flying aircrafts. Among the Vietnamese, it is considered to be the cause of an abnormally high incidence of miscarriages, skin diseases, cancers, birth defects, and congenital malformations (often extreme and grotesque).

Alterations in manufacturing procedures had reduced the dioxin content in Agent Orange later to minimal levels. Today, 2,4,5-T registrations have been cancelled and Agent Orange was voluntarily removed by the manufacturers in 1985.

Many United States, Australian, and New Zealand servicemen who suffered long exposure to Agent Orange in Vietnam later developed cancer and other health disorders. A class-action lawsuit was brought against seven herbicide makers that produced Agent Orange for the United States military. The suit was settled out of court with the establishment of a $180,000,000 fund to compensate some 250,000 claimants and their families. Separately, the United States Department of Veterans Affairs awarded compensation to about 1800 veterans.

Agent Orange has now been replaced by Agent White, a mixture of 2,4-D and picloram, which is longer lasting and more effective.

9.5. Pesticides and the Law

In the United States, The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) was passed in 1962 (amended in 1974, 1978, and 1988 *[200]*). This act divides all pesticides in four broad classes depending on their toxicity. The label of each pesticide has to contain a signal word depending on its toxicity. The criteria established by the FIFRA are given in Table 7.

According to the FIFRA, toxic category I pesticides must have the signal words DANGER and POISON (in red letters) and a skull and crossbones prominently displayed on the package label. The Spanish equivalent for danger, PELIGRO, must also appear on the labels of highly toxic chemicals. Toxic category II pesticides must have the signal word WARNING (AVISO in Spanish) displayed on the product label. Toxic category III pesticides are required to have the signal word CAUTION on the pesticide label. Toxic category IV pesticide products shall bear on the front panel the signal word CAUTION on the pesticide label. Pesticides formulated in petroleum solvents or other combustible liquids must also include the precautionary word FLAMMABLE on the product label. This was obviously done to prevent

Table 7
Criteria of Pesticide Toxicity, Established by the Federal Insecticide, Fungicide and Rodenticide Act of 1962

Category	Signal Word	Toxicity	Acute Oral LD50	Inhalation LC50	Dermal LD50
I	**DANGER** and **POISON**	High	0–50 mg/kg	Up to 0.2 mg/L	Up to 200 mg/kg
II	**WARNING**	Moderate	50–500 mg/kg	0.2–2 mg/L	200–2000 mg/kg
III	**CAUTION**	Low	500–5000 mg/kg	2–20 mg/L	2000–20,000 mg/kg
IV	**CAUTION**	Relatively safe	> 5000 mg/kg	> 20 mg/L	>20,000 mg/kg

LC/LD_{50}: concentration/dose which causes death in 50% of the exposed subjects.

cases of accidental poisoning, and similar acts exist in almost all countries. In India, a predominantly agricultural country, handling of insecticides is governed by The Insecticides Act 1968 and The Insecticide Rules, 1971 (amended in 1993) *(201)*. Section 19 of The Insecticide Rules, 1971 classifies insecticides on a similar basis. Section 19 also insists on affixing a label to the insecticide container in such a manner that it cannot be ordinarily removed. Among other things, it must contain a square, occupying not less than one-sixteenth of the total area of the face of the label, set at an angle of 45° (diamond shape). This square is to be divided into two equal triangles, the upper portion of which shall contain the signal word, and the lower portion the specified color. The classification of insecticides, signal words to be used, and the color of the identification band on the label according to The Insecticide Rules, 1971 of India are given in Table 8.

If a pesticide is misused in any way, the person who bought and stored the pesticide may be legally responsible. In the United States, The Food Quality Protection Act was passed in 1996 as a complementary set of regulations, which, among other important features, specifically recognizes the special situations and usages of pesticides for public health. These laws regulate the registration, manufacture, transportation, distribution, and use of pesticides. The regulations are administered by the Environmental Protection Agency.

Table 8
Classification of Insecticides, Signal Words To Be Used and Color of Identification Band To Be Used on the Label According to "The Insecticide Rules, 1971" of India

Classification of insecticide	LD50 (oral) in mg/kg of test animals	LD50 (dermal) in mg/kg of test animals	Signal word (to be incorporated in the upper portion of the square)	Color of identification band on the label (to be incorporated in the lower portion of the square)
1. Extremely toxic	1–50	1–200	*POISON*	Bright red
2. Highly toxic	51–500	201–2000	**POISON**	Bright yellow
3. Moderately toxic	501–5000	2001–20,000	**DANGER**	Bright blue
4. Slightly toxic	More than 5000	More than 20,000	**CAUTION**	Bright green

LD_{50}: lethal dose in 50% of the exposed subjects

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