Agricultural Poisons:

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Classification According to Toxicity:

1) Least toxic (generally not fatal):

i) Phenoxyacetic acid
ii) Cuprous oxide
iii) Tar oil emulsion
iv) Tea tree oil
v) Neem oil
vi) Jojoba oil
vii) Rosemary oil
viii) Petroleum washes.

2) Mildly toxic [Fatal dose > 10g]:

i) Chlorinated hydrocarbon insecticides
- DDT
- Gammexane
- Methoxychlor
- Aldrin

ii) Sodium chlorate

3) Highly toxic [fatal dose < 10g]:

i) Arsenic compounds
ii) Nicotine, sulphates, tannates
iii) HCN, KCN, NaCN
iv) Dinitrophenol, dinitro - orthocresol
v) Organophosphorus (OP) compounds
- ⇒ Tetraethylpyrophosphate (TEPP)
- ⇒ Hexaethyl tetraphosphate (HETP)
- ⇒ Parathion

Classification of Insecticides:

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1) Insecticides of vegetable origin:
   - i) Nicotine
   - ii) Pyrethrins
   - iii) Rotenone
2) Chemical Insecticides:
   - i) Inorganic – compounds of Arsenic, Barium, Mercury, etc.
   - ii) Organic – organophosphorus (OP) compounds
     - Carbamates
     - Organochlorines [oc]
     - Indane derivatives [aldrin, dieldrin]
   - iii) Chlorobenzene derivatives – DDT
   - iv) Benzene hexachloride / Lindane / gammexane
   - v) Chlorinated camphenes.

Classification of OP Compounds:

1) Alkyl phosphates:
   - Dimefox
   - Malathion
   - Trichlorfon
   - HETP
   - TEPP
   - Dimefox
2) Aryl phosphates:
   - Chlorthion
   - Methyl parathion
   - Paraoxon
   - Diazinon
   - Parathion (nitrostigmine)

OP Compounds:

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Absorption:

→ well-absorbed from — skin, lung, GIT, mucus membranes, etc.

Distribution: widely distributed in the body

→ readily crosses placenta

→ Lipophilic ∴ crosses the BBB.

Metabolism:

→ Major sites: liver & blood

Elimination:

→ Prolonged ⇒ over a week

Mechanism of Action: AchE - I

→ Powerful inhibitors of Acetylcholinesterase & pseudocholinesterase

$$Ach + H_2O \xrightarrow{AchE} Choline + acetate$$

OP

→ Bond formed between OP & AchE is strong & cannot be displaced even by high concentrations of Ach.

→ Deactivation of AchE → Accumulation of Ach molecules at { parasympathetic, ganglionic & neuromuscular synapses → Overstimulation

→ OP also inhibits Neuropathy Target Esterase [NTE] → OPIDP

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→ If ChE reactivators (oximes) are not given in time, ChE undergoes aging.

- OP-ChE complex undergoes dealkylation

↓

OP-ChE conjugate becomes extremely stable

↓

even oximes cannot react with ChE

∴ oximes must be given within first few hours of poisoning.

Acute Poisoning:

I] Clinical Features:

→ ocular exposure causes persistent miosis.

→ onset of symptoms is most rapid following inhalation

→ Order of impact: Secretory glands → Involuntary muscles → Voluntary muscles → Vital brain centres

a) Muscarinic Manifestations:

→ Cyanosis

→ Pupils: constricted

- Ciliary body: Blurred vision

→ Glands: ↑ secretions

- ↑ lacrimation, chromodacryorrhea (bloody tears)
- ↑ salivation

→ Bronchoconstriction, ↑ bronchial secretions (bronchorrhea), dyspnea

leading cause of death

→ Pulmonary edema

→ CVS: • Bradycardia • Hypotension • ECG changes — prolonged PR interval
— ST-T changes

→ GIT: • Anorexia • Nausea, vomiting • Diarrhea • Fecal incontinence

→ spontaneous abortion during pregnancy

→ Urinary incontinence

b) Nicotinic Manifestations:

→ Striated Muscles: • Initial contraction (cramps) → paralysis
• fasciculations

→ Sympathetic ganglia: • Hypertension • Tachycardia • Pallor
• Mydriasis

↳ opposite of muscarinic effects

Generally, Muscarinic effect > Ganglionic effect

c) CNS Manifestations:

→ Initially: • Ataxia • Emotional lability • Tremor
• Confusion • Slurred speech • Restlessness

→ Later: • Depression of respiratory & CVS centres
• Drowsiness • Hypothermia • Convulsions • Coma

II] Diagnosis:

a) Depression of ChE Activity:

	Normal Activity in Men	Normal Activity in Women
RBC ChE	0.76	0.75
Plasma ChE	0.95	0.81

→ RBC ChE is a better indicator of OP poisoning

• RBC ChE: True ChE ⇒ falls slowly & regenerates slowly

• Plasma ChE: Pseudo ChE ⇒ falls early & regenerates early.

Severity of poisoning	% of ChE activity depressed
Latent Poisoning	10 - 50 %
Mild Poisoning	50 - 80 %
Moderate Poisoning	80 - 90 %
Severe Poisoning	> 90 %

b) Blood:

→ RBC cholinesterase activity

→ Hyperglycemia

→ Hyperamylasemia

c) Urine:

→ p-Nitrophenol test: Steam distillate of urine + NaOH → Yellow colour → Indicates presence of p-Nitrophenol

[p-Nitrophenol is a metabolite of OP compounds & is excreted in urine]

→ Glucosuria

d) Thin Layer Chromatography

III] Management:

① Airway should be cleared of excessive secretions & secured

② Assess breathing & circulation & record 15-point Glasgow Coma Scale

③ Make patient lie down in left lateral position (with head lower than feet)

④ Administer oxygen (intubate in case of respiratory depress)

⑤ Set-up an infusion of 0.9% normal saline (Aim: SBP = 80 mm Hg ; urine output > 30 mL/h)

⑥ Remove contaminated clothes & thoroughly wash skin with soap & water

⑦ Perform gastric lavage once patient is stabilized

⑧ Give activated charcoal (50g in 200mL)

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Drugs used: • Atropine • Pralidoxime (2-PAM) • Benzodiazepines

In case of uncertain diagnosis, perform atropine test: inject 0.6-1 mg IV atropine ⇒ if pulse rate goes above 25/min or skin flushing develops ⇒ mild/no OP toxicity.

Atropine Bolus: inject 1.8-3 mg (3-5 mL) of atropine bolus

→ Check pulse, BP & chest crepitations after 5 min.

[**Aim:** HR > 80/min, SBP > 80 mm Hg, clear chest, no pinpoint pupils, dry axillae]

→ If not achieved, double dose of atropine every 5 min & review

→ once parameters start improving, repeat last dose/smaller dose

→ On persistent satisfactory improvement, plan atropine infusion

Atropine Infusion: calculate total dose of atropine required for rapid atropinization

→ start hourly atropine infusion at 10-20% of total dose required

(most patients do not need >3-5 mg/hr of atropine infusion)

→ Use 3-point checklist to reduce infusion rate by 20% every 4 hourly once the patient is stable [Secretions, Heart Rate, Pupils] (Bronchorrhoea is the most important sign for dose titrating)

Atropine Toxicity: Absent bowel sounds + fever + confusion

→ stop atropine for 60 min

→ re-start infusion at lower rate once temperature comes down

→ If atropine is C/I ⇒ use glycopyrrolate for bronchorrhoea.

Pralidoxime is ineffective as an antidote to carbamate anti-ChEs.

Pralidoxime (ChE reactivator): by removing phosphoryl group deposited by the OP.

→ **Bolus dose:** 30 mg/kg (1-2g for adults) in 100 mL Normal saline over 15-30 minutes

→ **Maintenance dose:** continuous infusion of 8-12 mg/kg/hr

→ administer pralidoxime until atropine is no longer required

Benzodiazepines: Diazepam 10mg slow IV push repeated as necessary (upto 30-40 mg diazepam/day can be given) ⇒ for agitation & seizures

Ventilatory support: if patient develops respiratory failure

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IV] Fatal Dose:

→ TEPP: 100 mg orally [50 mg IM]

→ OMPA, Parathion: 175 mg orally [80 mg IM]

→ HETP: 350 mg orally [60 mg IM]

→ Malathion, Diazinon: 1g orally

V] Fatal Period:

→ Untreated cases: 24 hours

→ Treatment given (but unsuccessful): 10 days

VI] Cause of Death:

→ **Respiratory failure**: due to

- Weakness & paralysis of muscles of respiration
- Bronchoconstriction & bronchorrhea.

VII] PM Appearance:

a) External:

→ **Signs of asphyxia:**

- Congestion of face
- Cyanosis
- Blood-stained froth at nose & mouth

→ Constricted pupils

→ **Kerosene-like odour**: from mouth, gastric contents, body

→ Insects & flies die immediately after they alight on an opened cadaver at autopsy.

b) Internal:

→ Gastric mucosa: • congested, haemorrhagic
• May have oily greenish scum

→ Respiratory passages: • congested
• contain frothy haemorrhagic exudate

→ Heart: • Soft • Flabby
• May show epicardial haemorrhages

→ Lungs: • Gross congestion
• Sub-pleural petechiae
• Haemorrhagic pulmonary edema

→ Brain: • Congested & edematous

→ Viscera: • Congested
• Petechial haemorrhages

Intermediate Syndrome:

→ delayed muscle weakness without fasciculations occuring 1-4 days after acute haemorrhage

* Signs & Symptoms:

→ Upper body weakness
→ Cranial nerve palsies
→ Areflexia

* Treatment:

→ mainly supportive, with airway protection

* Resolution:

→ Syndrome may automatically resolve in 5-18 days when burden of of metabolites diminishes.

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OPIDP [Delayed Sequelae]: Organo Phosphorus Induced Delayed Polyneuropathy

→ occurs due to inhibition of NTE
→ occurs within 1-4 weeks after exposure
→ Signs & symptoms: involvement of distal limb muscles

Chronic Poisoning:

→ develops months – years after continued exposure
→ People at-risk:
- occupational hazard in agricultural workers
- persons engaged in manufacturing & packaging OP compounds.
- Research workers

→ Absorption occurs through inhalation & skin contamination

Signs & Symptoms:

a) Neuropsychiatric Symptoms:
- Personality change
- Mood destabilization
- Suicidal thinking
- Cognitive impairment
- Anxiety
- Confusion
- Drowsiness
- Parkinsonism-like symptoms
- Muscle cramps
- Paraesthesias
- Weakness

b) Alcohol intolerance
c) Heightened sense of smell
d) Decreased exercise tolerance
e) Dipper's flu: One or more episodes of severe flu-like symptoms lasting more than three days
→ accompanied by hypersalivation, abdominal cramps, diarrhoea

Prevention: people at-risk should have baseline ChE testing for monitoring (especially RBC ChE).

MLI of OP:

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a) Suicide: very common

b) Homicide: rare (due to strong smell & bad taste)

c) OPs resist putrefaction: can be detected in viscera for a long time following death

d) Accident: quite common

e) Restricted Use Pesticide (RUP): RUP is available for purchase & use only by certified pesticide applicators

→ has a high degree of potential human & environmental hazard

Ex:
- Diazinon
- Fenitrothion
- Methyl parathion
- Monocrotophos

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Carbamates: organic compounds derived from carbamic acid (NH_2COOH)

→ marketed in the form of dusts or solutions

- Carbaryl / sevin
- Propuxur / Baygon
- Carbofuran
- Aminocarb

Toxicokinetics:

→ rapidly absorbed from small intestine or on inhalation
→ large volume of distribution in the body
→ metabolized in liver
→ Excreted in urine.
→ do not penetrate BBB

Signs & Symptoms: same as that of OP compounds, but much less pronounced. (∵ they are hydrolyzed spontaneously by cholinesterase within 24-48 h).

Management:

i) Atropine: 1st drug of choice
ii) Oximes: c/I (carbamate + oxime → carbamylated oxime → more potent ChE inhibitor than carbamate itself)
iii) Adjunct therapies (same as in OP compounds).

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Aluminium Phosphide: (AlP) Lethal solid fumigant pesticide, insecticide & rodenticide

→ available as dark brown/grayish green tablets of 3g each
→ aka rice tablets
→ on contact with moisture, each 3g tablet liberates 1g of phosphine (which kills insects & rodents in all stages of development)
→ Trade names: Alphos, Celphos, Quickphos

Toxicokinetics:

→ rapidly absorbed from GIT by simple diffusion
→ Phosphine (from AlP) is readily absorbed through lungs.
→ AlP is metabolized in the liver to phosphine (PH_3)
→ PH_3 is excreted in urine as hypophosphite & also through lungs in unchanged form.

Mechanism of Action:

$AlP + H_2O \rightarrow Al(OH)_3 + PH_3$ or $AlP + 3HCl \rightarrow AlCl_3 + PH_3$

(in air/stomach) (non-toxic) (toxic) (in stomach) (non-toxic) (toxic)

Mechanism of toxicity of liberated PH_3:

(1) Esophagus: esophageal strictures due to – its corrosive nature
– AlP tablets get stuck in esophageal lumen → local ulcerations

(2) Lungs: direct injury to alveolar capillary membrane
(3) Liver: disturbance of hepatic fat metabolism
(4) Heart: (not understood)
(5) Cellular level: PH_3 reacts with cytochrome c & cytochrome c oxidase → inhibition of mitochondrial oxygen uptake.

→ blockage of oxidative phosphorylation

→ formation of highly reactive hydroxyl free radicals → lipid peroxidation → oxidative stress → acute lung injury.

(6) Heme: PH_3 reacts with heme in Hb in the presence of oxygen

Signs & Symptoms:

If Ingestion: symptoms begin within 30 minutes

(1) GIT:
- metallic taste
- excessive thirst
- vomiting & diarrhoea
- burning epigastric pain
- Garlicky odour or odour of decaying fish
- Esophageal strictures (onset of dysphagia: 2-8 weeks of ingestion)
- tracheoesophageal fistula

(2) Hepatic:
- Hepatitis
- Jaundice
- Hepatomegaly

(3) Pancreas: Pancreatitis

(4) CNS:
- Restlessness
- Dizziness
- Coma
- Headache
- Convulsions
- Acute hypoxic encephalopathy

(5) Haematological:
- Intravascular hemolysis
- Methemoglobinemia
- Microangiopathic haemolytic anemia

(6) CVS: ECG abnormalities — rhythm disturbances, ST-T disturbances, conduction defects
- Arrhythmia
- Myocarditis
- Shock
- Profound & refractory hypotension
- Subendocardial infarction

(7) Respiratory:
- Cough
- Tachypnea, dyspnea
- Cyanosis
- Pulmonary edema
- Respiratory failure

(8) Renal: Renal failure

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(9) Metabolic: metabolic acidosis

(10) Miscellaneous: • Bleeding diathesis • DIC • Muscle wasting

II] Inhalation of PH_3:

1] Acute toxicity:

→ Mild toxicity: • Nausea, vomiting, diarrhea • Acute respiratory distress • Chest tightness • Dizziness • Fatigue

→ Moderate toxicity: • Ataxia • Diplopia • Jaundice • Tremor • Incoordination • Muscular weakness • Numbness • Paraesthesia

→ Severe toxicity: • Arrhythmias • CHF • Pulmonary edema • Convulsions • Coma

2] Chronic toxicity: (repeated exposure)

• Anemia • Bronchitis • Visual, speech, motor disturbances

III] Complications: • Pericarditis • Acute CHF • ARDS • Acute massive GIT bleeding

Management:

(1) Immediate:

→ patient should move to fresh air in case of occupational/accidental inhalation

→ decontamination of skin & eyes with plain water

→ confirm airway patency

→ start supplemental oxygen

→ check pulse ; establish IV access

→ Investigations – ECG, X-ray, ABG, electrolytes, LFT, RFT.

(2) Gastric lavage: (in case of ingestion) done only after ET intubation
→ $KMnO_4$ [1:10,000]

(3) 100g Activated Charcoal

(4) Antacids

(5) Vegetable oils & Liquid paraffin: Inhibit release of PH_3 from ingested AlP.

(6) Maintain adequate renal perfusion & urine output

(7) $MgSO_4$: MoA – stabilizes cell membrane (↓ arrhythmias)
– ↓ free radical stress
– corrects hypomagnesemia (↓ arrhythmias)
→ 1g stat → 1g every hour for 2 hours → 1-1.5g every 6h for 5-7 days

(8) Cathartics: Sorbitol [1-2 ml/kg]

(9) Haemodynamic support

(10) Managing Organ failures: O_2 therapy for hypoxia
→ ET intubation & mechanical ventilation for acute lung injury
→ IV methylene blue 1% 2mg/kg over 5 minutes for methemoglobinemia
→ IV sodium bicarbonate for metabolic acidosis
→ Hemodialysis (in case of renal failure)

Diagnostic Tests:

(1) Tests for Phosphine:

i) Gastric aspirate/contents (PM) 5 mL + 15 mL H_2O in a flask → cover mouth with filter paper impregnated with 0.1 N $AgNO_3$ → Heat at 50°C for 15 min → blackening of filter paper (due to formation of silver phosphide)

ii) Face mask impregnated with 0.1 N $AgNO_3$ → Patient breathes in & out for 15 min → blackening of filter paper (due to formation of silver phosphide)

iii) PM ⇒ Gas chromatography with a nitrogen-phosphorus detector.

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(2) ↑ Liver enzymes: SGOT, SGPT, ALP, Albumin

(3) Magnesium levels: hypomagnesemia (rarely: hypermagnesemia)

Fatal dose:

AlP:

→ Ingestion of 1-3 tablets (3-9g)

Phosphine: > 50 ppm : dangerous to life

400 - 600 ppm : lethal within 30 minutes

[Permissible exposure limit in working environment : < 0.3 ppm]

Fatal Period: 1 h – 4 days

Cause of Death:

MAC

Within 24 hours:
- Cardiogenic shock
- Hemodynamic instability
- Arrhythmias
- Myocardial injury

After 24 hours:
- Acidosis
- ARDS
- Refractory shock

PM Appearance:

I] Gross:

(1) Garlic odour: mouth, nostrils, stomach contents

(2) Blood-stained froth: mouth, nostrils

(3) Congestion: lower part of esophagus, stomach, duodenum, all internal organs

II] Histopathological: suggestive of cellular hypoxia

(1) Stomach:
- Congestion
- Leukocytic infiltration
- Edema
- Sloughing of gastric mucosa

(2) Heart : • Congestion • Edema • Focal necrosis • Leukocytic infiltration
• Areas of myocytolysis • Degeneration • Myocyte vacuolation

(3) Lungs: • Congestion • Edema • Thickened alveoli
• Desquamation of respiratory epithelium • Lymphocytic infiltration

(4) Brain : • Congestion • Edema • Degeneration of neurons
• Paucity of glial cells • Appearance of neurotic patches

(5) Liver: • Centrizonal haemorrhagic necrosis

(6) Renal : • Congestion • Acute tubular necrosis
• Cloudy swelling of renal tubular epithelium

(7) Suprarenal : • Congestion • Necrosis
• Haemorrhage • Lipid depletion in cortex

MLI :

→ AlP is a restricted use pesticide [RUP] in India.

→ most common cause of suicidal poisoning in northern India

→ Accidental poisoning — occasional

→ Homicidal : rare (peculiar smell)

hexachloride: gamma hexachlorobenzene (Lindane). (3) Cyclodienes and related compounds: aldrin, chlordane, chlordecone, dieldrin, endosulfan, endrin, hepatachlor, isobenan, mirex. (4) Toxaphene and related compounds. All of these pesticides are absorbed through skin, orally and via inhalation. DDT is the least well absorbed. These agents are highly lipid soluble. They are partially metabolised in the liver and directly excreted in the urine, faeces and milk. Endrin is rapidly metabolised and eliminated and does not persist in body tissues.

Action: They interfere with nerve impulse transmission. CNS is first stimulated and then depressed.

Fatal Dose: DDT; 30 g. ; gammexane 15 g. Lindane 15 g; chlordane 30 g.

ENDRIN

Endrin is a polycyclic, polychlorinated hydrocarbon belongs to the group of cyclodiene insecticides. It is a stereoisomer of dieldrin. It is soluble in aromatic hydrocarbons and ketones, sparingly in alcohols, but is not soluble in water. Its taste is bitter. It melts at 245°C. It is also called **" plant penicillin"**, because of its broad spectrum of activity against various insect pests. It is sold in the market under the trade names of Endrin-We-16, Endox-DB 50, Endtox EC-20, Endrex, Tafdrin, etc. These products contain about 20 to 50% of endrin mixed with petroleum hydrocarbon, such as aromax, which smells like kerosene. It is commonly used as sprays or as dusts, diluted with inert clays.

Symptoms : These begin within one to 6 hours. They are salivation, nausea, vomiting, abdominal pain, rarely diarrhoea, hoarseness of voice, coughing, froth at the mouth and nose, dyspnoea, headache, giddiness, restlessness, hyperirritability, dilated pupils, incoordination, ataxia, mental confusion, tremors, tonic and clonic convulsions, coma and death due to respiratory failure. In non-fatal cases, most of the persons feel well after twenty-four hours.

Chronic Poisoning : Long term exposure to some of these compounds results in cumulative toxicity characterised by loss of weight, weakness, ataxia, tremors, mental changes, oligospermia and increased tendency to leukaemias, purpura, aplastic anaemia and liver cancer.

Fatal Dose : 5 to 6 g. By ingestion it is 3 times as toxic as aldrin, dieldrin and 10 times as toxic as DDT.

Fatal Period : One to several hours.

Postmortem Appearances : The mouth and stomach contents smell of kerosene. Signs of asphyxia are present. Endrin resists putrefaction and can be detected in the viscera quite some time after death.

Treatment : (1) Clothing should be removed and skin washed with soap and water. (2) Gastric lavage, or the stomach evacuated by emetics and cathartics. (3) Give activated charcoal. (4) Cholestyramine is a non-absorbable bile acid binding anion exchange resin, which increases the faecal excretion of organochlorines. It is given 16 g. per day in divided doses for several days. (5) There is no specific antidote. (6) Maintain and assure adequate airway, breathing and circulation. (7) If the mental state is altered give dextrose, naloxone and thiamine. (8) Control convulsions with diazepam followed by phenobarbital. If necessary general anaesthesia is given. (9) Calcium gluconate is useful.

Circumstances of Poisoning : Human poisoning occurs from occupational or accidental exposure to endrin. Suicide is very common. Homicide is rare, but it is sometimes given mixed with food or sweets, or alcohol is used to conceal the smell. Accidental deaths are very rare.

CHLOROPHENOXYACETATES: They are plant harmone used as weed-killers. They include 2, 4, -D, MCPA, mecoprop, dichloroprop (DCPP), 2, 4, 5-T. They irritate skin, mouth, GIT and damage muscles, nerves and brain. They are absorbed through skin, lungs and GIT.

SYMPTOMS: Symptoms include: redness and irritation of skin and eyes, burning in mouth, coughing and choking, pain in abdomen, vomiting, diarrhoea, confusion, muscle weakness, twitchings, hypotension, fast breathing, convulsions, coma and death in few hours. If patient survives for more than a few hours, liver and kidney damage occurs.

TREATMENT: Symptomatic.

CHLORATE :

It is used as a weedkiller, in match heads an fireworks. Sodium salt (resembles table sugar) is toxic than potassium salt. Fatal dose is about 20 to 3 is a powerful oxidising agent, and it attacks all body It reacts with thiol groups on red cells and may ca to lyse. It oxidises haemoglobin to methaemoglobin. It