

# Medical Aspects of Pesticide and Herbicide Exposures (selected)

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# Objectives/Disclaimers

- Review selected pesticides and herbicides
  - Not a whirlwind list you won't remember, but will discuss a few high yield products that the Poison Center hears about a lot
- Structures are presented for perspective
  - If you don't like chemistry, then look away.....



# Carolinas Poison Center



- We are the state poison center
- Take calls from the public, law enforcement and from health care providers
  - Function as entity for reporting occupational pesticide exposures
- The CPC reports all severe pesticide poisonings (not just occupational) to Public health
- Medical Toxicologists are available 24/7/365 for consultation by other health care providers
- Education efforts to the public

# Ideal Product

- Lethal against target organism (plant or insect)
  - Limited toxicity against similar organisms
  - No toxicity in humans
- No resistance can develop vs. agent
- Agent degrades in environment in favorable time frame
- No product is perfect
  - Especially when you consider the human tendency to use things in ways never imagined

# Herbicides

- Designed for killing undesirable plants
- Several different categories
- In general, humans do not usually experience toxicity from herbicides.
  - But...

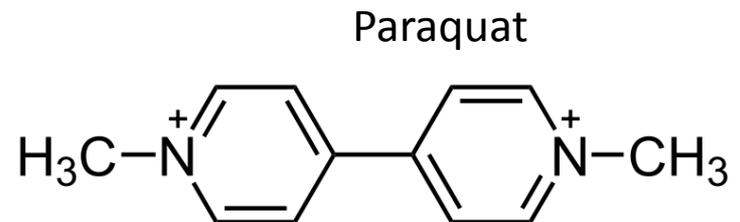
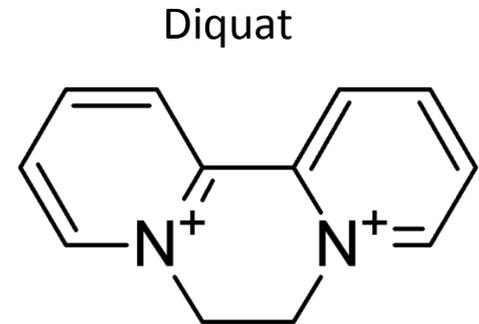


# Recent Case Example

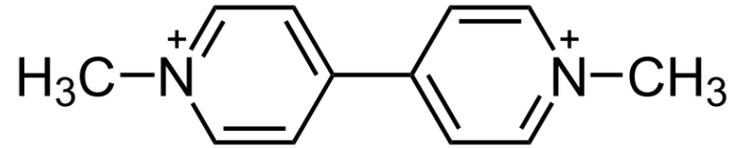
- A 61 year old man drank “a few tablespoons”/one mouthful of unknown weed killer he got from a friend in a water bottle
  - Was thirsty after the gym and just grabbed bottle by accident.
  - Bluish green color
- Throat pain, vomiting-brought up blue colored vomitus
- Started on antibiotics, steroids and discharged after 23 hr observation; felt embarrassed about whole event.
- Returns 4 days later with continued problems swallowing, mouth sores and breathing issues; labs revealed renal failure
- Bilateral chest x-ray infiltrates which progressed; pneumonia
- Vasopressors, steroids, cyclophosphamide, nitric oxide, N-acetyl cysteine, antibiotics, ventilator, and dialysis
- Died 21 days after the ingestion. (Black Friday)

# Bipyridyliums

- Consists of two compounds
  - Paraquat
  - Diquat
- Non-selective herbicides
- Diverts electrons in the plant during photosynthesis (Photosystem – I – electron diversion)
  - Meaning the electrons don't go to plant energy but to generate toxic oxygen species
- Rapidly deactivated with soil contact
- Fast acting herbicide
- Significant Human toxicity



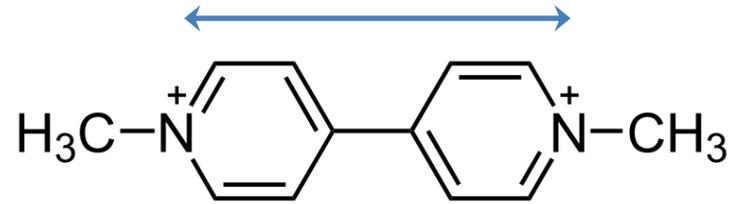
# Paraquat



- Used extensively around the world
  - Popular suicide method
- In US, it is available but is restricted to licensed applicators.
  - Multiple cases of toxicity from “shared” products
- For safety, dyed dark blue
- Concentrate quite deadly
- Respect even for dilute

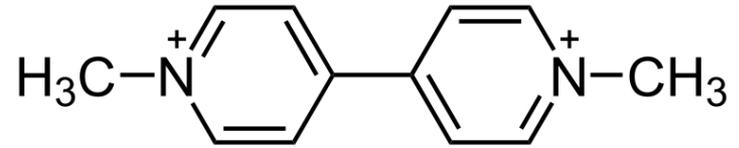


# Paraquat



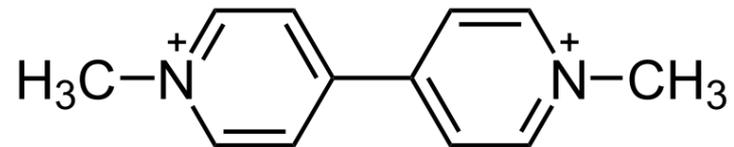
- Once absorbed, unfortunately selectively taken up by specialized lung cells (alveolar cells)
  - Undergoes redox cycling with oxygen within human lungs
    - Sort-of a controlled “burn”
    - Oxygen becomes toxic (more than the usual)
    - Similar killing mechanism as with plants
  - Results in toxic oxygen species (hydrogen peroxide)
    - Giving oxygen as therapy is the wrong answer.
  - Paraquat is removed from those cells very slowly
  - Unavoidable, progressive, irreversible lung injury over several days
- Sometimes more rapid death with larger doses (acidosis, renal failure, coma)

# Paraquat



- Not a risk most circumstances when dilute sprayed
  - Occasional dermal injury
- Weak link with chronic applicators and Parkinson's disease
  - But not consistent in all studies.
  - Given mechanism of action, lack of toxicity with the dilute product and inability to cross the blood brain barrier, somewhat suspect finding.

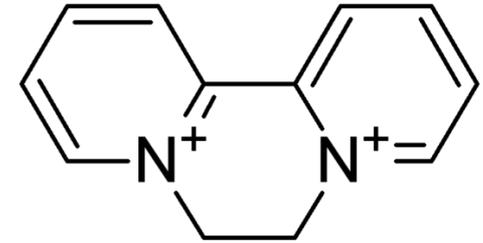
# Paraquat



- Renal elimination
  - “pumped out”; not metabolized
  - Paraquat also poisons kidneys
- Horrible corrosive mucosal injuries
- Can find in urine via spot test
  - Paraquat is also known as Methyl Viologen – indicator used for redox reactions



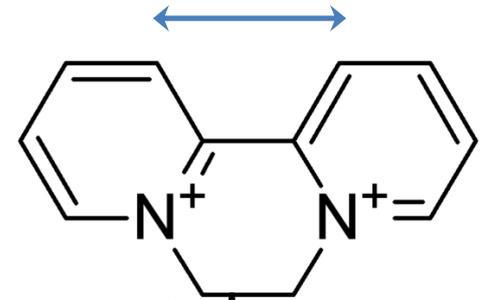
# Diquat



- Less dangerous of the two “quats”
- Often found combined with Glyphosate, another broad spectrum herbicide
  - Increases effectiveness
  - Rapid onset
  - Reduced resistance
- When diquat is diluted, not usually problematic

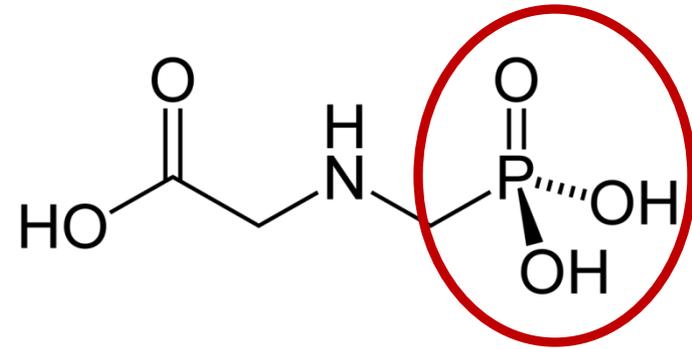


# Diquat



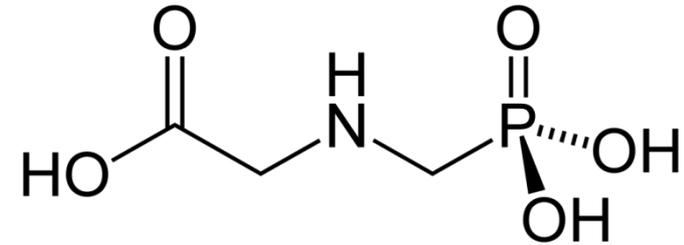
- Shape of molecule doesn't "Fit" the uptake pump in the lung cells
  - So no pulmonary injury
- But it does fit in uptake pump in renal cells
- Renal failure
- Brain stem infarction
- But less likely to be lethal even with unintentional concentrated ingestions (still kills)
- Much milder dermal irritation
- Can also perform the dithionite urine test

# Glyphosate



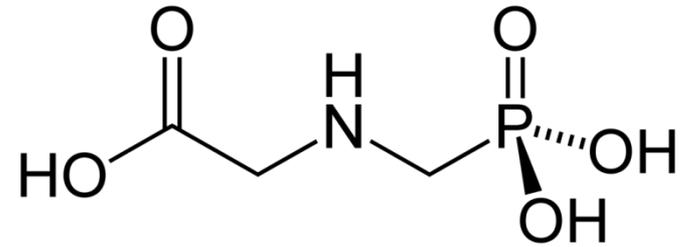
- Broad spectrum herbicide
  - One brand is Roundup<sup>®</sup>
- Inhibits a pathway (shikimic acid) that animals do not have.
- Organic phosphorus containing compound
  - But not an organophosphate.
- Genetically engineered crops with resistance to glyphosate now used
  - Spray the field, kill everything green that is not your engineered crop.
  - Benefits to this technique
- Doesn't kill plants as fast as other herbicides

# Glyphosate



- Is not metabolized and does not accumulate
- Is (almost) completely non-toxic in humans
- Requires formulation with surfactant (“soap”) to get into solution and into a plant.
- The *surfactant* is what is concerning when there is ingestion exposure to the concentrate

# Glyphosate



- One of the most common agricultural product exposures to poison centers
- Only really problems when there is ingestion of the concentrate (i.e. surfactant)
  - These cases are nearly always intentional
  - Gastrointestinal injury
  - Hypotension
  - Acidosis
- Dilute exposures are a non-issue in humans, even chronic exposures

# Selected Insecticides

- Organophosphates
- Carbamates
- Pyrethroids

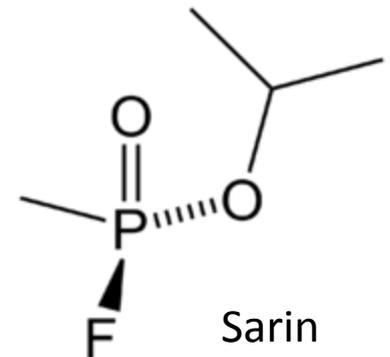
# Organophosphates

- Group of very important pesticides
- Used extensively around the world in huge quantities
- Some organophosphates in use (WHO classification)
  - Acephate
  - Chlorpyrifos\*
  - Diazinon\*
  - Dimethoate\*
  - Malathion (& medicinal)
  - Parathion\*\*\*
  - Phosmet\*
  - Phorate\*\*\*
- CPC gets plenty of calls that start with “I was cleaning out an old barn/shed when I found/spilled...X”



# Organophosphates

- Term used to describe a class of compound with cholinergic effects
  - “Organic phosphorus” compounds would include things like ATP and DNA
- Careful choosing side groups has resulted in compounds with selectivity against insects.
- “Nerve gases” are basically human insecticide
  - VX (not a gas), Sarin, Soman are nerve agents
  - Incredibly high lethality
  - Very similar process of causing injury
  - Similar therapies



# Organophosphates

- Inhibit several enzymes in the human body
- Two important enzymes are
  - Acetylcholinesterase
  - Neuropathy Target Esterase

# Organophosphates

- The organophosphate compound binds to the active site of acetylcholinesterase
- Part of the organophosphate breaks away.
- The enzyme now is inactivated and remains inactivated. Two possibilities now for the enzyme:
  - The part can leave/undergo hydrolysis and the enzyme can become active again (therapy)
  - The part can “age” and now be permanently bound to the enzyme

# Organophosphates

- **Acetylcholinesterase** enzyme responsible for breaking down acetylcholine and “ending” certain neuronal transmission
  - Acetylcholine used in muscle cells (nicotinic)
  - Acetylcholine used in certain secretion cells (muscarinic)
  - Sympathetic/parasympathetic systems
- By preventing the acetylcholinesterase enzyme from working, victims have persistent acetylcholine at synapses

# Organophosphates

- Elevated levels of acetylcholine causes a combination of toxicological syndromes -- Cholinergic toxicity
- DUMBBBELLS [Muscarinic contribution]
  - **D**iarrhea
  - **U**rination
  - **M**iosis (not always\*)-vision changes
  - **B**ronchorrhea
  - **B**ronchospasm
  - **B**radycardia (not always)
  - **E**xcitation of CNS-headache, seizures
  - **L**acrimation
  - **L**ots of vomiting
  - **S**alivation
- Weakness, Fasciculations, Tachycardia [Nicotinic contribution]

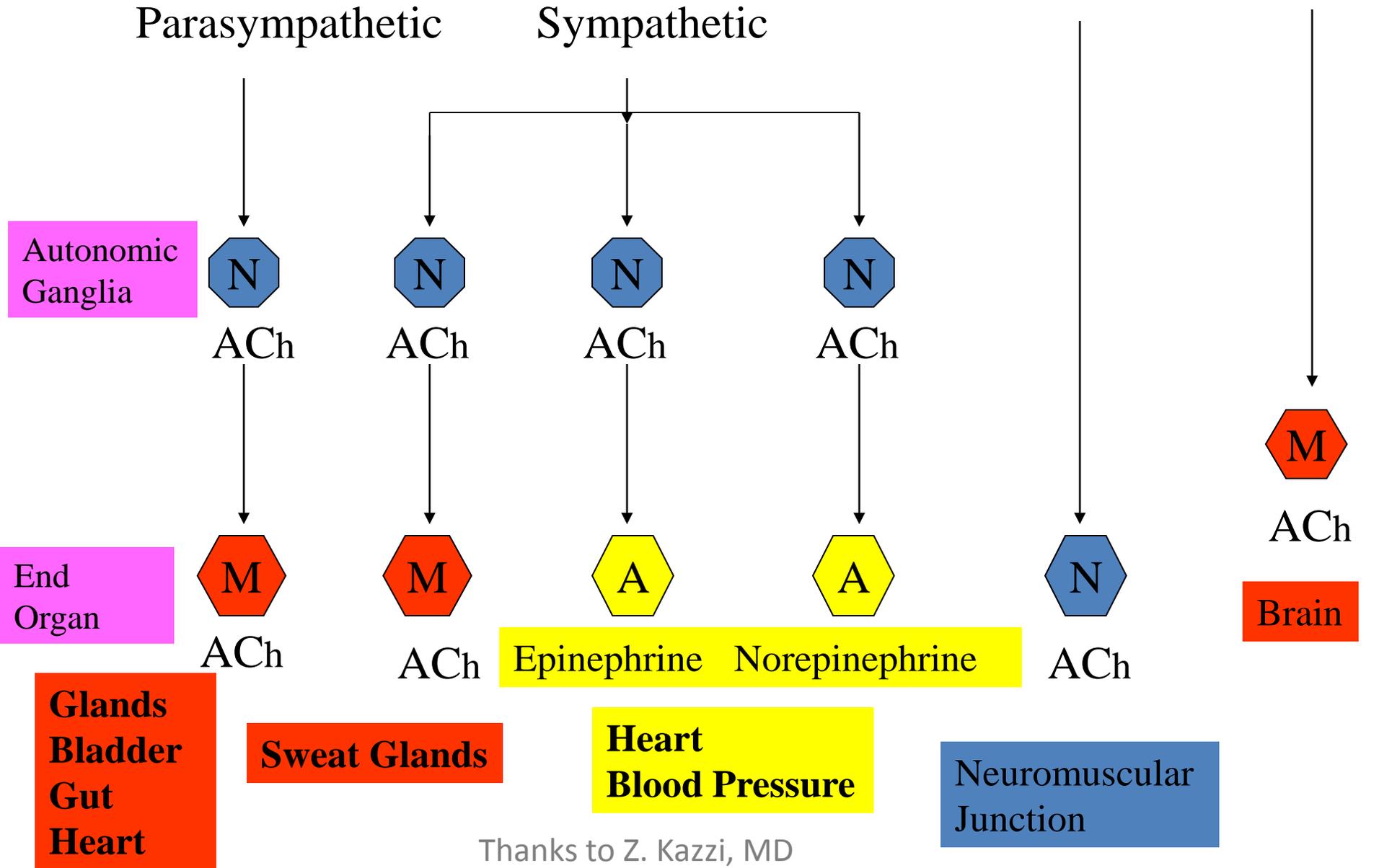


# Autonomic Nervous System

# Somatic Central

Parasympathetic

Sympathetic



Thanks to Z. Kazzi, MD

# Organophosphates

- Due to lipophilicity and conversion to active metabolite, recurrence of symptoms reported days after acute exposure to some agricultural OPs
  - Extending therapy for sufficient time
- Intermediate syndrome can develop several days after acute exposure
  - Sometimes some degree of recovery from cholinergic sx before it develops
  - Marked by weakness, cranial neuropathies
  - May take weeks to resolve
  - Not the same as insufficient therapy although there is possibly a link

# Organophosphates

- Chronic symptoms
  - Because of longer biological half life, repeated low level exposures can result in cholinergic illness
  - Neuropsychiatric changes reported in some populations (acute & chronic exposures)
    - Anxiety, sleep changes, changes in mentation
    - It is known that these changes can occur with acute exposure episodes, especially with war agents
    - Neuropsychiatric changes with chronic low level exposures are harder to define as these populations are not studied as well
  - Concerns for chronic exposures resulting in neurocognitive developmental delays in children.

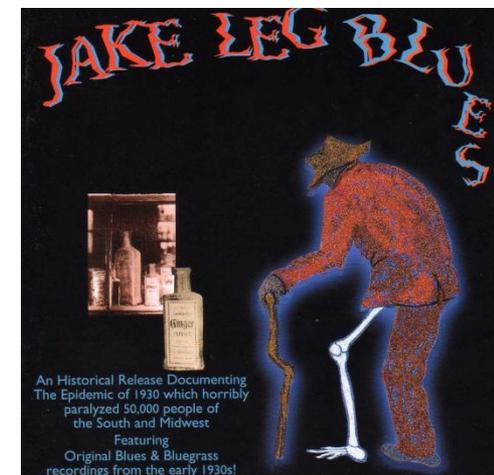
# Organophosphates



- Neuropathy target esterase (NTE) inhibition
- Compounds used in North America all have much greater affinity for Acetylcholinesterase than for the NTE
- This is good because---inhibition of NTE causes neuronal death
  - Loss of sensation and motor function
  - Degree of permanence to the injury
- Organophosphate induced delayed polyneuropathy (OPIDP)

# Organophosphates

## NTE



- Mass poisoning episode of Ginger Jake Leg Paralysis from TOCP
  - TOCP is an Organophosphate compound
  - Contaminated ginger extract
  - 1000s affected; records poor
  - Woke up unable to walk; never had cholinergic sx.
- The cholinergic symptoms serve as a “warning”
- Will not generally occur without episode of significant systemic poisoning with agricultural organophosphates.

# Organophosphates

- Diagnosis of exposure
  - History and exam
    - Concentrate/Dilute
    - Acute/Chronic
    - Route(s) of exposure
  - Serum cholinesterase (plasma cholinesterase) and Red Blood Cell cholinesterase can be done for acute diagnosis and chronic surveillance
  - Peripheral cholinesterases are similar to what is happening in the nerves---but not the same.

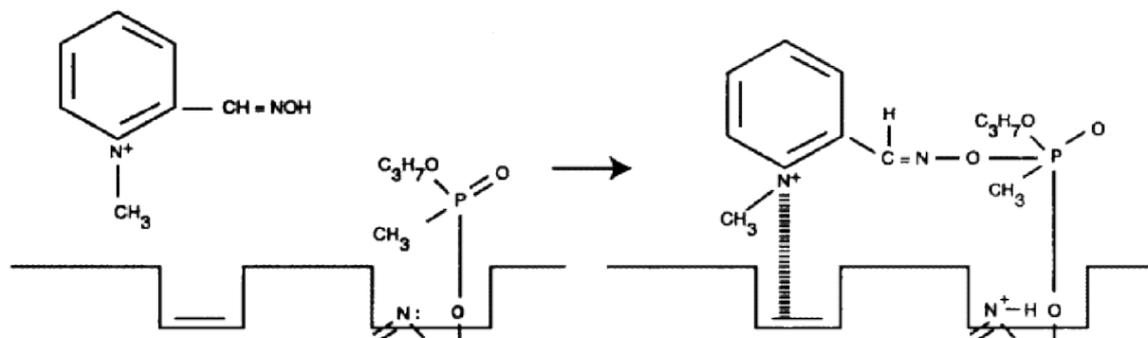
# Organophosphates

- Treatment
  - Remove from exposure;
    - Concentrated product will require decontamination and disposal of leather due to permeation
    - Solvent used for concentrated product is volatile; the OP has much less volatility
    - Protect your staff- limit dermal exposure (vomitus, dermal contamination, clothing)
    - Cases of ED staff developing “illness” following treating a patient with pesticide ingestion vomiting
  - Decontamination
    - Activated charcoal would work for the GI tract, but usually they are vomiting so much the value is questionable
  - ABCs; Most patients die an airway death
    - Intubation
    - Secretions
    - Ventilation becomes impossible- you can’t squeeze in enough air past the secretions.

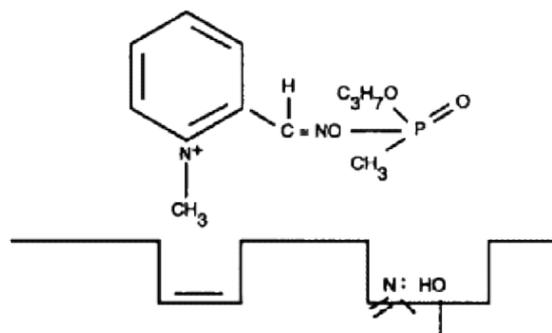
# Organophosphates

- Treatment
  - Muscarinic antagonist/blocker; anticholinergic
    - Atropine (IV probably best route, but inhaled/IM used)
    - Dose **much** above published doses
    - 100's of mg (50x+ usual doses) used\*
    - Dosed to **dry secretions to ventilate**- tachycardia is not a reason to stop
  - Diazepam (Valium<sup>®</sup>) for seizure prophylaxis

- Restore the acetylcholinesterase enzyme
  - Oxime therapy using pralidoxime / 2-PAM
  - Bolus followed by infusion
  - Removes the OP from not-aged enzyme

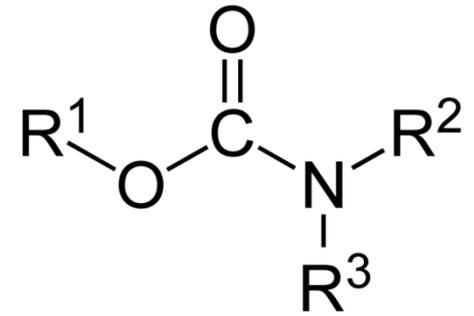


Mark I and Antidote Treatment  
 nerve Agent Auto injector (ATNAA)  
 are designed for military use and  
 have atropine and 2-PAM



Sarin

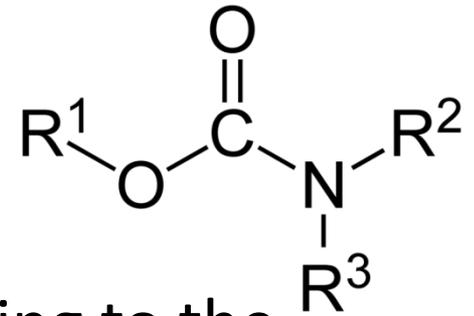
# Carbamates



- Insecticides similar to organophosphates
  - Medicinal ones include neostigmine and physostigmine
  - More toxic members include aldicarb, methomyl and propoxur
- Similar mechanism of toxicity to organophosphate
- Some have good water solubility (better than OP)
  - Can result in episodes of toxicity where it is incorrectly used on vegetables with high water content
  - Aldicarb



# Carbamates



- Inhibition of acetylcholinesterase by binding to the enzyme and rendering it inactive (same as OP)
- However, it does not “age” and carbamates will hydrolyze off the acetylcholinesterase without specific treatment
- No bio-accumulation in humans; enzyme recovery is fast
  - Less concern for chronic exposures
- Rare chronic neuropsychiatric effects with acute toxicity event as well as chronic exposure, but less severe than organophosphates
  - Sleep changes, anxiety, lethargy, vertigo, changes in decision making
  - Not well studied

# Carbamates

- Treatment is similar to organophosphates
- The role of 2-PAM is controversial, but is probably not needed
- I think of Carbamates as weak Organophosphates
- But intentional large ingestions of the concentrate are still rapidly lethal

# Pyrethroids

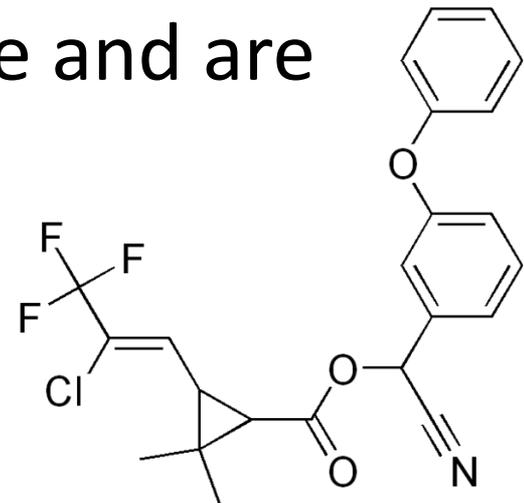
- Pyrethrins found in Chrysanthemum are natural insecticides
- Limitations in their stability and selectivity
- Synthetic derivatives are pyrethroids



# Pyrethroids

- First generation are sensitive to light and temperature changes
  - This is a good thing
  - Used for indoor pest control
  - Make up the majority of insecticide calls to CPC
- Second generation are more stable and are used outdoors in agriculture

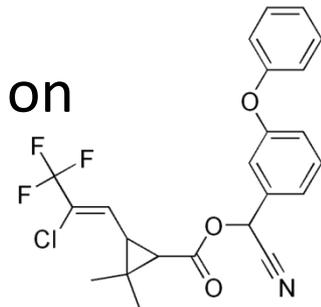
Cyhalothrin



# Pyrethroids

- Cause neuroexcitation by interaction with sodium channels
  - These channels are what allow for nerve conduction
  - Channels rapidly open then have “second” gate which slams closed
  - Pyrethroids slow *activation* and slow the *inactivation*
  - Also effect at chloride channels which cause additional excitation by the Type II Pyrethroids
- Rapidly paralyzes insects whose channels are more sensitive to these effects
- Some of this selectivity in the pyrethroids comes from control of chiral centers
  - Variability of toxicity with product mixtures based on quality control during synthesis

Cyhalothrin

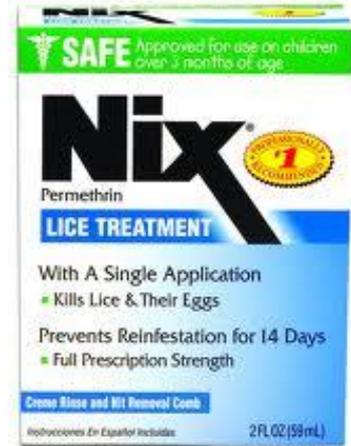


# Pyrethroids

- Rapidly metabolized in humans (hours-days)
  - No bio-accumulation
- Human toxicity can occur with high doses absorbed over a reasonably short period of time
- Greater peripheral nerve sensitivity in humans than central nervous system
- Differences in the rate which the pyrethroid “falls off” the sodium channel differentiate Type I vs. Type II Pyrethroids

# Pyrethroids

- Two types of pyrethroids
  - Type I (shorter binding, less toxic)
    - Permethrin (& medicinal), bioallethrin, cismethrin
  - Type II-(have cyano group, longer binding)
    - Cyhalothrin, cypermethrin, deltamethrin, fenvalerate
  - Some with mixed properties (I and II)
- Division based on effect on sodium channel
- Differences in symptoms
- Compounded with solvents which can add additional toxicity (aspiration, dermal irritation)



# Pyrethroids

- Type I (not seen much)
  - Fine tremor, reflex hyperexcitability, hyperthermia and sympathetic activation.
  - "T-syndrome" (Tremors).
- Type II [worse]
  - Salivation, coarse tremor, sympathetic activation, increased extensor tone, hyperexcitability, seizures, choreoathetosis, pulmonary edema, and coma.
  - "CS-syndrome" (choreoathetosis, seizures, salivation).
- Useful in helping differentiate from other pesticide toxidromes such as cholinergic toxicity
- Therapy will be mostly supportive following whatever decontamination can be performed.

# Pyrethroids

- Inhalational exposure can result in “localized” symptoms of sodium channel effects; runny nose, sneezing, occasional hypersensitivity reactions (cough, dyspnea, wheezing) as well as headache and dizziness.
- Ingestion is usually intentional and results in irritant symptoms, GI distress as well as the systemic effects. The solvent often contributes to toxicity in these situations.

# Pyrethroids

- Dermal absorption is poor, but localized symptoms (itching, paraesthesias/ sensory changes) common with Type I and II
  - Very common call to the CPC
- Treatment for dermal effects
  - Complete decontamination with soap and water
  - Vitamin E cream (probably either its lipophilicity or the cream itself).

# Questions

- Thank you for your attention
- Please do not hesitate to contact the Carolinas Poison Center for all your poisoning needs
- Not just for pesticides!