Pesticide Poisoning, Residues in the Indoor Environment, Assessment and Health Effects

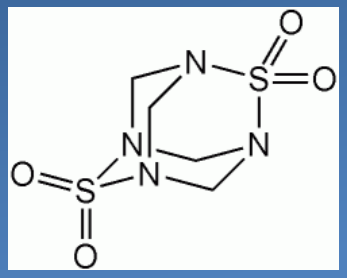
Cyrus Rangan MD, FAAP, FACMT
Director, Toxicology and Environmental Assessment, Los Angeles County Department of Public Health
Assistant Medical Director, California Poison Control System,
Medical Toxicologist, Children's Hospital Los Angeles

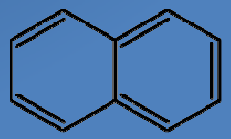
Learning Objectives

- Recognize the diversity of the chemistry and toxicology of common pesticides
  - Emphasis on indoor exposures
- Understand chemical properties of pesticides, and their impact on human exposure pathways
- Provide specific examples of clinically important pesticides that may be encountered indoors
  - Exposure pathways and scenarios
  - Exposure assessment
  - Clinical toxicology
- Recognize emerging areas of research in pesticide toxicology
  - Biomonitoring, health implications of chronic, low-level exposures

Specific Examples of Pesticides and Risks from Indoor Exposure

- Organophosphate insecticides
- N-methylcarbamate insecticides
- Mothballs
- Rodenticides





Pesticides

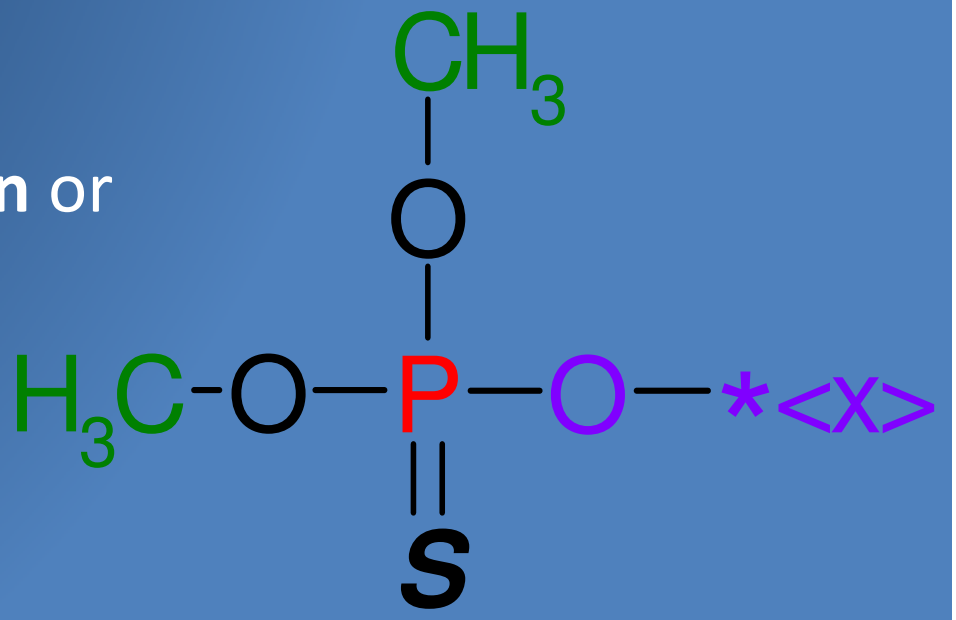
- Any substance intended for preventing, destroying, repelling, or mitigating any pest
  - Repellents (solid mothballs), insecticides (liquids, aerosols, vapors), rodenticides (solid baits, powders)

Residential Use of Pesticides

- High-risk subgroups
- Possible risks from chronic exposure
  - Asthma
  - Cancer
  - Endocrine disruption
- Concerns have led to significant regulatory decisions in past 15 years

Insecticides and the Indoor Environment: Organophosphates

- Common chemical structure
- Central phosphorus atom
- Double bond to either **oxygen** or ***sulfur***
- Two alkyl groups bound to oxygen
- A leaving group (X) bound to either oxygen or sulfur
  - Highly variable
  - Volatility and vapor pressure depend on chemistry of leaving group



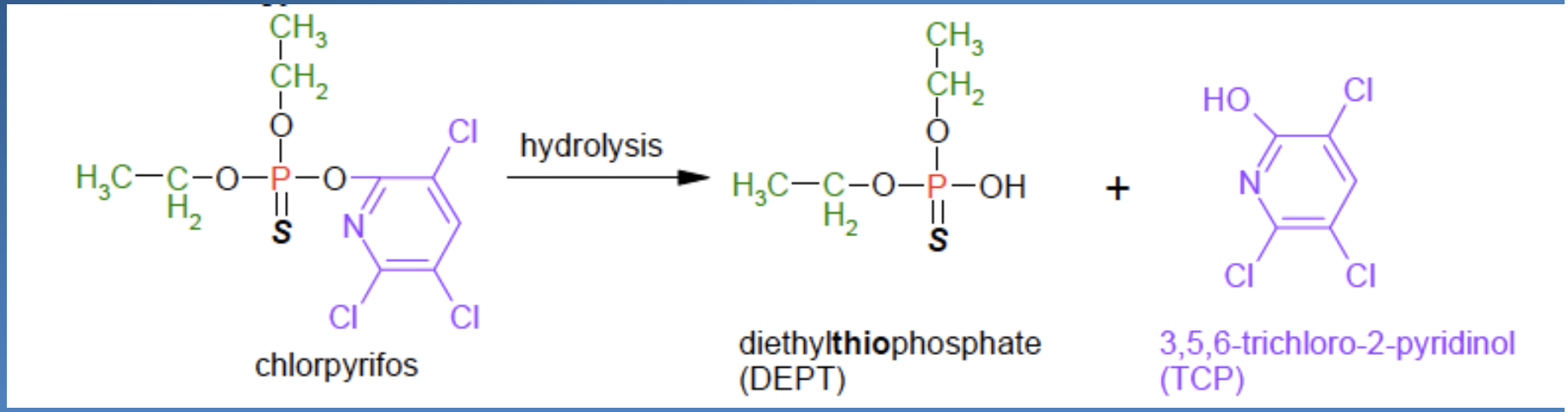
Organophosphate

Organophosphates: Exposure Pathways in the Indoor Environment

- Inhalation
  - Highest risk for insect strips (DDVP), and aerosol formulations
- Dermal contact
  - Bioavailability depends on specific organophosphate
  - Can cause systemic toxicity
- Ingestion
  - Hand-to-mouth activity with a treated surface
    - Important for pediatric exposures
- Agricultural workers (and families) as high-risk populations

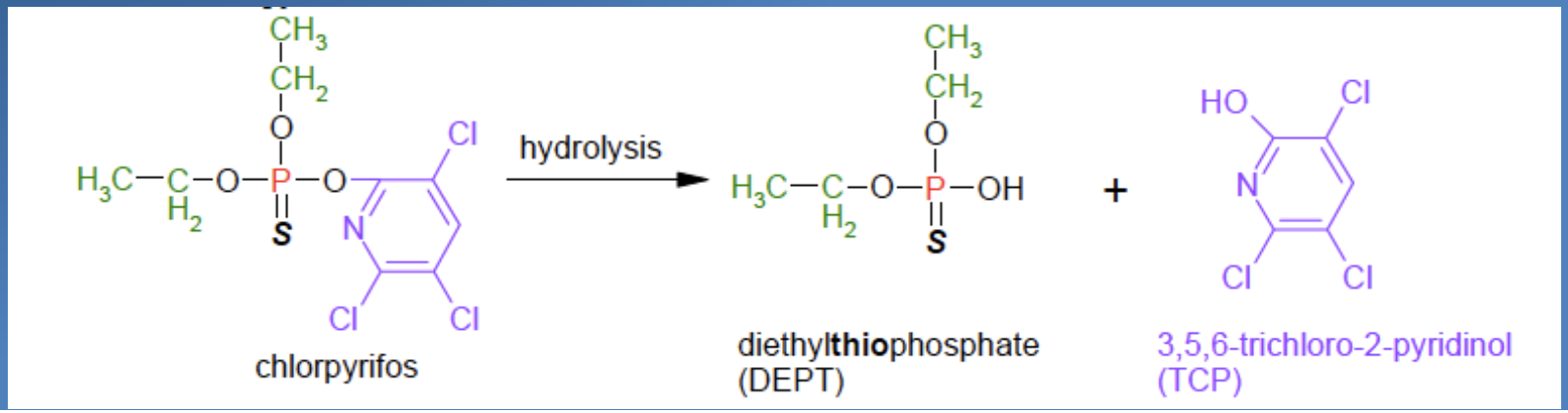
Chemical Fate of Organophosphates

- Organophosphates undergo chemical changes in the environment (indoors and outdoors)
- Transformation reactions result in detoxification
- Residues of active ingredient and detoxification residues can remain on surfaces indoors
- Chlorpyrifos example
  - Undergoes hydrolysis to dialkylphosphate and trichloropyridinol (TCP)



Organophosphate Residues in the Indoor Environment

- Children's Exposure to Persistent Pesticides Study (Morgan MK et al., J Expo Analysis Environ Epi. 2004;1-13)
- The Reliability of Using Urinary Biomarkers to Estimate Children's Exposures to Chlorpyrifos and Diazinon (Morgan MK et al., J Expo Analysis Environ Epi. 2010 (in press)
- Chlorpyrifos and degradation product (TCP) were detectable in 100% of dust and surface wipe samples in homes and daycare centers



Organophosphate Toxicokinetics: Absorption

what the body does to the pesticide

Absorption

↓

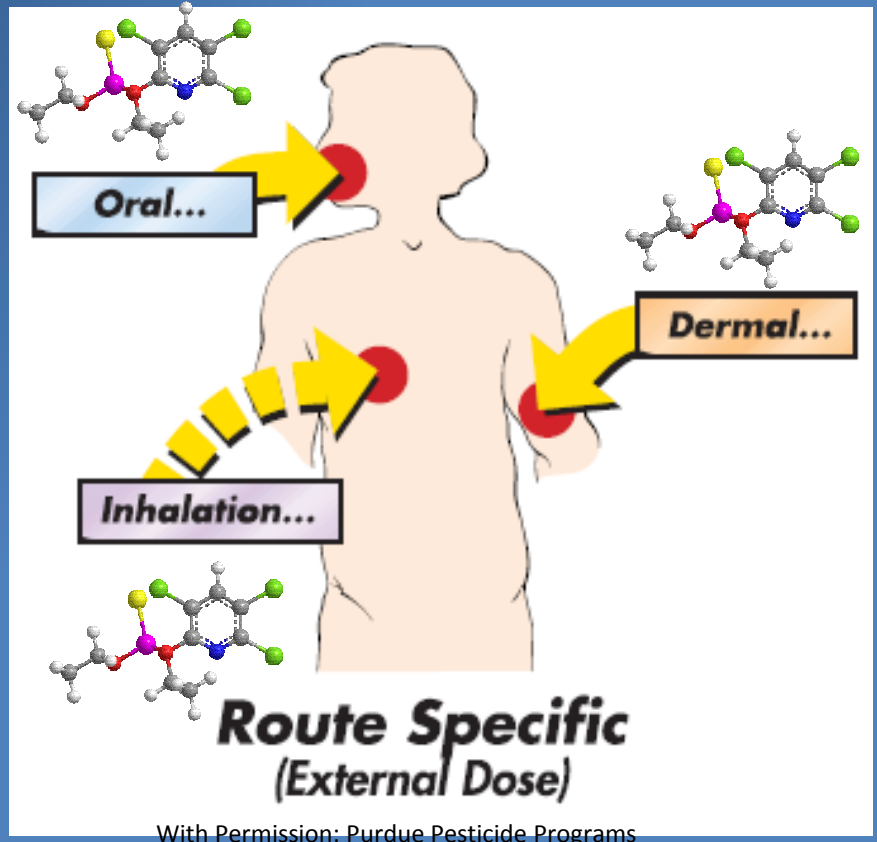
Distribution

↓

Metabolism

↓

Elimination



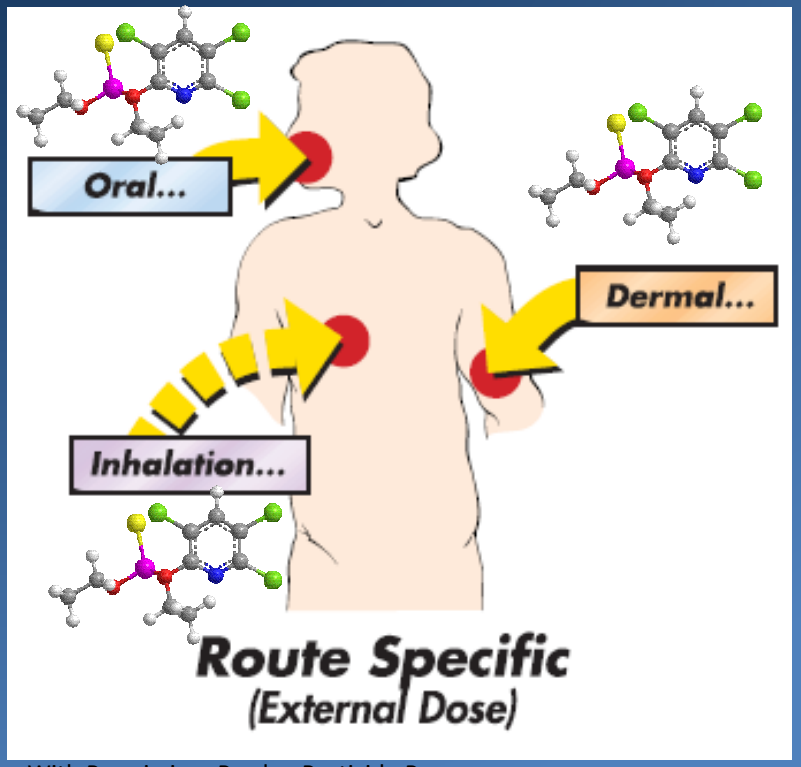
With Permission: Purdue Pesticide Programs

Internal dose depends on exposure pathway and bioavailability

- Contrast dermal exposure with oral and inhalation exposure

Organophosphate Toxicokinetics: Distribution to Nervous System

Absorption → **Distribution** → Target



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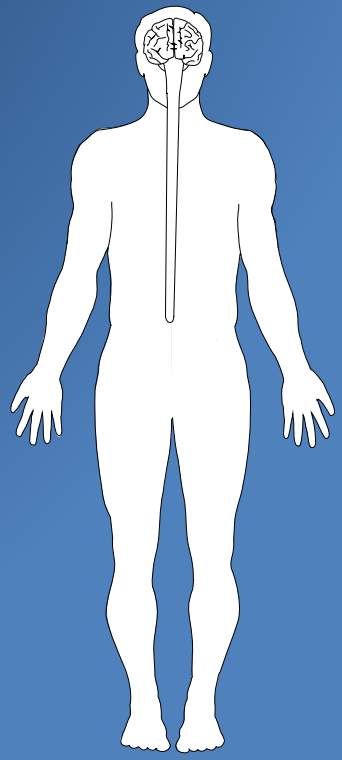
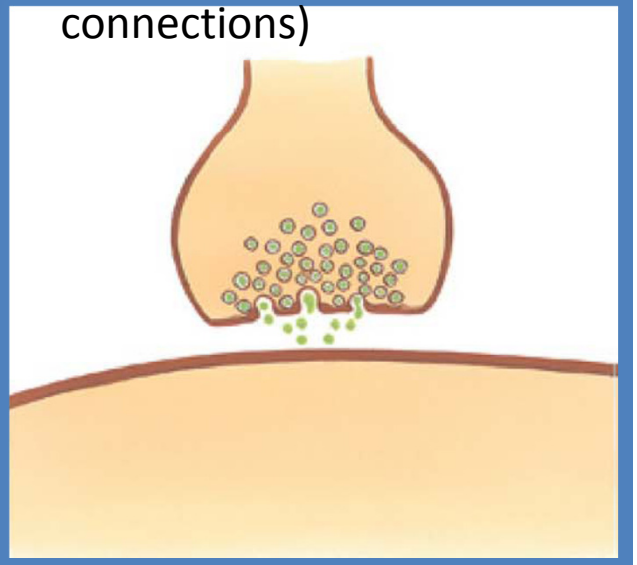
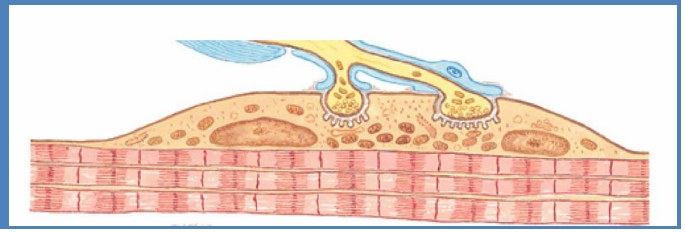


Synapse (nerve-nerve connections)

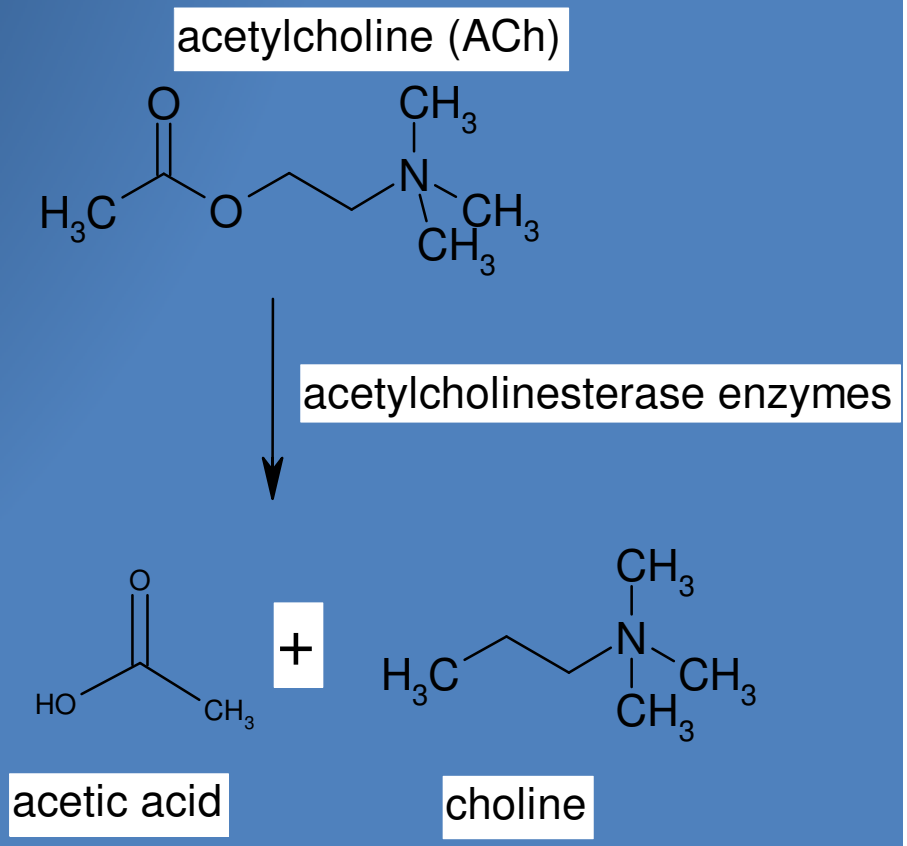


Nerve-Muscle Junction



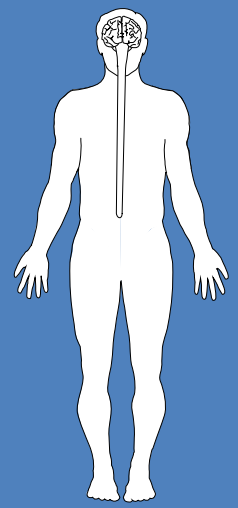
Organophosphate Toxicodynamics

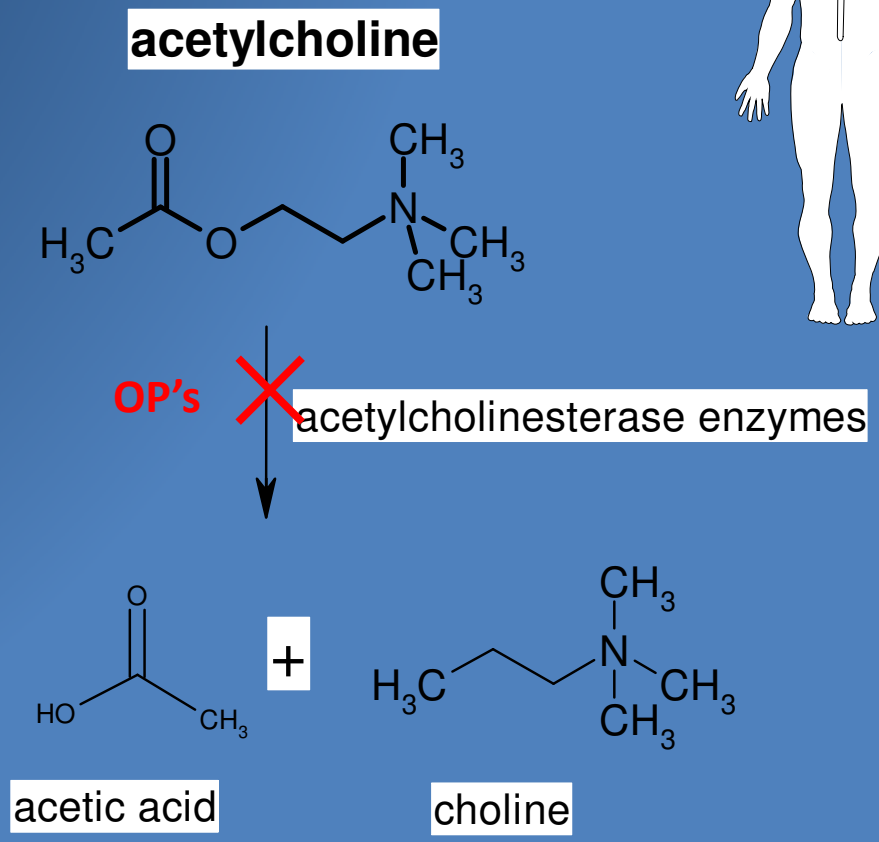
- Organophosphates are inhibitors of cholinesterase enzymes
  - Cholinesterase enzymes are found in insects and mammals
  - Different types of cholinesterase enzymes
    - Butyrylcholinesterase (in blood)
      - role in drug, xenobiotic metabolism
    - **Acetylcholinesterase (in nervous system)**
      - Role in neurotransmitter (acetylcholine) metabolism
  - OP's differ in their potency
    - High: methyl parathion
    - Lower: chlorpyrifos, malathion



Toxicodynamic Effects of Organophosphates

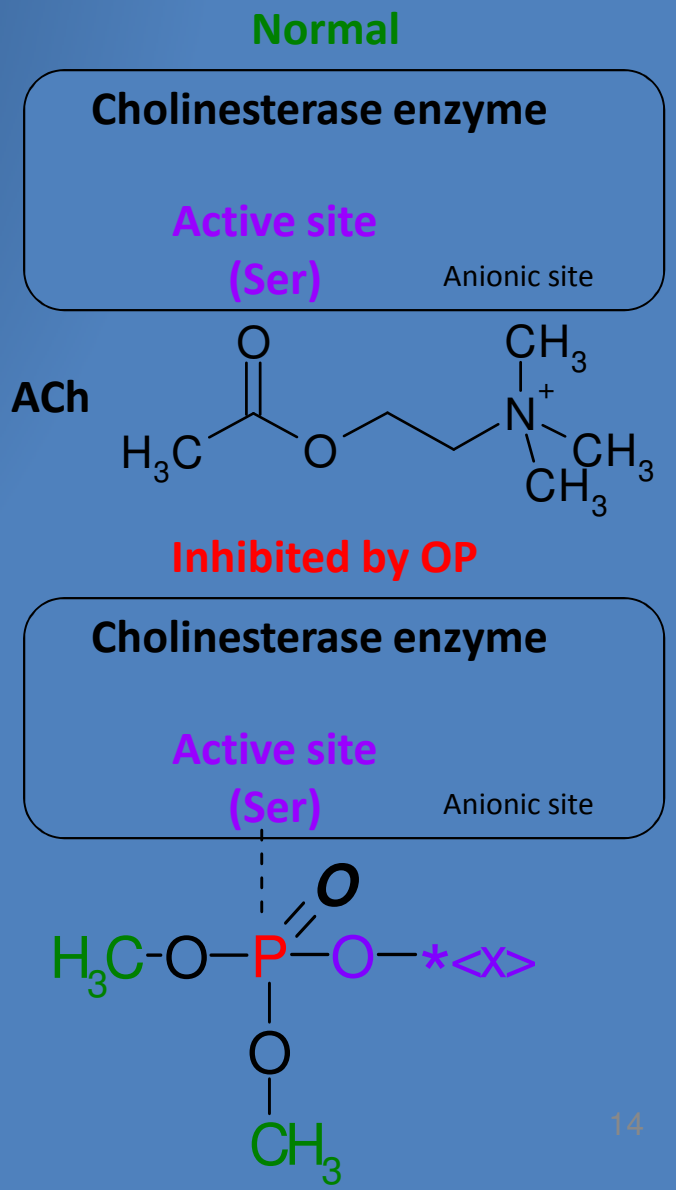
- Cholinesterase inhibitors block the metabolism of acetylcholine (ACh)
  - Leads to accumulation (excess) of acetylcholine in the nervous system
  - Excess acetylcholine leads to excessive activity at acetylcholine receptors in nervous system
    - Neuron-muscle junction
    - Parasympathetic (autonomic) nervous system
      - Responsible for "rest and digest" processes in body
    - Central nervous system (brain)





Organophosphate Toxicodynamics

- Serine (Ser) amino acid residue at active site of cholinesterase enzyme
  - Catalytic site for esterase activity
  - Breaks down ACh to choline and acetic acid
- OP's bind to, and phosphorylate the active site of cholinesterase
  - Competitively inhibits the enzyme from breaking down ACh
- Significant differences exist among OP's in their potency for cholinesterase inhibition
  - Methyl parathion (higher potency)
  - Chlorpyrifos, malathion (lower potency)

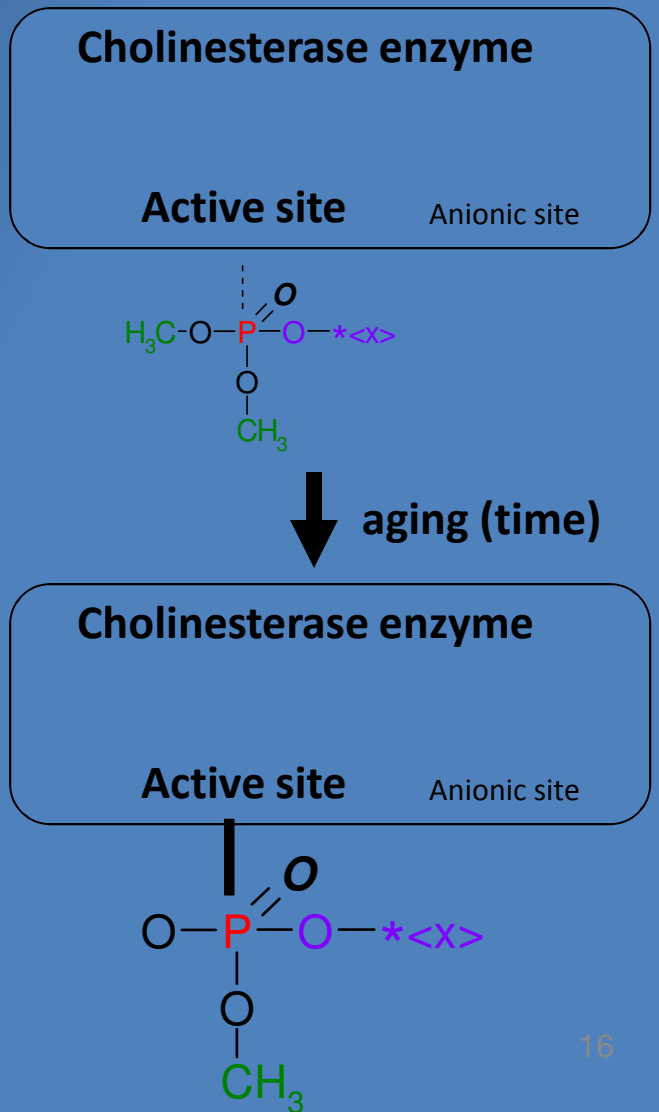


Effects of Cholinesterase Inhibitors (OP's) on the Nervous System

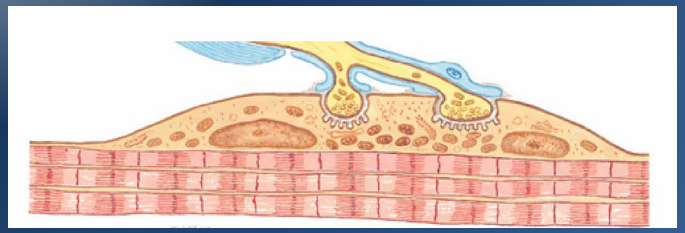
- ACh accumulates at neuron-muscle junction
  - Excessive muscle stimulation
  - Fasiculations (abnormal contractions) followed by
    - Weakness
    - Paralysis
- ACh accumulates in central nervous system
  - Altered mental status
  - Confusion, disorientation, delirium, seizures
- ACh accumulates at receptors for parasympathetic (autonomic) nervous system
  - "rest and digest" functions
  - Cholinergic toxidrome
    - SLUDGE mnemonic
      - Salivation, lacrimation, urination, defecation/diarrhea, gastrointestinal tract symptoms (nausea, vomiting), emesis/eyes (miosis)
  - Effects reversed by atropine
    - Atropine binds to, competitively blocks (antagonist at) acetylcholine receptors in parasympathetic nervous system

Organophosphate Toxicodynamics

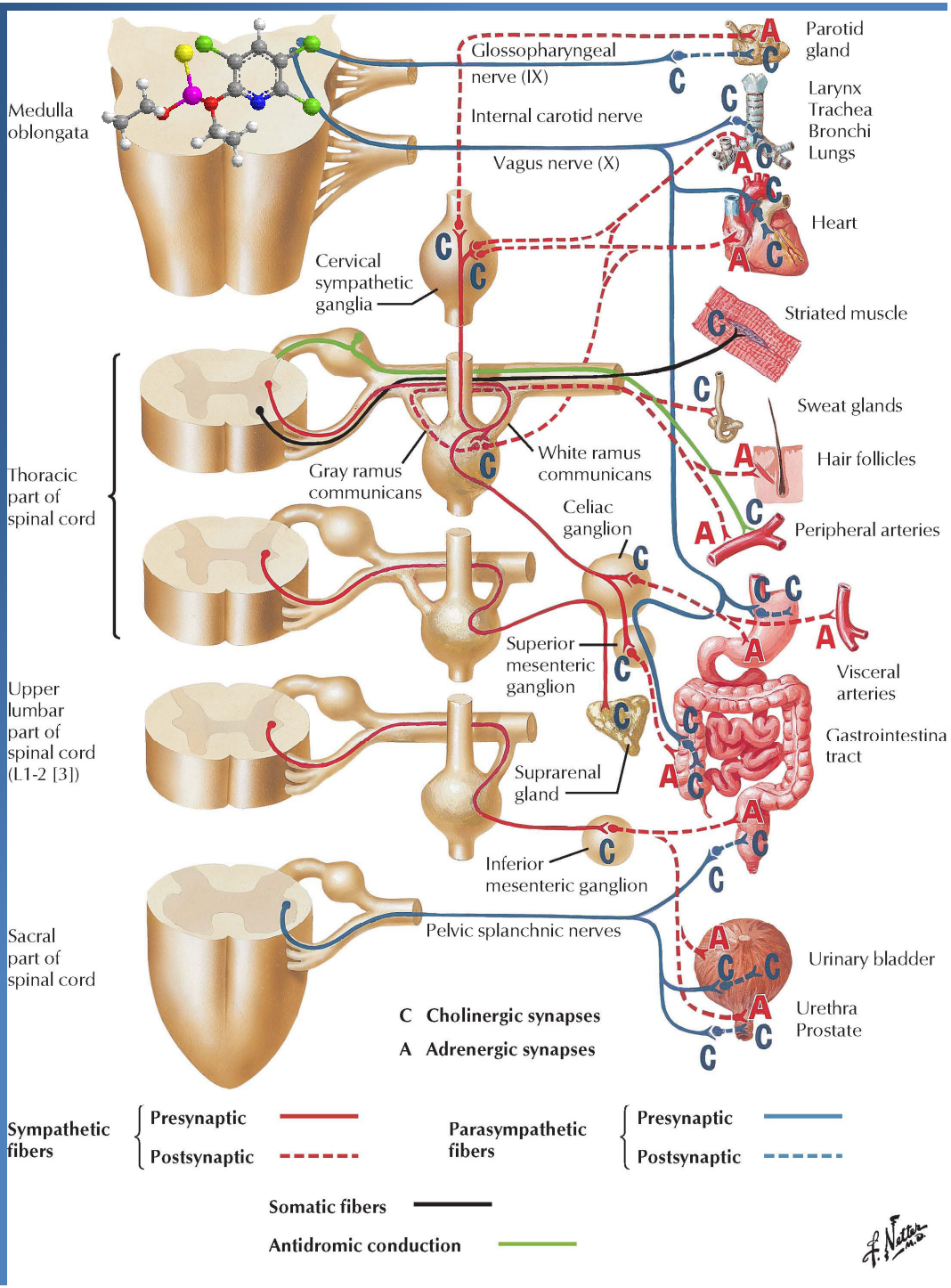
- Fate of inhibited cholinesterase enzyme
  - OP-active site bond can spontaneously hydrolyze, regenerating active enzyme
  - Nucleophilic attack at the phosphorylated enzyme can hydrolyze the OP-active site bond (regenerating enzyme)
    - *Antidote (2-PAM, a.k.a. pralidoxime) used for acute poisonings by OP insecticides*
    - *Modifies the toxicodynamic effects*
  - The OP-active site bond becomes more stable, and enzyme is **permanently inhibited**
    - "aging"
    - Regeneration requires new synthesis of cholinesterase enzymes



Organophosphate Toxicodynamics

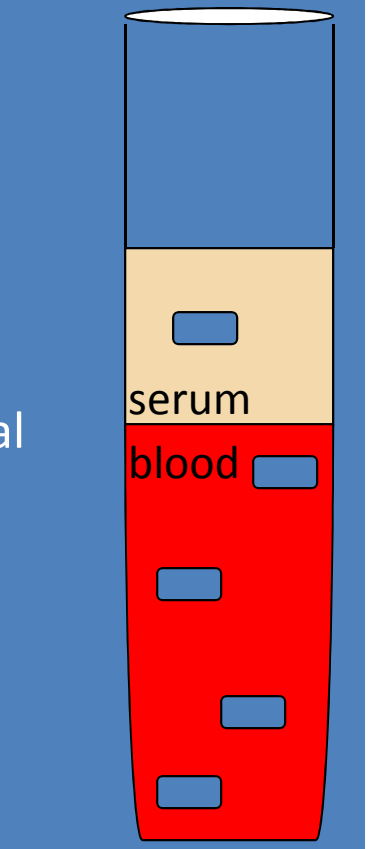


- Acetylcholine as neurotransmitter
  - Nerve-muscle junction
    - Nicotinic ACh receptors
  - Neurotransmitter in PNS (parasympathetic)
    - Muscarinic ACh receptors
  - Neurotransmitter in CNS
- Organophosphates inhibit cholinesterase enzymes, causing accumulation of ACh in nervous system



Clinical and Laboratory Diagnosis of Organophosphate Poisoning

- Exposure history, clinical signs and symptoms
  - Recognize common exposure scenarios, high-risk populations
  - Assess for cholinergic signs and symptoms, and physical examination findings
- Cholinergic symptoms correlate with extent of cholinesterase enzyme inhibition
  - Can develop when enzyme inhibited to less than 70-80% of usual activity
- Cholinesterase enzyme activity (extent of inhibition) can be measured in the blood
  - Serum (pseudocholinesterase)
  - Red blood cells (RBC cholinesterase)
    - Correlates better with enzyme activity in nervous system
    - A more specific (but indirect) **biomarker of effect**



Methyl parathion: Adverse Health Effects from Indoor Misuse

- 1994-6: Ohio (Lorain County)
  - Hundreds of residences affected
  - Cost to clean-up greater than $20 million
- Illegal misuse of methyl parathion by unlicensed pesticide applicators

http://www.atsdr.cdc.gov/alerts/961213.html

Methyl parathion: Adverse Health Effects from Indoor Misuse

- Rubin, et al. (2002)
- Symptoms reported after application
  - Headache, nausea, diarrhea, dizziness, abdominal cramping, sweating, salivation, confusion
  - Higher proportion of children affected
  - Some cases were not recognized as organophosphate poisoning
    - Gastroenteritis, dehydration, URI

Methyl parathion: Adverse Health Effects from Indoor Misuse

- Rubin, et al. (2002)
- Case series
  - 43 year old female with multiple ED visits over a 1 year period
  - Had monthly spraying in her residence
  - Primary complaint of wheezing, headache, coughing
  - One visit with nausea, vomiting
  - No fever or abnormal vitals
  - Physical examination unremarkable

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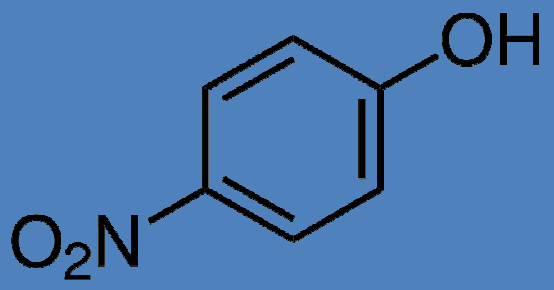
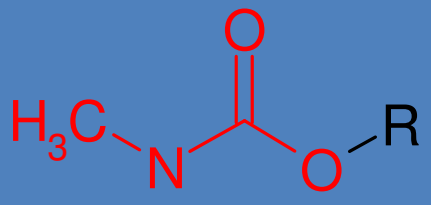


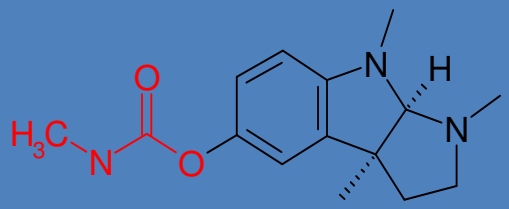
Pesticide Residues in the Home: Organophosphates

- Organophosphates are no longer registered for most indoor residential uses in the U.S.
- Importance of misapplications, storage of old products
- Understand the importance of exposure history and physical exam findings
- Recognize the signs and symptoms of cholinergic toxidrome
- Applications and limitations of biomarkers (of exposure and effect)

Other Pesticide Residues in the Home: N-methyl carbamate Insecticides

- Chemistry
  - N-methyl carbamates
    - Esters of carbamic acid
- Some N-methyl carbamates occur naturally
  - Physostigmine (from the calabar bean)
    - Modern pharmaceutical uses
- Others widely used for crop protection

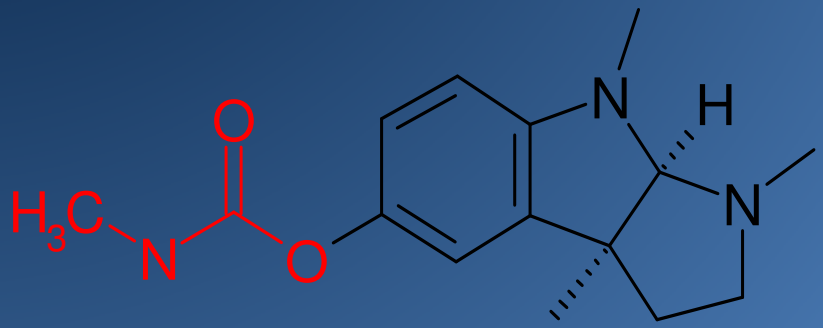




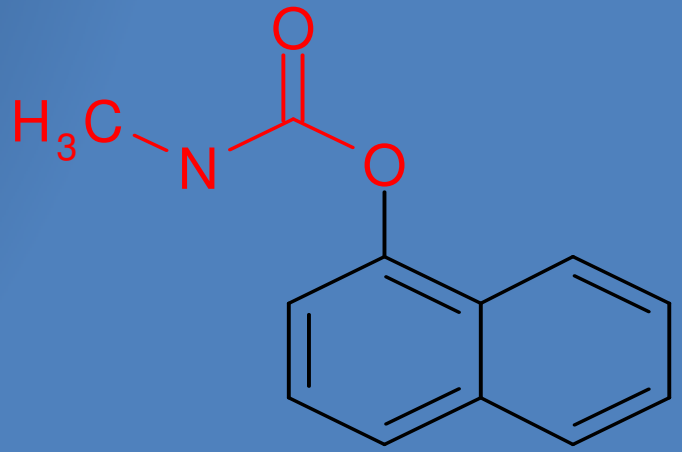
Physostigmine

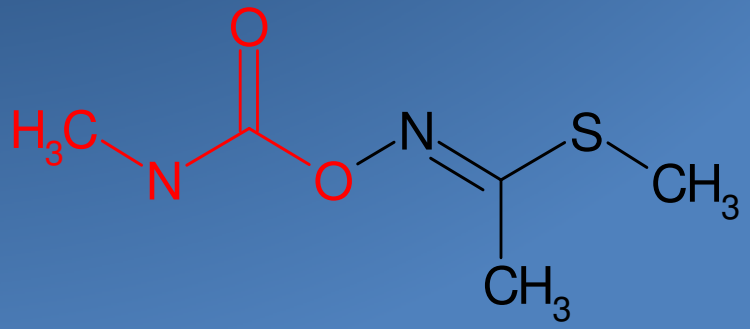
N-methyl Carbamates (Examples)

Physostigmine (drug)

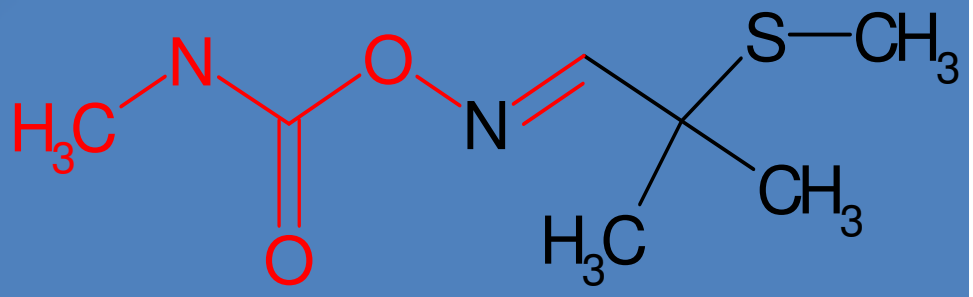


Carbaryl





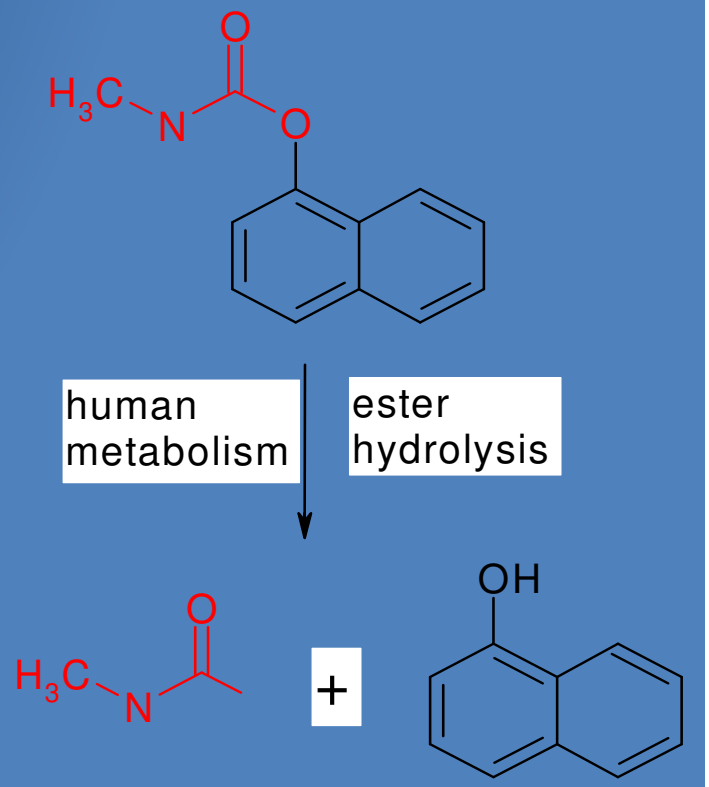
Aldicarb



Methomyl

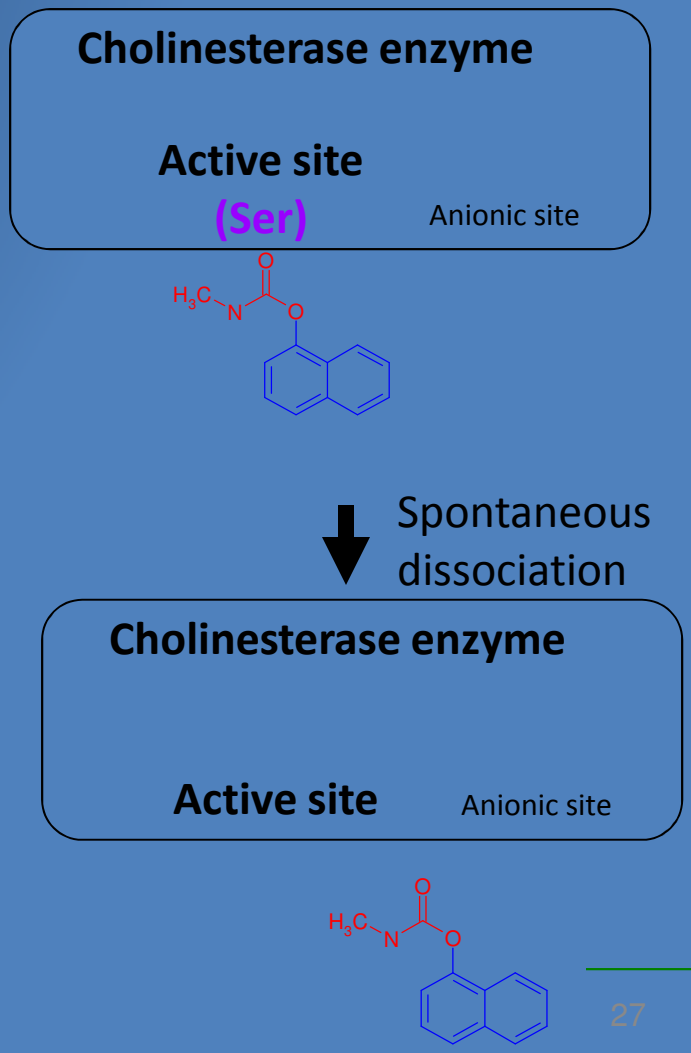
N-methyl Carbamate Toxicokinetics (Humans)

- Most are well-absorbed from ingestion pathways (orally bioavailable)
- Some (aldicarb) have significant dermal bioavailability
- Distribution varies by chemical structure
  - Generally greater than plasma volume
  - Some are charged (ionized) at physiological pH (pH=7.4)
    - Affects distribution to target organs
- Metabolic pathways include ester hydrolysis
  - Similar to what occurs in environment
- Elimination in urine
  - Not persistent compounds
  - Generally, short elimination $t_{1/2}$ (hours)



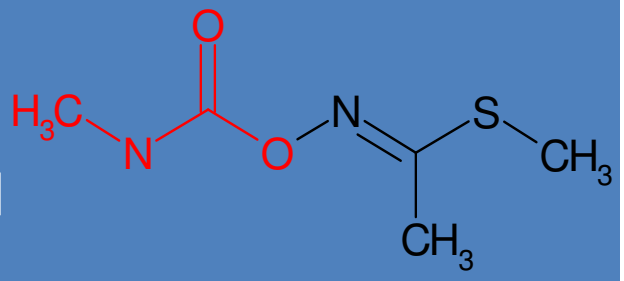
N-methyl carbamate Toxicodynamics

- **Reversible** inhibitors of cholinesterase enzymes
- Bind to active (esterase) site (serine residue) on cholinesterase enzymes
- Inhibits the active site of cholinesterase enzyme
- Interaction with inhibited enzyme is unstable, spontaneously dissociates to re-form **active enzyme**



Poisonings from Illegal Indoor use of N-methylcarbamates as Rodenticides

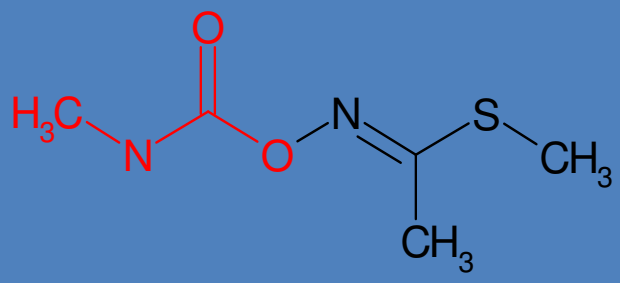
- Nelson, et al. (2001)
- Symptoms reported after application of *Tres Pasitos*
  - "Three Little Steps"
  - Rodenticide that could be legally purchased in Dominican Republic
  - Many victims had recently emigrated from Dominican Republic
  - Cluster of incidents resulting in acute cholinergic toxidrome
    - Included intentional (suicidal exposures) and accidental exposures from residential misapplication
  - Active ingredient was found to be aldicarb
    - Not registered for indoor uses in U.S.



Aldicarb

Poisonings from Illegal Indoor use Aldicarb (*Tres Pasitos*) as Rodenticide

- Nelson, et al. (2001)
- Symptoms reported after application
  - parents found 2 yr-old eating *Tres Pasitos* and rice mixture, which they had applied
  - Lethargic, vomiting, pulmonary rales, pinpoint pupils
  - child improved after 3 mg atropine, admitted to ICU
  - extubated following day and completely recovered



Aldicarb

Illegal Pesticide Incidents: Public Health Response

- Clinicians should be aware of regulatory and enforcement agencies for suspected pesticide poisoning incidents:
  - In some cases, pesticide poisoning is a reportable condition to public health agencies
  - http://www.npic.orst.edu/mcapro/PesticideIncidentReporting.pdf
  - EPA Common Illegal Pest Products: http://www.epa.gov/opp00001/health/illegalproducts/#products

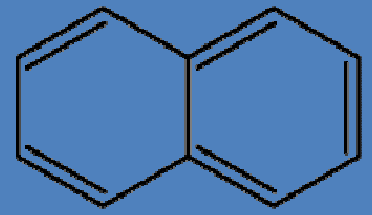
Tres Pasitos

Illegal Pesticide Incidents: Clean-Up and Enforcement Issues

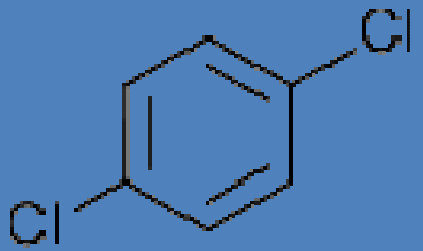
- Clean-up is complicated
  - Other ingredients in the formulation (not disclosed on label)
  - Manufacturer of product may be able to provide specific information
    - http://npic.orst.edu/manuf.htm
- Regulatory and enforcement agencies
  - Varies by state
  - http://npic.orst.edu/state1.htm

Other Important Pesticide Residues in the Indoor Environment: Mothballs

- Commonly contain naphthalene or paradichlorobenzene
  - Mothballs undergo sublimation
- Widely available for consumer use
- Misuse of mothball products is common
  - Examples: placement in air handling systems or crawlspaces
- Accidental (pediatric) exposures are also very common



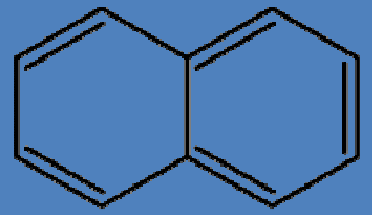
naphthalene



paradichlorobenzene

Pesticide Residues in the Indoor Environment: Naphthalene Mothballs

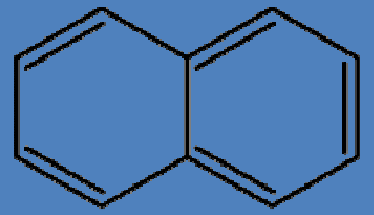
- Other potential sources of naphthalene indoors
  - Tobacco smoke, other products of combustion
- Presence of mothballs is an important contributor to indoor air levels of naphthalene
- ATSDR has established a minimum risk level (MRL) for naphthalene
  - 0.0007 parts per million (ppm)



naphthalene

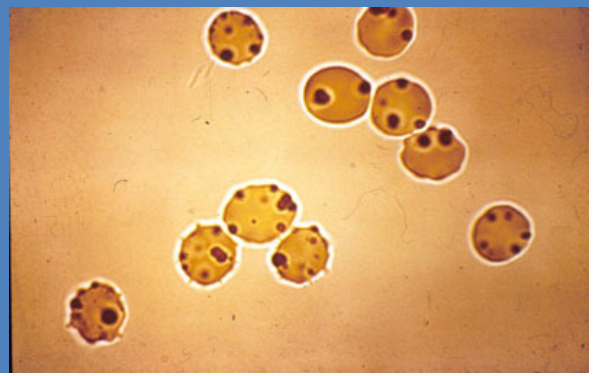
Pesticide Residues in the Indoor Environment: Naphthalene Toxicology

- Ingestion exposure is most common pathway for serious toxicity
- Hepatic metabolism
  - Metabolites produce oxidative stress
  - Oxidation of hemoglobin
    - Heinz Bodies
  - Increased susceptibility to hemolysis
  - Delay in onset of signs and symptoms
    - 1-2 days
  - Increased susceptibility among individuals with G6PD deficiency
- Other effects, airway injury/inflammation, narcosis



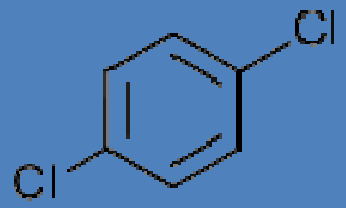
naphthalene

Heinz Bodies in RBC's



Other Important Pesticide : Paradichlorobenzene Mothballs

- Paradichlorobenzene is a very common ingredient in mothballs
- Similar patterns of exposure with naphthalene mothballs
- Toxicology is different
  - Hemolytic reactions are unlikely
  - Ingestion exposures
    - Nausea, vomiting
  - Inhalation exposures
    - Headache, mucous membrane irritation



paradichlorobenzene

Pesticide Residues in the Indoor Environment: Tetramine

- tetramethylene disulphotetramine
- odorless, tasteless, and water-soluble white crystalline powder
- Binds noncompetitively and irreversibly to the gamma-aminobutyric acid receptor on neuronal cell membranes and blocks chloride channels
- WHO classifies as an extremely hazardous pesticide

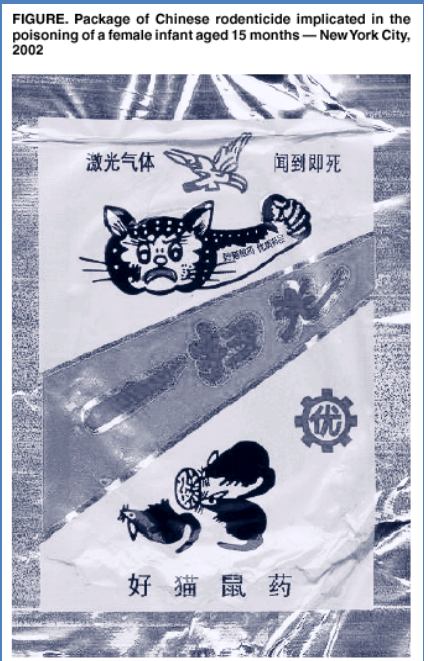
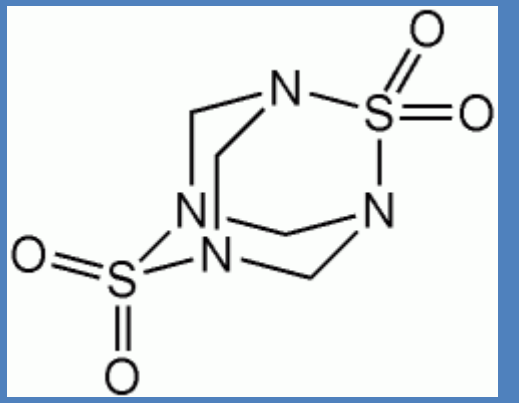


FIGURE. Package of Chinese rodenticide implicated in the poisoning of a female infant aged 15 months — New York City, 2002

Photo/New York City Poison Control Center



Tetramine: Adverse Health Effects from Indoor Misuse

- 2002: New York City
  - First reported exposure case in United States
  - 15-month-old infant found playing with white rodenticide powder that parents had bought from China and applied in their kitchen
  - 15 min. later, infant experienced generalized seizures, and taken to ER
    - Seizures refractory to lorazepam, phenobarbital, and pyridoxine

FIGURE. Package of Chinese rodenticide implicated in the poisoning of a female infant aged 15 months — New York City, 2002

Photo/New York City Poison Control Center

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5210a4.htm

Tetramine: Adverse Health Effects from Indoor Misuse

- Zhang, et al. (2010)
- Literature review of tetramine poisonings in China between 1998 to 2010
  - 40 cases (20 male/20 female)
  - Ages 5-62 years (median 35 years)
  - 10 of the 40 cases occurred by accidental exposure

FIGURE. Package of Chinese rodenticide implicated in the poisoning of a female infant aged 15 months — New York City, 2002

Photo/New York City Poison Control Center

Pesticide Residues in the Indoor Environment: Key Concepts

- Pesticides have multiple mechanisms of toxicity
  - Recognize toxidromes
  - Recognize common and serious clinical presentations
- Serious morbidity, mortality can arise from misuse, misapplication
  - Illegal applications
  - Unregistered pesticides
- Clinicians should participate in notifying public health authorities when appropriate

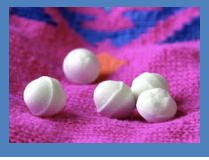
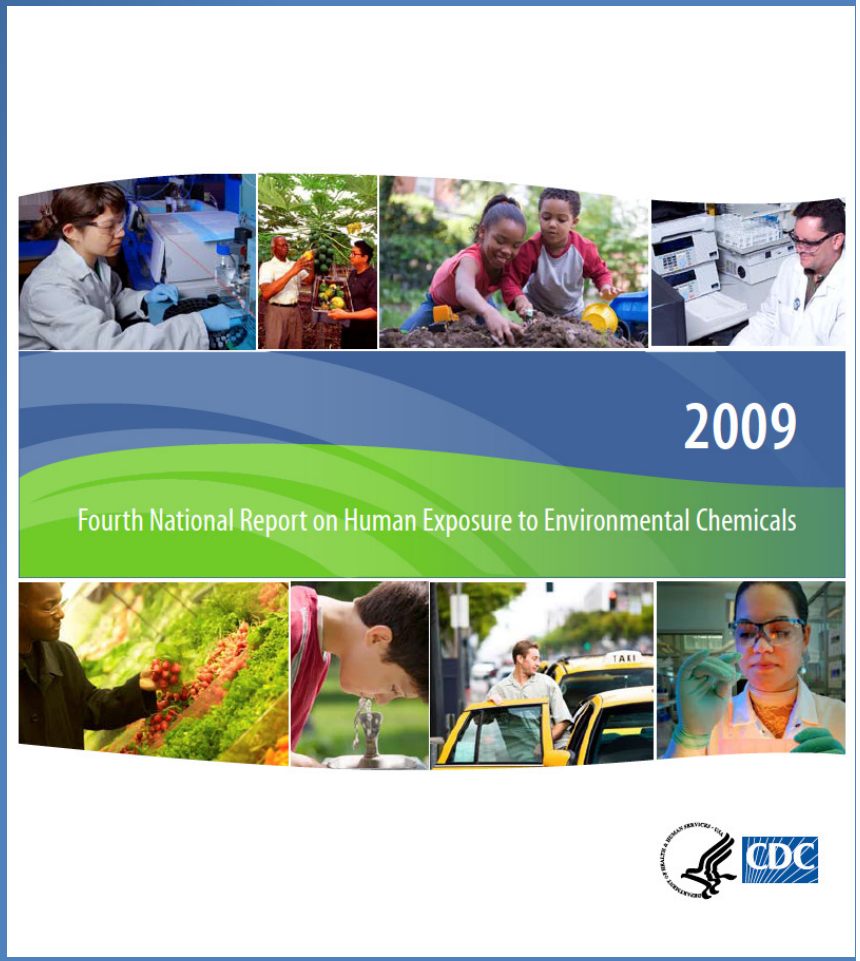


FIGURE. Package of Chinese rodenticide implicated in the poisoning of a female infant aged 15 months — New York City, 2002

Photo/New York City Poison Control Center

Current Areas of Research in Pesticide Toxicology: Biomonitoring

- Population-based estimates of human exposure to pesticides
  - Organophosphates
  - Pyrethroids
  - Herbicides
  - Organochlorines
- Discussion includes applications and limitations of biomarker methods



http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf

Current Areas of Research in Pesticide Toxicology: Endocrine Disruption

- Environmental chemicals that may mimic or antagonize the effects of endogenous hormones
  - Pharmaceutical example: diethylstilbestrol (DES) and vaginal cancer from synthetic estrogens
- Do pesticides have potential to interact with hormone receptors in humans?
  - Considerations of exposure, internal dose, and response
  - An area of ongoing research, and risk assessment considerations
  - EPA requires screening of pesticides for potential interactions with the endocrine system

Current Areas of Research: Cancer and Other Health Endpoints

- Health implications of chronic, low-level residential exposure to pesticides
- Epidemiological studies in high-risk occupations
  - Pesticide applicators
    - The Agricultural Health Study
    - http://aghealth.nci.nih.gov/
- Current and future studies focusing on children and environmental health
  - The National Children's Study
  - http://www.nationalchildrensstudy.gov/Pages/default.aspx

Literature for Further Review

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