

PESTICIDES-FUNGICIDES

Pásztiné Dr Gere Erzsébet

2020

FUNGICIDES

❖ INORGANIC COMPOUNDS

sulfur, barium-sulfide
copper-hydroxide, -sulfate
zinc-sulfate, iron-sulfate

❖ ORGANIC DERIVATIVES

pyrimidines, heterocyclic compounds
phenols, piperazines, benzimidazols

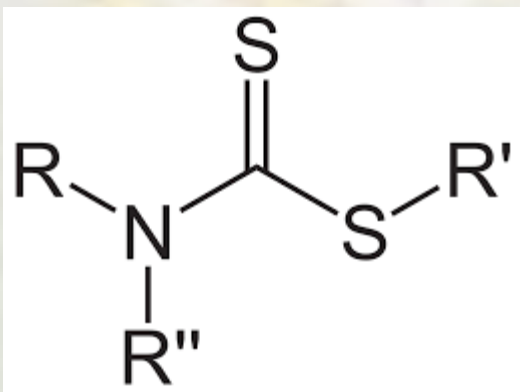
DITHIOCARBAMATES

TETRAMETHYL-THIURAM-DISULFIDE

⇒ generally low toxicity

⇒ poisonings in animals uncommon

DITHIOCARBAMATES



amino group

dimethyl, ethyl, propyl

SH → metal (Zn, Mn, Fe)

ring → ethylene-bis-dithiocarbamate (EBCD)

TMTD (linear)

dimethyl-dithiocarbamate (2)

cineb, maneb, mankoceb, propineb

DITHIOCARBAMATES

TOXICITY

Less toxic

Dithiocarbamate

PO LD 4000-6000 mg/kg

Prolonged uptake

5-10x lesser amount

Sheep: 250 mg/kg feed, 18 ws \emptyset
5000 mg/kg feed, 15x uptake ✓
(cineb)

Carcinogenic

TMTD

PO LD 200-1000 mg/kg
↙ poultry 40 mg/kg feed
leg weakness, egg production ↓

poultry 10-50 mg/kg feed toxic

Teratogenic

DITHIOCARBAMATES

Absorption

GI well

Distribution - Metabolism

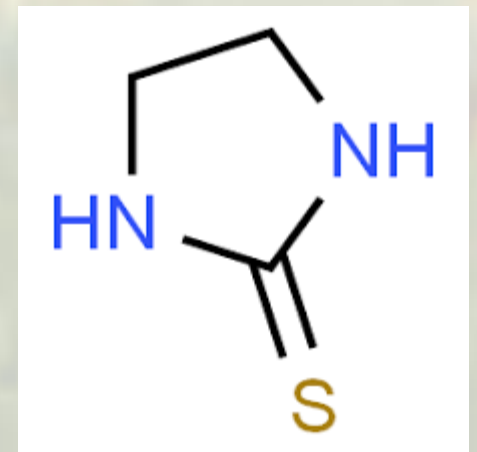
rapid (active metabolites)

carbon-disulfide (psycho/neurotoxic)

ethylene thiourea (neurotoxic, antityreoid)

Excretion

urine (mainly)



DITHIOCARBAMATES

MECHANISM of ACTION

Enzyme inhibition (parent molecule + metabolite)

Alcohol-dehydrogenase, AChE
phosphatase

⇒ **metabolic effects**

Dopamine- β -hydroxylase

→ disturb endogenous NA synthesis

⇒ tachycardia, hypotension

Aldehyde oxydase (**TMTD**) ⇒ acetaldehyde intoxication

DITHIOCARBAMATES

MECHANISM of ACTION

Inhibition the conversion of inorganic iodine to organic

→ goiter (hypertrophy/plasia)

in rats, mice, monkeys, dogs

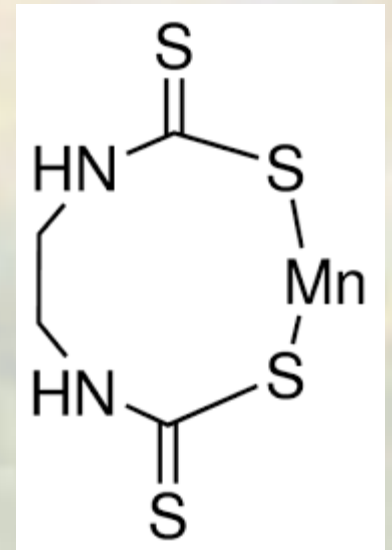
Reproductive problems (testis atrophy) – (prolonged)

Mutagenic, teratogenic, embriotoxic

Local irritative effect (skin, mucosa)

Peripheral demyelination

Degeneration (skeletal muscle/heart)



**MANEB: ANTITHYROID
EFFECTS**

DITHIOCARBAMATES

CLINICAL SIGNS

ACUTE

anorexia, diarrhoea, depression, cardiac failure
leg weakness, leg deformities (poultry)
reproductive problems, abortion
infertility (testis atrophy)

Poultry egg production ↓ (deformed, soft-shelled)

CHRONIC

growth retardation, loss of weight, goiter
+ acute (slight)

DITHIOCARBAMATES

POSTMORTEM FINDINGS

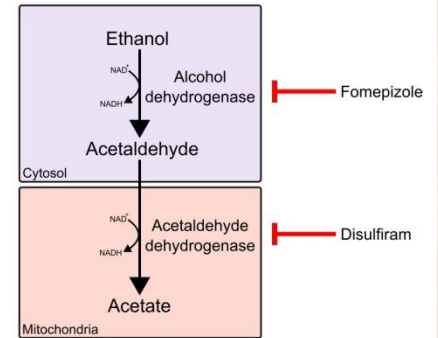
- Liver, kidney, muscle degeneration, hemorrhages
- Heart muscle Zenker-degeneration
- Skeletal muscle hyaline degeneration
- Spinal cord demyelination
- Thyroid gland hypertrophy/plasia, hemorrhage
- Poultry edema/necrotic changes in oviductus

DITHIOCARBAMATES

TREATMENT

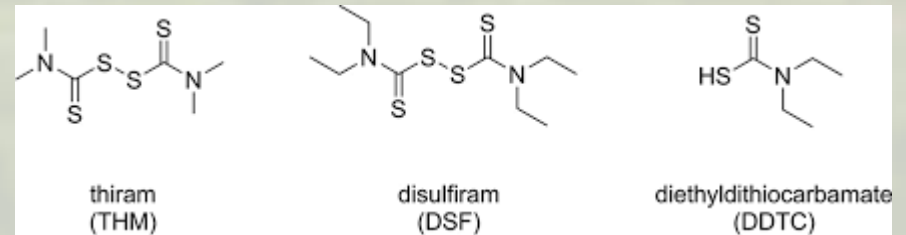
- Specific antidote Ø
- GI detoxification
activated charcoal, saline purgatives
- Symptomatic therapy
liver protecting agents, analeptics,
forced diuresis, multiple vitamin therapy
- ! Alcohol Ø

Ethanol Metabolism



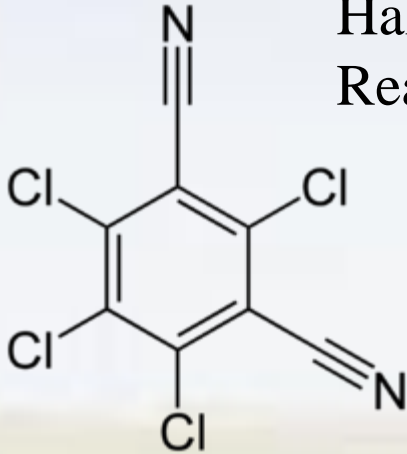
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Moises Dominguez



CLOROTHALONIL

Halogenated benzonitrile fungicide
Reactive toward SH group



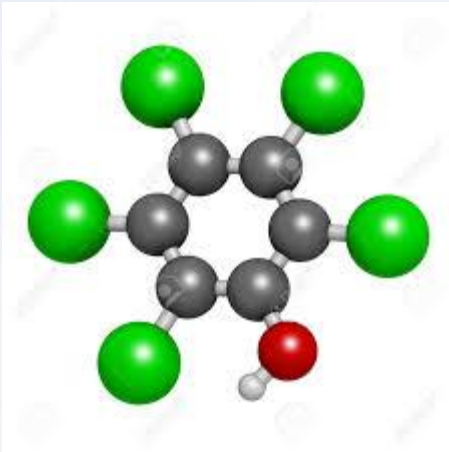
ABSORPTION: rapid, GIT (30%)

METABOLISM: glutathione conjugation (hepatic
GSH is decreased)

EXCRETION: Feces (80%) within 96 h

- Skin irritation (rat, rabbit)
- Ocular lesion (irreversible-rabbit)
- Decreased body weight and hematological parameters
- Degeneration of proximal tubular epithelium
- Carcinogenicity: Hyperplasia of forestomach in rodents (dogs, no forestomach)
- Toxicity is high in fish

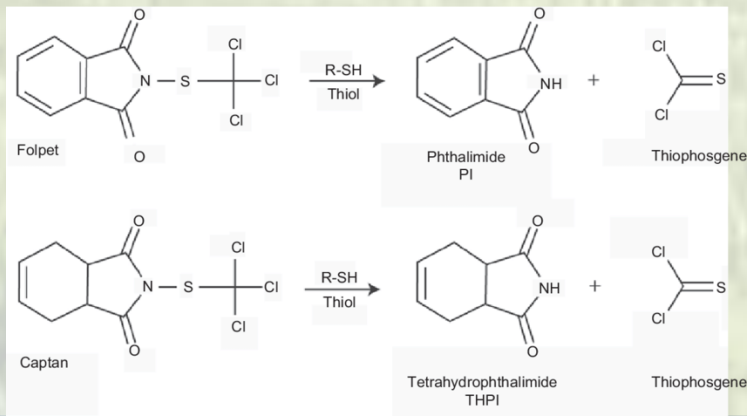
PCP



- Halogenated fungicide
- LD50=80-100 mg/kg highly hazardous in rats
- Lethal dose in sheep and in cattle: 120-140 mg/kg BW
- Mode of action: uncoupling of ox. phosphorylation (ATP↓, oxygen consumption ↑, depletion of energy reserves)
- TOXICITY:
 - ↑temperature, breathing rate, tremors, convulsions
 - Chronic: weight loss, reduced productivity (milk, eggs....)

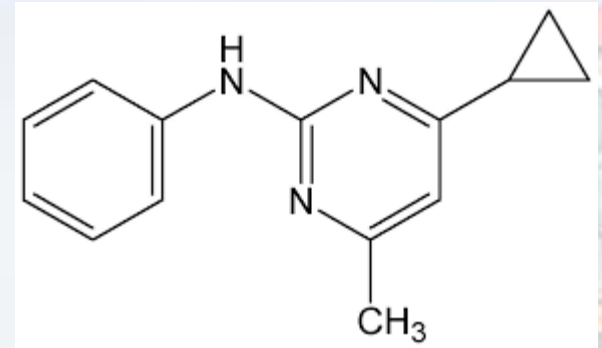
CAPTAN and FOLPET

- Chloroalkylthiodicarboximides
- Stomach: degradation, rapid excretion ($t_{1/2} = 4s$)
- No captan is in urine/blood
- No effect on systemic targets
- Reaction with SH to produce thiophosgene (SH, NH₂, OH group reaction)
- Crypt cell proliferation, villi cell loss, adenocarcinoma (continued irritation)
- Folpet: reduced food intake/diarrhoea
- Captan: cattle oral TD 250-500 mg/kg ascites, gastroenteritis, HUMAN: reproductive problems





CYPRODINIL



Anilinopyrimidine

ABSORPTION: rapid (GIT)- to lesser extent and more slowly in goats (to rats)

METABOLISM: complete

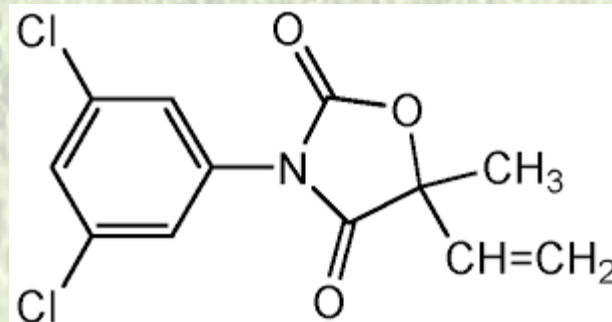
EXCRETION: feces and urine (milk minimal)

Toxicity: slightly hazardous LD50= 2g/kg

- No effect on development toxicity
- Not genotoxic
- No carcinogenic
- In dogs: hepatomegaly and increased thyroid weights

ENDOCRINE DISRUPTORS

- Clorothalonil:
 - Infertility in male and female rats via inhibition of CP450
 - Steroid metabolism
 - Alteration of sexual differentiation through antagonism of androgen receptors
- Vinclozalin:
 - Antiandrogenic
 - Competitive antagonist



OTHER FUNGICIDES WITH THE RISK CAUSING DEVELOPMENT TOXICITY

- Benzimidazoles: Fuberidazole
 - Moderately hazardous
 - LD50 in rats 350 mg/kg
 - ↓sperm count and testis weight in laboratory animals
- Conazoles:
 - Aza-, bromu-, propi-, tetraconazole LD50 in rats ~500 mg/kg
 - Variable multiple defects
- Morpholines:
 - Tridemorph
 - LD50 in rats 250 mg/kg
 - Malformations in rats and mice