INORGANIC HERBICIDES

- They are older, cheaper, more toxic and more likely to cause problems than newer compounds.
- Their use has been curtailed in developed countries.

1. Arsenicals (Inorganic arsenicals e.g Sodium arsenite, arsenic trioxide and Organic arsenicals e.g Methane arsonate, methyl arsenic acid)

- Used as dessicants and cotton defoliants
- Toxic dose in cattle/sheep is 22-55mg/kg

Treatment:

- Dimercaprol 3mg/kg i/m every 4-6 hours (small animals), 2.5-5mg/kg (large animals).
- Sodium thiosulfate 20-30g p/o in 300mls of water (cattle), one-fourth dose for sheep.

2. Ammonium Sulfamate

Clinical Signs:

- Sudden death, inappetance, weakness

Treatment:

- Lower rumen pH by dilution with copious amounts of water to which weak acetic acid (vinegar) has been added.

3. Borax

- Used as insecticide and soil sterilant
- The toxic dose is >0.5g/kg

Clinical Signs:

- Diarrhea, rapid prostration, convulsions

Treatment:

- Fluid therapy and supportive care

4. **Sodium Chlorate**

- Seldom used
- Constitutes fire hazard

Mechanism of action:

- Haemolysis of RBC and conversion of haemoglobin to methaemoglobin.

Treatment:

- Methylene blue 10mg/kg, blood transfusion, isotonic saline and mineral oil.

RODENTICIDE POISONING

- Rodenticides are agents which destroy rodent pests such as black rats (*Rattus rattus*) and mice (*Mus musculus*).
- An ideal rodenticide should

A. Be potent and palatable to the target animals

B. Not induce bait shyness

C. Not make the intoxicated animals go out in the open to die

D. Be specie specific

E. Cause death in such a manner that surviving rodents will not suspect.

Commonly employed rodenticides are:

1. Anticoagulant Rodenticides (Warfarin and Congeners)

- Potentially dangerous to all mammals and birds.
- These are the most frequent cause of poisoning in pets.
- All anticoagulants have the basic coumarin or indanedione nucleus. -The "first-generation" anticoagulants (warfarin, pindone) are rapidly inactivated by cytochrome P450 enzymes of the liver and are multiple-dose poisons requiring frequent feedings.
- The "second-generation" anticoagulants (brodifacoun and bromadiolone) are highly toxic to nontarget species (dogs, cats, and livestock) after a single feeding.
- The "intermediate" anticoagulants (chlorophacinone and diphacinone) require fewer feedings than "first-generation" group.

Sources of poisoning:

- Pets and wildlife may be poisoned directly from baits or indirectly by consumption of poisoned rodents.
- Intoxications in domestic animals have resulted from contamination of feed with anticoagulant concentrate, malicious use of these chemicals, and feed mixed in equipment used to prepare rodent bait.

Mechanism of toxicity:

- The anticoagulants antagonize vitamin K thereby interfering with the normal synthesis of coagulating proteins (clotting factors I, II, VII, IX, and X) in the liver; thus adequate amounts are not available to convert prothrombin into thrombin. A latent period, dependent on species, dose and activity, is required, during which clotting factors already present are used up.

Clinical signs:

- Anaemia, hematomas, melena, hemothorax, epistaxis, hemoptysis, hematuria, weakness, ataxia, colic, and polypnea, may be seen. Depression and anorexia occur in all species even before bleeding occurs.

Diagnosis:

- History of ingestion of the substance.
- A prolonged prothrombin, partial thromboplastin, or thrombin time in the presence of normal fibrinogen, fibrin degradation products, and platelet counts.

Differential Diagnosis:

- Disseminated intravascular coagulation
- Congenital factor deficiencies
- Platelet deficiencies

- Canine ehrlichiosis.

Treatment:

- Vitamin K_1 is antidotal. Recommended dose vary from 0.25 to 2.5 mg/kg in warfarin exposure, to 2.5 to 5mg/kg in the case of 2^{nd} gen. rodenticide intoxication. Vitamin K_1 is administered subcut. (with the smallest possible needle to minimize hemorrhage) in several locations to speed absorption. IV administration of vitamin K_1 is contraindicated as anaphylaxis may result. Frozen plasma (9ml/kg) or whole blood (20 ml/kg) IV is required to replace needed clotting factors and RBC if bleeding is severe. One week of vitamin K_1 treatment is usually sufficient for first-generation anticoagulants. For intermediate and second-generation anticoagulants or if anticoagulant type is unknown, treatment should continue for 4-6 weeks to control long-term effects. Administration of vitamin K_1 with a fat-containing ration such as canned dog food increases the bioavailability 4-5 times as compared with vitamin K_1 given alone.
- Supportive therapy

2. α- Naphthylthiourea (ANTU)

- A selective rodenticide
- Toxic to rats but harmless to human

Mechanism of action:

- Interferes with effective uptake of O_2 from pulmonary alveoli by producing extensive oedema of the lungs due to increased capillary permeability and seepage of fluid into the airways. This leads to formation of froth which further blocks the air passage and the poisoned animal drowns in its own fluid.

Dogs and pigs are occasionally poisoned, ruminants are resistant.

Clinical signs:

- Vomiting, hypersalivation, coughing, and dyspnea. Animals prefer to sit. Severe pulmonary edema, moist rales, and cyanosis are present. Death from hypoxia may occur within 2-4 hr of ingestion, while animals that survive 12hrs after, may recover.

Post-mortem lesions:

- Pulmonary edema and hydrothorax. Hyperemia of the tracheal mucosa, mild to moderate gastroenteritis, marked hyperemia of the kidneys, and a pale mottled liver are found in most cases.
- Tissue for chemical analysis must be obtained within 24hr.

Treatment:

- Emetics should be used only before respiratory distress is evident. Prognosis is grave when severe respiratory signs occur. Sodium thiosulfate (10% solution) is beneficial.

3. **Bromethalin:**

- A new non-anticoagulant, single-dose rodenticide, which is a neurotoxin.

Mechanism of action:

- It appears to uncouple oxidative phosphorylation in the CNS. CSF pressure increases, placing pressure on nerve axons, resulting in decreased nerve impulse conduction, paralysis and death. Bromethalin can cause either an acute or a chronic syndrome.

Clinical signs:

- Hyperexcitability, muscle tremors, grand mal seizures, hindlimb hyperreflexia, CNS depression and death may appear ~ 10hr after ingestion. Chronic effects are seen with

lower dosage and may appear 24-86 hr after ingestion. This syndrome is characterized by tremors, depression, ataxia, vomiting, and lateral recumbency.

- Bromethalin toxicosis should be considered when cerebral edema or posterior paralysis is present.

Treatment:

- Use of mannitol as an osmotic diuretic and corticosteroids have been suggested, but have shown little effect in bromethalin-poisoned dogs.
- Use of activated charcoal, perhaps for several days, may increase recovery rate.

CYANIDE POISON

Poison :- Any solid, liquid or gas that, when introduced into or applied to the body can interfere with the processes of the cells of the organism by its own inherent chemical properties without acting mechanically regardless of temperature.

Xenobiotic :- Any substances, harmful or not, that is foreign to the body.

Sources of cyanide poisons/Etiology

- Plants
- Fumigants
- Soil sterilizer
- Fertilizer

And rodenticides (e.g calcium cyanomide) ingestion of plants that contains cyanogenic glycosides. These are examples by feed the fruiting.

- *Trigloclin maritims* (arrow grass)
- *Hoecus lunatus* (velvet grass)
- *Sorghum spp.* (common sorghum)

- *Zeamays* (corn)
- *Linum spp* (flex)
- *Sambucus canadensis*
- *Pyrus malus apple*
- *Eucalyptus spp* At home cause to small animals or in implicated in toxicity.
- *Manihot esculantum*
- *Sorghum bicolar*
- *Pheseolus lunatus (*lime bear)
- *Passiflora feotida* (stinging poison flower)

Mechanism of Release of Cyanide and Cause of Toxicity

The cyanogenic glycosides in plants yield free hydrocyanic acid. (HCN).The free hydrocyanic acid also known as prussic acid, when is hydrolysed by *B. glycosidase* and *hydroxynitrile lyase* and when other plant cell structures are damaged e.g by freezing, chopping, chewing, stress frost, trampling etc The microbial flora and fauna that are inhabitants of the rumen would cause further release, thus discharging the free cyanide.

The toxic of HCN is attributed to the high affinity towards metalloporphyrin this contains enzymes. The HCN reacts with (Fe^{3+}) of cytochrome oxidase results in *CN-cytochrome oxidase complex*. This impairs respiratory electron chain resulting in *cytotoxic anorexia* and death.

PREDISPOSING FACTORS TO CYANIDE POISONING

1. Soil factors or edaphic factors

2. Season: - cyanogenic glycosides decrease in drought – stricken plants. More at rains or wet season when there are new shoot.

3. Herbicide Sprayer and Fertilizers: Increases the tendencies especially nitrates in phosphorus deficient soils. Cyanogene forage when sprayed with foliar herbicides such as 2,4– D, this increases the prussic acid concentrations for several weeks after application.

4. Feeding on frozen plants may cause a high release of cyanogenic glycosides.

5. Part of the plant eaten - for example in *Pyrus malus* the poison is more in the leaves and seeds and is less in the fleshy fruit.

6. Species factor: - It is common in large animals such as cattle (ruminants). The monogastrics are less likely to get poisoned. Hereford cattle - is the breed that is reported to be less susceptible than other breeds.

7. The processing of the material: when silage is not dried / increase toxicity if plant materials contain 20 mg HCN /100 gram, is considered toxic.

FORMS OF CYANIDES TOXICITY

Types:

1. **Acute:**

    - Excitement
    - Lacrimation

- Hypersalivation
- Bright red mucosa
- Nystagmus
- Death.

2. **Chronic**:

- Urination
- Incontenance

Clinical Findings Generally:

15 – 20 min to few hrs after the animal has consumed the forage.

- Excitement can be involved
- Rapid respiratory state
- Dyspnoea
- Tarchycardia
- Salivation
- Lacrimation (in excess)
- U – urination
- Vomiting (especially in pigs)
- Fasciculation in common and progresses to generalized spasm
- Animal staggers, struggles and falls.
- Asphyxra cyanides, the mucuos membrane bluish.(cyanotic)

The whole syndrome does not exceed 30-45min if lives up to 2hrs after onset of clinical signs, survives except if cyanide continuous absorbed from the gastro intestinal tract.

LESIONS

In acute and peracute cases, blood may be clear red initially but can be dark red if necropsy is delayed. Agonal haemorrhages in the heart.

- Mucuous membrane :- cyanotic
- Gastro intestinal
- Rumen may be distended with gas in the odour of "bitter almond"

Respiratory System

- Froth in trachea serosa surfaces of trachea mucosa and lungs may be congested or haemorrhagic.
- Liver:- Congestion with hemorrhages

C.N.S.

Multitude foci of degeneration or necrosis may be seen in the C.N.S. of dogs in chronically exposed to sublethal amount of cyanide.

Differential Diagnosis

- Nitrate poisoning
- Organophosphorus poisons
- Sulphur poison
- Nitrate poison.

Diagnosis

- Appropriate history
- Clinical signs
- Postmortem finding or necropsy

- Demonstration of cyanide poisoning in the rumen using smell “almond smell”

Taking appropriate samples, these samples include:

- Suspected plant
- Rumen and stomach content
- Heparinized whole blood
- Liver and muscle

Samples should be taken preferably not more than 4 hours after death.

Method of storage of samples used for diagnoses:

Sealed in air-tight container, refrigerated or frozen. In the absence of refrigeration, immersion of specimens in 1-3% mercury chloride.

Another way of diagnosis is by estimating the amount of cyanide in the food.

1. >2000ppm cyanide on HCN is considered very dangerous.
2. 750ppm HCN is considered hazardous
3. 500-750ppm is doubtful
4. <500ppm is considered safe.
5. <100ppm is considered very safe.

Picrate Paper is used to test the plants materials in stomach/rumen.

TREATMENT

What is used are as follows:

- $NaNo_3$ – sodium nitrate
- Sodium thiosulphase
- Dimethyl amino phenol (DMAP) or Hydroxalamine

Sodium Nitrate – (1 of 100ml of distilled water or isotonic solution) 20mg/kg. It could be repeated for 2-4hours or as needed.

Sodium thiosulphate at ≥500mg/kg I.V. plus 30g/cow to detoxify the rumen.

The basis of the use of $NaNo_2$ in I.V bring about vasodilatation and

counteracts the CN induced – vasospasm.

It combines with haemoglobin (Hb) and converts it to methaemoglobin (Fe^{3+}) competes with cyanide complexed cytochrome oxidase so preventing the combination of HCN in the cytochrome oxidase.

So, the sodium thiosulphate should be immediately given to detoxify the *cynamethaemoglobin* so that the already discharged cyanide from this compound *cynamethaemoglobin* react and combine with *thiosulphate* to produce *Thiocynate*. Artificial respiration with oxygen 100% should also be given along with sodium nitrate and sodium thiosulphate.

The use of sodium thiosulphate will fix the HCN present in the rumen as free cyanide in the blood decreases, additional cyanide dissociate from cyamethaemoglobin.

REVISION HINTS

1. List scientific names of 10 plants that might cause cyanide poisoning
2. Discuss cyanide poisoning under the following headlines:
    - Sources
    - Predisposing factors
    - Diagnosis
    - Sample collection

- Treatment

3. Write short notes on the following:
    - Estimating cyanide in pasture
    - Diagnosis of cyanide poisoning
    - Mechanism of toxicity of cyanide
    - Treatment
    - Supportive treatment.
4. Read between the lines to know all names of enzymes involved, doses of various regimens used for treatment of cyanide poisoning.

NITRATE/NITRITE POISONING

Animals resistant to nitrate poisoning are Equids:

Animals susceptible include: Ruminants, especially cattle, the reason is the microflora reduces the nitrates to Ammonia, young pigs are also vulnerable to this.

Note: Usually, questions are asked why is it that nitrites are treated with nitrates, the nitrite is an intermediate product. But is 10 times more toxic than nitrates.

Forms of toxicity

Acute, sub-acute, or chronic form of toxicity.

Acute toxicity – Effects:

- The cellular basis is this – Nitrate converted to nitrite ion and combines with Hb, iron is converted to Ferric state this form Methaemoglobin when there is 80% or >methaemoglobin.
- Secondary effect is Nitrate has vasodilatory effect and would interfere with Metabolic protein enzymes.
- It irritates the mucosal lining and causes abdominal pain and diarrhea.

The subacute/chronic effects:

- Lowered milk production
- Minor transitory goitrogenic effects.
- Abortion
- Fetoxicity
- Increase susceptibility to infection.

Chronic form controversial and lowered milk production does not occur in chronic form of the disease.

Source of nitrates/aetiology:

Fertilizers.

Preservatives, (prickling and bines)

Machination

Gun powder

Unacclimated animals might feed on plants containing this include:

- Zea mays
- Sunflower
- Sorghum
- Cereal grasses (oats, millet and rye)

Factors that affect Nitrate poisoning

1. Excess nitrate in plants is associated with damp weather condition and cool temperatures of $55^{o}F(13^{o}C)$.
2. In drought especially when plants are immature.
3. Decreased light, cloudy weather and shading associated with crowding conditions can cause increase in nitrates poisoning.
4. Edaphic factors: Low soil that is deficient in trace elements like m*olybdenum* and in macro elements like *sulphur* or *phosphorus*.
5. Anything that stunts growth increases nitrate accumulation in the lower parts of the plants.
6. Herbicides.

7. Nitrates are accumulated in lower stalks but are lesser in leaves and upper stalk.

Clinical finding/Percentage Methaemoglobin

- Rapid weak heart beat
- Subnormal body temperature
- Weakness
- Dyspnoea
- Tachypnea
- Brown or muddy cyanotic, mucous membrane.
- Frequent urination (Methemoglobinaemia)

Signs of non plant sources are:

- Pains, abdominal discomfort, diarrhea salivation, vomiting

The Acute form occurs when 80% or haemoglobin is converted to Methemoglobin 85%, this would result to dyspnea or dyspnoea. The lung would later recover but later worsen to Interstitial Pulmonary emphysema; If conditions are favorable, patient may recover in 10-14days but in adverse condition animal die.

Lesions:

- Chocolate – brown colour, although dark red lines may also be seen.

- Pin point haemorrhage in Serosal.

Diagnosis:

1. The specimen that is most preferred is plasma for pre-mortem specimen analysis of Plasma-protein-bound nitrate, because if the blood is clot, nitrate could be lost in the clot if serum was collected.

2. Other specimen may be postmortem

3. Methaemoglobin analysis (not reliable).

Interpretation: If the nitrate present in while blood other postmortem specimens is indicative of nitrate poisoning.

Post mortem specimens

Specimens to be taken are as follows:

- Ocular fluids
- Fetal pleural fluid.
- Thoracic fluids
- Fetal stomach content
- Maternal uterine fluid.

Method of storage and preservation

- Frozen in clean plastic or glass containers labeled before submission.
- Blood collected whole for methaemaglobin analysis is not frozen.

4. Standard analytical methods are required.

5. Field test for nitrate (presumptive) dipsticks are used to determine nitrate values.

Differential diagnoses

* Cyanide * pesticides * toxic gas

* Urea * toxic gases * H_2S and carbon monoxide

Some infectious diseases could be confused and non infectious.

Non infectious diseases:

- hypocalcemia
- Hypomagnesemia
- Pulmonary endenomatosis

Treatment of Nitrate poisoning

Low I.V. injection of methylene blue in distilled water or isotonic saline should be given of 22mg/kg or depending on severity of exposure. Lower dosage may be repeated in 20-30minutes. If the initial response is not satisfactory, higher dosage can be used.

Control: Animal may adapt to high nitrate content in feed, especially grazing summer animals such as sorghum Sudan hybrid.

- Multiple small feeding help animals adapt.
- Balanced diet and trace element and this prevent metabolic disorders and predisposed to this poisoning.
- High-nitrate forage may also be harvested and stored as ensilaged rather than dried hay or green shop, this reduces the nitrate content.

Revision Questions;

1. Discuss Nitrate poisoning under the following headlines
    a) Predisposing factors.
    b) Mechanism of toxicity
    c) diagnosis.
    d) Treatment.

2a. In which way is nitrite and nitrate related and discuss the mechanism of toxicity of nitrates and nitrites.

2b. Discuss the forms of toxicities of nitrates.

2c. Differentiate the clinical signs of cyanide poisoning and nitrate poisoning.

2d. Discuss the control of nitrate poisoning.

3. Discuss the diagnosis of nitrate poisoning.