7: Metals, metalloids, halogens, minerals and other inorganic substances [Industrial-origin toxins]

Definitions [adapted from Lewis' Dictionary of Toxicology 1998 and Blood & Studdert (1999)]

Metal: Any element that is electropositive and reactive, tending to lose electrons on reaction (forms positive ions in aqueous solution). Most are also marked by being solid and having lustre, malleability, ductility and conductivity of electricity and heat. Their oxides and hydroxides are basic.

Heavy metal: A variously defined term, often used in the literature without definition.

Strictly, a metal with a density exceeding 5 g/cm^{-3}. This is an arbitrary definition and includes 53 naturally-occurring elements and 16 synthetic elements with widely different chemical properties. It includes elements of the lanthanide and actinide series which are not accepted as heavy metals by most authors because of their chemical behaviour. Metals fitting this definition are antimony, manganese, arsenic, bismuth, cadmium, chromium, cobalt, copper, gallium, gold, indium, iridium, iron, lead, manganese, mercury, nickel, palladium, platinum, rhodium, silver, thallium, tin, titanium, vanadium and zinc.

Of more utility for toxicological purposes, a metal with a density exceeding 5 g/cm^{-3} that (1) binds preferentially to ligands that contain nitrogen or sulphur as opposed to those that bind preferentially to ligands that contain oxygen, and (2) those that are borderline with respect to ligand selection. This definition includes those of toxicological significance such as mercury, chromium, cadmium, arsenic (sometimes classed as a metalloid), copper, nickel, zinc and lead.

They are environmentally persistent, toxic even at low concentrations and tend to bioaccumulate.

Metalloid: Any chemical element with properties intermediate between metals and non-metals. The metalloid elements are boron, silicon, germanium, arsenic, antimony, tellurium and astatine.

Mineral: Any naturally-occurring non-organic homogeneous solid substance. Also, a substance obtained by mining.

Halogens: Highly electronegative elements of group VIIA of the periodic table: fluorine, chlorine, bromine, iodine, astatine.

Plant-metal interactions

A recent development in studies of heavy metals in the environment has been the realisation that the interaction of plants and microbes with heavy metals can be beneficial as well as hazardous (Brooks 1998). Two aspects are of interest: **hyperaccumulation** and **hypervolatilisation**. Both are relevant to remediation of land sites contaminated with heavy metals. Hyperaccumulation is relevant to the potential for toxicity of grazing animals. Metals, metalloids and halogens that are hyperaccumulated by plants include arsenic, cadmium, cobalt, copper, iodine, lead, manganese, nickel, selenium, thallium and zinc.

References:

Brooks RR (ed.) (1998) *Plants that Hyperaccumulate Heavy Metals. Their role in phytoremediation, microbiology, archaeology, mineral exploration and phytomining.* CAB International, Wallingford, Oxon OX10 8DE, UK. ISBN 0 85199 236 6

METALS & METALLOIDS

Lead (Plumbism)

Core data

Common sources:

- lead-acid batteries
- sump oil, oil filters
- lead paint on old buildings
- lead shot

Animals affected:

- mainly cattle & dogs
- waterfowl, raptors
- young more susceptible

Modes of action:
- inhibits enzyme systems with free sulphydryl (-SH) groups
- binds to brain capillary endothelial cells → ↑ capillary permeability → oedema
- blocks haem synthesis → anaemia
- in blood, > 95% Pb bound to erythrocytes → ↑ fragility → anaemia

Poisoning circumstances:
- ingestion deliberate: cattle – batteries, sump oil
- ingestion accidental: dogs – paint dust; waterfowl – Pb shot in gizzard

Main effects:
- cattle: nervous signs (including mania, tremors, head-pressing, circling)
- dogs: vomiting, colic, diarrhoea and/or nervous signs
- cats: non-specific (including anorexia, vomiting, weight loss, abdominal pain)
- pathology: ± cerebral oedema, anaemia, acid-fast intranuclear inclusions (kidney)

Diagnosis:
- Pb assay unclotted blood, liver, kidney
- urine Pb concentration increases after chelation therapy

Therapy:
- control seizures
- remove remaining Pb fragments from GI tract
- chelating agent (calcium disodium versenate [CaEDTA], D-penicillamine)
- thiamine hydrochloride
- Pb deposited in bone (reservoir → relapses after therapy) – monitor blood Pb

Prevention:
- deny access to sources
- lead shot replaced by alternatives for wildfowl hunting

Plumbum (Latin = lead); Pb

Lead remains a major cause of acute poisoning in both companion and production animals worldwide.
Once widely used because it had a low melting point, was easily worked and durable when exposed to weather. It was used for water pipes and roof flashing, toys, solder, etc.
Suggested as one of the contributing causes for the decline of the Roman Empire (wine, sweeteners used in food, medicaments, lead water pipes, pottery glazes, among other Pb sources) and well recognised for its poisonous properties in the ancient world (Nriagu 1983). The ancient Roman author of *Natural History*, Pliny the Elder, recorded dogs as particularly susceptible to lead poisoning (Nriagu 1983).
Currently, there is concern about the effects of lead exposure on children with 5% of US children having blood lead concentrations of 10 μg Pb/dl or higher, thus falling into the category of subclinical Pb toxicity with consequent serious irreversible deleterious effects on brain function manifest as lowered intelligence, diminished school performance, hearing deficits and growth retardation (Lanphear 1998). To balance that, the proportion of US people with blood lead concentrations exceeding 10 μg Pb/dl has dropped dramatically with time and the reduction in use of leaded fuels ((Robertson 2000).

Sources:

- **lead-acid batteries** → farm animals (mostly cattle)
- **sump** (crank case) **oil**, lubricating grease, oil filters → farm animals (mostly cattle)
- **lead–based paint** (superseded but still on old buildings painted pre-1970; renovation of such buildings makes paint available through dust and paint chips) → dogs, cats, farm animals, humans (children)
- **lead shot** (shotgun pellets) → wildfowl including particularly magpie geese in Northern Territory, some populations of which have been reduced significantly by lead poisoning (Bell 1991, Whiteheas & Tschirner 1991). See reference list on wildlife Pb poisoning in Australia (below)
  - lead shot has been banned (USA 1991, some European countries) and replaced by either steel , bismuth-tin alloy or tungsten-iron alloy shot in USA, zinc, molybdenum-

plastic mixture, silver-coated lead in Europe; concerns that silver-coated lead may prove toxic in bird gizzards once the silver coating wears off (Kleiner 1997)
- shooting ranges (Craig *et al.* 1999)

- other domestic sources: solder, linoleum, golf balls, fishing sinkers, putty → dogs
- urban air & vegetation contaminated from industrial and vehicular emissions (tetra-alkyl Pb as anti-knock agent in petrol being phased out) → dogs, children (chronic effects)

Organolead compounds (mostly tetraethyl- and tetra methyl-lead) have been used as antiknock additives in petrol since 1923. Combustion of leaded fuel produces lead emissions in a number of halogenated forms, namely PbCl.Br, α- and β- forms of NH_4Cl.Br and $2NH_4$ Cl.PbCl.Br. When P is present in fuel, about 20% of the exhaust lead is expelled as 3Pb3 (PO_4) 2.PbCl.Br. Lead-free petrol has been available in Australia since 1975 and all new cars have been required by law to use only lead-free fuel since 1987, so environmental contamination from this source is expected to decrease with time (Halliwell *et al.* 2000).

- lead mines and smelters → pasture contamination (for example, Moloney 1998, Moloney *et al.* 1999)
- lead-based parasiticides (lead arsenate (*q.v.*)) used on orchards & vegetable crops

Toxicity:

- most commonly **cattle, dogs**. Adult poultry & pigs relatively resistant.
- wild species including fruit bats (Sutton & Wilson 1983), wedge-tailed eagle (Nimmo-Wilkie & Booth 1998) , bald eagles (Langelier *Et al.* 1991), swans (Cooke & Cooke 1999), magpie geese (Bell 1991)
- young animals more susceptible
- dogs with short hair coats may be more susceptible (Prescott 1983)
-acute toxic dose (calves): 200 mg/kg; minimum toxic dose (adult cattle): 6-7 mg/kg/day for several months
- < 2.0% of ingested lead is absorbed
- stored in liver, excreted in bile and urine (& milk)
- may form insoluble complexes kidney > liver (acid-fast intranuclear inclusion bodies)
- **deposited in bone** (especially metaphyses of growing animals) → reservoir

Mode of action:

- inhibits enzyme systems with free sulphydryl (-SH, thiol, mercapto) groups
- → blocks delta-aminolevulinic acid hydratase and ferrochelatase in haem synthesis → anaemia (↑ nucleated RBCs, ± basophilic stippling)
  → porphyrinuria
  → ↑ urinary delta-aminolevulinic acid (δ-ALA)
- in blood, > 95% Pb bound to erythrocytes → ↑ fragility → contributes to anaemia (prolonged exposure)
- binds to brain capillary endothelial cells → ↑capillary permeability (growing capillaries → young animals most susceptible) → oedema. Acute poisoning → brain damage - tips of gyri most susceptible (cf. thiamine deficiency → base of sulci most affected - rarely diagnostically significant).
- low grade kidney damage

Conditions of poisoning:

- ingestion deliberate (cattle - batteries, sump oil; dogs - linoleum, fishing sinkers)
- ingestion accidental (dogs, cats - paint flakes; wildfowl - pellets in gizzard; grinding action and low pH act to solubilise ingested shot; cattle – grazing pastures contaminated from mining operations [Moloney *et al.* 1999])
- wedge-tailed eagle (Nimmo-Wilkie & Booth 1998) thought due to shotgun pellets from prey species (wildfowl, rabbits); bald eagles poisoned by shotgun pellets ingested with tissues of prey in USA & Canada (Langelier *Et al.* 1991)
- shot-gun pellets embedded in tissues from non-fatal wounding may result in toxicity in wild birds (Platt *et al.* 1999)

Clinical signs:

- onset 2-3 days (oils, greases) to 2-3 weeks after ingestion
- insidious onset makes diagnosis difficult (Prescott 1983)
- course of illness 2-3 hrs ("sudden death") to days

- **cattle**
    - early signs - depression, anorexia, gut atony, colic, ± diarrhoea
    - **nervous signs** - dullness, circling, head-pressing, ear twitching, head-bobbing, blinking, tremors, mania, convulsions, death
    - in some cases, the absence of overt neurological abnormalities in sub-acute to chronic intake of Pb may make diagnosis difficult (Moloney *et al.* 1999)
- **dogs**
    - some have only gastrointestinal signs (higher doses), others only nervous signs (lower doses over longer time)
    - *gastrointestinal signs*: anorexia, salivation, persistent vomiting, severe colic and diarrhoea, sudden death
    - *nervous signs*: hyperaesthesia, hysteria, fear reactions, episodes of running & barking, intermittent convulsions, ± stupor, ± blindness, death
- **cats**
    - signs often **non-specific & non-localising** (anorexia >> vomiting, depression/lethargy >> weight loss > abdominal pain, 3rd eyelid prolapse, constipation) (Prescott 1983, Maddison *et al.* 1993)
    - nervous signs *rarely* reported; hyper-excitability + fits (Prescott 1983), epileptiform seizures (van Alstine *et al.* 1993)
- **waterfowl** with lead shot poisoning often found **paralysed** & emaciated
- **horses**
    - acute poisoning: tremors, posterior ataxia, intermittent violent convulsions, sudden death
    - **chronic** exposure: **peripheral neuropathy** → laryngeal hemiplegia, dysphagia, aspiration pneumonia
- lambs chronic intake → osteoporosis, hydronephrosis

Pathology:

- Necropsy
    - usually no specific lesions [swollen kidneys, mild enteritis, ± flattened cerebral gyrae]
    - possibly dehydration, emaciation
    - ruminants may have lead fragments (car battery plates) in reticulum
    - sump oil in ruminoreticulum
    - lead pellets in gizzards of waterfowl, raptors
- Histologically
    - ± **cerebral oedema**
    - ± laminar cortical necrosis (polioencephalomalacia)
    - ± **acid-fast intranuclear inclusion bodies**: kidney cortex epithelium > hepatocytes, osteoclasts of canine metaphyseal bone (Papaioannou *et al.* 1998); the longer the course of the intoxication, the more likely inclusions are to occur.
    - birds ± peripheral neuropathy (Platt *et al.* 1999), degenerative arteritis, cardiomyopathy (Langelier *et al* 1991)

Diagnosis:

- assay Pb in whole blood (5 ml unclotted), faeces, liver, kidney, suspected source
- assay Zn protoporphyrin in blood - correlates better with syndrome than blood Pb (Kowalczyk *et al* 1981)
- assay delta-aminolevulinic acid (δ-ALA) in urine (> 90 μmol/L)
- radiographs →
    - ± radiodense fragments/objects in GI tract (or other tissues in the case of gunshot wounds) ; only 15% of lead-poisoned eagles in North America had lead shot in the stomach (Redig 1984 cited by Langelier *et al.* 1991)
    - ± epiphyseal Pb line (rarely seen)
- *ante mortem* whole blood concentrations > 0.4μg Pb/ml (2 μM/l)
- until recently, urban dogs frequently had blood Pb concentrations around 0.15 -0.2 μg/ml, cats (inner Sydney, *ca.*1992) 0.07-1.43 μmol/L (0.014-0.29 μg/ml)
- threshold for determining excess exposure to Pb in humans (children) = 10 μg/dl (0.1 μg/ml) (Lanphear 1998)
- **urine concentrations ↑ after chelation therapy** → supports tentative diagnosis
- *post mortem* liver, kidney concentrations > 5 mg Pb/kg wet weight (dog, bird), >10 (adult cattle), >20 (calf kidney)

Therapy:

- **control seizures** (dog - diazepam, barbiturates; livestock - barbiturates, chloral hydrate)
- **remove remaining Pb fragments from GI tract**: lavage, enema, surgery as required (removal from reticulum of cattle very difficult)
- → $MgSO_4$ (Epsom salts) or Na_2SO_4 orally → precipitate intraluminal Pb (limited value)
- then → **chelating agent** (calcium disodium versenate (CaEDTA), D-penicillamine) → non-toxic water-soluble complexes with Pb in intracellular fluid & bone → rapid excretion in urine & bile
- check blood Pb concentration 10 days after start of treatment; if indicated, give further treatment courses for 5 days at 10 day intervals
- monitor renal function during treatment, provide adequate drinking water

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Calcium disodium versenate treatment protocol:
Calsenate®
Precautions: Maximum continuous course 5 days [nephrotoxic, depletes Zn reserves]. Maximum total dose (dog) 2g/day. Rapid Pb mobilisation from bone may → ↑ signs / sudden death. May → pain at injection site. 20% (200 mg/mL) solution → slow IV injection [↑HR, RR or muscle tremor = toxic reaction]

Dose: 80 mg/kg (0.4 mL/kg)/day ***in 2-4 divided doses*** for 3-5 days
Horse: 180 mL/450kg daily
Cattle: 140 ml/350kg daily
Dog: 2 ml/5kg daily. Maximum 2g (10 mL)/day, regardless of body weight.

Further 5 day courses may be needed for severe cases. Wait 10 days between courses to avoid renal & GI tract toxicity.

D-penicillamide treatment protocol:
May be used as an alternative or adjunct chelator.
9-12 mg/kg 4 times daily for 7 days, leave for 7 days, repeat if required.

- **thiamine hydrochloride** (vitamin B_1) → ↓ deposition of Pb in CNS & PNS + mobilises intracellular Pb into extracellular fluid/blood → ↑ excretion in bile & urine when used with CaEDTA therapy [5 mg/kg slow IV twice daily for 1-2 weeks; monitor for untoward reactions]
- some treatment protocols include IM dimercaprol (BAL) (see notes on As poisoning for doses and adverse effects)

Prevention & Control:

- dispose of / prevent access to sources
- dealing with lead-painted surfaces during renovation. Advice may be had from the Lead Advisory Service website www.lead.org.au or Freecall 1800 626 086
  - lead test kits for paint are available from some paint manufacturers and specialist paint stores
  - prevent dust or fume formation when removing old paint by keeping surfaces wet (do not heat-strip, dry sand or dry scrape)
  - collect old paint and dispose of through an appropriate chemical waste facility
- lead shot banned for wildfowl hunting in USA in 1991 & replaced by steel, bismuth-tin, tungsten-iron, tungsten-polymer, tungsten-matrix and tin shot (US Fish & Wildlife Service 1999)

References:

Os191, Se211, Puls (1994a) 146-159, VM8/1469
Bloom H, Noller BN, Shenman G (1976) A survey of blood lead levels in dogs and cats. *Aust. Vet. J.* **52**:312-316.
Cooke SW, Cooke ZR (1999) Study of lead and zinc toxicity in swans. *Vet. Rec.* **145**:352.
Craig JR, Rimstidt JD, Bonnaffon CA, Collins TK, Scanlon PF (1999) Surface water transport of lead at a shooting range. *Bull. Environ. Contam. Toxicol.* **63**:312-319.

Halliwell D, Turoczy N, Stagnitti F (2000) Lead concentrations in *Eucalyptus* sp. in a small coastal town. *Bull. Environ. Contam. Toxicol.* **65**:583-590. [Study in Warrnambool, Vic]
Kleiner K (1997) Good news for ducks. *New Scientist* **155** (2097):11.
Kowalczyk DF *et al.* (1981) The value of zinc protoporphyrin in equine lead poisoning: a case report. *Vet. Human Toxicol.* **23**:12-15.
Langelier KM, Andress CE, Grey TK, Wooldridge C, Lewis RJ, Marchetti R (1991) Lead poisoning in bald eagles in British Columbia. *Can. Vet. J.* **32**:108-109.
Lanphear BP (1998) The paradox of lead poisoning prevention. *Science* **281**:1617-1618.
Maddison JE, Hawke CG, Watson ADJ (1993) Parameters of lead exposure and clinicopathology of lead toxicity in urban cats. *Aust. Vet. Practit.* **23**:210-216.
Moloney B (1998) Lead intoxication in cattle grazing in a paddock containing an ore treatment plant. *Vet. Pathol. Report (ASVP Newsletter)* No.49 p.11
Moloney B, Curran G, Marshall J (1999) Chronic lead toxicity in cattle in an extensive grazing situation. *Proc. Aust. Soc. Vet. Pathol. Conf.* p.33.
Nriagu JO (1983) *Lead and Lead Poisoning in Antiquity.* John Wiley & Sons, Inc., New York.
Papaioannou N, Vlemmas I, Balaskas N, Tsangaris T (1998) Histopathological [ultrastructural] lesions in lead intoxicated dogs. *Vet. Human Toxicol.* **40**:203-207.
Platt SR, Helmick KE, Graham J, Bennett RA, Phillips L, Chrisman CL, Ginn PE (1999) Peripheral neuropathy in a turkey vulture with lead toxicosis. *J. Am. Vet. Med. Assoc.* **214**:1218-1220.
Prescott CW (1983) Clinical findings in dogs and cats with lead poisoning. *Aust. Vet. J.* **60**:270-271.
Robertson WO (2000) A reminiscence about 'Lead non-poisoning". *Vet. Human Toxicol.* **42**:372-373.
Rolton CE, Horton BJ, Pass DA (1978) Evaluation of tests for the diagnosis of lead exposure in sheep. *Aust. Vet. J.* **54**:393-397.
US Fish & Wildlife Service (1999) Service approves non-toxic shot for upcoming waterfowl season. USFWS News release 19 August 1999
van Alstine WG, Wickliffe LW, Everson RJ, DeNicola DB (1993) Acute lead toxicosis in a household of cats. *J. Vet. Diagn. Invest.* **5**:496-498.

Australian wildlife lead poisoning

Bell M (1991) Lead poisoning in magpie geese. *Vet. Path. Report (Newsletter Aust. Soc. Vet. Path.)*, No.30 (March), p.25-25.
Harper MJ, Hindmarsh M (1990) Lead poisoning in magpie geese *Anseranas semipalmata* from ingested lead pellets at Bool Lagoon Game Reserve (South Australia). *Aust. Wildl. Res.* **17**:141-145.
Kingsford RT, Flanjak J, Black S (1989) Lead shot and ducks on Lake Cowral. *Aust. Wildl. Res.***16**:167-172.
Koh TS, Harper MJ (1988) Lead poisoning in black swans *Cygnus atratus* exposed to spent lead shot at Bool Lagoon Game Reserve, South Australia. *Aust. Wildl. Res.* **15**:395-403.
Lavery HJ (1971) Lead poisoning as a possible cause of death in waterfowl in northern Queensland. *Emu* **71**:138-139.
Nimmo-Wilkie JS, Booth R (1998) Lead poisoning in a wedge tailed eagle. *Vet. Pathol. Report (ASVP Newsletter)* No.50 p.11.
Norman FI (1976) The incidence of lead shotgun pellets in waterfowl (Anatidae and Rallidae) examined in south-eastern Australia between 1957 and 1973. *Aust. Wildl. Res.* **3**:61-71.
Sutton RH, Wilson PD (1983) Lead poisoning in grey-headed fruit bats (*Pteropus poliocephalus*). *J. Wildlife Dis.* **19**:294-296.
Whitehead PJ, Tschirner K (1991) Lead shot ingestion and lead poisoning of magpie geese *Anseranas semipalmata* foraging in a northern Australian hunting reserve. *Biological Conservation* **58**:99-118.

☑ Arsenic (inorganic)

Core data

Common source:

- superseded acaricide
- old cattle dips
- ash from CCA-treated timber

Animals affected: mostly cattle
Poisoning circumstances: access to contaminated sites
Main effects: severe gastroenteritis
Diagnosis: assay liver, kidney for As
Therapy:

- prognosis poor-grave
- sodium thiosulphate
- dimercaprol (BAL)
- D-penicillamine

The Greeks had a word for it: αρσενικον (arsenikon). And arsenic was a favourite tool of assassins and murderers until forensic toxicology was established in the 19th century and developed assays for the substance. In the world of Australian agriculture, arsenic, ultimately combined with bluestone (copper sulphate) to close the reticular groove and direct the dose into the abomasum, was the only available defense against gastrointestinal helminth infestations of sheep and cattle until after the

Second World War, and accidental overdose was a common cause of death for treated animals. Until the 1970s, arsenic was the most commonly applied treatment for ectoparasites of sheep and cattle (Albiston 1975).

Chemical structure:

the element arsenic (As), a metalloid
Arsenic trioxide (trivalent As)
Lead arsenate (pentavalent As)

Sources:

- superseded **acaricide,** insecticide (termiticide), fungicide (orchards) & herbicide formulations of arsenic trioxide (As_2O_3), lead arsenate
- residues in and around old disused dips and holding tanks. Most arsenical dipping and jetting solutions contain sodium arsenite (Radostits *et al.* 1994).
- contaminated buildings and surroundings where arsenical compounds for farm use were stored previously and farm rubbish dumps used for disposal
- ash from burnt CCA preservative-treated timber. The treatment is applied under vacuum and imparts a light green colour to the wood. [CCA = chromated copper arsenate or copper-chrome-arsenic formulations; wood preservative containing no more than 16% each (weight/volume) of copper sulphate, potassium dichromate and arsenic pentoxide.] (Thatcher *et al.* 1985, Hullinger *et al.* 1998)
- old mine tailings
- natural outcrops of As-containing ores (e.g. in NE Vic [Ian Wilkie, personal communication 1996])
- arsenic pyrites associated with areas of volcanic activity (e.g. in NZ [Hopkirk 1987])
- lead arsenate (a superseded insecticide used in orchards) (Stair *et al.* 1995)

Toxicity:

- Mostly livestock (**cattle**, sheep, horses)
- Susceptibility parasites > mammals > poultry
- As → relatively strong bonds with pairs of adjacent sulphydyl groups → particularly affects enzymes involved in cellular respiration (especially pyruvate oxidase). Tissues rich in these enzyme systems most susceptible (alimentary tract wall, liver, kidney, spleen, lung). Toxicity → capillary damage in alimentary tract wall → fluid loss, haemorrhage
- absorbed As becomes concentrated in the liver, from which it is slowly released and distributed to other tissues, particularly the kidneys. As disappears readily from the soft tissues, but can be stored in keratinised tissues such as skin, hair and hooves (Seawright 1989). As is mainly excreted in urine, persisting for 1-2 weeks in horses and cattle (Seawright 1989, Humphreys 1988). In most species, 40-70% of absorbed inorganic As is excreted in urine within 48 hr (Vahter 1983). In dogs, 40-45% of injected inorganic As is excreted in 100 min (Tsukamoto *et al.* 1983). Half-life of As of 2-10 hr in dogs (Hollins *et al.* 1979) .
- As is known as a carcinogen causing skin neoplasia in humans (Klaassen 1996), but this effect is not recorded in domestic animals. Contamination of bore water supplies with As is a serious concern in Bangladesh (of the order of 1 mg As/L; recommended upper limit of 10 μg/L) (Pearce 1995, 2000).

Conditions of poisoning:

- cattle and sheep apparently relish the taste of arsenic salts, particularly if mineral deficient (Albiston 1975)
- access to contaminated sites, e.g.
  - soil around old acaricide dip sites. Toxicity may follow rainfall if animals are held in dip yards and, in feeding, pull up plants by the roots from the softened earth and thus consume the attached soil. Contaminated soil can also be eaten after being splashed onto plants by raindrops.
  - farm buildings, either old and disused or still in use, that previously were used to store arsenical preparations where spillage occurred
  - carelessly discarded old containers for arsenical acaricides, insecticides, herbicides, fungicides.
  - contaminated timber floors where sheep hides were previously treated (NZ case, dog: Bruere 1980)
  - contaminated water in areas of volcanic activity (Hopkirk 1987)
- ingestion of ash from burnt CCA-treated timber (Harradine 1990)

- accidental skin application in mistake for other compounds (Robertson *et al.* 1984)

Clinical signs:

- Acute (severe gastroenteritis)
  - onset 20-50 hr after ingestion
  - death may occur before signs are observed. Usual course 3-4 hr.
  - severe abdominal pain (restlessness, groaning, teeth grinding, salivation, rumen atony)
  - ± vomiting
  - profuse diarrhoea, dehydration
  - clonic convulsions precede death
- Subacute (gastroenteritis)
  - course 2-7 days
  - signs as above +
    - dysentery
    - muscle tremor, incoordination

- Chronic (ill thrift) - rare
  - lethargy
  - emaciation
  - dry staring coat, easily shed
  - congested ('brick red') mucosae
  - ± local skin necrosis

Chronic poisoning is described in reference texts, but this is poisoning from chronic intake of small quantities of As, a phenomenon most often seen in humans. There is no mention of chronic effects following a single large exposure to As. Natural chronic toxicity from inorganic arsenicals is generally not described in domestic animals (Osweiler 1996), but has been induced experimentally (dogs: Byron *et al.* 1967, Neiger & Osweiler 1989, Neiger & Osweiler 1992).

Chronic skin exposure of dogs to arsenical compounds as contaminants of soil or other surroundings has caused dermatitis (Bruere 1980, Evinger & Blakemore 1984). Historically, soil under some shearing sheds in New Zealand contaminated by arsenical sheep dip dripping from sheep is reputed to have caused dermatitis in sheepdogs that rested in their shade (Bruere 1990, Dalefield R 1999, personal communication VETTOX)
Half-life of As of 2-10 hr in dogs (Hollins *et al.* 1979) indicates removal from the source as an adequate therapeutic measure, rather than use of potentially toxic chelating compounds such as dimercaprol (Evinger & Blakemore 1984).

Pathology:

- marked hyperaemia & patchy submucosa haemorrhage in abomasum, duodenum
- watery, mucoid content further down tract, often with some blood
- ± haemorrhage/ulceration of gall bladder mucosa
- ± periacinar hepatocyte necrosis (Harradine 1990, Mackie & Mitchell 1999)

Diagnosis:

- syndrome of gastroenteritis with minor signs of nervous system involvement
- assay liver, kidney, faeces, urine, ingesta, suspected sources
- > 10 mg As/kg liver wet weight is considered diagnostic
- urine and hair are suggested as the most useful specimens for assay if attempting to confirm low-level chronic inorganic arsenic exposure (in dogs); > 30 μg As/g in urine is firm evidence of significant exposure (Neiger & Osweiler 1992)

Therapy:

- prognosis poor-grave; literature is inconclusive on antidotes
- rehydration therapy is essential
- specific rational treatment is parenteral administration of substances containing a large number of sulphydryl groups (2,3-dimercaptopropanol = Dimercaprol = BAL [British anti-Lewisite], D-penicillamine, sodium thiosulphate) to compete for available As. See box below. [In case you were wondering, Lewisite = $C_2H_2AsCl_3$, a vesicant chemical warfare agent, named after US chemist W. Lee Lewis 1878-1943]
- BAL is toxic itself , is administered in oil and can cause serious injection site reactions

Dimercaprol (BAL) treatment protocol:
10% solution in oil: 2.5-5.0 mg/kg IM every 4 hr for 2 days; 3 times on day 3; twice for next 10 days or until recovery. Note: 5.0 mg/kg on first day in severe cases.

D-penicillamine treatment protocol:
10-15 mg/kg *per os* every 12 hr for 7 days. Dose 30 min before feeding to avoid binding dietary minerals. Note: may require antiemetic premed; beware penicillin allergies.

Sodium thiosulphate treatment protocol:
20% aqueous solution: 30-40 mg/kg IV 2-3 times daily until recovery (usually 3-4 days). Double this dose can be given orally as an alternative.

Prevention and control:

- As is very persistent in soil, so contaminated sites will remain hazardous for years/decades and should be fenced off from grazing animals

  Maximum tolerable dietary concentrations for animals is recommended as 50 mg of inorganic arsenic/kg of feed (US National Academy of Sciences, Washington 1980). Translating this into a "safe" figure for soil if quite difficult because soil is not directly eaten except accidentally as, for example, mud splashed onto plants or attached to the roots of plants that are eaten whole after being pulled from softened ground after rain. A rough rule-of-thumb may be 100 mg inorganic arsenic/kg of soil.

- bioremediation using sulphur-reducing bacteria has been tested on run-off from mine tailings (Coles M, personal communication 2000); this may have future application to small contaminated sites
- *Pteris vittata* L. (brake fern, ladder brake, Chinese brake) hyperaccumulates As from contaminated sites and may be useful in bioremediation (Ma *et al.* 2001). This fern species is recorded from Q, WA, NSW and Vic and is very widespread in tropical to warm-temperate parts of the Old World (Kramer & McCarthy 1998) as well as in North America (Ma *et al.* 2001).
- CCA-treated timber waste should be disposed of by burial, not burning (Norton & Lightley 1992).

References:

Review literature:

Hu19, Os181, Se195, VM8/1480, K697

Albiston HE (1975) *Diseases of Domestic Animals in Australia. Some Metabolic Diseases, Deficiencies and Toxaemias.* Service Publication (Animal Quarantine) Number 12, Australian Department of Health. Australian Government Publishing Service, Canberra. pp.125-128.

Nriagu JO (ed.) (1994) *Arsenic in the Environment. Part I: Cycling and Characterisation. Part II: Human Health and Ecosystem Effects.* [Volumes 26 & 27 of Advances in Environmental Science and Technology]John Wiley & Sons Inc., New York.

General literature:

Bruere SN (1980) Arsenical poisoning in farm dogs. *N. Z. Vet. J.* **28**:220.

Bruere AN, Cooper BS, Dillon EA (1990) *Veterinary Clinical Toxicology.* Publication 127, Foundation for Continuing Education of the New Zealand Veterinary Association, Massey University, Palmerston North. p.20.

Byron WR, Bierbower GW, Brouwer JB, Hansen WH (1967) Pathological changes in rats and dogs from two-year feeding of sodium arsenite or sodium arsenate. *Toxicol. Appl. Pharmacol.* **10**:132-147.

Evinger JV, Blakemore JC (1984) Dermatitis in a dog associated with exposure to an arsenic compound. *J. Am. Vet. Med. Assoc.* **184**:1281-1282.

Harradine I (1990) Arsenic poisoning of cattle. *Post-Grad. Committee in Vet Science, University of Sydney: Control & Therapy Series*. Mailing 156, No.2931.

Hollins JG, Charbonneau SM, Bryce F *et al.* (1979) Whole blood retention and excretion of [^{74}As] arsenic acid in the adult beagle dog. *Toxicol. Lett.* **4**:7-13.

Hopkirk RG (1987) Arsenic poisoning in dairy cattle from naturally occurring arsenic pyrites. *N. Z. Vet. J.* **35**:170-172.

Hullinger G, Sangster L, Colvin B, Frazier K (1998) Bovine arsenic toxicosis from ingestion of ashed copper-chrome-arsenate treated timber. *Vet. Human Toxicol.* **40**:147-148.

Kramer KU, McCarthy PM (1998) Pteridaceae. *Flora of Australia* **48**:241-248.

Ma LQ, Komar KM, Tu C, Zhang WH, Cai Y, Kennelley ED (2001) A fern that hyperaccumulates arsenic. *Nature* **409**:579.
Mackie J, Mitchell G (1999) Hepatocellular necrosis associated with arsenic toxicity in cattle. *Proc. Aust. Soc. Vet. Pathol. Conf.* p.32.
Neiger RD, Osweiler GD (1989) Effect of subacute low level dietary sodium arsenite on dogs. *Fundamental Appl. Toxicol.* **13**:439-451.
Neiger RD, Osweiler GD (1992) Arsenic concentrations in tissues and body fluids of dogs on chronic low-level dietary sodium arsenite. *J. Vet. Diagn. Invest.* **4**:334-337.
Norton J, Leightley LE (1992) Safety and the use of CCA-treated timber. *Queensland Forest Service Timber Note No.13.* (revised March 1992) 2 pp.
Pace LW, Turnquist SE, Casteel SW, Johnson PJ, Frankeny RL (1997) Acute arsenic toxicosis in five horses. *Vet. Pathol.* **34**:160-164.
Pearce F (1995) Death and the devil's water. *New Scientist* **147** (1995):14-15.
Pearce F (2000) Danger in every drop. *New Scientist* **165** (2225):16-17.
Robertson ID, Harms WE, Ketterer PJ (1984) Accidental arsenical toxicity of cattle. *Aust. Vet. J.* **61**:366-367.
Stair EL, Kirkpatrick JG, Whitenack DL (1995) Lead arsenate poisoning in a herd of beef cattle. *J. Am. Vet. Med. Assoc.* **207**:341-343.
Thatcher CD, Meldrum JB, Wikse SE, Whittier WD (1985) Arsenic toxicosis and suspected chromium toxicosis in a herd of cattle. *J. Am. Vet. Med. Assoc.* **187**:179-181
Tsukamoto H, Parker HR, Peoples SA (1983) Metabolism and renal handling of sodium arsenate in dogs. *Am. J. Vet. Res.* **44**:2331-2335.
Vahter M (1983) Metabolism of arsenic. In *Biological and Environmental Effects of Arsenic.* Fowler BA (ed.), Elsevier, New York. pp.171-198. [cited by Neiger & Osweiler 1992]

Copper

Core data

Syndromes:
- chronic copper poisoning (primary and hepatogenous)
- acute copper poisoning
- peracute copper poisoning

Common sources:
- pasture (+ pyrrolizidine alkaloids in hepatogenous chronic copper poisoning)
- compounded feeds
- copper compounds as anthelmintics, molluscicides, fertilisers
- injectable Cu

Animals affected: sheep (British breed) > sheep (Merino) > cattle > pigs

Mode of action:

Chronic copper poisoning
- slow liver Cu accumulation
- then triggering event → mass Cu release into blood
- → acute haemolysis

Acute copper poisoning – local alimentary tract irritation

Poisoning circumstances:

Chronic copper poisoning

Cu accumulation:
- feeding rations compounded for less susceptible species
- feeding poultry litter
- clover-dominated pasture
- pig manure/poultry litter on pasture

Triggering events (poorly understood stress):
↓ nutritional plane, ↓ temperature, birth, lactation, forced exercise, handling

Acute copper poisoning: overdose with oral Cu

Main effects:

Chronic copper poisoning
- pallor, jaundice, haemoglobinuria
- death 24-48 hr (including "sudden death")
- dark kidneys (Hb nephrosis)

Acute copper poisoning – acute diarrhoea, convulsions, death

Diagnosis: syndrome + Cu assay liver, kidney, blood

Therapy:

Chronic copper poisoning: add Mo + S to feed

Prevention:
Chronic copper poisoning: remove Cu source; pasture fertiliser with added Mo

Syndrome names:

The toxicity of copper in domestic animals can occur in a number of forms, namely

- primary **chronic copper poisoning**
- plant-associated hepatogenous (or secondary) chronic copper poisoning, also known as toxaemic jaundice
- primary **acute copper poisoning**
- peracute copper toxicity from copper injections

The most common of these syndromes are the two chronic copper poisoning syndromes.

Chemical structure: the element copper (Cu)
Sources:

- soil/pasture
  - rarely, results from industrial air pollution of pastures from mining/smelting operations (Gummow *et al.* 1991; Grobler 1999)
- compounded feeds
- injections for Cu deficiency
- $CuSO_4$ over-used PO as an anthelmintic
- $CuSO_4$ (anthelmintic, molluscicide), fungicides, fertilisers/top-dressings
- poultry litter
- sunflower meal with Cu:Mb ratio > 10; sunflower crop fertilized with Cu (Garcia-Fernández *et al.* 1999)

Toxicity:

Chronic copper poisoning

- continued ingestion of small amounts of Cu over a long period (months) → ↑↑ liver Cu. Triggering event → mass release of Cu into bloodstream → **acute intravascular haemolytic crisis** - mortality = *ca.* 100% - pigs → death from anaemia (GI haemorrhage)
- hepatocyte Cu loading not uniform in cell population → lysosomal Cu storage mechanism overloaded → uncontrolled Cu ↑ in cytosol → Cu-induced lipid peroxidation of membranes → hepatocyte death - very heavily-loaded cells die in increasing numbers during pre-haemolytic period → debris scavenged by Kuppfer cells → hypertrophy with yellow granules ("golden macrophages")
- species susceptibility: **sheep** (British breeds & crosses) > sheep (Merino), ?goats > calves > adult cattle > pigs > horses. Sheep most susceptible because of less efficient Cu excretory mechanisms.
- maximum dietary Cu concentrations tolerated (with normal concentrations of Mb, SO_4, Zn & Fe): sheep < 20 mg/kg; cattle 100; pigs 250; fowls & turkeys 300, horses 800 (Ammerman *et al.* 1980)
- diet factors reducing Cu absorption when in high concentration:
  ruminants - molybdenum, sulphate
  pigs - zinc, iron
- Se deficiency (sheep) and high Ca intakes (→ Zn deficiency?) → ↑ susceptibility
- a genetic defect (autosomal recessive) affecting up to 60% of Bedlington Terriers (and West Highland white terriers?) leads to hepatic Cu accumulation with age, hepatic damage and haemolytic crisis in some dogs; cases reported in USA (Twedt *et al.* 1988) and Australia (Robertson *et al.* 1983, Watson *et al.* 1983); reviewed by Thornburg (2000)

Plant-associated chronic copper poisoning

Pyrrolizidine alkaloid poisoning (*q.v.*) predisposes ovine hepatocytes to increased Cu uptake, thus boosting the incidence of chronic copper poisoning.

Acute copper poisoning

- excess cupric ions → local irritation of alimentary tract
- toxic oral dose 25-50 mg/kg in lambs, 130 in adult sheep, 200 in adult cattle
- susceptibility: sheep > cattle > pigs > poultry

Peracute copper poisoning

Overdose with injectable Cu EDTA preparations → massive liver necrosis, sudden death (Mylrea & Byrne 1974)

Conditions of poisoning:

Chronic copper poisoning

Cu accumulation:

- soils rich in Cu → high pasture concentrations
- clover-dominated pastures for sheep (high Cu, low Mo)
- pasture polluted by smelter fumes or drippings from corroded overhead cables
- pasture fertilised with pig manure/poultry litter
- feeding grain treated with Cu-based fungicides
- inclusion of excessive Cu in mineral supplements or giving excessive Cu injections
- contamination of dried milk powder for calves in manufacturing plant with brass fittings
- feeding sheep with rations compounded for other livestock (cattle, pigs) or with poultry litter
- feeding cattle with rations compounded for pigs or with poultry litter (Tokarnia *et al.* 2000)

Triggering events (incompletely understood stress):

- falling plane of nutrition
- low temperatures
- parturition, lactation
- mustering, travelling, shearing

Acute copper poisoning

- accidental dosing with large amounts of soluble Cu salts
- contamination of food plants with fungicidal sprays containing Cu
- overdose with Cu-containing anthelmintics
- contamination of drinking water with $CuSO_4$ during snail eradication
- too liberal provision of Cu-containing mineral supplements
- grazing pastures too soon after Cu top-dressing to correct Cu deficiency

Clinical signs (ruminants):

Chronic copper poisoning

- anorexia, thirst
- pallor & jaundice of mucus membranes
- haemoglobinuria
- depression, death in 24-48 hr (including "sudden death")

Acute copper poisoning

- vomiting (non-herbivores)
- acute abdominal pain
- hypersalivation
- acute diarrhoea - bluish-green faeces
- convulsions, collapse, death

Pathology:

Chronic copper poisoning

Clinical pathology:

- ↑ liver & blood Cu concentrations (liver Cu greater in caudate lobe)
  - *Pre*-haemolytic crisis liver Cu concentrations: up to 16 mmol/kg (1000 mg/kg) dry matter in sheep [normal <5.5 mmol/kg, 200 mg/kg], 30 mmol/kg in calves, 95 mmol/kg (4000 mg/kg) in pigs [normal 40-50 mg/kg]
  - *Post*-haemolytic crisis diagnostic liver Cu concentrations: > 8 mmol/kg dry matter (sheep)
  - During haemolysis, blood Cu concentrations 80-115 μmol/L (sheep) [normal 16 μmol/L, 0.75-1.35 mg/kg]
- ↑ liver-associated serum enzymes - sheep ↑ AST up to 6 weeks before haemolytic crisis → monitor

- haemolysis → ↓ PCV, haemoglobinuria

Necropsy (ruminants):
- jaundice
- pallor
- swollen yellow liver - periacinar necrosis (from hypoxia resulting from anaemia), "golden macrophages"
- gall bladder distended with thick bile
- swollen spleen
- swollen dark (black) kidneys - haemoglobinuric nephrosis
- haemoglobinuria

Necropsy (pigs):
- jaundice
- pallor
- gastrointestinal ulceration & haemorrhage
- yellow, ochre or bronze-coloured fibrotic liver
- bronze-coloured kidneys

Acute copper poisoning
- Cu + chlorophyll → **bluish-green** compound discolouring gut contents

Diagnosis:

Chronic copper poisoning
- clinical & necropsy findings
- assay liver, kidney, blood Cu
  - liver Cu > 150 mg/kg wet weight; kidney Cu > 15 mg/kg wet weight; serum/whole blood Cu > 1.5 ppm (Os187)
  - cattle liver Cu > 560 mg/kg dry matter; kidney Cu > 40 mg/kg dry matter (Humphreys 38)
  - pigs liver Cu > 500 mg/kg dry matter (JG Allen, personal communication 2001)
- genetic markers are being sought for the inherited copper toxicity of Bedlington terriers. A microsatellite marker has been identified, but its detection should be employed diagnostically with caution (Haywood *et al.* 2000)

Acute copper poisoning

history of administration/access, discoloured GI contents, Cu assay

Therapy (ruminants):

Chronic copper poisoning
- reduce body Cu stores below critical values

→ supplement feed with Mo & S
- Mo & sulphate rumen metabolism → Cu-thiomolybdate complexes → ↓ Cu absorption → ↑ faecal Cu excretion; some thiomolybdates absorbed → systemic Cu-thiomolybdate complexes → biliary (& some urinary) excretion

→ IV tetrathiomolybdate - chelates and boosts biliary excretion of Cu, helps prevent Cu entering RBCs

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Therapeutic protocols (ruminants): body copper load reduction

Feed Mo & S supplementation

- daily 50-500 mg ammonium molybdate + 0.3-1.0 g anhydrous sodium sulphate for 3 weeks

Chelation therapy

IV tetrathiomolybdate (not commercially available?) @ 2.4 mg/kg
- ammonium tetrathiomolybdate (33.5 mg/ml saline) in 3 doses at 2 day intervals. Dose in mls = live weight (kg) ÷ 20

OR

SC tetrathiomolybdate @ 3.4 mg/kg in 3 doses at 2 day intervals (Humphries *et al.* 1988)

OR

PO penicillamine @ 50 mg/kg daily for up to 6 days (van Saun 1988, Soli *et al.* 1978)

[other chelating agents including calcium versenate (disodium calcium ethylenediamine tetraacetate), 2-3 –dimercapto-1-propanol and dimethyl dithiocarbamate are relatively ineffective (van Saun 1988)]

Therapy (Bedlington terriers):

- low copper diet
- chelation therapy alternatives:
  - D-penicillamine (Robertson *et al.* 1983, Watson *et al.* 1983)
  - 2,3,2-tetramine (Twedt *et al.* 1988)

Acute copper poisoning

GI sedatives, supportive treatment for shock

Control (ruminants):

Chronic copper poisoning

- remove the Cu source if possible
- monitor serum AST concentrations
- top-dress pasture
  - Mo-superphosphate (280 g Mo/ha)
  - lime → ↑ pasture Mo but no ↑ in Cu
  - *N.B. excess Mo → Cu deficiency*
- pastures for sheep → Cu:Mo ratio < 10:1 & dry matter S content > 0.2%

Acute copper poisoning

- Cu-top-dressed pastures: do not graze for 3 weeks or until after heavy rain
- as anthelmintic → no more than 9.3 mg $CuSO_4$ /kg live weight in single dose to sheep < 1 year old

References:

Review literature

Os185, Se201, Humphreys 38, VM8/1495 & 1499

Ammerman CB, Fontenot JP, Fox MRP, Hutchinson HD, Lepore P, Stowe HD, Thompson DJ, Ullrey DE (1980) *Mineral Tolerance of Domestic Animals.* National Academy of Sciences, Washington DC. pp.162-183.

Greene LW, Huston JE (1999) Copper toxicosis in sheep: a review. *Sheep & Goat Research J.* **15**:120-125.

Bedlington Terrier literature

Haywood S, Fuentealba IC, Kemp SJ (2000) Copper toxicosis in Bedlington terriers (Correspondence). *Vet. Rec.* **146**:383-384.

Robertson HM, Studdert VP, Reuter RE (1983) Inherited copper toxicosis in Bedlington terriers. *Aust. Vet. J.* **60**:235-238.

Thornburg LP (2000) A perspective on copper and liver disease in the dog. *J. Vet. Diagn. Invest.* **12**:101-110.

Twedt DC, Hunsaker HA, Allen KGD (1988) Use of 2,3,2-tetramine as a hepatic copper chelating agent for treatment of copper hepatotoxicosis in Bedlington terriers. *J. Am. Vet. Med. Assoc.* **192**:52-56.

Watson ADJ, Middleton DJ, Ilkiw JE (1983) Copper storage disease with intravascular haemolysis in a Bedlington terrier. *Aust. Vet. J.* **60**:305-307.

General literature

Garcia-Fernández AJ, Motas-Guzmán M, Navas I, María-Mojica P, Romero D (1999) Sunflower meal as cause of chronic copper poisoning in lambs in south-eastern Spain. *Can. Vet. J.* **40**:799-801.

Goonaratne SR, Christensen DA (1997) Effect of chelating agents on the excretion of copper, zinc and iron in the bile and urine of sheep. *Vet. J.* **153**:171-178.

Grobler DG (1999) Copper poisoning in wild ruminants in the Kruger National Park: geobotanical and environmental investigation.. *Onderstepoort J. Vet. Res.* **66**:81-93.

Gummow B, Botha CJ, Basson AT, Bastianello SS (1991) Copper toxicity in ruminants: air pollution as a possible cause. *Onderstepoort J. Vet. Res.* **58**:33-39.

Humphries WR, Morrice PC, Bremner I (1988) A convenient method for the treatment of chronic copper poisoning in sheep using subcutaneous ammonium tetrathiomolybdate. *Vet. Rec.* **123**:51-53.

Lewis NJ, Fallah-Rad AH, Connor ML (1997) Copper toxicity in confinement-housed ram lambs. *Can. Vet. J.* **38**:496-498

Mylrea PJ, Byrne DT (1974) An outbreak of acute copper poisoning in calves. *Aust. Vet. J.* **50**:169-172.

Rooney DR, Uren NC, Leaver DD (1977) Some aspects of fertiliser use in relation to animal health and the environment. *Aust. Vet. J.* **53**:9-16.

Soli NA, Froslie A, Aaseth J (1978) The mobilization of copper in sheep by chelating agents. *Acta Vet. Scand.* **19**:422-429.

Stogdale L (1978) Chronic copper poisoning in dairy cows. *Aust. Vet. J.* **54**:139-141.

Tokarnia CH, Döbereiner J, Peixoto PV, Moraes SS (2000) Outbreak of copper poisoning in cattle fed poultry litter. *Vet. Human Toxicol.* **42**:92-95.

van Saun RJ (1988) Copper toxicosis in sheep. *Mod. Vet. Prac.* **69**:3-7.

Iron

Core data

Common sources:

- iron supplements (injectable, oral)
- molluscicide (Fe-EDTA)

Animals affected:

- pig, cattle, foals
- dog (?)

Mode of action:

- direct oxidant mucosa damage
- mitochondrial damage
- cardiovascular collapse

Poisoning circumstances:

- overdose
- ingestion of molluscicide pellets (very large dose required)

Main effects:

- haemorrhagic gastroenteritis
- liver necrosis
- shock

Diagnosis: history + serum iron assay

Therapy:

- oral Mg $(OH)_2$
- emetic to dogs ingesting molluscicide pellets
- chelation – desferrioxamine (deferoxamine)
- oral ascorbic acid

Chemical structure: the element iron (Fe), a metal

Sources:

- oral supplements (ferrous fumarate, ferrous sulphate, ferric phosphate, ferrous carbonate)
- injectable iron preparations (ferric ammonium citrate, iron-dextran complexes)
- molluscicide (Multiguard® = Fe-EDTA complex; 60 g Fe-EDTA/kg product) – significant poisoning of dogs considered unlikely (Young 1999)

Mechanism of toxicity:

- elemental iron is corrosive, strong oxidant → direct mucosal damage
- excess oral dose overwhelms selective absorptive mechanism of intestine mucosa → excess absorption, overwhelms transferrin iron-binding capacity → excess iron circulates free in plasma
- mitochondrial damage → hepatic necrosis
- ↑ capillary permeability → cardiovascular collapse

Toxicity:

- cases recorded in pigs, cattle (Holter *et al.* 1990), foals (Mullaney & Brown 1988)
- toxicity of injectables > oral preparations
- oral preparations: moderate toxicity @ 20-60 mg/kg, lethal @ >200 mg/kg
- Fe-EDTA rat oral LD_{50} = 5 g/kg; 500 g pack of Multiguard® molluscicide contains 30 g Fe-EDTA (Young 1999)
- certain bird species (including Indian hill mynahs [*Gracula religiosa*], toucans [*Ramphastos* spp.], hornbills, some psittacines, birds of paradise) appear to be susceptible to hepatic haemosiderosis in captivity (Cork 2000)

Sudden death from injectable iron preparations may present several syndromes:

- severe depression, shock & acidosis from excessive circulating iron
- peracute anaphylactic-like reaction probably related to histamine release immediately after injection
- staggering, collapse with convulsions with necropsy revealing hepatic necrosis and perirenal and cerebral oedema (Holter *et al.* 1990)

Conditions of poisoning:

- accidental ingestion, overdose
- foals in first few days of life more susceptible; toxic PO dose = 16 mg/kg ferrous fumarate; vitamin E & Se deficiencies may predispose (Mullaney & Brown 1988)
- dogs ingesting Fe-EDTA molluscicide pellets are unlikely to obtain a lethal dose (Young 1999)

Clinical signs: Oral intake [For injectables, see notes under sudden death syndromes]

Within 6 hr of ingestion

- lethargy, vomiting, **haemorrhagic diarrhoea**
- occasional acute haemolysis occurs

Apparent improvement for 6-24 hr

After 24 hr

- diarrhoea, dehydration
- liver necrosis
- shock, acidosis, coma

Pathology:

- necrosis, ulceration of alimentary mucosa
- enteritis (contents fluid to haemorrhagic)
- **liver necrosis**, jaundice
- ± haemoglobinuria

Diagnosis:

- assay serum iron - concentrations 50-100% above normal values (100-300 μg/dL) suggest toxicosis
- assay liver iron - normal values vary widely (up to 900 mg/kg wet weight in puppies; newborn piglets 100-200 mg/kg; supplemented piglets 600 mg/kg; adults <400 mg/kg)

Therapy:

- decontaminate alimentary tract (< 4 hrs after ingestion + no GI signs) - PO milk of magnesia [$Mg(OH)_2$] → Fe precipitated as insoluble iron hydroxide; N.B. activate charcoal is **not** effective
  - an emetic should be given to dogs that have recently ingested Fe-EDTA molluscicide pellets (Young 1999); apomorphine, not sodium carbonate (washing soda) (Anon 1997)
- supportive measures for shock, dehydration, acidosis
- chelation therapy
  - continue until serum Fe concentration > 300 μg/dl; may need therapy for 3-4 days
  - – desferrioxamine (deferoxamine) [Desferal®] IV as a constant rate infusion @ no more than15 mg/kg/hr (avoid rapid administration) or IM 40 mg/kg @ 4-8 hr intervals; total dose should not exceed 6 g in 24 hr] (Anon. 1997)
  - possible alternative chelator: deferiprone, dosed PO @ 150 mg/kg (Barr *et al.* 1999)
- + ascorbic acid PO → ↑ iron excretion during chelation therapy (urine is reddish-brown from excess iron during early chelation therapy)
- monitor serum iron concentrations (3-4 days)

References:

Os188 & 190, VM8/1504

Adams J (1999) Iron poisoning in a dog from snail pellets. *Post-Graduate Foundation in Veterinary Science of the University of Sydney, Control & Therapy Series*, Mailing 210, Article 4156. p.1119-1120.

Anon. (1996) Caution urged when using snail baits. *AVA Information Sheet.* Issue No.2, 18 December 1996. Australian Veterinary Association, Artarmon. 4pp.

Anon. (1997) Multiguard snail and slug bait. *AVA Information Sheet.* Issue No.6, 11 June 1997. Australian Veterinary Association, Artarmon. 3pp.

Barr J, Berkovitch M, Tavori I, Kariv N, Schejter A, Eshel G (1999) Acute iron intoxication: the efficacy of deferiprone and sodium bicarbonate in the prevention of iron absorption from the digestive tract. *Vet. Human Toxicol.* **41**:308-3311. [Study in rats for application in humans]

Cork SC (2000) Iron storage diseases in birds. *Avian Pathol.* **29**:7-12.

Holter JA, Carson TL, Witte ST (1990) Acute iron intoxication in a herd of young bulls. *J. Vet. Diagn. Invest.* **2**:229-230.

Mullaney TP, Brown CM (1988) Iron toxicity in neonatal foals. *Equine Vet. J.* **20**:119-124.

Young C (1999) Iron EDTA complex. *Post-Grad. Committee in Vet Science, University of Sydney: Control & Therapy Series*. Mailing 211, No.4183 pp.1140-1143.

☑ *Mercury - inorganic compounds & vapour*

Core data

Common sources: ointments, blisters, antiseptics, fungicides containing Hg salts or organic Hg compounds
Animals affected: all
Mode of action:

- direct irritation of alimentary tract
- excretion through kidney → nephrosis
- excretion through large intestinal mucosa → colitis

Poisoning circumstances:

- licking of topically-applied ointments or blisters
- accidental feeding
- percutaneous absorption (blisters)

Main effects:

- acute: vomiting, diarrhoea, colic ± early death
- survivors: stomatitis, nephrosis, colitis (± ulcerative)

Diagnosis: assay stomach contents, urine, blood, kidney
Therapy: as for As

Chemical structure: the element mercury (Hg), a metal
Sources:

- **ointments** containing mercuric oxide (HgO), mercuric iodide (HgI_2), mercuric nitrate ($Hg(NO_3)_2.2H_2O$)
- mercuric chloride (corrosive sublimate, $HgCl_2$) as an **antiseptic**
- mercurous chloride (calomel, Hg_2Cl_2) - insoluble, relatively non-toxic (Simpson *et al.* 1997)
- alkoxyalkylmercurial & arylmercurial **fungicides** (organic mercurials) break down in the body → inorganic Hg
- volatilisation of metallic Hg exposed to air

Toxicity:

Ingested mercury

- oral toxic dose $HgCl_2$: 8 g (horse, cow), 4 g (sheep), 0.2-0.35 g (dog)
- oral toxic dose Hg_2Cl_2 : 12-16 g (horse), 8-12 g (cow), 1-2 g (sheep), 0.4-2.0 g (dog)
- directly irritant to alimentary tract
- excretion through kidney → **nephrosis**
- excretion through large intestinal mucosa → **colitis**
- excretion from the body (gut, kidneys) is slow → accumulation from relatively low doses

Mercury vapour

- safe concentration in air < 0.05 mg Hg/m^3
- toxic concentrations 0.1-0.2 mg Hg/m^3 or above (may reach 13 mg/m^3 @ 20°C in enclosed space)
- high concentrations → acute chemical pneumonitis
- **lower concentrations** → absorption into blood through alveolar wall → much deposited in kidney as inorganic salts, some passes blood-brain barrier as elemental uncharged Hg

Conditions of poisoning:

Ingested mercury

- licking of topically-applied ointments or blisters (see below)
- accidental feeding
- percutaneous absorption e.g. applying blisters with dimethyl sulphoxide (DMSO)

In the past, a *blister* or *counterirritant* was applied to horses' legs as a paste of cantharides (substances obtained from dried *Cantharis vesicatoria* [= *Lytta vesicatoria*] beetles; Spanish fly) or mercuric salts to produce superficial irritation intended to relieve the effects of deeper inflammatory change such as in strained tendons or ligaments. Firing (burning the skin and superficial tissues with a hot iron) was an alternative

counterirritant. Naturally, less traumatic methods are used by veterinarians today. However, some lay people continue to use such methods.

Mercury vapour

-volatilisation of metallic Hg exposed to air
- animals treated with topical Hg preparations & kept in closed stalls

Clinical signs:

Ingested mercury

Early signs - acute poisoning - vomiting, diarrhoea, colic ± early death
Subsequent signs - survivors

- stomatitis
- ± mild-to-severe dysentery
- acute nephrosis
  - proteinuria, glucosuria
  - anuria, renal failure

Mercury vapour

Higher concentrations: dyspnoea, coughing, nasal discharge, fever, ± bleeding from oral mucosa, ± dermatosis
Lower concentrations: intention tremor, hypersensitivity to external stimuli (erethism), ± salivation & gingivitis

Pathology:

Ingested mercury

- nephrosis, gastroenteritis ± ulcerations, gingivitis

Mercury vapour

Higher concentrations: pulmonary oedema, acute pneumonitis, ± nephrosis

Diagnosis:

- history of exposure; nephrosis
- assay stomach contents/vomitus, blood, urine, kidney, (hair)

Therapy:

Ingested mercury

- as for As (see notes under sudden death syndromes); remove source (ointments)

Mercury vapour

Higher concentrations: usually reversible on termination of exposure

References: Os197, Se217, VM8/1487

Simpson VR, Stuart NC, Munro R, Hunt A, Livesey CT (1997) Poisoning of dairy heifers by mercurous chloride. *Vet. Rec.* **140**:549-552.

Mercury - organic (methyl mercury)

Syndrome name: Originally = Minamata disease of humans

Sources:

- inorganic Hg in industrial discharges into water bodies → conversion to methyl mercury by methanogenic bacteria in muds of river beds, lakes and seas. Methyl Hg water soluble, readily enters food chain/web → bioaccumulation → high concentrations in higher order consumers (sharks, other carnivorous fish, aquatic mammals). Methyl Hg bound to cysteine residues in structural proteins → widespread in animal tissues (including muscle)
- fungicidal seed dressings for grain

Toxicity:

- 1.0 ppm US FDA upper limit of acceptable methyl Hg in commercial fish for human food (10 times lower than lowest concentration associated with adult human poisoning incidents)
- recorded incidents: humans, cats, pigs
- pigs- daily intake 0.4 mg/kg, 20-90 days → signs → death in *ca.*8 days
- cats- experimental daily intake 0.6 mg/kg, 70 days → signs
- nervous signs when brain methyl Hg > 10 mg/kg
- → cell death in cerebrum, cerebellum & spinal cord fibre degeneration
- methyl Hg deposits in dorsal spinal root ganglia → cell death, fibre tract degeneration → disturbed proprioception

Conditions of poisoning:
- diets containing large proportion of heavily contaminated animal tissue
  - Minamata area, Japan (1940s-1950s) → humans, cats
  - Canada (1960s) → humans
  - Amazon River basin, Brazil (late1990s) → humans; Hg sources = gold mining, deforestation with Hg leaching from soils (Pearce 1999)
  - Hobart, Tasmania (1970s) → cats (3 yrs barracouta consumption)
- accidental ingestion of fungicide-treated grain
  - USA (1969-70) → pigs; affected pigs → humans
  - Iraq (1972) → humans

Clinical signs (pigs, cats):
- anorexia, weight loss/↓ growth rate
- ataxia, hypermetria, knuckling
- intention tremors
- aimless wandering, blindness, chewing without prehension
- paresis, clonic convulsions, coma, death

Pathology:
- no gross lesions ± nephrosis
- histopathology →
  - cerebrum & cerebellum neurone degeneration/death
  - spinal cord white matter degeneration (dorsal & lateral > ventral tracts)

Diagnosis:
- clinical syndrome, pathology
- Hg assay - blood, hair, urine, kidney

Therapy:
- CNS damage irreversible
- Se supplementation → ↓ effects on CNS ??
- chelation (D-penicillamine) → clearance from blood (see notes on Pb poisoning above & on As poisoning under sudden death syndromes)

Prevention & Control:
- meat from poisoned livestock unsuitable for human consumption
- monitor local environment (sharks, marlin - 1970s some high Hg Vic, NSW, Q)
- sand flathead good indicator fish species in southern Australia
- cat blood Hg concentrations can indicate degree of contamination of local fish population

References:

Se217, VM8/1487
D'Itri PA, D'Itri FM (1977) *Mercury Contamination: A Human Tragedy.* John Wiley & Sons, New York.
Gruber TA, Costigan P, Wilkinson GT, Seawright AA (1978) Chronic methylmercurialism in the cat. *Aust. Vet. J.* **54**:155-160.
Pearce F (1999) A nightmare revisited. *New Scientist* **161**(2172):4

☑ *Zinc*

Core data

Common sources:
- galvanised metal,
- Zn salts as prophylactics
- topical pharmaceuticals

Animals affected:
- sheep, cattle
- caged birds

Mode of action: undefined

Poisoning circumstances:
- ruminants: overdose of prophylactic Zn salts *vs.* sporidesmin
- sheep: drinking footrot baths
- parrots: eating galvanised metal flakes from cage wire

Main effects:
- pancreatic atrophy/necrosis/fibrosis
- nephrosis

- Heinz body haemolytic anaemia

Diagnosis:

- pathology + assay blood, kidney
- radiograph bird alimentary tract

Therapy:

- remove source from diet & alimentary tract
- chelation as for Pb, As

Prevention:

new cage wire:

- remove metal flakes
- scrub/soak in vinegar
- then wash before use

Chemical structure: the element zinc (Zn), a metal

Sources:

- galvanised containers, new wire cages, roofing nails
- prophylactic medication: $ZnSO_4$ (e.g. footrot footbaths for sheep [Jelinek *et al.* 2001])or ZnO, calamine lotion ($ZnCO_3 + Fe_2O_3$ as colouring), ZnO-containing topical pharmaceuticals
- Zn-based paint (50-55% Zn)
- coins (mainly US coinage: pennies minted after 1982 contain >99% Zn [Os204])
- fishing sinkers (Cooke & Cooke 1999)
- Zn shot (candidate replacement for Pb shot) (Levengood *et al.* 1999)
- smelters; industrial pollution of pastures (horses)

Toxicity:

- usually of low toxicity
- young animals more susceptible
- sheep, cattle, dogs, piglets, foals
- caged birds (particularly parrots), swans (Cooke & Cooke 1999), ducks (Levengood *et al.* 1999)
- sheep: death from doses of 20-180 mg/kg in from 35-1 weeks respectively
- pigs: maximum tolerated concentration in diet 0.1%
- young animals → interference with mineral metabolism → osteodystrophy (piglets, foals); Zn-induced copper deficiency in foals

Mode of action:

- undefined
- possible pathogenic mechanisms affecting pancreatic acinar cells include interaction with important divalent cations (e.g. Ca, Cu) to inhibit their cellular function, Zn-induced membrane changes, Zn-induced release of secretagogues (e.g. cholecystokinin) and Zn-induced release of corticosteroids (Zazacos & van Vleet 1989)
- Zn-induced copper deficiency in foals

Conditions of poisoning:

- cattle / sheep overdose of $ZnSO_4$, ZnO used as prophylactics for preventing sporidesmin or phomopsin toxicity [low margin of safety]. Drenching → closure of oesophageal groove → direct damage to abomasal mucosa → ill-thrift
- sheep drinking $ZnSO_4$ from footrot footbaths
- birds eating flakes of galvanised metal from cage wire. New cage wire most risky. (Reece *et al.* 1985)
- cattle licking Zn-based paint
- cattle fed brewer's grain from galvanised containers (Ellis *et al.* 1984)
- milk in galvanised containers → Zn lactate. 0.1 % → piglet toxicity
- dogs swallowing certain coins (US pennies minted after 1982), licking topical skin treatments
- contamination of pasture near smelters (when Zn & Pb are present in toxic amounts together, Zn toxicity develops rather than Pb toxicity)
- waterfowl ingesting Zn shot (Levengood *et al.* 1999)
- horse pasture contamination near Zn smelter (Newcastle, NSW) (Eamens *et al.* 1984)

Clinical signs:

- severity varies with dose
- very large dose → direct irritation of alimentary tract
  - vomiting, colic, diarrhoea, collapse

- lesser doses
    - loss of weight
    - ± diarrhoea
    - ↓ milk yield
    - ± somnolence, recumbency (hypocalcaemia)
    - polyuria, excessive thirst (nephrosis)
    - pallor, ± red urine (haemolytic anaemia)
    - lameness (osteodystrophy, arthritis - young animals)
    - pink discoloration of feathers (swans) (Cooke & Cooke 1999)
- chronic intake (horses)
    - lameness → recumbency
    - ill-thrift
    - bony joint enlargements

Pathology:

Ruminants, birds:

- **exocrine pancreatic atrophy / necrosis / fibrosis** (islets of Langerhans are usually spared)
- abomasal ulceration
- nephrosis, ± visceral gout (birds)
- Heinz body haemolytic anaemia
- ± arthritis, osteodystrophy
- ± hepatic haemosiderosis (birds)
- ± gastrointestinal haemorrhage (birds)

Horses:

- degenerative joint lesions
- osteoporosis

Diagnosis:

- assay blood, liver, kidney, suspected source (results variable) + pathology
- ↑ blood Zn concentrations [cattle 3.0-15.0 ppm] (rapidly return to normal after Zn source removed)
- normal serum/plasma and liver zinc concentrations vary significantly between genera of parrots and toxic concentrations can be considerably below those for poultry (that is, liver Zn > 200 mg/kg) (Puschner *et al.* 1999)
- in parrots, serum/plasma Zn > 2.0 ppm indicates possible toxicity and further evaluation of Zn exposure is warranted. Exceptions are cockatoos and Eclectus parrots which have higher normal concentrations (0.25-3.41 & 0.41-2.63 respectively) (Puschner *et al.* 1999)
- radiographs → ± zinc flakes in bird proventriculus & gizzard
- diagnosis and differential diagnosis of pancreatic disease in birds is discussed by Doneley (2001) with emphasis on serum amylase assay and pancreatic biopsy.

Therapy:

- remove source of Zn from environment / diet
- remove Zn flakes from bird alimentary tract (surgery, purging)
- careful chelation therapy may be appropriate (e.g. CaEDTA, D-penicillamine)- see As & Pb under sudden death & nervous syndromes
- supportive measures (fluids etc.)

Prevention (caged birds):

- scrub or soak new galvanised cage wire with vinegar (acetic acid → Zn acetate), then wash in clean water before use for bird cages
- mechanically remove all Zn flakes from cage wire
- weathering of galvanised wire alone is insufficient to reduce Zn availability
- BHP (Waratah brand) makes a green aviary wire which is polymer coated over a smooth zinc coat (T. Blowfield 2000, personal communication, AVAList)

References: Os204, Se228, VM8/1502

Allen JG, Masters HG, Peet RL, Mullins KR, Lewis RD, Skirrow SZ, Fry J (1983) Zinc toxicity in ruminants. *J. Comp. Path.* **93:**363-377**.**

Allen JG, Morcombe PW, Masters HG, Petterson DS, Robertson TA (1986) Acute zinc toxicity in sheep. *Aust. Vet. J.* **63**:93-95.

Cooke SW, Cooke ZR (1999) Study of lead and zinc toxicity in swans. *Vet. Rec.* **145**:352.

Doneley R (1992) Zinc toxicity in caged and aviary birds – "new wire disease". *Aust. Vet. Practit.* **22**:6-11. [8 parrots]

Doneley RJT (2001) Acute pancreatitis in parrots. *Aust. Vet. J.* **79**:409-411.
Eamens GJ *et al.* (1984) Skeletal abnormalities in young horses associated with zinc toxicity and hypocuprosis. *Aust. Vet. J.* **61**:205-207, 247.
Ellis TM , Masters HG, Dolling MJ (1984) Elevation of zinc levels of brewer's grain stored in galvanised troughs. *Aust. Vet. J.* **61**:239-240.
Inns JH (1995) Zinc toxicity in a dog following ingestion of zinc oxide and calamine. *Aust. Vet. Practit.* **25**:118-121.
Jelinek PD, Depiazzi LJ, Galvin DA, Spicer IT, Palmer MA, Pitman DR (2001) Eradication of ovine footrot by repeated daily footbathing in a solution of zinc sulphate with surfactant. *Aust. Vet. J.* **79**:431-434.
Levengood JM, Sanderson GC, Anderson WL, Foley GL, Skowron LM, Brown PW, Seets JW (1999) Acute toxicity of ingested zinc shot to game-farm Mallards. *Illinois Natural History Survey Bulletin* **36**:0-36 [Abstract 8437 *Vet. Bull.* 1999]
Puschner B, St.Leger J, Galey FD (1999) Normal and toxic zinc concentrations in serum/plasma and liver of psittacines with respect to genus differences. *J. Vet. Diagn. Invest.* **11**:522-527.
Reece RL, Scott PC, Forsyth WM, Gould JA, Barr DA (1985) Toxicity episodes involving agricultural chemicals and other substances in birds in Victoria, Australia. *Vet. Rec.* **117**:525-527. [Peach-faced lovebirds]
Reece RL, Dickson DB, Burrowes PJ (1996) Zinc toxicity (new wire disease) in aviary birds. *Aust. Vet. J.* **63**:199. [Peach-faced lovebirds]
Zazacos EA, van Vleet JF (1989) Sequential ultrastructural changes of the pancreas in zinc toxicosis in ducklings. *Am. J. Pathol.* **134**:581-595.

☑ Selenium

Core data

Syndromes:

- sudden death
- ill-thrift, abortion, infertility
- porcine poliomyelomalacia
- chronic selenosis – hair & hoof loss

Common sources:

- feed supplements
- selenium-containing pharmaceuticals
- selenium-accumulating plants

Animals affected:

- pigs
- poultry
- sheep (cattle)
- horses

Mode of action:

- porcine myelomalacia - possible mediation through nicotinamide deficiency
- chronic selenosis - Se replaces S in amino acids, interferes with keratinisation

Poisoning circumstances:

- accidental overdose
- eating selenium-accumulating plants

Main effects:

- sudden death – pulmonary oedema (heart failure), nephrosis
- ill-thrift – includes myocardial damage, nephrosis, depressed growth & immunity, reproductive failure
- hair & hoof loss
- Porcine myelomalacia
  - ➢ posterior ataxia & paralysis
  - ➢ symmetrical poliomyelomalacia

Diagnosis: assay feed, liver, kidney
Therapy: nil
Prevention: nil

Syndrome names:

Selenium poisoning has different manifestations depending on dose and animal species involved. Known syndromes are

- sudden death
- ill-thrift, abortions, depressed immunity
- porcine poliomyelomalacia

- chronic selenosis: hair & hoof loss from plant and other sources of selenium (*q.v.*)

Chemical structure: Selenium is a metaloid element chemically similar to sulphur

Sources:

Pharmaceuticals: sodium selenite & sodium selenate drenches or injections as prophylaxis against white muscle disease.

Feed additives/supplements, for example, as prophylaxis against white muscle disease, hepatosis dietetica and mulberry heart disease.

Selenium-accumulator plants causing chronic selenosis (*q.v.*) in USA (*Astragalus* spp., *Stanleya*), in Australia (*Neptunia amplexicaulis, Morinda reticulata*)

Industrial emissions from smelting of Zn & Pb (Huang & Gulson 2002)

Toxicity:

Sudden death:

- ruminants (mainly sheep)
- susceptibility lambs > adults
- some flocks very sensitive to Se toxicity
- original recommendations: 5 mg to ewes before mating, 5 mg before lambing, 1 mg to lambs at 2 weeks, then 5 mg at 3-monthly intervals
- some lamb deaths reported after single doses Na selenite of 5 mg parenterally (0.4-1.0 mg/kg) or 10-15 mg orally (1.0-2.2 mg/kg)
- predisposing factors may include low dietary protein, Co deficiency, stress
- LD_{50} 0.5 – 0.7 mg/kg

Ill-thrift:

- sheep (5mg every 2 weeks, 72 weeks)
- chickens

Porcine poliomyelomalacia:

- 5 mg/kg *lowest* daily dietary concentration → toxicity (recommended maximum 0.3 mg/kg)
- > 20 mg/kg in diet may → acute toxicity
- recent toxicity incidents have occurred with diets containing
  - 55-196 mg/kg → signs in 24 hrs, deaths in 2-5 days
  - 26-29 mg/kg (=12-32 mg Se/kg liveweight/day) → signs in 6-12 weeks

Mode of action:

Sudden death & *Ill-thrift*: unrecorded

Porcine poliomyelomalacia: unclear, but possibly related to induction of a nicotinamide deficiency which particularly affects glia (see notes on polioencephalomalacia for a similar glial pathogenesis) (Summers *et al.* 1995)

Conditions of poisoning:

Sudden death & *Ill-thrift*:

deliberate or accidental overdose

misreading or careless reading of dosage instructions

Porcine poliomyelomalacia:

- mistakes in feed formulation
- pigs fed rejected commercial dog food containing factory floor sweepings (Penrith 1995)

Clinical signs:

Sudden death:

- **sudden death** within 24 hr of dosing, continuing up to 7 days
- lethargy, tachypnoea, dyspnoea, frothing at the mouth & nostrils

Ill-thrift:

- poor weight gains, weight loss, death
- reduced reproductive rate (sheep)
- abortions (cattle) (Yaeger *et al.* 1998)
- depressed immunity (cattle) (Raisbeck *et al.* 1998, Yaeger *et al.* 1998)

Porcine poliomyelomalacia:

- ± anorexia, depression, vomiting
- **posterior ataxia & paralysis** (dog-sitting [paraplegia], quadriplegia) → lateral recumbency
- terminal dyspnoea, cyanosis, tachycardia

- ± rough hair coat; coronitis ± hoof sloughing (cf. effects of Se under skin syndromes)

Pathology:

Sudden death:

- ↑ serum/plasma urea, creatinine
- hydrothorax
- **pulmonary oedema** (tracheobronchial foam)
- nephrosis

Ill-thrift:

Sheep (WA) - nephrosis, myocardial necrosis & calcification, hepatic haemosiderosis (complicated by Co deficiency)

Birds – pancreatic lesions reported in aquatic birds (Green & Albers 1997)

Porcine poliomyelomalacia:

- **symmetrical poliomyelomalacia** in ventral horns
- ± degeneration in cardiac & skeletal muscle

Diagnosis:

Se dosing or exposure history + syndrome

Se assay: blood, liver [normal 0.25-1.5 mg/kg], kidney [normal 0.9-3.0 mg/kg]; feed

Therapy: nil

Prevention & Control:

Ill-thrift:

Chickens (USA) - add dietary cysteine & phenylarsenicals → ↓ effects (Lowry & Baker 1989)

In Australia the Maximum Permissible Concentration of selenium in edible offal is 2 mg/kg and in meat 1 mg/kg, wet weight.

Porcine poliomyelomalacia:

- affected pig groups should not be marketed until blood Se normal (*ca.*6-8 weeks after exposure); condemn liver, kidney, skin/hair at slaughter
- blood Se half-life estimated at 12 days; 60 day per-slaughter withholding period should ensure tissues safe for human consumption (Davidson-York *et al.* 1999) ; In Australia the Maximum Permissible Concentration of selenium in edible offal is 2 mg/kg and in meat 1 mg/kg, wet weight.

References:

Os201, Se115 & 117, VM8/1484

Davidson-York D, Galey FD, Blanchard P, Gardner IA (1999) Selenium elimination in pigs after an outbreak of selenium toxicosis. *J. Vet. Diagn. Invest.* **11**:352-357.

Green DE, Albers PH (1997) Diagnostic criteria for selenium toxicosis in aquatic birds: histologic lesions. *J. Wildl. Dis.* **33**:385-404.

Huang YJ, Gulson BL (2002) Selenium in soils, spermatophytes and bryophytes around a Zn-Pb smelter, New South Wales, Australia. *The Science of the Total Environment* **293**:129-141.

Lowry KR & Baker DH (1989) *J Anim Sci* **67**:959

Penrith M (1995) *J. S. Af. Vet. Assoc.* **66**:47

Raisbeck MF, Schamber RA, Belden EL (1998) Immunotoxic effects of selenium in mammals. Chapter 53 in *Toxic Plants and Other Natural Toxicants*. eds Garland T, Barr AC. CAB International, Wallingford. pp. 260-266.

Smith BJ, Donovan GA, Rae DO (1999) Selenium toxicosis in a flock of Katahdin hair sheep. *Can. Vet. J.* **40**:192-194.

Summers BA, Cummings JF, de Lahunta A (1995) *Veterinary Neuropathology*. Mosby-Year Book, Inc., St.Louis, Missouri, p.260

Wilson TM, Scholz RW, Drake TR (1983) Selenium toxicity and porcine focal symmetrical poliomyelomalacia: description of a field outbreak and experimental reproduction. *Can. J. Comp. Med.* **47**:412-421.

Yaeger MJ, Neiger RD, Holler L, Fraser TL, Hurley DJ, Palmer IS (1998) The effect of subclinical selenium toxicosis on pregnant beef cattle. *J. Vet. Diagn. Invest.* **10**:268-273.

Molybdenum

Syndrome names:

- acute molybdenum poisoning of ruminants (liver & kidney necrosis)
- teart in cattle

Chemical structure: transition element; metaloid

Sources:

Acute poisoning:

Molybdenum is used as an additive to superphosphate pasture fertiliser (Mo-super)

Teart:

naturally high Mo soils

pasture contamination from mining & smelting operations
excessive application of Mo-containing fertilisers
lime supplementation → ↑ pasture Mo but no ↑ in Cu

Organ systems affected:

Acute poisoning: Liver, Kidney

Teart: Alimentary tract, Blood

Toxicity:

Acute poisoning:

cattle: ration contained 7400 mg/kg Mb; sheep also susceptible at the same order of magnitude (Swan *et al.* 1998)

Teart:

Mode of action:

Acute poisoning:

Teart:

Thiomolybdates → local irritation of alimentary tract

Conditions of poisoning:

Acute poisoning:

Accidental substitution of sodium molybdate for sodium bicarbonate in feedlot ration (Swan *et al.* 1998)

Teart:

High Mo pastures - pasture Cu:Mo ratio < 2:1

Clinical signs:

Acute poisoning (Swan *et al.* 1998):

sudden death
reduced feed intake/feed refusal
lethargy
ataxia progressing to recumbency
profuse ocular discharge & salivation
scant mucoid faeces

Teart:

emaciation
liquid diarrhoea full of gas bubbles
swollen genitalia
anaemia
loss of coat colour
osteoporosis (long-standing cases)

Pathology:

Acute poisoning (Swan *et al.* 1998):

severe periacinar necrosis of hepatocytes
severe necrosis of renal tubular epithelial cells

Teart:

Diagnosis:

Acute poisoning:

Liver Mb = 6-12 mg/kg wet weight (normal 0.6-1.6 mg/kg) + pathology (Swan *et al.* 1998)

Teart:

Therapy:

Acute poisoning: nil

Teart: Cu supplementation → precipitation of insoluble, non-irritant Cu-thiomolybdates, reverses systemic Cu deficiency

Prevention & control:

Acute poisoning: care with feed formulation

Teart:

References:

Os199, Se203, VM8/1493

Swan DA, Creeper JH, White CL, Ridings M, Smith GM, Costa ND (1998) Molybdenum poisoning in feedlot cattle. *Aust. Vet. J.* **76**:345-349.

Cadmium

Chemical structure: the element cadmium (Cd), a heavy metal

Sources:

- phosphatic fertilizers (monoammonium phosphates [MAP]may contain > 400 mg Cd/kg P)
- plants fertilized with cadmium-contaminated sewerage sludge or fertilizers
- pasture contamination from mining & smelting operations
- nickel-cadmium batteries
- antiseborrheic shampoos (cadmium sulphide)
- certain fungicides (cadmium chloride or succinate - may contain up to 12.3% elemental cadmium)

Toxicity:

- oral acute LD_{50} (dogs, rodents) = 39-107 mg/kg
- maximum tolerable dietary concentration for domestic animals = 0.5 ppm
- Cd induces synthesis of the protein metallothionein and binds to it in tissues → sequestration
- free cadmium nephrotoxic
- < 10% absorbed from alimentary tract; concentrated in kidney tubules
- **very long biological half-life** (decades)
- dietary interactions with Zn, Cu may → deficiencies if these elements marginal; conversely adding Zn to diets reduces Cd uptake
- Cd residues in offal (cattle, sheep, pig) for human consumption of concern; 1997 Australia New Zealand Food Authority (ANZFA) maximum permissible concentration in kidney = 2.5 mg Cd/kg fresh weight, in liver 1.25, in meat 0.05; residues influenced by fertilizer use and P supplementation practices

Conditions of poisoning:

- feed contamination, accidental ingestion of fungicides - livestock
- ingestion of Ni-Cad batteries - dogs

Clinical signs:

- reduced growth rates
- anaemia
- proteinuria, glucosuria
- arthropathy, osteoporosis
- abortion
- testicular & ovarian hypoplasia
- large doses → vomiting, diarrhoea

Pathology: **nephrosis**, hepatic damage

Diagnosis: assay kidney, urine

Therapy:

- no specific therapy; supportive measures
- adding EDTA complex to chicken diets decreased liver & kidney Cd concentrations (Mlodkowski & Telk 1997)

Reference: Os205, VM8/1505

Mlodkowski M, Telk L (1997) [An attempt to decrease cadmium accumulation in animal tissue by means of antagonistic influence of other mineral elements and complexing compound] *Roczniki Naukowe Zootechniki* **24**:243-249 (in Polish) [1998 *Nutrition Abstracts & Reviews (Series B)* **68**; Abstract 5197]

Rooney DR, Uren NC, Leaver DD (1977) Some aspects of fertiliser use in relation to animal health and the environment. *Aust. Vet. J.* **53**:9-16.

Manganese

Manganism (chronic manganese poisoning) is recognised in humans in industrial situations: apathy, anorexia, muscular weakness of the legs, irritability, headache, psychosis & Parkinsonism; neural effects are related to the effects of manganese on dopamine neurotransmission in the brain (Lewis 1998).

References:

Neser JA, de Vries MA, de Vries M, van der Merwe AJ, Loock AH, Smith HJC, Elsenbroek JH, van der Vyver FH, Delport R (1998) Enzootic geophagia and hepatitis of calves and the possible role of manganese poisoning. Chapter 29 in *Toxic Plants and Other Natural Toxicants*, edited by T Garland and AC Barr, CAB International, Wallingford UK, pp. 137-142.

Thallium (q.v.)

HALOGENS

☑ *Fluorine compounds*

Core data

Common sources:

- artesian bore water
- rock phosphates
- airborne industrial emissions – pasture contamination
- volcanic activity – pasture contamination

Animals affected: kangaroos > cattle > sheep > horses > pigs, poultry

Mode of action: broad enzyme inhibition affecting mainly ameloblasts, odontoblasts, osteoblasts

Poisoning circumstances:

- sheep - F concentrated by evaporation from artesian bore drains
- cattle – high F mineral supplements; pasture contamination

Main effects:

- dental fluorosis: mottled, pitted teeth, uneven teeth wear, emaciation
- skeletal fluorosis: lameness, unnatural posture, emaciation

Diagnosis:

- radiographs, histopathology (bone lesions)
- assay feed, water, urine, bones, teeth

Therapy: nil

Prevention:

- earth tanks for water supply
- ↓ evaporation of bore water (piped system)
- feed F < 40 mg/kg
- Al, Ca added → ↓F absorption from gut

Syndrome names:

There are two syndromes recognised as associated with intake of fluorine compounds

- **fluorosis** or chronic fluoride poisoning affecting bones and teeth
- **subacute fluoride poisoning** affecting kidney function, also known as superphosphate poisoning

Chemical structure: the element fluorine (F) is a highly corrosive gas

Sources:

Fluorosis

- F-rich **artesian bore water**
  - soluble forms of F released into underground water from granite rocks at high temperature & pressure + high sodium carbonate or bicarbonate concentrations + active ion exchange process
  - western and northern Queensland water F concentrations vary from negligible to 14 ppm, many 5-10 ppm (McCosker & Winks 1994)
  - F-rich artesian water areas in Queensland: Julia Creek-Cloncurry, Hughenden-Croydon, Longreach, Blackall northwards, Roma, Eulo-Hungerford (McCosker & Winks 1994)
  - evaporation from bore drains → 3-4 fold↑ concentration (up to 32 ppm)
  - along bore drains, soil may have 30-40 ppm F & plants may have up to 40 ppm F in dry matter
  - cases in India: cattle, buffalos, goats, sheep; water F 1.5-4.0 ppm (Choubisa 1999)
- F-rich **rock phosphates**

- up to 4% F recorded; F content varies with source, e.g. Christmas Island 1.78-1.83%F, Nauru 2.38%F, Duchess (NW Qld) 3.06%F (Blaney & Gartner 1983)
- F present in rock phosphate as fluoroapatite; processing to superphosphate or dicalcium phosphate (DCP) → solubilisation as calcium fluoride

- **gypsum** (Bourke & Ottway 1998)
- pasture contamination from **point-source airborne industrial emissions**
  - aluminium, steel, mineral supplements, fertiliser production, brick manufacture
  - brown coal-fired power plants (Kierdorf & Kierdorf 1999)
  - F-containing material heated to high temperatures expels fluorides → air; in air, fluorides + particulates + water → settle on vegetation (direct inhalation insignificant)
  - kangaroos in Portland area, Victoria (Clarke *et al.* 2002), cattle in Colac district (Victoria) & water buffaloes in India from brick manufacturing (Singh & Swarup 1994)
- pasture contamination from **volcanic activity**
  - Iceland, South America (Araya *et al.* 1990, 1993), New Zealand
  - pasture can remain hazardous for at least 2 years after cessation of the eruption (Araya *et al.* 1993)
- vegetation grown on **F-rich soils** (rare)
  - plants accumulate F poorly
  - natural F concentrations: grains 1-3 ppm, forage 1-36 ppm (mean < 4 ppm)
- pasture contamination from F-rich **fertilizer application** (superphosphates *etc.*) leading to long-term F-accumulation in soils. While pasture plants do not take up significant amounts of F from soils, soil particle contamination of pasture accounts for over 50% of ingested F in grazing livestock. Ingestion of soil containing 326-1461 μg F/g is likely to lead to chronic fluorosis in sheep & cattle. It is estimated that the use of F-rich fertilizers could produce this situation within decades in certain countries such as New Zealand. (Cronin *et al.* 2000)

Subacute poisoning

- superphosphate fertiliser used as top dressing on pasture; applied at 125-750 kg/ha; contains about 1-3% F
- volcanic ash (New Zealand, Iceland, South America); NZ ash contained 24-34 mg F/kg

Toxicity:

Fluorosis

- susceptibility: kangaroos > cattle > sheep > horses > pigs, poultry
- young animals most susceptible
- toxic diet concentrations = 30-60 ppm F
- vitamin C deficiency exacerbates fluorosis in guinea pigs
- Ca, Mg, Al ions + F → insoluble compounds in gut → ↓ absorption
- absorbed F excreted rapidly in urine or **96-99% stored in bones** (& teeth in young animals)
- F ions displace OH radicals from bone hydroxyapatite crystal structure → fluoroapatite; very slow F release from fluoroapatite → virtual permanent F in bones & teeth
- **dental fluorosis** → damage to permanent teeth during development (matrix laid down by damaged ameloblasts & odontoblasts fails to accept minerals normally → enamel hypoplasia, poor mineralisation of dentine) → inadequate prehension & mastication → emaciation
- **skeletal fluorosis** → disrupted osteogenesis (defective osteoblastic activity → inadequate matrix, defective irregular mineralisation), accelerated bone remodelling, production of abnormal bone (exostosis, sclerosis) ± accelerated resorption (osteoporosis) → lameness

Subacute poisoning

- **sheep**, cattle

- superphosphate sheep LD_{50} = 5-6 g/kg (fatal dose for most sheep 200-300 g) = 70-90 mg F/kg
- NaF sheep LD_{50} = 100-300 mg/kg (45-135 mg F/kg)
- NaF cattle toxic dose = 1.0-1.5 mg F/kg

Mode of action:

Fluorosis:

- F → broad enzyme inhibition; high bone F concentration → most effect on osteocytes, osteoblasts, ameloblasts, odontoblasts → greatest effect where metabolic activity & remodelling processes greatest

Subacute poisoning:

details uncertain; direct damage to renal tubular epithelium

Conditions of poisoning:

Fluorosis

- kangaroos – pasture contamination from industrial emissions; population of Eastern Grey kangaroos in the vicinity of the Portland aluminium smelter, Victoria (Clarke *et al.* 2002)
- sheep - artesian water, western Queensland + evaporative concentration in bore drains
- cattle - high-F mineral supplements fed, pasture contamination (industrial, volcanic)
- guinea pigs - high-F rock phosphate used in diets (130-400 ppm F in diet)

Subacute poisoning

- application of fertiliser to very **short pasture** (<3 cm) during **fine winter weather** (fertiliser adheres to leaf blades) or deposition of volcanic ash on pasture
- predominantly pregnant & lactating **ewes**
- under-nutrition of animals
- no alternative fodder available

Clinical signs:

Fluorosis

onset months-years after initial exposure

Cattle, sheep & horses

- mottled, discoloured (brown, black) or pitted enamel; abnormally rapid, uneven teeth wear → "broken mouthed" at early age
- lameness, unnatural posture, generalised stiffness (Griffith-Jones 1977)
- weight loss → emaciation

Guinea pigs

- excessive salivation ("slobbers")
- weight loss → emaciation, death

Kangaroos - lameness

Subacute poisoning:

- onset within 1 week of application of fertiliser/volcanic eruption
- anorexia, thirst
- **diarrhoea** (faeces watery, yellow to brown, foetid)
- weakness, ataxia, incoordination
- death in 24-48 hr after onset

Pathology:

Fluorosis:

Cattle, sheep & horses

- teeth as above + periodic radiolucent regions
- first bone lesions bilateral on medial surfaces of proximal third of metatarsals; then mandible, metacarpals, ribs affected
- diffuse enlargement, chalky with roughened periosteal surface
- histopathology may include cortical thickening, periosteal hyperostosis, uneven mineralisation, resorption of endosteal bone, excessive osteoid

Guinea pigs

- mal-apposition of molars → overgrowth → prevents mastication
- nephrosis + renal calcification → ↓ F excretion → exacerbation of syndrome

Kangaroos (Clarke *et al.* 2002)
- osteophytosis of distal tibia and fibula, tarsal bones, metatarsus IV & proximal coccygeal vertebrae
- osteopaenia of the femur, tibia & metatarsus IV
- incisor enamel hypoplasia, staining and abnormal teeth wear including uneven wear of molars
- abnormal bone matrix mineralisation & mottling
- microradiography reveals 'black osteons', a known manifestation of fluorosis

Subacute poisoning:
- hyperphosphataemia, uraemia, aciduria
- **nephrosis** (dilated tubules with flattened eosinophilic epithelium, casts)
- ± gastrointestinal ulceration

Diagnosis:

Fluorosis:
- radiograph lower limb bones
- histopathology of bony lesions
- assays
  - feed & water
  - urine (reflects recent exposure): cattle 15-20 ppm F (normal 2-6 ppm)
  - bone (biopsy, necropsy) or teeth
    - F concentration cancellous > cortical bone
    - sample sites: metatarsals, metacarpals, ribs, pelvis, mandible, coccygeal vertebrae
    - sheep up to 7000 ppm (normal 100-250 ppm F) - highest in mandibular ramus
    - adult cattle 2000-8000 ppm (normal 1000-1500 ppm on dry fat-free basis)

Subacute poisoning:
- access to superphosphate or volcanic ash + nephrosis
- differentiate from salmonellosis & metabolic disease

Therapy: Nil

Prevention & Control:

Fluorosis:

Total F consumption for cattle (feed + water) should not exceed 1 mg/kg/day (McCosker & Winks 1994)

Feed F concentration can be up to 40 ppm in dry matter, where water supplies are free of F (McCosker & Winks 1994)

Artesian water F
- **earth tanks** ("dams") for storage of surface water → ↓ reliance on artesian water
- open free-flowing artesian bores are being converted progressively to **controlled-flow piped systems** to prevent evaporative losses
- water with > 8 mg F / litre should not be used for livestock; water with > 4 mg F / litre should be used with care (any P supplementation should use low-F or F-free materials) (McCosker & Winks 1994)

Feed supplements
- rock phosphate minimum P:F ratio of 100:1 → incorporation in feeds at normal rates (0.1-0.3%) without risk of fluorosis
- aluminium sulphate (6% - Milhaud & van Weering 1997) , aluminium chloride, calcium aluminate, calcium carbonate → ↓ F absorption from gut
- rock phosphate sold for livestock feed in Queensland must not contain > 2% F

Prevent grazing around industrial plants, e.g. 2-3 km zone around plants in Netherlands designated unsuitable for grazing, plus monitoring of surrounding pastures and herds and supplementation with aluminium sulphate prevented cases (Milhaud & van Weering 1997)

Government regulation of industrial emissions leading to effective emission control measures: e.g. Germany – for power plants/large combustion plants, the allowable annual mean atmospheric F concentration = 1 μgF/m^3 and allowable peak concentration = 3 μgF/m^3 (Kierdorf & Kierdorf 1999).

Phytoremediation using water plants is proposed to reduce F concentrations in water as an approach to control fluorosis in humans in the Indian subcontinent (Sinha *et al.* 2000)

Subacute poisoning:

avoid predisposing conditions

References:

Os221, Se208, VM8/1489 & 1530

Araya *et al.* (1990) Bovine fluorosis following volcanic activity in the southern Andes. *Vet Rec* **126**:641-642.

Araya O, Wittwer F, Villa A (1993) Evolution of fluoride concentrations in cattle and grass following a volcanic eruption. *Vet. Human Toxicol.* **35**:437-440.

Blaney BJ, Gartner RJW (1983) Fluorine absorption by cattle fed rock phosphates containing various concentrations of aluminium and iron. In Farrell DJ, Vohra P (eds.) *Recent Advances in Animal Nutrition in Australia 1983.* University of New England Publishing Unit, Armidale. p. 3A.

Bourke CA, Ottway SJ (1998) Chronic gypsum fertilizer ingestion as a significant contributor to a multifactorial cattle mortality. *Aust. Vet. J.* **76**:565-569.

Cronin SJ, Manoharan V, Hedley MJ, Loganathan P (2000) Fluoride: a review of its fate, bioavailability, and risks of fluorosis in grazed-pasture systems in New Zealand. *N. Z. J. Agric. Res.* **43**:295-321.

Choubisa SL (1999) Some observations on endemic fluorosis in domestic animals in southern Rajasthan (India). *Vet. Res. Commun.* **23**:457-465.

Clarke EJ, Beveridge I, Slocombe RF, Coulson G (2002) Fluorosis as a probable cause of chronic lameness in Eastern Grey kangaroos (*Macropus giganteus*). *Proceedings, Aust. Soc. Vet. Pathol. Annual Conference.* p.11.

East NE (1993) Accidental superphosphate fertilizer poisoning in pregnant ewes. *JAVMA* **203**:1176-1177

Griffith-Jones W (1977) Fluorosis in dairy cattle. *Vet Rec* **100**:84-89. UK. Upper hind limb lameness most frequent sign. Fluorine from rock phosphate diet supplements.

Kierdorf H, Kierdorf U (1999) Reduction of fluoride deposition in the vicinity of a brown coal-fired power plant as indicated by bone fluoride concentrations of roe deer (*Capreolus capreolus*). *Bull. Environ. Contam. Toxicol.* **63**:473-477.

McCosker T, Winks L (1994) *Phosphorus Nutrition of Beef Cattle in Northern Australia.* Department of Primary Industries, Brisbane. pp. 20-22, 24, 80.

Milhaud G, van Weering HJ (1997) Prevention de la fluorose bovine et ovine d'origine industrielle. *Rec. Med. Vet.* **173**:53-58.

O'Hara PJ *et al.* (1982) Superphosphate poisoning of sheep: a study of natural outbreaks; experimental studies; the role of fluoride. *N. Z. Vet. J.* **30**:153-155, 165-169, 199-201

Parsonson IM, Carter PD, Cruickshanks J (1975) Chronic fluorosis in laboratory guinea pigs. *Aust. Vet. J.* **51**:362-363.

Rooney DR, Uren NC, Leaver DD (1977) Some aspects of fertiliser use in relation to animal health and the environment. *Aust. Vet. J.* **53**:9-16.

Shanks DF (1997) Clinical implications of volcanic eruptions on livestock – Case studies following the 1995 and 1996 eruptions of Mt.Ruapehu. *Proc. 27th Seminar of the Society of Sheep and Beef Cattle Veterinarians of the New Zealand Veterinary Association*, Publication 175, Veterinary Continuing Education, Massey University, Palmerston North, p.1-13.

Singh JL, Swarup D (1994) Fluorosis in buffaloes. *Vet Rec* **135**:260-261.

Sinha S, Saxena R, Singh S (2000) Fluoride removal from water by *Hydrilla verticillata* (l.f.) Royle and its toxic effects. *Bull. Environ. Contam. Toxicol.* **65**:683-690.

☑ Iodine

Core data

Syndrome names: iodism

Common sources:

- feed supplements including seaweed (marine algae)
- antiseptic solutions

Animals affected: horses, cattle, sheep, poultry

Mode of action:

- not precisely described
- depressed immune function

Poisoning circumstances:

- accidental overdose
- over-enthusiastic feed supplementation

Main effects:

- excessive lacrimation

- chronic coughing / bronchopneumonia
- poor hair coat

Diagnosis: history of supplementation + blood & milk iodine assay
Therapy: remove excess iodine source
Prevention: observe recommended maximum dietary concentrations

Syndrome name: iodism
Chemical structure: the element iodine (I), a halogen
Sources:

- feed supplements including ethylenediamine dihydroiodide (EDDI)
- antiseptic solutions including iodophores (teat dips)
- seaweed (marine algae) as a feed supplement (Quick 2000). Marine algae are known to concentrate iodine (Brooks 1998).

Toxicity:

- horses, cattle, sheep, poultry
- all species have a wide margin of safety (Ammerman *et al.* 1980)
- cows: natural clinical cases from intakes of 250-600 mg EDDI/head/day (Olson *et al.* 1984)
- calves: depressed growth rates @ > 50 ppm in rations, respiratory signs @ > 100 ppm (Newton *et al.* 1974)
- lambs: depressed growth rates @ 100 mg/kg/day PO, respiratory signs @ > 150 mg/kg/day (McCauley *et al.*1973)
- pigs: depressed growth rates @ >400 ppm in rations; pregnant sows tolerated 25oo ppm for 30 days pre-farrowing (Ammerman *et al.* 1980)
- breeder poultry: reduced and delayed hatchability @ 50 ppm; egg production stopped by 5000 ppm (Ammerman *et al.* 1980); sexual maturity in 12 week-old cockerels delayed @ 5000 ppm (Wilson & Harms 1972)
- mares: goitrous foals born @ 48-432 mg/day

Mode of action:

- not precisely described
- depressed immune function

Conditions of poisoning:

- excessive and prolonged supplementation, for example with EDDI or other supplements to prevent footrot, actinomycosis/actinobacillosis in cattle or as an expectorant in mild respiratory infections
- thoroughbred horses in training supplemented with seaweed (kelp) @ 30 g seaweed meal/day resulting in 8 times the recommended feed concentrations (Quick 2000)

Clinical signs:
Horse (Quick 2000)

- excessive lacrimation
- copious nasal discharge
- chronic coughing
- intermittent thyroid enlargement
- poor hair coat
- progressive weight loss
- foals born goitrous and with leg weakness (Baker & Lindsey 1968, Drew *et al.* 1975)

Cattle (Hillman & Curtis 1980, Olson *et al.* 1984)

- hyperthermia
- lacrimation, conjunctivitis
- nasal discharge, coughing, bronchopneumonia (particularly in calves)
- salivation
- hair loss (around eyes), rough hair coat, scaly dermatitis
- exophthalmus
- hock injuries
- reduced fertility
- reduced growth rate
- reduced milk production
- increased incidence of infections, lymphopaenia

Sheep (McCauley *et al.* 1973)

- hyperthermia

- coughing
- reduced growth rate

Pathology:

Horse

serum I 117 μg/dl [normal 5-10] (Quick 2000)

Cattle

- ↑ milk iodine concentrations: range 0.3-6.4 ppm (normal 0.1-1.0) (Hillman & Curtis 1980)
- ↑ serum iodine concentrations: range 17.0-121.0 μg/dl (normal 5.7-19.5) (Olson *et al.* 1984)
- high normal serum urea concentrations

Diagnosis: history of supplementation + blood & milk iodine assay

Therapy: remove excess iodine source

Prevention & control:

- maximum dietary concentrations (Ammerman *et al.* 1980)
  - horses: 5 ppm
  - calves: 25 ppm
  - cows: 50 ppm
  - poultry: 300 ppm
  - pigs: 400 ppm

References:

Review literature

Humphreys 47, VM8/1505

Ammerman CB, Fontenot JP, Fox MRS, Hutchinson HD, Lepore P, Stowe HD, Thompson DJ, Ullrey DE (1980) *Mineral Tolerance of Domestic Animals.* National Academy of Sciences, Washinton D.C. pp. 227-241.

Stowe CM (1981) Iodine, iodides and iodism. *J. Am. Vet. Med. Assoc.* **179**:334-335.

General literature

Baker HJ, Lindsey JR (1968) Equine goitre due to excess dietary iodide. *J. Am. Vet. Med. Assoc.* **153**:1618.

Brooks RR (ed.) (1998) *Plants that Hyperaccumulate Heavy Metals. Their role in phytoremediation, microbiology, archaeology, mineral exploration and phytomining.* CAB International, Wallingford, Oxon

Drew B, Barber WP, Williams DG (1975) The effect of excess iodine on pregnant mares and foals. *Vet. Rec.* **97**:93.

Hillman D, Curtis AR (1980) Chronic iodine toxicity in dairy cattle: blood chemistry, leukocytes, and milk iodine. *J. Dairy Sci.* **63**:55-63.

McCauley EH, Linn JG, Goodrich RD (1973) Experimentally induced iodine toxicosis in lambs. *Am. J. Vet. Res.* **34**:65.

Newton GL, Barrick ER, Harvey RW, Wise MB (1974) Iodine toxicity. Physiological effects of elevated dietary iodine on calves. *J. Anim. Sci.* **38**:449.

Olsen WG, Stevens JB, Anderson J, Haggard DW (1984) Iodine toxicosis in six herds of dairy cattle. *J. Am. Vet. Med. Assoc.* **184**:179-181.

Quick M (2000) Paper on iodism of race horses presented at the 2000 Aust. Equine Vet. Assn. Bain-Fallon Memorial Lectures. Abstract in *The Veterinarian* October 2000 Issue, p. 17.

Wilson HR, Harms RH (1972) *Poultry Sci.* **51**:742-746.

Bromine

Chemical structure:

Sources:

sodium bromide

Organ systems affected:

Toxicity:

goats

Mode of action:

Conditions of poisoning:

accidental access to sodium bromide by goats

Clinical signs:

somnolence, lateral recumbency, drooping ears, eyelids & tail
dribbling urine

Pathology:

increased concentration of plasma bromine (+ spurious increased concentration of chloride)

Diagnosis:

Therapy:

Prevention & control:

References:

Review literature

VM8:1506

General literature
Liggett AD *et al.* (1985) *J. Am. Vet. Med. Assoc.* **187**:72

OTHER INORGANIC SUBSTANCES

Sulphur

See notes on sulphur under feed additives.

8: Pesticides [Industrial-origin toxins]

RODENTICIDES & OTHER VERTEBRATE PESTICIDES

Coumarin derivatives (anticoagulant rodenticides)

Core data

Common sources: rodenticides
- 1st generation: warfarin, coumatetralyl (multiple daily doses for toxicity)
- 2nd generation: brodifacoum, bromadiolone, flocoumafen (single dose toxic)

Animals affected: dogs (cats, pigs, ruminants, horses, marsupials)
Mode of action:
- competitive inhibition of vitamin K epoxide reductase
- reduced vitamin K essential for coagulation factor activation

Poisoning circumstances:
- 1^o : eating rodent baits (cereal-based) or feed contamination
- 2^o : eating poisoned rodents

Main effects:
- haemorrhage in most mobile tissues or those most subject to trauma
- lameness, SC haematomas, pallor, dyspnoea, sudden death

Diagnosis: ↑prothrombin time + normal platelets
Therapy:
- vitamin K_1 ± blood transfusion; monitor prothrombin time
- 2nd generation compounds required prolonged therapy

Chemical structure:

synthetic compounds derived from 4-hydroxycoumarin or indan-1,3-dione
microbial action on 4-hydroxycoumarin → dicoumarol (= 3,3'-methylene-bis[4-hydroxycoumarin]) (e.g. in mouldy sweet clover (*Melilotus* sp.) [*q.v.*])
4-hydroxycoumarin derivatives: Warfarin, Coumatetralyl, Brodifacoum, Flocoumafen
Indan-1,3-dione derivatives: Pindone, Diphacinone

Sources:

The most commonly-available commercial **rodenticides**
First generation → "natural" selection of resistance in rodents (↑↑ hepatic microsomal mixed function oxidase degradation capacity)
- **warfarin** [Ratsak® 0.5g warfarin/kg; Ratblitz®], first introduced in early 1950s for use against *Rattus norvegicus*; less toxic to other rodent species
- **coumatetralyl** [Racumin® 0.37g coumatetralyl/kg]
- indandiones (diphacinone [Diphacin®], chlorophacinone)
- pindone [PIN-25®, Pival®]
- coumachlor

Second generation - longer half-lives than warfarin, developed to deal with warfarin resistance in rodents (some of which are now developing resistance to some of these compounds [Pelz *et al.* 1995])
- **brodifacoum** [Talon® 0.05g brodifacoum/kg; Rat Kill® 0.05g/kg; Ratsak 1 Shot® 0.05g/kg; Klerat®]
- **bromadiolone** [Bromakil® 0.05g bromadialone/kg; Brolone®, Bromard®, Rat-Attack®, Stoprat Plus®]
- **flocoumafen** [Storm® 0.05g flocoumafen/kg]
- coumafuryl [Fumarin®]
- difethialone
- difenacoum

Toxicity:

- **coagulopathy**
- species susceptibility pig > cat > dog > ruminant, horse > poultry.
  Cases in poultry are rare (Reece *et al.* 1985, Munger *et al.* 1993).

Cases in horses have occurred. Brodifacoum LD_{50} adult horse = 1-2 kg rodenticide pellets (0.05g brodifacoum/kg) (Boermans *et al.* 1991, McConnico *et al.* 1997).

- marsupials (brush-tailed possum) (Eason *et al.* 1996; Littin *et al.* 2002) and birds of prey (e.g. barn owls) susceptible
- first vs. second generation
  - warfarin: **multiple** consecutive small daily doses
  - second generation: persistent & toxic after **single** exposure
- mechanism of action:
  - **competitively inhibit vitamin K 2,3-epoxide reductase**
  - reduced vitamin K is essential for final carboxylation and activation of clotting factors II (prothrombin), VII (proconvertin), IX (Christmas factor) and X (Stuart factor)
  - coagulation system activity is maintained until natural decay of the clotting factors occurs (24-36 hr after intake of toxin)
- bound to plasma albumin , so **potentiated by**
  - drugs also bound to albumin (e.g. phenylbutazone)
  - conditions → ↓ albumin (e.g. renal, hepatic insufficiency)
  - drugs → ↓ vitamin K synthesis in the intestines (e.g. sulphonamides, broad-spectrum antibiotics)

Conditions of poisoning:

- **primary** poisoning (**eating cereal baits or feed contamination**) - pigs, dogs, horses (Boermans *et al.* 1991, McConnico *et al.* 1997), possums, poultry, granivorous wild birds (Reece *et al.* 1985)
- **secondary** poisoning (**eating poisoned rodents**) - dogs, cats, barn owls
  1 adult brown rat (*Rattus norvegicus*) may contain 5 mg - enough to poison a small to medium sized dog
  rodents resistant to these compounds are increasing worldwide, thus carry larger amounts of the toxins and potentially threaten populations of predatory birds and mammals such as barn owls, foxes, weasels, stoats (Newton I *et al.*. 1999)
- for a discussion of rodent baiting techniques in agriculture and elsewhere, see Buckle & Smith (1994), Buckle (1999); sustained baiting (first generation compounds) and pulsed baiting (second generation compounds)

Clinical signs:

- onset first generation: 4-5 days; second generation 1-3 days
- ± acute onset → **sudden death** (animal found dead) from massive haemorrhage (brain, pericardium, mediastinum, pleural & abdominal cavities)
- more commonly →
  - weakness, exercise intolerance, lethargy, tachycardia (from anaemia)
  - **pallor of mucosae**
  - **subcutaneous haematomata**
  - **lameness** (bleeding in & around joints)
  - dyspnoea [thoracic radiographs → pleural effusion, generalised patchy interstitial/alveolar pulmonary infiltrates, tracheal narrowing, increased mediastinal soft tissue opacity (Berry *et al.* 1993)]
  - external haemorrhage (including epistaxis, haematemesis, melena, haematuria, haemorrhagic diarrhoea or profuse bleeding from minor wounds)
  - ± scleral, conjunctival, intraocular haemorrhage
  - pericardial effusion + cardiac tamponade without other signs of haemorrhage (rare) (Petrus & Henik 1999)

Pathology:

- haematology/coagulation studies: anaemia, ↑**prothrombin time (PT)**, ↑activated coagulation time (ACT), ↑activated partial thromboplastin time (APTT), platelets normal, fibrinogen normal

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Reference ranges for coagulation tests (seconds)

Test	Dog	Cat
PT	6-10	7-12
APTT	11-15	10-15

ACT	65-95	<65

- necropsy: **widespread haemorrhage** (concentrated in tissues most in motion during life or most susceptible to minor trauma - subcutis, joints, lungs, heart, intestines) including haemoperitoneum, haemothorax and pulmonary haemorrhage (DuVall *et al.* 1989)

Diagnosis:

- history of access, clinical syndrome, ↑PT with **normal platelets** & fibrinogen
- assay stomach contents, liver, blood (serum), baits: techniques include HPLC, GC/MS (DuVall *et al.* 1989), liquid chromatography (Felice *et al.* 1991)
- dye from pellets (green, purple, blue) may be apparent in faeces or vomitus (green indistinguishable from green dye in metaldehyde pellets, blue indistinguishable from that in carbamate molluscicide pellets - see notes on metaldehyde & carbamates)
- favourable response to vitamin K therapy
- differential diagnosis in dogs in northern Australia should include canine infectious cyclic thrombocytopaenia caused by *Ehrlichia platys* infecting megakaryocytes (Brown *et al.* 2001, Irwin 2001).

Therapy:

- → **vitamin K_1** (phytomenadione) [K1®, Koagulon®, Konakion®] much more effective than synthetic K_3 (menadiol).
- monitor progress using PT. Continue treatment until the toxin is cleared. Therapy much more prolonged if second generation compounds involved [half-lives in dogs: warfarin 14.5 hours, brodifacoum 6 days. Half-life of brodifacoum in horses = 1.22 days (Boermans *et al.* 1991)]
- → blood products if anaemia significant or if local supportive therapy to control bleeding inadequate

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Anticoagulant rodenticide treatment protocol (dog)

If soon after ingestion, induce vomiting, lavage stomach & instil activated charcoal @ 1g/5ml water.

→ O_2 if required. Consider chest radiographs if dyspnoea continues.

→ IV blood product (frozen or fresh plasma, cryosupernatant), or if severe anaemia, whole blood @ 10-20 ml/kg. Monitor ACT or PT to decide if more blood products needed.

→ vitamin K_1 @ 3 mg/kg (large dog) - 5 mg/kg (small dog) SC twice per day until coagulation times are normal, then continue @ 2-3 mg/kg/day p/o in divided doses for 1 week (warfarin) or @ 5 mg/kg for up to 30 days (second generation compounds). Monitor response with PT; continue therapy if PT elevated.

Milder cases may need only vitamin K_1.

Anticoagulant rodenticide treatment protocol (adult horse – brodifacoum [McConnico *et al.* 1997])

→ activated charcoal PO (nasogastric tube) (2.2 kg dose) and mineral oil (2L) alternately every 4hrs for 24 hr

→ vitamin K_1 @ 2.5 mg/kg SC every 12 hr for 36 hr and then PO for remainder of therapy duration

Monitor PT (normal < 12 sec) & APTT (normal < 51 sec) daily

Add lucerne (*Medicago sativa*) to diet (as a source of vitamin K_1)

Stable the horse, allowing restricted outside exercise in small yard 2-4 hr daily

Duration of therapy may be 3-5 weeks depending on dose ingested

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References: Os276, Se 308

Berry CR *et al.* (1993) Thoracic radiographic features of anticoagulant rodenticide toxicity in fourteen dogs. *Vet. Radiology & Ultrasound* **34**:391-396

Boermans HJ, Johnstone I, Black WD, Murphy M (1991) Clinical signs, laboratory changes and toxicokinetics of brodifacoum in the horse. *Can. J. Vet. Res.* **55**:21-27.

Brown GK, Martin AR, Roberts TK, Aitken RJ (2001) Detection of *Ehrlichia platys* in dogs in Australia. *Aust. Vet. J.* **79**:554-558.

Buckle AP (1999) Rodenticides – Their role in rodent pest management in tropical agriculture. Chapter 7 in Singleton GR, Hinds LA, Leirs H, Zhang Z (eds) *Ecologically-based Management of Rodent Pests.* Australian Centre for International Agricultural Research, Canberra. pp.163-177.
Buckle AP, Smith RH (eds) (1994) *Rodent Pests and their control.* CAB International, Walingford UK.
Clark P, Parry BW (1996) Vitamin K antagonism in companion animals. *Aust. Vet. Practit.* **26**:118-126.
DuVall MD, Murphy MJ, Ray AC, Reagor JC (1989) Case studies on second-generation anticoagulant rodenticide toxicities in non-target species. *J. Vet. Diagn. Invest.* **1**:66-68.
Eason CT, Wright GR, Batcheler D (1996) Anticoagulant effects and the persistence of brodifacoum in possums (*Trichosurus vulpecula*). *N. Z. J. Agric. Res.* **39**:397-400.
Felice LJ, Chalermchaikit T, Murphy MJ (1991) Multicomponent determination of 4-hydroxycoumarin anticoagulant rodenticides in blood serum by liquid chromatography with fluorescence detection. *J. Analytical Toxicol.* **15**:126-129.
Irwin PJ (2001) The first report of canine ehrlichiosis in Australia. *Aust. Vet. J.* **79**:552-553.
Littin KE, O'Connor CE, Gregory NG, Mellor DJ, Eason CT (2002) Behaviour, coagulopathy and pathology of brushtail possums (*Trichosurus vulpecula*) poisoned with brodifacoum. *Wildlife Research* **29** (3): 259-267.
McConnico RS, Copedge K, Bischoff KL (1997) Brodifacoum toxicosis in two horses. *J. Am. Vet. Med. Assoc.* **211**:882-886.
Munger LL, Su JJ, Barnes HJ (1993) Coumafuryl (Fumarin®) toxicity in chicks. *Avian Dis.* **37**:622-624.
Newton I *et al.* (1999) *Advances in Vertebrate Pest Management* in press [cited in *New Scientist* **161**(2170):4]
Pelz H-J, Hänisch D, Lauenstein G (1995) Resistance to anticoagulant rodenticides in Germany and future strategies to control *Rattus norvegicus. Pestic. Sci.* **43**:61-67.
Petrus DJ, Henik RA (1999) Pericardial effusion and cardiac tamponade secondary to brodifacoum toxicosis in a dog. *J. Am. Vet. Med. Assoc.* **215**:647-648.
Reece RL, Scott PC, Forsyth WM, Gould JA, Barr DA (1985) Toxicity episodes involving agricultural chemicals and other substances in birds in Victoria, Australia. *Vet. Rec.* **117**:525-527.

Phosphides of zinc, aluminium or calcium

Sources:

- **rodenticides** (mostly superseded) as baits at concentrations of 2-5% (most commonly 2-2.5% (Buckle 1999); 0.75-2.5% (Twigg *et al.* 2002)

  currently used to control

  - rat infestation of sugar cane fields in Queensland for prevention of direct damage to cane and of leptospirosis of workers (Weil's disease) (RJ Parker, Department of Natural Resources, personal communication, 2001)
  - house mice in broad-acre cereal, pulse and horticultural crops in Australia – the zinc phosphide wheat bait MOUSEOFF® (Animal Control Technologies, Victoria) was registered in July 2000 for broadacre control of mice in crops (Twigg *et al.* 2002).

- **grain fumigants** (Phostox® tablets)

Toxicity:

Caution: Veterinarians attending poisoned animals may inhale sufficient phosphine gas from stomach contents to be clinically affected with neurological symptoms including dizziness, weakness, paraesthesias of the face and limbs and muscular tremors, resolving after about an hour (Drolet *et al.* 1996). Phosphine gas is considered an occupational hazard at > 0.3 ppm, and as the gas has an olfactory threshold of 1.5-3.0 ppm, detection of the odour should be taken as warning of potential health risk; serious illness will occur at 7 ppm and deaths have been reported from grain fumigation (Wilson *et al.* 1980).

- **dogs**, pig,
- horse (Drolet *et al.* 1996)
- poultry (Blaxland & Gordon 1945, Hare & Orr 1945)
- wild birds & hares (reported from Holland) (Gotink & van Ulsen 1952)
- ruminants are expected to be somewhat less susceptible due to the higher pH of rumen fluid compared with monogastric stomach secretions (Guale *et al.* 1994)
- lethal dose in most species 20-50 mg/kg
- more toxic when consumed with a meal or on a full stomach when gastric acid secretion is active (Johnson & Voss 1952). Dog toxicity on an empty stomach = 300 mg/kg vs. 40 mg/kg on a full stomach

Mode of action:

Gastric acid liberates phosphine gas (PH_3) with an odour of acetylene or decaying fish (garlic-like)

Conditions of poisoning:

- access to rodent control baits; uncommon in Australia, but likely to increase (Twigg *et al.* 2002); used in Asia (Buckle 1999)

- in fasted dogs, vomiting may prevent severe intoxication
- ingestion of poisoned rodents (Stowe *et al.* 1978)
- exposure to phosphine gas used as a grain fumigant

Clinical signs:

- onset in 15-20 min, death usually within 48 hrs. Animals surviving for 3 days are said to have a good prognosis (Stephenson 1967)
- vomiting (repeated), depression followed by dyspnoea
- signs of abdominal pain
- hyperactivity (hyperkinesis) such as convulsive running and vocalising
- muscle tremors progressing to convulsions
- clonic-tonic convulsions may suggest strychnine poisoning, but the course of illness is usually much longer.
- coma

Horse: anorexia, sweating, hyperaesthesia, muscle tremors, colic, tachycardia, hyperpnoea, collapse, convulsions, third degree heart block, ventricular fibrillation & death. White smoke with an odour of garlic was obtained by stomach tube. (Drolet *et al.* 1996).

Pathology:

Necropsy findings are usually non-specific and may include

- congested, yellowish (fatty) liver
- intense irritation of the stomach mucosa (congestion, oedema, petechiation)
- hyperaemia of all organs (Stowe *et al.*1978)

Horse: ecchymoses of parietal pleura, pulmonary congestion and oedema, hepatic lipidosis, congested kidneys and spleen, congested pharyngeal, stomach and intestinal mucosae, oedema of the small intestinal submucosa. Stomach contents included pale beige fluid with a strong odour. (Drolet *et al.* 1996).

Diagnosis:

Assay the ingesta/vomitus and the suspected source if available. Because phosphine is volatile, samples of stomach contents must be sealed in air-tight containers and frozen before shipment to a laboratory, packed to arrive frozen (Guale *et al.* 1994). Carcase tissues are said to be unsuitable for assay, but Stowe *et al.* (1978) reported a positive test on liver from one case.

Therapy:

There is no specific treatment. Control convulsions & decontaminate.

If toxin has been recently consumed

- emetic, gastric lavage
- alkalise stomach content with sodium bicarbonate by lavage & *per os* 24 hr

References: Os282, Se231, VM8/1520

Blaxland JD, Gordon RF (1945) Zinc phosphide poisoning in poultry. *Br. Vet. J.* **101**:108-110.

Buckle AP (1999) Rodenticides – Their role in rodent pest management in tropical agriculture. Chapter 7 in Singleton GR, Hinds LA, Leirs H, Zhang Z (eds) *Ecologically-based Management of Rodent Pests.* Australian Centre for International Agricultural Research, Canberra. pp.163-177.

Casteel SW, Bailey EM Jr (1986) A review of zinc phosphide poisoning. *Vet. Human Toxicol.* **28**:151-154.

Drolet R, Laverty S, Braselton WE, Lord N (1996) Zinc phosphide poisoning in a horse. *Eq. Vet. J.* **28**:161-162.

Gotink WM, van Ulsen FW (1952) A massive mortality of game animals by poisoning with zinc phosphide. *Tijdschr. Diergeneeskd.* **77**:214-219.

Guale FG, Stair EL, Johnson BW, Edwards WC, Haliburton JC (1994) Laboratory diagnosis of zinc phosphide poisoning. *Vet. Human Toxicol.* **36**:517-518.

Hare T, Orr AB (1945) Poultry poisoned by zinc phosphide. *Vet. Rec.* **57**:17.

Ingram PL (1945) Zinc phosphide poisoning in a colt. *Vet. Rec.* **57**:103-104.

Johnson HD, Voss E (1952) Toxicological studies of zinc phosphide. *J. Pharmacol. Sci.* **41**:468-472.

Stephenson JBP (1967) Zinc phosphide poisoning. *Arch. Environ. Health* **15**:83-88.

Stowe CM, Nelson R, Werdin R, Fanfmann G, Frederick P, Weaver G, Arendt TD (1978) Zinc phosphide poisoning in dogs. *J. Am. Vet. Med. Assoc.* **173**:270.

Twigg LE, Martin GR, Stevens TS (2002) Effect of lengthy storage on the palatability and efficacy of zinc phosphide wheat bait used for controlling house mice. *Wildl. Res.* **29**:141-149.

Wilson R, Lovejoy FH, Jaeger RJ, Landrigan PL (1980) Acute phosphine poisoning aboard a grain freighter. *J. Am. Med. Assoc.* **244**:148-150.

💣☑ Fluoroacetate (1080)

See notes under plant toxins

💣☑ Strychnine

See notes under plant alkaloids

💣☑ Cholecalciferol (vitamin D_3)

See notes under feed additives

Phosphorus

Sources: Yellow & white P. Rodenticide (mostly superseded) → baits
Toxicity:
- gastrointestinal tract irritant and hepatotoxin
- toxicity enhanced when finely divided & dispersed in oil or fat
- **Dogs**, pigs.

Conditions of poisoning:
- bait consumption; material not very attractive to well-fed animals (dogs)
- poisonings likely to be secondary, from eating poisoned rodents

Clinical signs:
- may vomit the offending material soon after consumption and then remain well
- or → signs of gastroenteritis in 1-2 hr, followed by severe liver injury 2-4 days after consumption

Pathology:
- stomach congestion & haemorrhage
- pale jaundiced swollen haemorrhagic liver (hepatocyte necrosis)

Diagnosis:
- assay ingesta/vomitus (garlic odour, fume, phosphorescent), suspected source
- tissues unsuitable for assay.

Therapy:
- no specific treatment
- if toxin recently consumed
  - emetic + purgative (non-oil based)
  - astringents + rehydration therapy
- if signs of liver failure have appeared → symptomatic treatment

References: Os288, Se223, VM8/1486

Bromethalin

Sources: rodenticide in grain-based pellets; used against warfarin-resistant rodents
Toxicity:
- cats and dogs
- cat oral LD_{50} = 1.8 mg/kg; dog oral LD_{50} = 4.7 mg/kg

Mode of action:
- uncouples oxidative phosphorylation → lack of ATP supply

Conditions of poisoning: consumption of inappropriately-placed rodent baits by pets
Clinical signs:

High dose (at or above LD_{50})
- onset within 24 hr
- severe muscle tremors
- hyperthermia
- hyperexcitability
- focal motor and generalised seizures

Low dose (below LD_{50})
- onset 1-5 days
- hind limb ataxia and/or paresis , paralysis
- and/or progressive CNS depression

Pathology:

Necropsy

- acute syndrome - ± cerebral oedema, pulmonary congestion

Histopathology

- diffuse spongiosis of white matter
- optic nerve vacuolation

Diagnosis: assay baits, stomach contents, liver

Therapy: prognosis guarded

- detoxication - emesis, activated charcoal (repeated for 2-3 days to interrupt enterohepatic circulation), saline cathartic
- supportive therapy
  - reduce cerebral oedema: mannitol (IV 250 mg/kg every 6 hr) + dexamethasone (2 mg/kg every 6 hr)
  - oral fluids
  - control seizures: diazepam or phenobarbital

References: Os286

4-aminopyridine

Sources:

- feral / wild bird control substance (bird "repellent") for crop protection
- used as grain baits impregnated with 4-aminopyridine (Scatterbird® = 0.5% w/w 4-AP)
- also marketed in USA as Avitrol®; banned for pigeon control in New York (V.R. Beasley, personal communication VETTOX 1999)

Toxicity:

- birds, cattle, horses, humans
- 4-AP pigeon oral LD_{50} = 8mg/kg; rat oral LD_{50} = 20 mg/kg; dog oral LD_{50} = 3.7 mg/kg;
- secondary intoxication of scavengers of bird carcases poisoned by 4-aminopyridine, e.g. dogs, rats, raptors, is unlikely (Schafer *et al.* 1974)

Mode of action:

- potassium channel blocker & α_2 adrenergic antagonist $\rightarrow \uparrow$ transmission at neuromuscular junctions
- a small proportion of a bird flock become affected with nervous dysfunction $\rightarrow$ alarm signals $\rightarrow$ panic reaction in remainder of the flock
- useful as an antidote to saxitoxin (*q.v.*) and tetrodotoxin (*q.v.*) poisonings

Conditions of poisoning:

- birds: deliberate baiting for crop protection; manufacturer's instructions are to feed unbaited grain for several days, then include a small quantity of baited grain to intoxicate a few birds and scare off the remainder of the flock; large mortalities can be induced if these instructions are not followed and all grain fed is baited.
- mammals: accidental access to treated grain / contaminated water

Clinical signs:

Birds (Oehme 1987)

- onset 0.25 – 4.0 hr after ingestion
- initial behaviour changes: rapid raising of shoulders and blinking, followed by ataxia
- tremors / convulsions accompanied by audible vocalisations from involuntary muscle contractions
- recumbency, hyperventilation

Cattle (Nicholson 1981)

- onset 12-24 hrs after ingestion
- frequent defaecation, tenesmus
- ataxia, incoordination
- ± tremors
- ± retropulsion (walking backwards) with head lowered & a fixed stare (hallucinations?) exacerbated by handling

Horses (Ray *et al.* 1978)

- onset 4-6 hrs after ingestion
- apprehension

- retropulsion
- fluttering of third eyelid
- sweating
- convulsions
- death within 2 hrs of onset

Pathology: no data

Diagnosis:

- access + syndrome
- assay stomach contents, kidney, liver, urine (Casteel & Thomas 1990)

Therapy:

- no specific data
- dose with an α_2 agonist (e.g. detomidine [Dormosedan®] in horses)

Prevention & control: deny access to susceptible animals

References:

VM8/1521

Casteel SW, Thomas BR (1990) A high-performance liquid chromatography method for determination of 4-aminopyridine in tissues and urine. *J. Vet. Diagn. Invest.* **2**:132-134.

Nicholson SS (1981) Suspected 4-aminopyridine toxicosis in cattle. *J. Amer. Vet. Med. Assoc.* **178**:1277.

Oehme FW (1987) Clinical toxicology of birds. *Proc. Vet. Clin. Toxicol.* **103**:485.

Ray AC, Dwyer JN, Fambro GW, Reagor JC (1978) Clinical signs and chemical confirmation of 4-aminopyridine poisoning in horses. *Am. J. Vet. Res.* **39**:329-331.

Schafer EW, Brunton RD, Lockyer NF (1974) Secondary hazards to animals feeding on red-winged blackbirds killed with 4-aminopyridine baits. *J. Wildl. Management* **38**:424-426.

Alphanaphthylthiourea (ANTU)

Sources:

- rodenticide (superseded)
- used as sausage or bread mash containing 2% ANTU

Toxicity:

- effective only in the brown rat (*Rattus norvegicus*); LD_{50} (domestic rats) = 2.5-6.25 mg/kg (Dieke & Richter 1946)
- wide species difference in toxicity: single oral lethal doses =
  - dog 10-40 mg/kg
  - pig 20-50 mg/kg
  - horse 30-80 mg/kg
  - cat 75-100 mg/kg
  - fowl 2500-5000 mg/kg (Kotz & Bubien 1962)
- ruminants resistant: doses >50 mg/kg given without effect
- dogs:
  - increase in susceptibility at or just after puberty (Jones *et al.* 1949) with single oral lethal dose for 5-10 month old dogs = 85-100 mg/kg; similar effect in rats (Dieke & Richter 1946)
  - ANTU has central & local emetic effect in dogs; if stomach partly full when ANTU ingested, gastric irritation prevented and dose retained longer, better absorbed and more likely to cause death (Jones *et al.* 1949)
- toxicity to rats increases with increasing(!) particle size (50-55 or 100-110 μm diameter > 5 μm)

Mode of action: causes greatly increased permeability of lung capillaries

Conditions of poisoning: - access to baits

Clinical signs: (Jones *et al.* 1949)

- indefinite: in dogs, respiratory distress ± gastric irritation
- death in 6-48 hr

Pathology: (Jones *et al.* 1949; Lopes 1967) (rats – Vivet *et al.* 1983)

- pulmonary oedema
- hydrothorax
- hydropericardium
- catarrhal gastroenteritis
- severe renal hyperaemia

Diagnosis:

- access history + pathology
- assay of stomach contents/tissues only useful within 24 hr of ingestion of large doses

Therapy:

- no satisfactory treatment
- emetics (apomorphine) or gastric lavage, but not useful after lung pathology established (Jones *et al.* 1949)
- suggestions (efficacy unknown) have included silicone aerosols to prevent foaming in bronchioles (Curry & Nickerson 1952) and sulphydral group donors (particularly N-amylmercaptan) (Guilhon 1953)

References:

Hu178, VM8/1519
Curry CF, Nickerson M (1952) *J. Pharmac.* **106**:Abstract, 379.
Dieke SH, Richter CP (1946) *Proc. Soc. Exp. Biol. Med.* **62**:22.
Guilhon J (1953) *Proc. XVth Int. Vet. Congr., Pt 1* **1**:473.
Jones LM, Smith DA, Smith HA (1949) *Am. J. Vet. Res.* **10**:160.
Kotz J, Bubien Z (1962) *Weterynaria (Wroclaw)* **118**:69.
Lopes AC (1967) *Pesq. Agropec. Bras.* **2**:287-291.
Vivet P, Brun-Pascaud M, Mansour H, Pocidalo JJ (1983) *Br. J. Exp. Path.* **64**:361-366.

Thallium

Chemical structure: the element thallium (Tl), a metal

Sources:

Previously used as a rodenticide (thallous sulphate 0.25% or greater). Withdrawn from sale in Australia in 1993 (Lucas & Baker 1999). Rare cases of intoxication continue to occur sporadically in Australia (Lucas & Baker 1999)

Toxicity:

- dogs, cats
- single oral toxic dose thallous sulphate = 10-20 mg/kg
- thallium mimics potassium in biological systems
- the most toxic cumulative cation (heavy metal)
- mechanism(s) of toxicity not understood (general cellular poison)

Conditions of poisoning:

- direct ingestion of baits
- ingestion of poisoned rodents

Clinical signs:

Acute → **vomiting, colic, diarrhoea**, dyspnoea in 2 days, death in 7 days

Subacute (more typical syndrome) → vomiting, paresis, **dermatitis, hair loss** (begins at corners of mouth & eyes → muzzle & head, axillae, flanks, ventrum, perineum, limbs, foot pads), ulcerative **stomatitis** in 3-7 days → **hyperaesthesia, ataxia** → tremors, weakness, emaciation, coma, death in 10-14 days

Chronic → **alopecia** (marked in dogs, less so in cats but fur readily plucked)

Pathology:

Acute

- severe haemorrhagic **gastroenteritis**
- bronchitis, necrotising pneumonia
- cardiac & skeletal muscle focal degeneration/necrosis
- nephrosis
- mild centrilobular hepatic necrosis, fatty change

Subacute

- skin hyperaemia
- **hyper-, para- & dys-keratosis** + secondary infection + hair loss
- **brain oedema**, neurone chromatolysis ± lymphocytic cuffs in basal ganglia, pons & temporal cortex
- peripheral nerve degeneration
- lung consolidation, oedema, bronchitis

Diagnosis:

- signs & pathology indicative
- assay urine, faeces, kidney, liver

Therapy:

- if diagnosis is achieved early in the course of intoxication, give oral Prussian blue (ferric ferrocyanide; potassium ferric hexacyanoferrate) → ↑ thallium excretion in faeces by intercepting the enterohepatic circulation
- Prussian blue with small crystal size is a better antidote (Kravzov *et al.* 1993)
- standard anti-heavy metal therapies are ineffective; e.g. 2,3-dimercapto-1-propanesulfonic acid is ineffective compared with Prussian blue (Mulkey & Oehme 2000)
- symptomatic measures useful (blood transfusions, fluids, antibiotics, vitamins)
- infusion of 35 mmol/L KCl solution (+ sodium bicarbonate to counter acidosis) → ↑ thallium excretion in urine

References:

Os207, Se225, Humphreys 73

Kravzov J, Rios C, Altagracia M, Monroy-Noyola A, Lopez F (1993) Relationship between physicochemical properties of Prussian blue and its efficacy as antidote against thallium poisoning. *J. Appl. Toxicol.* **13**:213-216.

Lucas J, Baker R (1999) Dermatological lesions in four cats with thallium toxicosis. *Proc. Aust. Soc. Vet. Pathol. Conf.* p.31.

Mulkey JP, Oehme FW (1993) A review of thallium toxicity. *Vet. Human Toxicol.* **35**:445-453.

Mulkey JP, Oehme FW (2000) Are 2,3-dimercapto-1-propanesulfonic acid or Prussian blue beneficial in acute thallotoxicosis in rats? *Vet. Human Toxicol.* **42**:325-329.

INSECTICIDES & ACARICIDES

☑ Organophosphorus insecticides/acaricides (acute toxicity)

Core data

Common sources: insecticides, acaricides
Animals affected: mammals, birds
Mode of action:

- binds acetylcholinesterase (AChE) → inhibition → accumulation of acetylcholine (ACh) in neuroeffector junctions → overstimulation of parasympathetic nervous system (muscarinic, nicotinic or CNS effects of ACh)
- "aging" of bound AChE → bond irreversible by oxime antidote

Poisoning circumstances: overdose (accidental or malicious)
Main effects:

- Muscarinic: pupil constriction, excess salivation, diarrhoea, bronchoconstriction
- Nicotinic: muscle fasciculation, tetany
- CNS: convulsions, coma
- subclinical pancreatitis

Diagnosis:

- ↓↓ blood AChE/plasma pseudocholinesterase
- ↓↓ brain cholinesterase

Therapy:

- atropine + oximes (e.g. 2-PAM) reverses muscarinic effects
- prevent further absorption (wash skin, emetic, adsorbent)

Chemical structure:

OPs = organic triesters of phosphoric, thiophosphoric or dithiophosphoric acids
2 chemical types: those requiring biotransformation for action & those not requiring it (earlier compounds)

Examples of organophosphorus insecticides:

Chlorpyrifos (Dursban®)
Coumaphos (Asuntol®)
Diazinon
Dichlorvos
Dimethoate
Ethion
Famphur
Fenthion
Isofenphos
Malathion
Parathion
Phosmet
Trichlorfon
Chlorfenvinphos [agricultural uses banned and veterinary uses restricted in Australia (Anon 2001)]

Sources:

formulations for use on/in animals: dips, sprays, pour-on skin applications, powders, drenches, flea-collars/medallions
formulations for use on plants
several used for deliberate poisoning of feral animals (pigs), pets or wildlife (birds), e.g. fenthion (McKenzie *et al.* 1996), fenthion-ethyl (Luci-jet®), mevinphos (Phosdrin®) (Brady 1997)

Toxicity/Mode of action:

- young animals more susceptible than adults (liver & ruminal microbial OP metabolism → detoxification)

- OPs phosphorylate acetylcholine esterase (AChE) molecules, binding virtually permanently → inhibition
- OP-phosphorylated AChE undergoes "aging" in a few hours → even more tightly bound & not susceptible to release (hydrolysis) by oxime antidotes
- AChE inhibition → accumulation of acetylcholine (ACh) in synapses, neuromuscular or other neuroeffector junctions → overstimulation of parasympathetic nervous system (muscarinic, nicotinic or CNS effects of ACh)
- return of optimal AChE function in tissue depends on slow replacement (20-30 days) of phosphorylated AChE molecules by new molecules
- most OPs rapidly metabolised & excreted, so → no chronic effects from OP accumulation (cf. organochlorine compounds)
- repeated small doses may → cumulative AChE inhibition (because difficult to reverse) → toxicity when critical point exceeded

Very complex relationship between enzymic metabolism & toxicity of OPs result in occasional toxicity from normally safe doses

- compounds needing biotransformation are less predictable in action because they depend on the state of biotransformation mechanisms (insect/tick, host)
- detoxication may be glutathione dependent: ↓ tissue glutathione → ↑ toxicity
- major detoxication route of some OPs, aliesterases, may be competitively inhibited by variety of compounds (including isomers of OPs such as malathion); these inhibitors may develop spontaneously in storage → unexpected ↑ toxicity; applies to OP formulations past their product expiry date (Taylor 1998)

Conditions of poisoning:

- excessive skin application
- accidental ingestion or overdose
- presumed malicious poisoning, e.g. native birds (McKenzie *et al.* 1996, Ladds & Gabor 2000)
- application of OPs contaminated by water and/or past their product expiry date (Taylor 1998) - break-down products of diazinon in water include tetraethyl monothiopyrophosphate and like compounds which are highly toxic to animals causing acetylcholinesterase inhibition. TEPP (tetraethyl pyrophosphate) has been used as an insecticide but is not used on animals because of very high toxicity. Any discolouration or cloudiness of OP concentrates should be interpreted as evidence of possible water contamination or breakdown to more toxic compounds.
- formulation error with inclusion of unintended highly toxic OP in cattle pour-on formulation (rare) (Braselton *et al.* 2000)

Clinical signs: (**bold** = commonly reported signs)

Muscarinic effects (receptors in smooth muscles, heart, exocrine glands)

- **constricted pupils (miosis)**
- bronchoconstriction, excess bronchial secretions → dyspnoea
- **excessive salivation**
- lacrimation
- ↑ sweating (where possible)
- ↑ GI tone & peristalsis → **diarrhoea**, vomiting, abdominal pain
- involuntary urination
- bradycardia

Nicotinic effects (receptors in skeletal muscles, autonomic ganglia)

- mild weakness, easily tired
- **involuntary twitching, fasciculations**, cramps
- generalised tetany → stiff gait, tendency to fall
- tachycardia
- ↑ blood pressure

CNS effects

- restlessness
- tremor
- generalised weakness, ataxia
- convulsions
- depression of respiratory & circulatory centres, coma

Death is due to respiratory failure (combined effects above), usually within 24 hr of onset

Sudden death (within 1 hr of exposure) can occur with highly toxic breakdown products of diazinon (see above) or with poisoning by large doses of OPs

Subclinical pancreatitis; elevated serum amylase & lipase seen in dogs & humans (Dalefield *et al.* 1999)

Pathology:

- non-specific changes (pulmonary oedema, ↑ fluid in GI tract)
- pancreatitis in dogs & humans (Dalefield *et al.* 1999); elevated serum amylase & lipase

Diagnosis:

- exposure history, clinical syndrome
- ↓↓ blood AChE / plasma pseudocholinesterase activity (former more reliable) to < 25% of normal
  - N.B. OP exposure can → low AChE activity without clinical signs (e.g. flea collars)
  - whole blood AChE will vary with PCV – possible confusion in anaemic patients

  Cats: Cholinesterases are present in both erythrocytes and plasma in different proportions depending on animal species. In cats, most activity is in the plasma in contrast to most other species where activity is mainly in erythrocytes. In most species, assay of whole blood cholinesterase is considerably less sensitive than assay of pseudocholinesterase in plasma, making the former the better indicator of serious (toxic) exposure to OPs. Plasma pseudocholinesterase, being more sensitive, can be seriously depressed or extinguished by non-toxic exposures to OPs such as the therapeutic use of flea collars/medallions. So, whole blood cholinesterase assays which are meaningful as indicators of toxicity in most species are much less so in cats. (Beasley *et al.* 1997)

- monitor serum amylase and lipase in dogs
- at necropsy
  - assay of stomach contents for OP
  - ↓ AChE in caudate nucleus (in floor of lateral ventricles of brain) or cerebral cortex (samples should *not* be fixed)

  Mount & Oehme (1981) measured normal acetylcholinesterase activities in various parts of the brains of normal cattle, sheep and pigs using a modified Ellman method:

Animal species	Brain portion	Cholinesterase activity* (mean ± SD) [range]
Cattle [n = 21]	Cerebrum	3.01 ± 0.14 [1.91 – 4.28]
	Brain stem	3.42 ± 0.21 [2.48 – 7.00]
	Cerebellum	2.36 ± 0.06 [1.69 – 2.92]
	"Whole brain" [= mean of cerebrum, brain stem and cerebellum values for each animal averaged over the number of animals examined]	2.93 ± 0.09 [2.40 – 4.00]
Sheep [n = 13]	Cerebrum	3.32 ± 0.16 [2.48 – 4.50]
	Brain stem	3.93 ± 0.13 [2.92 – 4.50]
	Cerebellum	6.77 ± 0.64 [1.98 – 9.34]
	"Whole brain"	4.67 ±0.21 [2.91 – 5.66]
Pigs [n = 15]	Cerebrum	3.88 ± 0.27 [1.58 – 5.96]
	Brain stem	4.48 ± 0.18 [3.38 – 6.52]
	Cerebellum	2.89 ± 0.09 [2.25 – 3.49]
	"Whole brain"	3.75 ± 0.11 [2.63 – 4.36]

* μmoles acetylthiocholine hydrolysed/min/g brain tissue (wet weight) at 25^{o}C

Mount and Oehme (1981) reported cholinesterase values were stable for several days at 25°C, 4°C and –22°C and that in poisoned animals, values declined by 50-80% below normal.

Normal cerebral cholinesterase activities in a range of mammals and birds in Canada have recently been reported by Blakely & Yole (2002) using a modified Ellman method:

Animal species [Sample numbers assayed]	Cholinesterase activity* (mean ± SD)
Cattle [n = 33]	2.47 ± 0.76
Pigs [n = 8]	2.72 ± 1.24
Horses [n = 3]	2.31 ± 0.57
Sheep [n = 4]	4.57 ± 2.63
Dog [n = 13]	3.21 ± 1.60
Cat [n = 8]	7.30 ± 2.51
Goat [n = 1]	2.09
Fowl [n = 2]	12.72 ± 2.45
Duck [n = 1]	9.4

* μmoles acetylthiocholine hydrolysed/min/g cerebrum (wet weight) at 25°C

Variations in brain cholinesterase activity between species can be large, making interpretation without knowing normal values for particular species difficult or impossible. In general, birds appear to have greater activity than mammals.

Harlin *et al.* (1989) reported values for cholinesterase activity in cattle retina as a possibly more conveniently-sampled alternative to brain. Retinal cholinesterase in 51 normal cattle eyes were 19.57 ± 3.13 μmoles acetylthiocholine hydrolysed/min/g. Retinal values in 10 cattle poisoned by terbufos were 5.01 ± 3.51 μmoles acetylthiocholine hydrolysed/min/g, representing a mean inhibition of 76% (range 49-96%).

Therapy:

Specific therapy with atropine & oxime

- **atropine** [suggested 1mg/kg (half IV, half SC), but in practice the dose can be given to effect by monitoring pupillary dilation] → blocks excess ACh effects by competitively blocking muscarinic receptors → immediate relief from acute *muscarinic* signs; OP-poisoned animals are tolerant of doses of atropine larger than normal therapeutic ones
- then **oxime** e.g. 2-PAM [20 mg/kg (slow IV)], pralidoxime iodide → hydrolyses phosphorylated AChE → rapid return to normal if toxicity < few hours old (phosphorylated OP not "aged") (oximes without prior atropine → only minimal effects)

Prevent further absorption of toxin as appropriate

- wash OP from skin
- induce vomiting, dose with activated charcoal

Control convulsions (if present): give anticonvulsants; use a benzodiazepine drug first, then a barbiturate if convulsions are not effectively controlled

vs. Pancreatitis in dogs: chlorpromazine? (Dalefield *et al.* 1999)

Birds: larger doses of atropine (25-50 mg/kg) and 2-PAM (50-100 mg/kg) are recommended, but there may be variation in response depending on the OP/carbamate involved (Shlosberg *et al.* 1997)

References:

Review literature

Os231, Se262, VM8/1514

Meerdink GL (1989) Organophosphorus and carbamate insecticide poisoning in large animals. *Vet. Clinics N. Am.: Food Anim. Pract.* **5** (2):375-389.

Mosha RD (1993) The toxicology of organophosphorus insecticides: a review. *Vet. Bull.* **63** (11):1039-1050.

Sanchez-Hernandez JC (2001) Wildlife exposure to organophosphorus insecticides. *Rev. Environ. Contam. Toxicol.* **172**:21-63.

General literature

Anon. (2001) Chlorfenvinphos chemicals: NRA crackdown. *Aust. Vet. J.* **79**:513.

Beasley VR, Dorman DC, Fikes JD, Diana SG, Woshner V (1997) *A Systems-affected Approach to Veterinary Toxicology.* University of Illinois, Urbana-Champlain p.297-303.

Blakely BR, Yole MJ (2002) Species differences in normal brain cholinesterase activities of animals (*sic*) and birds. *Vet. Human Toxicol.* **44**:129-132.

Brady J (1997) Warning – mevinphos. *Vic. Vet.* Winter Issue, p.27.

Braselton WE, Johnson JL, Carlson MP, Schneider NR (2000) Gas chromatography/mass spectrometry identification and quantification of isazophos in a famphur pour-on and in bovine tissues after a toxic exposure. *J. Vet. Diagn. Invest.* **12**:15-20.

Dalefield RR, Fickbohm B, Oehme FW (1999) Possible therapeutic effect of chlorpromazine on canine pancreatitis resulting from organophosphate toxicosis. *N.Z. Vet. J.* **47**:75-76.

Dobson KJ (1977) Trichlorfon toxicity in pigs. *Aust. Vet. J.* **53**:115-117.

Fairbrother A, Marden BT, Bennett JK, Hooper MJ (1991) Methods used in determination of cholinesterase activity. Chapter 3 in Mineau P (ed.) *Cholinesterase-inhibiting insecticides. Their impact on wildlife and the environment.* (Chemicals in Agriculture Volume 2). Elsevier, Amsterdam. pp.35-71.

Harlin KS, Hamdy S, Beasley VR (1989) Preliminary studies with bovine retina cholinesterase determination in organophosphorus insecticide poisoning. *J. Vet. Diagn. Invest.* **1**:356-358.

Ladds P, Gabor L (2000) Cases of general interest – wildlife. *Vet. Path. Report (ASVP Newsletter)* No.55 p.18. [Tasmania, mortality in gulls; 7.1 mg mevinphos/kg gut contents]

McKenzie RA, Lanham AEL, Taylor JD, Gibson JA, Pierce RJ (1996) Fenthion poisoning of native birds in southern Queensland. *Aust. Vet. J.* **74**:321-323.

Mount ME, Oehme FW (1981) Brain cholinesterase activity in healthy cattle, swine, and sheep and in cattle and sheep exposed to cholinesterase-inhibiting insecticides. *Am. J. Vet. Res.* **42**:1345-1350.

Seawright AA, Costigan P (1977) Some toxicity aspects of dichlorvos flea collars in cats. *Aust. Vet. J.* **53**:509-514.

Shlosberg A, Bellaiche M, Hanji V, Ershov E (1997) New treatment regimens in organophosphate (diazinon) and carbamate (methomyl) insecticide-induced toxicosis in fowl. *Vet. Human Toxicol.* **39**:347-350.

Taylor LF (1998) Cattle deaths prompt fly control warning. *DPI News Release.* 23 March 1998 [aged diazinon poisoned cattle in 2 incidents]

Chronic exposure of humans to OPs has been associated with concerns of toxicity including so-called chronic organophosphate-induced neuropsychiatric disorder (COPIND). A chronic neurotoxicity has been experimentally induced in hens with fenthion dermal application (Tuler & Bowen 1999)

References:

Jamal GA (1995) Long term neurotoxic effects of organophosphate compounds. *Adverse drug React. Toxicol. Rev.* **14**:85-99.

Jamal GA (1997) Neurological syndromes of organophosphorus compounds. *Adverse Drug React. Toxicol. Rev.* **16**:133-170.

Tuler SM, Bowen JM (1999) Chronic fenthion toxicity in laying hens. *Vet. Human Toxicol.* **41**:302-307.

Organophosphorus compounds (delayed neurotoxicity)

Syndrome name(s): organophosphorus-induced delayed neuropathy (OPIDN)

Sources:

- triaryl phosphates (including triorthocresyl phosphate - TOCP) - additives to **lubricating & hydraulic oils** for use under high temperatures & pressures (cattle)
  - hepatic metabolism → toxic cyclic derivative of TOCP
- haloxon **anthelmintic** (sheep, pigs, foals)
- trichlorophon **insecticide** vs. *Hypoderma bovis* (cattle, Canada)
- isophenphos (restricted use as **seed dressing**, France) → pigs, UK

Toxicity:

- some OPs may phosphorylate (inhibit) esters other than AChE, including a nerve cell esterase ("neurotoxic esterase", neuropathy target esterase or NTE). 70-80% inhibition → sensory & motor myelinopathy & peripheral neuropathy *without* → AChE inhibition
- all species affected; fowls > mammals (cattle, pigs, humans)
- susceptibility adult > young
- 500 mg triaryl phosphate/kg → paralysis in mature cow in 26 days

Conditions of poisoning:

- single or multiple ingestion/dose/dermal application of sources
- feed storage in containers previously used for oils (cattle)
- waste oil used to treat dermatitis (cattle)
- overdose (x 3-6 therapeutic) of haloxon in sheep with low plasma aromatic esterase activity
- normal haloxon dose in some pigs, Arabian foals
- seed wheat dressed with isophenphos used as pig feed (UK)

Clinical signs:

- onset 2-25days after dosing/ingestion; course *ca.*3 weeks before slow regeneration (usually incomplete)
- **posterior ataxia** (proprioception deficit)
- → posterior paralysis (severe cases also involve forelimbs)
- ± urinary incontinence
- Arabian foals → acute laryngeal paralysis
- pigs → posterior ataxia + dyspnoea/voice alteration (recurrent laryngeal nerve degeneration)

Pathology:
- axonopathy ("dying-back") presenting as Wallerian degeneration of spinal cord white matter
- pigs (+ Arabian foals?) → + recurrent laryngeal nerve degeneration

Diagnosis:
- exposure history, clinical syndrome, pathology
- AChE activity usually not ↓

Therapy: nil

References:

Se264,274, VM8/1514, VM8/1530
Barrett DS, Oehme FW, Kruckenberg SM (1985) A review of organophosphorus ester-induced delayed neurotoxicity. *Vet. Human Toxicol.* **27**:22-37.

Carbamates

Core data

Common sources:
- insecticides, acaricides
- molluscicide (methiocarb)

Animals affected: all species

Mode of action:
- inhibits acetylcholinesterase
- but no irreversible binding cf. OP

Poisoning circumstances:
- overdose, accidental ingestion
- snail baits in home gardens (dogs, cats); spring-summer, weekends

Main effects: as for OP

Diagnosis: as for OP but reduced cholinesterase activity is very transient, blue dye in molluscicide pellets

Therapy: as for OP (oximes contraindicated in carbaryl toxicity)

Sources:
- physostigmine (a carbamate ester) from *Physostigma venenosum* (Calbar bean), West Africa
- **insecticides & acaricides** (including carbaryl [Sevin®], aldicarb, propoxur [Baygon®], promacyl) → livestock, dogs, cats
- **molluscicide** (methiocarb = Baysol Snail and Slug Killer®) → dogs, cats
- some herbicides

Toxicity:
- young animals more susceptible than adults (less liver detoxication capacity)
- **anticholinesterase** action
- directly toxic without hepatic activation (cf. OPs)
- carbamylated AChE readily hydrolysed → active enzyme (cf. OPs → "permanent" inhibition), thus → ↑↑ margin between dose causing poisoning and dose causing death → recovery within hours
- rapidly metabolised in liver (microsomal enzymes) → clearance from body in 2-3 days
  - some metabolites as or more toxic than parent
  - microsomal enzyme inhibitors may → ↑ toxicity
- most break down in sunlight → herbicide concentrations ↓↓ after sprayed on pasture

Conditions of poisoning:
- accidental or careless treatment at abnormally-high dose rates
- molluscicide in **home gardens** (dogs, cats)

Clinical signs: as for OPs above

Pathology: as for OPs above
Diagnosis:

- as for OPs above
- **N.B.** the carbamate-cholinesterase bond is labile and often spontaneously dissociates before or during laboratory assay resulting in normal cholinesterase values being detected; so, interpret normal laboratory cholinesterase determination results with caution in suspected carbamate toxicity cases
- blue dye in stomach contents (vomitus), faeces from methiocarb molluscicide pellets

Therapy:

- atropine and oximes as for OPs above
- oximes contra-indicated **only** in carbaryl poisoning, but should do no serious harm (Dawson 1994) - may exacerbate toxicity [oximes bind to ionic site of AChE, not to carbamyl moiety, thus → temporary AChE inactivation]

Birds: larger doses of atropine (25-50 mg/kg) and 2-PAM (50-100 mg/kg) are recommended, but there may be variation in response depending on the OP/carbamate involved (Shlosberg *et al.* 1997)

Prevention & control: see notes on metaldehyde for information on molluscicide pellet safety
References:

Os231, Se280, VM8/1514, VM8/1520-methiocarb
Dawson RM (1994) *Vet Rec* **134**:687
Frazier K, Hullinger G, Hines M, Liggett A, Sangster L (1999) 162 cases of aldicarb intoxication in Georgia domestic animals from 1988-1998. *Vet. Human Toxicol.* **41**:233-235.
Shlosberg A, Bellaiche M, Hanji V, Ershov E (1997) New treatment regimens in organophosphate (diazinon) and carbamate (methomyl) insecticide-induced toxicosis in fowl. *Vet. Human Toxicol.* **39**:347-350.

☑ *Chlorinated hydrocarbon (organochlorine) insecticides/acaricides*

Core data

Common sources: withdrawn insecticides/acaricides
Reasons for withdrawal from use:

- persistence in tissue (uncertainty of chronic effects on humans)
- bioaccumulation & ecotoxicity
- acquired resistance in target insect/tick species

Animals affected:

- all species
- bioaccumulation → raptors, pelicans

Mode of action:

- diffuse stimulants & depressants of CNS
- environmental persistence → bioaccumulation (highly lipid soluble)

Poisoning circumstances:

- overdose or accidental ingestion (historical)
- harmlessly (?) accumulate in adipose issue; ↓ nutritional plane → redistribution to CNS → toxicity

Main effects:

- hypersensitivity, muscle fasciculation, abnormal behaviour, seizures, pyrexia
- bioaccumulation (birds):
  - reproductive anomalies
  - ↑egg-shell fragility
  - hatchling toxicity (yolk accumulation)

Diagnosis: assay brain, suspected source
Therapy:

- remove source
- control seizures
- reduce pyrexia

These compounds were widely used during the period between the 1940s and 1960s. They were effective insecticides and acaricides, not unduly toxic to the host species. They were progressively **withdrawn from most uses**, mainly because of

- **persistence** (leaving residues in animal and plant tissues), and the **uncertainty of subsequent chronic effects in humans**, such as neoplasia
- **bioaccumulation & ecotoxicity**
- **acquired resistance** in the target insect or tick species

and this means that their current uses are very restricted, usually to particular crop pests for which no effective alternatives are available.

Sources:

Insecticides and acaricides

- chlorinated ethane derivatives [Se255]: DDT, DDE, methoxychlor (generally low toxicity)
- cyclodienes [Se257]: aldrin, dieldrin, endrin, chlordane, endosulfan, heptachlor, toxaphene (toxic → severe convulsions of sudden onset)
- hexachlorocyclohexanes [Se260]: gamma-BHC or lindane (Gammexane®)

Toxicity:

- all animal species affected; species susceptibility varies between compounds
- highly lipid soluble, non-water soluble → applied to animal skin as emulsions, poorly absorbed

Mode of action:

- diffuse stimulants & depressants of CNS → neuromuscular signs
- act on motor & sensory nerve fibres and on motor cortex → depolarisation → generalised fine muscle tremors → persistent coarse body tremor
- basis of CNS depression, convulsions is unclear

Conditions of poisoning:

- excessive skin application
- ingestion of compounds directly or as feed contaminants
- absorbed compounds → **sequestration in adipose tissue** (e.g. platypuses [Munday *et al.* 1998, 2002], pelicans [McKenzie *et al.* 1982])
  - animals in good condition or on rising nutritional plane → ↓ susceptibility to poisoning
  - falling nutritional plane → redistribution to CNS → acute toxicity (Australian pelicans, Brisbane River 1977-9) (McKenzie *et al.* 1982) *or* redistribution within the remaining adipose tissue resulting in greatly increased concentrations in this tissue without adverse effects on the animal (Munday *et al.* 2002)
- excretion in milk; may → poisoning of suckling young
- **bioaccumulation** → chronic effects in higher level consumers in food chain/web
  - enhanced hepatic microsomal mixed-function oxidase activity → altered rates of metabolism of steroid hormones → **reproductive anomalies**
  - interfere with energy-dependent Ca transport in egg-shell formation → ↑ **egg-shell fragility** → ↓ hatchings (raptors, brown pelicans)
  - yolk accumulation → **acute toxicity in hatchlings**

Clinical signs:

- onset minutes-hours-days after exposure
- signs may progressively increase in severity or have sudden severe onset
  - depression
  - **hypersensitivity** to external stimuli
  - **muscle fasciculation** of face and neck → intermittent limb spasms (tonic-clonic contractions)
  - **behavioural abnormalities**: apparent blindness, unexplained shying, abnormal posture
  - excessive salivation, continuous chewing
  - **seizures**, usually following disturbance
  - marked **terminal pyrexia** (CNS mediated & muscle spasms)
  - death in coma or after seizure

Pathology: non-specific changes

Diagnosis:

- assay brain, suspected source for suspected compounds
- large amounts of compounds in adipose tissue or liver (major storage sites) do *not alone* support a diagnosis

Therapy: - no specific therapy available

- **remove source**

-skin exposure: wash off remaining compound
- ingestion: induce vomiting, gastric lavage, then dose with activated charcoal (avoid oily purgatives that may promote absorption)
- **control seizures** (barbiturates, diazepam)
- modify pyrexia (physical cooling)

References:

Os237, Se251, VM8/1511
Main DC (1978) Endrin toxicity in cagebirds. *Aust. Vet. J.* **54**:198-199.
McKenzie RA, Freudigmann CL, Mawhinney H, Eaves LE, Green PE, Rees GJ (1982) Dieldrin poisoning and botulism in Australian pelicans (*Pelecanus conspicillatus*). *Aust. Vet. J.* **58**:148-152.
Munday BL, Stewart NJ, Södergren A (1998) Occurrence of polychlorinated biphenyls and organochlorine pesticides in platypuses (*Ornithorhynchus anatinus*) in Tasmania. *Aust. Vet. J.* **76**:129-130.
Munday BL, Stewart NJ, Södergren A (2002) Variations in residues of persistent organic pollutants in a platypus (*Ornithorhynchus anatinus*) at consecutive samplings. *Aust. Vet. J.* **80**:299-300.

Paradichlorobenzene (mothballs)

Organochlorine insecticide of relatively low toxicity.
Substituted for naphthalene in insect repellents (moth balls)
Metabolised to hepatotoxic phenol.
Clinical signs: vomiting (odour of mothballs), CNS stimulation including seizures, liver damage (rare)
Therapy: control seizures, monitor liver function, administer activated charcoal + saline cathartic
References: Gfeller & Messonnier 207

Chlorinated naphthalenes

Historically common in cattle in USA (chlorachneiform dermatosis)
Sources:
previously as wood preservatives, in lubricating oils, varnishes, ceramics, electrical insulators; solvents for contact insecticides
pentachloronaphthalene **very persistent** in treated timber
Toxicity:
cattle: single oral dose of 6 mg/kg → chronic illness & death
other species much less susceptible
routes of exposure: oral, respiratory, dermal
pathology **resembles avitaminosis A**; plasma & liver vitamin A concentrations fall
Conditions of poisoning (rare Australian & New Zealand cases):
environmental contamination with sump oil
feed contamination with wood preservatives
Clinical signs:
first: **excess lachrymation & salivation**
then: depression, anorexia, weight loss
skin dry, wrinkled & thickened ± **hair loss** (particularly anterior parts of animal)
± flattened, raised papillary proliferations on oral mucosa, tongue & hard palate
± terminal diarrhoea
Pathology:
hyperkeratosis of skin & hair follicles
papillary proliferations in mouth, oesophagus & forestomach mucosae
nodular proliferative lesions in gall bladder, bile duct & pancreatic duct mucosae
nephrosis + interstitial fibrosis
Diagnosis: history; pathology; feed/environment assay
Therapy: Nil; prognosis poor
Prevention & Control: No specific measures
References: Se245, VM8/1529

MOLLUSCICIDES

Metaldehyde

Core data

Common sources: molluscicide
Animals affected: dog, cat [farm livestock, poultry]
Mode of action:

- stomach hydrolysis → acetaldehyde → liver oxidation. If rate of absorption exceeds rate of oxidation → toxicity.
- acetaldehyde crosses blood-brain barrier → ↓ γ-aminobutyric acid (GABA), ↑ monoamine oxidase activity → ? tremors/convulsions

Poisoning circumstances:

- ingestion from gardens and storage areas
- spring-summer, weekends

Main effects:

- hyperaesthesia, muscle tremors
- convulsions (not induced by external stimuli)
- nystagmus (cats)
- pyrexia

Diagnosis:

- syndrome, access
- green dye in pellets
- assay stomach contents

Therapy:

- control convulsions
- emesis/gastric lavage
- activated charcoal,

Prevention:

- bittering & repellent agents in pellets
- Fe-EDTA molluscicide pellets much less toxic to pets

One of the most common poisonings of dogs, cats [82% of poisonings seen in Melbourne veterinary practices, August 1983-February 1984 (Studdert 1985)].

Chemical structure:
Cyclic tetramer of acetaldehyde
Sources:
- molluscicides used in home gardens against slugs & snails [see also carbamates (methiocarb) under nervous syndromes]
- used in bran-based pellets
- Defender® Pellets Snail & Slug Killer, Yates Blitzem® Snail & Slug Pellets - both 15 g/kg metaldehyde in 500 g packs

Toxicity:
- **dogs, cats**, horses, cattle, sheep, poultry, children, parrots (Reece *et al.* 1985)
- *ca.* 100 mg/kg minimum oral lethal to dogs [for 10-20 kg dogs = 63-125 g pellets] (Booze & Oehme 1985) LD_{50} = 60-500 mg/kg
- *ca.* 200 mg/kg lethal to cattle
- rapid hydrolysis in stomach → acetaldehyde → rapid absorption → liver oxidation. If rate of absorption exceeds rate of oxidation → toxicity.
- acetaldehyde easily crosses blood-brain barrier → ↓ γ-aminobutyric acid (GABA) [inhibitory neurotransmitter], ↑ monoamine oxidase activity → ? tremors/convulsions

Conditions of poisoning:
- pellets palatable & attractive to dogs (& cats to a lesser extent) *which actively seek them for consumption. Being poisoned will not deter this behaviour.*
- access to gardens or storage areas containing bait pellets (carnivores **&** herbivores)

- poisoning in pets occurs soon after pellets applied to gardens → clusters of cases over weekends (highest concentration of gardening activity) & during spring-summer

Clinical signs:

- onset: a few minutes to several hours after ingestion
- anxiety, depression
- salivation, vomiting
- incoordination, hyperaesthesia, **muscle tremors**, prostration with limbs extended in continuous spasms, **convulsions**, opisthotonus
- convulsions, spasms **not** provoked by external stimuli (cf. strychnine)
- **nystagmus** (cats)
- tachycardia, tachypnoea, dyspnoea
- cyanosis, coma, **pyrexia**
- acidosis
- ± diarrhoea, colic
- ± blindness (temporary)
- ± signs of liver damage in recovered cases

Pathology:

- non-specific (GI tract mucosal petechiae, lung congestion)
- ± odour of acetaldehyde (formaldehyde-like) in stomach contents
- ± green dye from pellets in stomach contents
- ± hepatocellular degeneration

Diagnosis:

- **access history**, clinical syndrome
- **green dye** in vomitus, faeces or saliva (cf. blue dye in methiocarb molluscicide pellets)
- assay vomitus/lavage fluid/stomach contents for metaldehyde

Therapy:

Dog, cat

- control convulsions (facilitates gastric lavage)

Muscle relaxation therapies in metaldehyde poisoning of dogs
diazepam (Pamlin®, Valium®): 2.5-20.0 mg IV as needed (2-5 mg/kg)
or methocarbamol (Robaxin®): 150 mg/kg IV or Xylazine: 1.1 mg/kg IV
OR barbiturates to effect (with caution - compete with acetaldehyde for hepatic detoxication enzyme systems)

- induce vomiting (if patient conscious)
- gastric lavage with milk, lime water or sodium bicarbonate solution, & then → activated charcoal
- intubate trachea, → O_2 + artificial respiration in cases of respiratory failure
- → IV fluids for acidosis correction & rehydration (Ringer's lactate or normal saline with bicarbonate supplementation)

Cattle

- control convulsions/tremors (xylazine, barbiturates)
- → activated charcoal + cathartic + fluids

Prevention & Control:

- Defender Petrepel® & Yates Blitzem® pellets contain a bittering agent (Bitrex® = denatonium benzoate; 250 ppm) to deter ingestion by dogs & children
- Defender Petrepel® pellets contain a repellent agent (Alamask®; 1%) to deter ingestion by dogs & cats
- instructions on containers advise to scatter, not heap, pellets, **but** dogs *will* seek out and eat enough individual pellets to be poisoned, in some cases despite this and *despite bittering or repellent agents in pellets.*
- physical protection of pellets such that molluscs have access, but dogs do not. There have been several appliances designed for this purpose. One (Tonelli 2002) is a short length of 25mm polypipe with a series of holes bored in it to allow snail access, plugged at both

ends with corks and firmly pegged to the ground with a piece of bent wire at each end; place pellets in the pipe; remove end corks and flush out dead molluscs when required.

- molluscicide pellets containing Fe-EDTA are much less toxic to mammals (see notes on iron)
- other less toxic methods of snail/slug control could be employed: Snail Stop® (a copper silicate compound for spraying on soil and plants)

References:

Os250, Se333, VM8/1520

Booze TF, Oehme FW (1985) Metaldehyde toxicity: a review. *Vet. Hum. Toxicol.* **27**:11-19.

Miller RM (1972) Metaldehyde poisoning in horses (two case reports). *Vet. Med./ Small Anim. Clin.* October:1141.

Reece RL, Scott PC, Forsyth WM, Gould JA, Barr DA (1985) Toxicity episodes involving agricultural chemicals and other substances in birds in Victoria, Australia. *Vet. Rec.* **117**:525-527. [king parrots]

Stubbings DP, Edginton AB, Lyon DG, Spence JB, Clark MH (1976) Three cases of metaldehyde poisoning in cattle. *Vet. Rec.* **98**:356-357.

Studdert VP (1985) Epidemiological features of snail and slug bait poisoning in dogs and cats *Aust. Vet. J.* **62**:269-271.

Tonelli P (2002) Snail solution. "Pete's Mailbag", *Gardening Australia Magazine.* February Issue, p.21.

Carbamates

See notes under insecticides

Iron

See notes under metals

HERBICIDES

Dipyridyl (bipyridyl) herbicides

Features of dipyridyl herbicides

- highly active on plants at low application rates
- rapid action on wide range of plants
- **soil contact → rapid inactivation** by absorption into colloidal clay particles
- rapid photodecomposition → **no residues on plants**
- useful in zero-till agriculture (spray one day, plant the next without ploughing)
- animals may safely eat treated plants
- all → GIT damage
- *only paraquat → lung damage*

Paraquat (a dipyridyl herbicide)

Core data

Common sources: herbicide
Animals affected: all mammals
Mode of action: destroys alveolar lining cells through free radicals
Poisoning circumstances: ingestion of concentrated compound
Main effects:

- GI mucosal erosions
- renal damage
- then irreversible pulmonary fibrosis

Diagnosis: access + histopathology + tissue assay
Therapy: early detoxication measures or nil
Prevention:

- safe storage and clear labelling of concentrate
- prevent access to treated plants for at least 24 hr

Chemical structure:

A dipyridyl (bipyridyl) herbicide

Sources: paraquat herbicide formulations (e.g. Gramoxone® ICI)

Toxicity:

- **numerous human deaths** from accidental or deliberate ingestion
- rare in domestic animals; cases recorded in Australia include Johnson & Huxtable (1976) [cats & dog], Pahl (1997) [cat]
- LD_{50} (acute oral) mg/kg: cats 35, cattle 50, pigs 75, sheep 100, poultry 200
- sheep lethal intraruminal dose is > 45 mg/kg, with death in 2-5 days (Smalley & Radeleff 1970)
- pig oral LD_{50} is 50 mg/kg (Smalley & Radeleff 1970)
- minor absorption of ingested dose (*ca.* 5-10%)
- absorbed paraquat is actively taken up by alveolar cells in **lungs**, and actively secreted by **kidney** tubular epithelium. Direct toxic damage to the renal tubules by paraquat reduces this excretion capacity and prolongs exposure of other organs to toxic concentrations (Webb 1983).

Mode of action:

- paraquat accepts electrons from various electron transport chains → stable free radical that reacts with O_2 → excessive production of toxic superoxide anions (O_2^-) by redox cycling and then hydrogen peroxide by superoxide dismutase → membrane disruption, fibrosis [see notes on Cellular Mechanisms of Toxicity]. Similar effects from O_2 toxicity in human infants.
- alveolar lining epithelium (types I & II pneumocytes) destroyed → ↓ surfactant, alveolar collapse, fluid into alveoli, hyaline membranes
- in few days, proliferation of fibroblasts in damaged alveoli → fibrosis

Conditions of poisoning:

ingestion of paraquat **concentrate**

cattle grazing recently-sprayed pasture (Edds & Dudley 1976)

dogs and cats exposed to garden plants/weeds treated with paraquat (Johnson & Huxtable 1976, Darke *et al.* 1977)

dogs eating from carcases baited with paraquat to kill foxes (UK) (Darke *et al.* 1977)

malicious poisonings of dogs, cats and pigs are on record (Rogers *et al.* 1973, Longstaffe *et al.* 1981, Bischoff *et al.* 1998). Rogers *et al.* (1973) note that paraquat remains toxic in intentionally-contaminated pig feed for at least a month.

Clinical signs:

Early signs

- vomiting, acute abdominal pain, diarrhoea

Followed within 24 hr by

- erosions, inflammation of buccal mucosa
- **dyspnoea**, depression, death in severe cases
- ± signs of renal dysfunction or failure

Apparent improvement after 1-2 days, then relapse several days later → **death** from severe dyspnoea

Pathology:

Necropsy

- GIT - *acute*: **mucosal erosions** (buccal, gastric, intestinal), bluish-green ingesta (stable free radical formed by microbes)
- lungs - *acute*: congestion, oedema; *chronic*: **fibrosis**, atelectasis, oedema
- kidneys - pale, swollen

Histopathology

- lungs (dogs: Kelly *et al.* 1978)
  - *acute*: oedema, haemorrhage, hyaline membranes; ultrastructural examination reveals loss of both Types I and II pneumocytes
  - *chronic*: interstitial and intra-alveolar fibrosis
- kidney cortical tubular necrosis in many cases
- ± liver, adrenal cortex (zona glomerulosa) & myocardial necrosis

Diagnosis:

- history of access + syndrome + pathology
- assay of tissues

Darke *et al.* (1977): assay method based on Calderbank & Yuen (1965) was positive in 4 of 10 dogs examined; success rate: urine > kidney > liver.

Bischoff *et al.* (1998): assay method based on Sunshine (1975) was positive in all of 7 dogs; in acute stages used vomitus, stomach contents or suspected baits; in acutely dead animals used kidney, liver and lung

Longstaffe *et al.* (1981) noted that in the more acute (and probably malicious) poisonings, tissue paraquat concentrations were relatively easily detected (lung: 0.94-40.2 mg/kg, liver 0.36-44.8, kidney 1.20-47.6) while in more chronic (and probably accidental) poisoning, tissue concentrations were often undetectable (< 0.0005 mg/kg).

Screening test for paraquat and diquat on urine (Calderbank & Yuen 1965; D. Holstege, personal communication VETTOX Discussion List 5 Feb 1999):

- Take 25 ml urine and adjust the pH to > 10 with ammonium hydroxide.
- Pull the urine through a 0.5 or 1 g silica gel column (any type).
- Add a couple of scoops of sodium dithionite to the top and pull 1 ml ammonium hydroxide through the column.
- Paraquat is revealed as a blue line migrating down from the top of the column.
- Diquat is revealed as a green line.

Therapy:

- **early** intervention *may* be worthwhile
- O_2 therapy is *contraindicated* (exacerbates toxicity)
- prevent further absorption through gastric lavage, adsorbents (activated charcoal, etc.), purgatives

- promote urinary excretion through forced diuresis using diuretics and fluids
- the use of anti-inflammatory drugs (corticosteroids) to reduce the fibrosis in lungs is of questionable value

Prevention & Control:

- safe storage and clear labelling of paraquat concentrate
- deny pets access to sprayed garden areas for at least 24 hrs after spraying

References: Os263, Se326

Bischoff K, Brizzee-Buxton B, Gatto N, Edwards WC, Stair EL, Logan C (1998) Malicious paraquat poisoning in Oklahoma dogs. *Vet. Human Toxicol.* **40**:151-153.

Calderbank A, Yuen SH (1965) An ion-exchange method for determining paraquat residues in food crops. *Analyst* **90**:99-106.

Darke PGG, Gibbs C, Kelly DF, Morgan DG, Pearson H, Weaver BMQ (1977) Acute respiratory distress in the dog associated with paraquat poisoning. *Vet. Rec.* **100**:275-277.

Dial CAB, Dial NA (1995) Lethal effects of the consumption of field levels of paraquat-contaminated plants on frog tadpoles. *Bull. Environ. Contam. Toxicol.* **55**:870-877.

Edds GT, Dudley WR Jr (1976) Paraquat toxicity in cattle. *Florida Vet. J.* **6**:23, 26-27.

Johnson RP, Huxtable CR (1976) Paraquat poisoning in a dog and cat. *Vet. Rec.* **98**:189-191. [cases in Sydney, Australia]

Kelly DF, Morgan DG, Darke PGG, Gibbs C, Pearson H, Weaver BMQ (1978) Pathology of acute respiratory distress in the dog associated with paraquat poisoning. *J. Comp. Path.* **88**:275-294.

Kiorpes AL, Winter RB, Hodgson DS, Galitzer SJ, Savides MC (1982) Pathophysiological effects of paraquat intoxication in domestic ruminants: low dose studies. *Vet. Human Toxicol.* **24**:81-85.

Longstaffe JA, Humphreys DJ, Hayward AHS, Stodulski JBJ (1981) Paraquat poisoning in dogs and cats – differences between accidental and malicious poisoning. *J. Small Anim. Practice* **22**:153-156.

Manzo L, Gregotti C, Di Nucci A, Richelmi P (1979) Toxicology of paraquat and related bipyridyls: biochemical, clinical and therapeutic aspects. *Vet. Human Toxicol.* **21**:404-410.

Pahl G (1997) Suspected paraquat poisoning in a cat. *Post-Grad. Committee in Vet Science, University of Sydney: Control & Therapy Series*. Mailing 197, No.3941.

Rogers PAM, Spillane TA, Fenlon M, Henaghan T (1973) Suspected paraquat poisoning in pigs and dogs. *Vet. Rec.* **93**:44-45.

Smalley HE, Radeleff RD (1970) Comparative toxicity of the herbicide paraquat in laboratory and farm animals. [Abstract] *Toxicol. Appl. Pharmacol.***17**:305.

Stevens MA, Waley JK (1966) *J. Sci. Fd. Agric.* **17**:472-. [experimental; cattle]

Sunshine I (ed.) (1975) *CRC Methodology for Analytical Toxicology.* CRC Press, Clevelend. p.294. [cited by Bischoff *et al.* 1998]

Webb DB (1083) Nephrotoxicity of paraquat in the sheep and the associated reduction in paraquat secretion. *Toxicol. Appl. Pharmacol.* **68**:282-289.

Diquat, morphamquat (dipyridyl herbicides)

Sources: diquat, morphamquat

Toxicity:

- rare, cattle-diquat case on record
- *only paraquat → lung damage*; all → GIT damage

Conditions of poisoning: ingestion of herbicide **concentrates**

Clinical signs: vomiting, acute abdominal pain, diarrhoea, erosion of buccal mucosa

Pathology: **GIT - mucosal erosions & inflammation** (buccal, gastric, intestinal); highly-coloured **green fluid** in abomasum (stable free radical from microbial action)

Diagnosis: exposure history, pathology

Therapy: gastric lavage, adsorbents, purgatives

Prevention & Control: safe storage & clear labelling of concentrates

References: Os263, Se326

Glyphosate

Chemical structure:

N-(phosphonomethyl) glycine

Sources: an aminophosphonate herbicide (Roundup®, Zero®)

Toxicity:

dogs, cats, cattle, horses

this compound has a **very low mammalian toxicity**: rat acute oral LD_{50} = 5600 mg/kg; human minimum lethal dose = 1 g/kg

in several cases, ingestion of significant amounts produced no clinical illness

glyphosate is well excreted by mammalian kidneys

amphibians appear to be more susceptible, with data available for Australian frog species (Mann & Bidwell 1999, Giesy *et al.* 2000)

Mode of action: unknown; appears to be direct irritation of the alimentary tract

Conditions of poisoning:

accidental ingestion of solutions of glyphosate (concentrate or diluted preparations)

persistence on sprayed plants is low, making this a less likely source of intoxication

Clinical signs (dogs):

spontaneous **vomiting** (60% of 25 cases) within a few minutes to 2 hrs of ingestion

hypersalivation with **buccal irritation** (26% of cases)

mild **diarrhoea** (16% of cases)

signs occurring rarely: prostration, paresis unassociated with shock or CNS depression, haematemesis, melena, hypothermia, mydriasis, conjunctivitis (after direct contact with glyphosate)

no fatal cases recorded

Pathology: non recorded

Diagnosis: access & clinical signs

Therapy:

ingested material: activated charcoal + osmotic diuretics (10% mannitol) while maintaining hydration

eyes: irrigate before anti-inflammatory medication

References:

Burgat V, Keck G, Pineau X (1998) Glyphosate toxicosis in domestic animals: a survey from the data of the Centre National d'Informations Toxicologiques Veterinaires (CNITV). *Vet. Human. Toxicol.* **40**:363-367.

Giesy JP, Dobson S, Solomon KR (2000) Ecotoxicological risk assessment for Roundup® herbicide. *Rev. Environ. Contam. Toxicol.* **167**:35-120.

Mann RM, Bidwell JR (1999) The toxicity of glyphosate and several glyphosate formulations to four species of south-western Australian frogs. *Arch. Environ. Contam. Toxicol.* **36**: 193-199.

*Arsenic (*q.v.*)*