9: Feed components or additives [Industrial-origin toxins]

Urea (ammonia)

Core data

Common source: non-protein nitrogen feed supplement
Animals affected: ruminants
Poisoning circumstances:
- excess/too rapid intake
- ruminal flora unadapted (adaptation rapidly lost)

Main effects:
- hyperammonaemia
- abdominal pain
- hyperaesthesia
- collapse with struggling

Diagnosis:
- history
- NH_3 assay of *frozen* plasma
- NH_3 assay of rumen contents + battery acid or *frozen* rumen contents
- feed urea assay

Therapy:
- empty rumen or dose with water + acetic acid
- check for relapses

Chemical structure:
ammonia = NH_3
urea = $CO(NH_2)_2$; synthesised industrially from CO_2 and NH_3

Sources:
- feed supplements containing urea as a non-protein nitrogen source
- fertiliser

Toxicity:
- **ruminants** (urea should not exceed 3% in concentrate ration).
- cattle lethal dose 1.0-1.5 g/kg in those accustomed to urea, may be 0.4g/kg in others
- tolerance rapidly lost (3 days), reduced by starvation or low protein ration
- horse lethal dose 3.5 g urea/kg (Hinz *et al.* 1970); natural cases in horses unreported
- Normally:
  - ruminal bacterial ureases split urea → $NH_3 + CO_2$
  - further ruminal bacterial metabolism converts NH_3 → bacterial protein
  - NH_3 absorbed into portal blood is reconverted to urea by hepatic enzymes
- Excessive urea intake or insufficient capacity of ruminal bacteria to metabolise NH_3
  → ↑ NH_3 absorption into portal blood
  - high rumen pH → less NH_3 as the ion and more as gas which readily diffuses across cell membranes
- If amount of NH_3 absorbed exceeds the hepatic capacity for reconversion to urea
  → ↑↑ NH_3 concentration in general circulation → NH_3 toxicity
  - signs occur at plasma concentrations of 13-20 μg NH_3 /ml, death at 50 μg /ml.

Conditions of poisoning:
- excessive/too rapid intake of urea-containing feedstuff
  - feed mixing errors, malfunction of dispensing mechanisms
  - individual variations in tolerance (ruminal bacterial capacity)
- soya beans contain urease and promote urea → NH_3

Clinical signs:
Ruminants
- onset 10-30 min after toxic dose. Case fatality rate high.
- severe cases → rapid death
  - abdominal pain signs, ruminal tympany, dyspnoea
  - hypersensitivity to external stimuli → aggression

- drooling saliva
- muscle tremor, weakness
- violent struggling & vocalisation

- less severe → lethargy, recumbency

Horses (Hinz *et al.* 1970)

- onset 0.5 – 3 hr after ingestion
-aimless wandering, incoordination
- head-pressing
- extensor rigidity
- recumbency (sternal or lateral)
- pupil dilation, sluggish response to light
- ± clonic convulsions
- death 30-90 minutes from onset

Pathology:

- non-specific changes only
  - agonal petechiation, rapid *post mortem* bloat, pulmonary oedema

Diagnosis:

- history of access to urea + syndrome
- assay plasma NH_3 concentration in live animal (prevent NH_3 loss - highly volatile)
  - sample blood into anticoagulant and separate plasma immediately in an air-tight tube
  - **freeze plasma immediately** and submit to the lab *to arrive frozen*. Warn the lab to expect the samples!
  - > 2 mg NH_3 / 100 mL (1.17 mmol/L) significant
- assay rumen fluid NH_3 concentration (use methods to prevent NH_3 loss – it is highly volatile)
  - > 80 mg NH_3 / 100 mL (45 mmol/L) significant
  - collect 20 ml rumen fluid *as soon after death as possible*
  - *immediately* add 4 drops of car battery acid (35% sulphuric acid) to acidify the sample [or add an equal volume of 0.2N HCl or 1-2 drops saturated $HgCl_2$]. If using the battery acid option, also submit a separate sample container with another 4 drops of battery acid (no rumen contents) to act as a blank for the assay procedure. This is to guard against the unlikely situation of ammonia contamination of the acid. Ammonia is fairly ubiquitous, can diffuse through plastics and will accumulate in acid with virtually no upper limit. The amount of acid added (1 drop = about 0.05 ml) should stabilise 20 ml samples containing at least 115 mM ammonia/L. Concentrated sulphuric acid is 36N and 1 L can hold 36 moles (612 g) of ammonia (K McGuigan, personal communication 2000).
  - OR freeze immediately and submit to the laboratory *to arrive frozen*. Warn the lab to expect the samples!
- assay feed source/supplement to confirm excess urea concentration

Therapy:

- **empty rumen** *via* large bore stomach tube or rumenotomy
- OR (less efficient) decrease urea metabolism by decreasing temperature, diluting and decreasing pH by
  - → **water** - 20-40 L for adult cattle
  - & → **6% acetic acid** (vinegar) - up to 12 L for adult cattle
  - watch affected animals closely - **relapses** may occur 30 min after conservative treatment

Prevention & control:

- introduce urea to ration slowly
- include adequate carbohydrate in ration

References: Os341, Se305, VM8/1522

Hinz HF, Lowe JE, Clifford AJ, Visek WJ (1970) Ammonia intoxication resulting from urea ingestion by ponies. *J. Am. Vet. Med. Assoc.* **157**:963-966.

☑ Sulphur (S-associated polioencephalomalacia of ruminants)

Core data
Syndrome names: molasses poisoning
Common sources:
- molasses
- sulphates & elemental sulphur (diet including drinking water)

Animals affected: sheep, cattle
Mode of action: poorly understood – rumen thiamine destruction? absorbed H_2S inhibits cellular respiration?
Poisoning circumstances: diets high in S, particularly as sulphates
Main effect: polioencephalomalacia
Diagnosis: pathology
Therapy/Management: thiamine (may not be effective)
Prevention: increase dietary thiamine

Compare this syndrome with that of thiamine deficiency of dogs and cats fed meat preserved with sulphur dioxide (Studdert & Labuc 1991, Steel 1997). See also Thiaminase.

Syndrome names:

"molasses poisoning"

so-called "blind staggers", attributed to Se intoxication in USA for decades, is now recognised as not a Se intoxication, but most commonly polioencephalomalacia (S-associated) or due to other encephalopathies (O'Toole *et al.* 1996). The geochemistry associated with Se-accumulator plants often produces water with a high S content in the same landscape (Raisbeck *et al.* 1993).

Sources:

- **molasses** - large S content from sulphuric acid used in sugar refining (Raisbeck 1999)
- various **sulphates**
  - ammonium sulphate (urinary acidifier → ↓ urolithiasis)
  - gypsum [$CaSO_4$. $2H_2O$] (dietary additive → control total daily intake)
  - drinking water containing Na_2SO_4 > 1000 ppm; sulphate is one of the major anionic components of saline surface waters in the arid rangelands of North America (Raisbeck 1999)
- elemental **sulphur** (Bulgin *et al.* 1996)
  - flowers of sulphur (Cu antagonist in sheep feed)
  - used in traditional folk medicine for external and internal parasites (Raisbeck 1999)
- **manure gas** (H_2S) (Dahme *et al.* 1983, Hooser *et al.* 2000)
- H_2S from petroleum, sour gas and geothermal wells (Raisbeck 1999)
- certain plants
  - probably plants in the family Brassicaceae: *Brassica* spp. (rape, kale etc.), *Rapistrum rugosum* (turnip weed)
  - possibly *Phalaris aquatica*

Toxicity: review - Olkowski (1997)

- **sheep, cattle**

Ingestion of virtually all forms of S results in some degree of alimentary production of H_2S in ruminants and possibly horses. Monogastrics are less at risk from SO_4 but can produce H_2S from elemental S. Depending on the dose of S and other poorly-defined dietary factors, sufficient H_2S may be formed to produce either acute or chronic poisoning (Raisbeck 1999)

- pathogenesis poorly understood, but involves excess production of sulphide ion (S^{2-}) and H_2S:
  - possible absorption of H_2S produced in rumen by microbial metabolism of sulphates (S reduction mechanisms) → inhibition of cellular respiration / hypoxia (more critical in brain?)
  - H_2S → destruction of thiamine in rumen? In some studies, no evidence of thiamine deficiency has been demonstrated (Gould 1998).
  - inhalation of eructated ruminal H_2S may be significant (as much as 60% of eructations may be inhaled)
  - microbial S reduction capacity is enhanced by high-S diets (Gould 1998)
  - The physicochemical conditions in the rumen influence H_2S production and absorption. The pKa of H_2S is about 7. Thus the balance between hydrosulphide anion (HS^-), predominantly in rumen fluid, and H_2S, predominantly in the gas cap, is determined by rumen pH. Acid conditions

typical of high-grain feedlot rations favour increased H_2S production. (Raisbeck 1999)

- recommended dietary S concentration for cattle = < 0.3% (maximum tolerated 0.4%) (NRC 1996)
- H_2S concentrations of 1000-2000 ppm cause respiratory paralysis and death in minutes; at concentrations >2000, H_2S directly paralyses the respiratory centre; 1-2 breaths lead to respiratory paralysis, generalised convulsions and death

Conditions of poisoning:

- incompletely understood
- ruminants are at greatest risk in the first 3 weeks after introduction to a diet rich in S, then the ruminal flora adapts and cases are rare (Raisbeck 1999)
- diets high in sulphur, particularly as sulphates (including molasses)
- grazing crops/weeds of the Family Brassicaceae (e.g. Hill & Ebbert 1997)
- diets low in Cu, Zn, Fe & Mo may predispose
- low rumen pH $\rightarrow \uparrow H_2S$ in gas cap
- inhalation of manure gas: agitation of manure in pits beneath animal confinement facilities $\rightarrow$ release of gas bubbles trapped in the manure (Hooser *et al.* 2000)

Clinical signs:

- sudden death (H_2S inhalation)
- odour of H_2S in eructated rumen gas
- anorexia, depression
- cyanosis, dyspnoea (acute manifestations)
- intermittent excitement, apparent blindness, head pressing, convulsions

Pathology:

- odour of H_2S in rumen is transient and may be absent after a few hours *post mortem* (Raisbeck 1999)
- **polioencephalomalacia**
  - autofluorescence of lesions under UV illumination @ 365 nm wavelength; autofluorescent substance localised in mitochondria (Shibahara *et al.* 1999)
- pneumonia
- mucosa of animals receiving mineral supplements (Cu, Fe) may be blackened by metal sulphides. (Raisbeck 1999)
- ± hepatic necrosis & haemorrhage (experimental cases) (Raisbeck 1999)

Diagnosis:

- pathology
- dietary S analysis (include water); total dietary S concentrations > 0.4% are consistent with S intoxication (Raisbeck 1999)
- H_2S assay of ruminal gas cap in in-contact clinically-normal cattle; ruminal gas cap H_2S concentrations > 2000 ppm can precede polioencephalomalacia development; normal < 500 ppm (Gould *et al.* 1997; Gould 1998)
- ruminal fluid S^{2-} assay – preserve immediately with 1 volume 5% zinc acetate to 20 volumes rumen fluid to prevent volatilisation

Therapy: cases not always responsive to thiamine administration

Prevention & Control:

- increased dietary thiamine can be protective
- use ammonium chloride as urinary acidifier

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☑ Polyether Ionophore antibiotics

Core data

Common source:
- compounded feeds
- poultry litter
- monensin, salinomycin, maduramicin, lasalocid, narasin

Animals affected: horses >> sheep > pigs > cattle, dogs, cats

Poisoning circumstances:
- feeding & formulation errors
- interaction with other therapeutics

Main effects:
- striated muscle damage
  - cardiac (horse, fowl)
  - skeletal (sheep, pig, dog)
  - both (cattle)
- peripheral polyneuropathy

Diagnosis:
- histopathology
- feed history
- assay feed residue

Therapy: non-specific

Compounds:
- **monensin**, salinomycin, narasin (methylsalinomycin), lasalocid, maduramicin, semduramicin, laidlomycin propionate
- Australian manufacturers & trade names: monensin (Elanco: Rumensin®, Elancoban®), salinomycin (Pfizer: Coxistac®), narasin (Elanco: Maxiban,® Monteban®), lasalocid (Roche: Avatec®)
- monensin
  - produced by the fungus *Streptomyces cinnamonensis*
  - developed as poultry coccidiostat
  - growth promoter for cattle

Sources:
- **compounded feeds**
  - growth promotants in feedlot ruminants; inhibitors of major lactic acid-producing bacteria in the rumen (prevention of ruminal acidosis in feedlots) (Oehme & Pickrell 1999)

- coccidiostats in poultry
- antibloat agent in dairy cattle

- medicaments in slow-release capsules for intra-ruminal dosing
- poultry litter

Toxicity:

- interfere with sodium ion flux across biological membranes [ionophore = any molecule that increases the permeability of cell membranes to a specific ion; ionophore antibiotics form lipid-soluble complexes with mono- or di-valent cations, facilitating their transport across membranes]
- → **muscle damage** (all **striated muscle** susceptible) → heart failure, paresis
- main damage predominantly in **heart** (horse, fowl) or predominantly in **skeletal muscle** (sheep, pigs, dogs, ostriches (Baird *et al.* 1997), turkeys), or equally in skeletal & heart (cattle).
- → **peripheral polyneuropathy** + myocardial degeneration in cats ingesting salinomycin (van der Linde-Sipman *et al.* 1999) and (probably) dogs ingesting lasalocid (Safran *et al.* 1993)

Dogs fed **lasalocid**-contaminated food (166-210 mg/kg product) developed progressive paresis and paralysis of hind limbs often followed by quadriplegia and dyspnoea. Experimentally, lasalocid at 10-15 mg/kg product was toxic. (Safran *et al.* 1993)

Cats in the Netherlands in 1996 ingesting **salinomycin** as a contaminant of commercial dry cat food (13-21 mg salinomycin/kg product) developed myocardial degeneration and distal polyneuropathy manifest as acute posterior paralysis followed in severe cases by anterior paralysis and respiratory failure (van der Linde-Sipman *et al.* 1999).

- wide variation in susceptibility, low safety margin (therapeutic vs. toxic doses)
- monogastrics (**horses** most susceptible) > ruminants, dogs, cats > turkeys > fowls
  - signs begin at monensin doses of 1 mg/kg (**horse**), 4 (sheep), 7.5 (pig), 10 (cattle)
  - monensin LD_{50} 2-3 mg/kg (**horse**),12 (sheep), 20 (dog), 24 (goat), 16-50 (pig), 20-80 (cattle)
  - lasalocid doses of 10 mg/kg and above have caused toxicity in cattle (Galitzer *et al.* 1986a,b, Blanchard *et al.* 1993) and dogs (Carson TL personal communication VETTOX 1999); lethal dose for dogs 20-30 mg/kg (Carson TL personal communication VETTOX 1999)
- general ranking of toxicity: salinomycin < lasalocid < narasin < monensin < maduramicin (Oehme & Pickrell 1999)

Conditions of poisoning:

- failure to dilute a concentrate
- mixing errors, for example intoxication of dairy calves with calf-rearing mix containing monensin at 10,000 mg instead of 1000 mg/kg (Gabor *et al.* 2001)
- settling out of ionophore within liquid supplements → uneven distribution and lethal concentrations (Schweitzer *et al.* 1984)
- feeding the wrong material, e.g. cattle feed to horses, poultry feed to turkeys (Gordon & McKenzie 2000)
- cattle/sheep fed poultry litter from farms using salinomycin/maduramicin coccidiostat; maduramicin is usually present in poultry litter at the original feed concentration, while monensin is usually present at 25% of that concentration (Oehme & Pickrell 1999)
- mixing horse feed in feed mills after making cattle feed. Molasses (as binder & to improve palatability) is a good scouring agent → first bagful sometimes contains high concentrations of ingredients flushed out of chutes/ducts
- ex-label use (overdose) of lasalocid to prevent cryptosporidiosis in neonatal calves (Benson JE *et al.* 1998)
- dogs/cats fed contaminated commercial diets (Wilson 1980, Safran *et al.* 1993, van der Linde-Sipman *et al.* 1999)
- dogs chewing intra-ruminal slow-release devices containing monensin (Condon & McKenzie 2002)
- interaction with other therapeutics or feed components can potentiate toxicity of ionophores fed at recommended (normally non-toxic) rates

- mechanism of action probably through slowing the rate of ionophore clearance through the hepatic xenobiotic biotransformation enzyme systems, thus causing accumulation of toxic concentrations in the body
- macrolide antibiotics
- tiamulin at therapeutic doses (swine dysentery) boosts monensin or salinomycin toxicity for pigs (van Vleet *et al.* 1987) and poultry (Umemura *et al.* 1984a)
- oleandomycin boosts monensin toxicity for poultry (Umemura *et al.* 1984b)
- erythromycin, clarithromycin boost monensin toxicity for cattle (Basaraba *et al.* 1999)
- furazolidone boosts lasalocid or monensin toxicity for poultry (Czarnecki 1990)
- neomycin-permethrin (Nation & Roth 1993)
- animal protein
- interaction with mycotoxin contaminants of feed
- T-2 (trichothecene) lowered the narasin LD_{50} by > 40% (Oehme & Pickrell 1999)

Clinical signs: variation between species [pigs (van Vleet *et al.* 1983b); cattle (van Vleet *et al.* 1983c); horses (Reef 1998)]
- ± sudden death (severe cardiac damage)
- muscular weakness (muscle tremor)/paralysis, incoordination, recumbency
- ± diarrhoea
- ± tachycardia, dyspnoea
- ± myoglobinuria (mammals)
- chronic heart failure → subcutaneous oedema, ascites, diarrhoea, dyspnoea, jugular distension, tachycardia
- horses: oedema of the face and swelling of masseter muscles may occur (Rollinson *et al.* 1987) (cf. persin toxicity)
- ± death up to weeks later

Pathology: variation between species [pigs (van Vleet *et al.* 1983b); cattle (van Vleet *et al.* 1983c); poultry (Dowling 1992)]
- ↑↑ serum CPK, AST
- ± myoglobinuria, myoglobinuric nephrosis
- cardiac & skeletal **muscle necrosis** ± → fibrosis
- ± extracardiac lesions of acute heart failure or chronic cardiovascular insufficiency (lung oedema, ascites, anasarca, liver necrosis)
- ± peripheral polyneuropathy (cats, dogs; salinomycin, lasalocid); in cats, involving both motor and sensory nerves (primary axonal degeneration followed by secondary myelin sheath degeneration) plus myocardial degeneration occurred (van der Linde-Sipman *et al.* 1999). Some cats had minor degenerative skeletal muscle lesions and degenerative changes in dorsal funiculi of spinal cord (van der Linde-Sipman *et al.* 1999).

Diagnosis:
- history of new feed batch or source
- histopathology of cardiac & skeletal muscles
- assay feed residue (if available), stomach contents (sudden death cases)

Monensin + narasin assay available (feed only) from Eli-Lilly Australia (Elanco Animal Health), 112 Wharf Rd., West Ryde, Sydney NSW 2114; Phone 02 9325 4555/ 1800 226324 Fax 02 9325 4420; Cost (1998) $60 for a single test; Salinomycin assay available from Pfizer Animal Health, PO Box 57 West Ryde NSW 2114; Phone (02) 9850 3333
- differentiate from exertional rhabdomyolysis, vitamin E/Se deficiency, *Senna* spp. poisoning, gossypol poisoning, porcine stress syndrome, botulism (particularly in species where effects on skeletal muscle or peripheral nerves predominate e.g. dogs, cats); horses with head oedema – avocado (persin) poisoning, Hendravirus infection, African horse sickness

Therapy:
- no specific treatment (vitamin E/Se ineffective)
- rest with sedation if applicable (monitor heart & kidney function)
- some poisoned animals completely recover

Prevention:

- care with feed formulation and interactions with other drugs
- pre-treatment with vitamin E and selenium can modify, but not abolish, the effects of monensin toxicity in pigs (van Vleet *et al.* 1983a, 1987) and cattle (van Vleet *et al.* 1985).

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Os 338, Se 335, VM8/1524

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☑ *Sodium ion (commonly sodium chloride)*

Core data

Common sources: diets high in Na (various salts)
Animals affected: pigs, poultry, ruminants
Mode of action: hypothesis:

- high brain Na + damage to blood-brain Na transport mechanism
- → cerebral oedema when body rehydration occurs

Poisoning circumstances:

- large salt intake + restricted fresh drinking water supply
- signs usually initiated by resumption of water supply

Main effects:

- seizures (pigs – repeated at set intervals), apparent blindness
- cerebral oedema
- pigs only - eosinophilic meningoencephalitis

Diagnosis:

- syndrome
- brain pathology
- assay CSF/brain/aqueous humour Na

Therapy: cautious restoration of fresh water supply
Prevention: uninterrupted fresh water supply

Sir Humphrey Davy
Abominated gravy.
He lived in the odium
Of having discovered Sodium.

Edmund Clerihew Bentley 1890 [His first Clerihew]

Syndrome names:

Salt poisoning
Water deprivation-salt (Na ion) poisoning
"Water intoxication" - not to be confused with excess cold water intake causing haemolysis in calves (*q.v.*)
Oedema disease (poultry)

Chemical structure: NaCl
Sources: diets high in Na (various salts – chloride, bicarbonate, sulphate)
- compounded feeds
- drinking water

Toxicity:

- pigs, poultry, ruminants, dog [only 1 case recorded; Khanna *et al.* 1997]
- depends on fresh water supply at time of salt ingestion - unlimited supply → salt poisoning very unlikely
- pigs: normally 0.5-1.0% salt in diets; tolerate 13% salt in diet if adequate water supply
- poultry: young poultry (chickens) are more susceptible than adults
  - chickens: minimum toxic concentration in feed = 3% (Sibbald *et al.* 1962)
  - turkey poults < 21 days old; minimum toxic feed concentration 3-4% (Bigland 1950, Dewar & Siller 1971)
- cattle: tolerate 2% salt in drinking water for several months

Effects of various concentrations of salt exposure on cattle* (from van Leeuwen 1999):

Salt concentration (ppm) †	Effects on cattle
< 1000	No effect
1000-3000	Temporary diarrhoea; reduced water intake and milk production (peak & persistency); serum Na concentrations may be normal.
3000-5000	May stimulate food refusal in animals unaccustomed to it.
5000-7000	May produce reproductive failures.
7000-10 000	Unsafe, especially in younger animals & in hot weather due to increased water loss. Neurological and severe gastrointestinal signs begin.
>10 000	Unsafe for all ages. Neurological and severe gastrointestinal signs.

* Data are based on the assumption that **either** the diet **or** the water source is contaminated with large amounts of salt. If **both** are highly contaminated, clinical signs may occur at concentrations half as large as those indicated.
† Different laboratories report NaCl concentrations using different units: ppm, %, mg/L. In water samples, electrical conductivity of total salts (an approximation of NaCl concentration) is also often reported, using united millimhos/cm (mmho/cm), micromhos/cm (μmho/cm) or deciSiemens/m (dS/m). Conversion between the units can be effected through the formulae:

- 1% = 10 000 ppm
- 1 mg/L = 1 ppm
- 1 mmho/cm = 1000 μmho/cm
- 1 mmho/cm = 640 ppm
- 1 mmho/cm = 1 dS/m

Despite the data in the above table, cattle and sheep have been known to survive on water containing as much as 17 000 ppm NaCl, if the salt concentration rises gradually. Cattle have survived on a total dietary salt intake of 130 000 ppm (in dry matter), if salt concentrations rise gradually and they have continuous access to fresh drinking water. (van Leeuwen 1999)

Mechanism of toxicity

Mammals (proposed):

- normally plasma Na slightly > CSF Na → diffusion of Na to CSF, active Na transport (energy-dependent) back to plasma.
- water deprivation → dehydration, haemoconcentration → ↑ plasma Na conc. → ↑ CSF Na conc. → inhibition of anaerobic glycolysis at blood-brain barrier → ↓ energy available for active Na transport to plasma from CSF → retention of high CSF/brain Na
- rehydration
  → excretion of excess plasma Na in urine
  → water drawn into hypertonic brain tissue → swelling & oedema
- dysfunctional blood-brain barrier → no return of excess Na to plasma → persistence of brain oedema → clinical signs

Poultry:

suggested hypertension + direct effect on electrical activity of cardiac muscle cells (Onderka & Bhatnagar 1982)

Conditions of poisoning:

Pigs:

- **large salt intake + restricted fresh drinking water supply** from various causes including:
  - medication of water → unpalatability
  - frozen water supply
  - overcrowding → insufficient water for some animals
  - moving to strange environment → unable to find water supply (e.g. drinking nipples)
- onset most likely *after* restoration/provision of access to unlimited fresh water
- pigs given unlimited supplies of whey abnormally high in salt

Cattle:

- cattle fed large amounts of salt in highly palatable form → **rapid intake**
- cattle grazing pasture periodically inundated by salt water (salt marsh pasture) (van Leeuwen 1999)

Poultry:

- feed formulation error
- high sodium concentration in drinking water
- chickens fed wet mash containing > 2% salt (see also notes under heart failure syndromes)
- possible build-up of salt in poultry feeders by gravitation (Bigland 1950)
- egg albumen as protein source in feed for turkey poults (Dewar & Siller 1971)

Clinical signs:

Pig → series of **seizures** repeated at specific time intervals in each affected animal + normal between seizures

- twitching of face & ears → spreads over back & neck → adopts sitting position → head drawn slowly back & upwards, muscle tremors extend to posterior of body → head continues to be drawn back until → falls into lateral recumbency + violent running/paddling + dyspnoea, cyanosis → recovers → resumes feet & may walk away normally.
- other signs may include
  - vomiting (common)
  - attempts to climb walls of pens
  - apparent blindness
  - unidirectional circling
- some pigs simply remain recumbent & comatose
- recovered pigs may → ill-thrift, continued ataxia, mild residual neurological abnormalities, aimless wandering

Cattle

- hyperexcitable, seizures with paddling, opisthotonus
- apparent blindness, unresponsive to surroundings
- incoordination, knuckling of fetlocks
- head pressing, standing motionless with arched back, circling
- muscle tremors
- urinary incontinence, ± diarrhoea
- death in 24 hrs

subacute effects include female infertility

Chickens

- sudden death
- depression
- excessive thirst, increased water consumption
- fluid discharges from beak
- diarrhoea / loose wet faeces
- increased respiratory rate, dyspnoea
- tendency to ataxia & paralysis

Pathology:

Mammals:

- **cerebral oedema**
- ± cerebrocortical mid-laminar necrosis/ polioencephalomalacia & vacuolation
- **pigs only → eosinophilic meningoencephalitis**
  - eosinophils migrate into perivascular spaces of cerebral cortex & meninges within first 48 hrs → migrate back in next 3-4 days

Poultry:

- subcutaneous oedema (ventral)
- **ascites**
- hydropericardium
- **cardiac dilation** (bilateral ventricular dilation)
- pulmonary oedema
- liver congestion, fibrin on liver surface
- congestion & oedema of intestinal walls

Diagnosis:

- feed/water availability + distinctive clinical syndrome in pigs + brain pathology (pigs - eosinophilic meningoencephalitis)
- assay feed *and* water Na concentrations
- plasma/CSF Na > 160 mEq/L; brain Na > 1800 mg/kg
- cattle: aqueous humour Na > 160 mEq/L

Therapy:

- prognosis poor
- cautious restoration of fresh water in small increments to dehydrated pigs
- replace the high Na source

Prevention & Control:

- provide uninterrupted adequate fresh water supply

References:

Os355, Se338, VM8/1499

Ammerman CB *et al.* (1980) Sodium chloride. *Mineral Tolerance of Domestic Animals*, National Academy of Sciences, Washington D.C., pp.441-458.

Bigland CH (1950) Ascites and oedema of brooded turkey poults in Alberta. *Can. J. Comp. Med.* **14**:144-156.

Dewar WA, Siller WG (1971) Sodium toxicity resulting from feeding hen egg albumen powder to turkey poults. *Br. Poult. Sci.* **12**:535-543.

Khanna C, Boermans HJ, Wilcock B (1997) Fatal hypernatremia in a dog from salt ingestion. *J Am Anim Hosp Assoc* **33**:113-117.

Onderka DK, Bhatnagar (1982) Ultrastructural changes of sodium chloride-induced cardiomyopathy in turkey poults. *Avian Dis.* **26**:835-841.

Sibbald IR, Pepper WF, Slinger SJ (1962) Sodium chloride in the feed and drinking water of chicks. *Poultry Sci.* **41**:541-545.

Trueman KF, Clague DC (1978) Sodium chloride poisoning in cattle. *Aust. Vet. J.* **54**:89-91.

van Leeuwen JA (1999) Salt poisoning in beef cattle on coastal pasture on Prince Edward Island. *Can. Vet. J.* **40**:347-348

☑ Cholecalciferol (vitamin D_3) & ergocalciferol (vitamin D_2)

Core data

Common sources:

- rodenticides
- feed additive
- [some plants]

Animals affected: dog, cat, pig, cattle

Mode of action: hypercalcaemia

Poisoning circumstances:

- ingestion of rodenticide pellets by non-target species
- overdose in feeds

Main effects:

- hypercalcaemia
- soft tissue calcification
- renal failure

Diagnosis: access + hypercalcaemia

Therapy:

- prognosis guarded
- detoxification: emesis + activated charcoal & saline cathartic, repeated
- reduce hypercalcaemia: diuresis + corticosteroid + disodium pamidronate (Aredia®) or calcitonin

Syndrome name: hypervitaminosis D

Sources:

- **rodenticide** in cereal-based pellets (e.g. cholecalciferol = Quintox®, Racumin D® [Bayer] produces delayed toxicosis & death in rodents 1-3 days after a single ingestion; ergocalciferol = Sorexa CD® requires multiple feeds for toxicity]
  - cholecalciferol (vitamin D_3) is more toxic than ergocalciferol (vitamin D_2) (Harrington & Page 1983)
- **feed additives**, vitamin supplements
- **plant** calcinogenic glycosides (*q.v.*)
- calcipotriol -vitamin D analogue used as human topical anti-psoriasis drug (Daivonex® ointment CSL) (Campbell *et al.* 1997)

Mechanism of toxicity:

→ **hypercalcaemia** → heart conduction dysfunction → ↓ HR (cardiac failure may occur @ serum Ca > 14 mg/dl)

→ **soft tissue mineralisation**; critical tissues = arterioles, renal tubules

→ direct cellular degeneration, necrosis (e.g. renal tubules) @ high vitamin D doses

Toxicity:

- dogs under 12 kg & cats most at risk from rodenticide form (cholecalciferol) of toxicity

- dog & cat - toxicity starts at 0.5-3 mg/kg; lethal doses start at 10-20 mg/kg [acute dog LD_{50} using technical grade cholecalciferol = 85 mg/kg - gives false impression of safety; LD_{50} = 13 mg/kg with anecdotal reports suggesting clinical signs with as little as 2 mg/kg (Rumbeiha *et al.* 1999)] - rodenticide baits contain 750 mg cholecalciferol/kg
- acute toxicity → death within 2-5 days of onset
- accumulation of lower doses can → toxicity
- normal dietary requirements for domestic mammals: 200-400 IU/kg diet (1μg vitamin D = 40 IU)
- long term feeding (>60 days): maximum safe level = 4-10 times the dietary requirement
- short term: most species tolerate up to 100 times the dietary requirement

Conditions of poisoning (acute form):

- ingestion of rodenticide by non-target species (dogs, young male cats); toxicity from ingestion of poisoned rodents is unlikely
- accidental or deliberate overdose in feeds (pigs, horses, cattle)
- accidental ingestion of calcipotriol ointment (human topical anti-psoriasis drug) (Campbell 1997)

Clinical signs (acute form):

- onset often 12-36 hr after ingestion of *acute* toxic dose; worsen 24-36 hr after onset
- initially often vague, mild or moderate - depression, anorexia, vomiting, polydipsia, polyuria, constipation or diarrhoea, melena
- **renal failure** → polyuria, hyposthenuria (=↓SG), [+ azotaemia in severe acute cases]
- **heart sounds slow & prominent**

Pathology:

Clinical pathology

- ↑**serum Ca** > 2 mg/dl (3 mmol/L) [dog normal 2.25-2.83 mmol/L]
- ↑serum P - may precede ↑Ca by 12 hr; could → early indication
- **azotaemia**, urine SG 1.002-1.006 [dog & cat normal 1.018 – 1.050]

Necropsy/histopathology

- pale streaks and plaques in tissues & large blood vessels (mineralisation)
- **mineralisation** often in renal tubules, coronary arteries, gastric mucosa, parietal pleura, pulmonary bronchioles, pancreas, urinary bladder
- ± renal tubular necrosis
- haemorrhagic gastritis (pigs – Long 1984)
- diffuse interstitial pneumonia (pigs – Long 1984)

Diagnosis:

- access + hypercalcaemia (+ tissue mineralisation)
- differential diagnoses of hypercalcaemia in dogs & cats include lymphosarcoma and other malignancies, hypoadrenocorticism, chronic renal failure, primary hyperparathyroidism (Rumbieha *et al.* 1999)

Therapy: **prognosis guarded**

- **detoxification** ASAP (preferably within 3 hrs of ingestion) including repeated activated charcoal to interrupt enterohepatic recycling of toxin
- **monitor** serum Ca, urea & creatinine; urine SG; heart sounds & ECG for minimum 2 weeks
- **treat hypercalcaemia**
  - *diuresis* to promote Ca excretion
  - *corticosteroid* to inhibit release of osteoclast-activating factors, reduce intestinal Ca absorption, promote urinary Ca excretion
  - *disodium pamidronate* (aminohydroxy-propylidene biphosphonate) (Rumbeiha *et al.* 1999, 2000) *or calcitonin* to reduce excessive serum Ca concentrations (>14 mg/dl) or when hypercalcaemia is prolonged; prolonged therapy may be required with calcitonin; a second biphosphonate, clodronate (dichloromethylene biphosphate), is reported to be useful (case report, one dog only: Petrie 1966); high doses of pamidronate (≥ 10 mg/kg) are nephrotoxic in dogs (Rumbeiha *et al.* 2000)

Therapeutic protocol for cholecalciferol toxicosis

Detoxification

- emesis or gastric lavage
- activated charcoal (1 g/kg) + osmotic cathartic
- continued activated charcoal (0.5-1.0 g/kg three times daily for 1-2 days)

Hypercalcaemia reduction

- diuresis - fluid therapy with normal saline + furosemide (IV 5 mg/kg followed by 3 mg/kg three times daily) [furosemide preferred to thiazide diuretics which may promote hypercalcaemia] - may need to continue for 4-14 days
- corticosteroid - e.g. prednisolone 2-6 mg/kg 2-3 times daily

and - disodium pamidronate (Aredia®) @ 2.0 mg/kg by IV infusion in normal saline over 2 hr; a second infusion may be needed 4 days after the first – monitor serum Ca concentrations (Rumbeiha *et al.* 1999)

or - calcitonin (salmon - Calsynar®, Miacalcic®, porcine - Calcitare®, human synthetic - Cibacalcin®) initially SC 4-6 IU/kg every 3 hr until serum Ca is reduced; dose may be increased to 10-20 IU/kg if initial dose ineffective [read product literature for adverse effects *etc.*]; dosing may be required for 3-4 weeks

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References:

Os279

Campbell A (1997) Calcipotriol poisoning in dogs. *Vet. Rec.* **141**:27-28.

Capen CC, Cole CR, Hibbs JW (1966) The pathology of hypervitaminosis D in cattle. *Path. Vet.* **3**:350-378.

Harrington DD, Page EH (1983) Acute vitamin D_3 toxicosis in horses: case reports and experimental studies of the comparative toxicity of vitamins D_2 and D_3. *J. Am. Vet. Med. Assoc.* **182**:1358-1369.

Long GG (1984) Acute toxicosis in swine associated with excessive dietary intake of vitamin D. *J. Am. Vet. Med. Assoc.* **184**:164-170.

Petrie G (1966) Management of hypercalcaemia using dichloromethylene biphosphate (clodronate). Abstract, *Proc. Br. Small Anim. Vet. Assoc. Annu. Congr.* p.80.

Roder JD, Stair EL (1999) An overview of cholecalciferol toxicosis. *Vet. Human Toxicol.* **41**:343-344.

Rumbeiha WK, Kruger JM, Fitzgerald SF, Nachreiner RF, Kaneene JB, Braselton WE, Chiapuzio CL (1999) Use of pamidronate to reverse vitamin D_3-induced toxicosis in dogs. *Am. J. Vet. Res.* **60**:1092-1097.

Rumbeiha WK, Fitzgerald SD, Kruger JM, Braselton WE, Nachreiner R, Kaneene JB, Frese KK (2000) Use of pamidronate disodium to reduce cholecalciferol-induced toxicosis in dogs. *Am. J. Vet. Res.* **61**:9-13.

Thomas JB, Hood JC, Gaschk F (1990) Cholecalciferol rodenticide toxicity in a domestic cat. *Aust. Vet. J.* **67**:274-275

☑ *Organic arsenical (phenylarsonic; benzenearsonic) compounds (pentavalent As)*

Core data

Common sources: growth promotants/swine dysentery prophylaxis with arsanilic acid, roxarsone
Animals affected: pigs, poultry
Mode of action: unknown
Poisoning circumstances:

- overdose
- substitution of roxarsone for arsenilic acid at same rate
- dehydration predisposes (↓ urinary excretion)

Main effects:

- transient ataxia, incoordination
- permanent blindness (pig)

Diagnosis: assay liver, feed
Therapy: remove from diet ASAP
Prevention: prevent dehydration during access

Sources:

- pig & poultry growth promotants / pig swine dysentery prophylactic/therapeutic
  - **arsanilic acid** (4-amino-phenylarsonic acid)
  - 3-nitro-hydroxyphenylarsonic acid (**roxarsone**, 3-Nitro®, Nitromix-100®)
  - 4-nitro-phenylarsonic acid (nitarsone, 4-nitro)
  - p-ureidobenzenearsonic acid (cabarsone)

Toxicity:

- pigs, turkeys, fowls
- much less toxic than inorganic As or organic trivalent arsenicals

- toxicity (pigs) roxarsone > arsanilic acid
- rapid renal excretion

In calves, large doses of arsanilic acid can cause signs typical of inorganic arsenic poisoning (Osweiler *et al.* 1985)

Mode of action:

- mechanism of therapeutic/toxic actions unknown → peripheral nerve degeneration

Conditions of poisoning:

- accidental overdosing (mistakes in feed formulation)
- substitution of roxarsone for arsanilic acid at same rate [pig diets arsanilic acid 50-100 ppm growth promotion, 250-400 swine dysentery (5-6 days); pig diets roxarsone 25-45 ppm growth promotion; turkey diets roxarsone maximum 300-400 ppm]
- pigs onset
  - 3-10 days when diet contains > 1000 ppm arsanilic acid
  - 3-6 weeks when diet contains 250 ppm
- diarrhoea or limited water supply predispose by → dehydration → ↓ urine volume → ↓ excretion of arsanilic acid

Clinical signs:

Pigs

- not usually fatal
- **ataxia**, **incoordination** (wide-based stance with low head, swaying, loss of balance, muscle tremors, goose-stepping, knuckling over, ± circling)
- wide-eyed, staring, ± apparent **blindness** (permanent despite recovery otherwise)
- appetite retained, drink normally, poor weight gains
- ± posterior paralysis, quadriplegia
- ± vocalisation ("screaming")
- ± transient diarrhoea

Turkeys, Fowls

- locomotor disturbances

OR haemorrhagic gastroenteritis (cf. inorganic As)

Pathology:

- no necropsy lesions (± distended urinary bladder)
- degeneration of peripheral nerves (reversible) e.g. sciatic nerves
- degeneration of optic nerves/tracts in blind pigs

Diagnosis:

- assay liver, feed
- liver As 3-10 mg/kg (**only** if still on suspected diet)

Therapy:

- reversible if removed quickly from toxic diet → recovery 2-3 weeks
- ensure adequate water supply, control diarrhoea
- blindness is permanent

References: Os181, Se311, VM8/1480

Knight PR (1975) Neurotoxicosis in pigs caused by excessive arsanilic acid ingestion: clinical observations. *Aust. Vet. J.* **51**:540.

Osweiler GD *et al.* (1985) *Clinical and Diagnostic Veterinary Toxicology.*

*Selenium (*q.v.*)*

☑ *Vitamin A (*q.v.*)*

See under Mammals (above)

Dialkylimidazoles (indole alkaloids) - Ammoniated forage toxicity

Syndrome names: ammoniated forage toxicity, ammoniated hay toxicity, bovine hysteria, bovine bonkers

Chemical structure:

- toxic dialkylimidazoles include (Sivertsen & Muller 1999)
  - 4-methyl imidazole
  - 1,2-dimethylimidazole
  - 1,4-dimethylimidazole

- 1,5-dimethylimidazole
- 2,4-dimethylimidazole
- 2-ethyl-4-methylimidazole

- substituted imidazoles form from soluble carbohydrates and ammonia; factors affecting the reaction include concentrations of ammonia & moisture and temperature (Johns *et al.* 1984)

Sources:

- fodder (roughages, hay) treated with anhydrous ammonia to increase digestibility, crude protein content and intake; ammonia also inhibits mould growth and allows storage of forages at moisture contents that would spoil under normal conditions (Johns *et al.* 1984)
- ammoniated molasses

Toxicity:

- cattle, sheep affected
- cases reported from North America, Scandinavia

Mode of action: not clearly described

Conditions of poisoning:

- ruminants fed high-quality grasses (cereal grain hay, sorghum hay, immature grass hay) or molasses treated with ammonia at 2-3 or > 4% of its weight as the primary feedstuff; toxicity not recorded on corn silage or low-quality ammoniated forages including late-cut mature grass, corn stalks, straw or soybean stubble (Johns *et al.* 1984, Weiss *et al.* 1986)
- calves (or lambs) fed milk from cows consuming ammoniated forage (Weiss *et al.* 1986)

Clinical signs:

- hyperexcitability; affected animals difficult to handle
- circling, running into obstacles
- convulsions

Pathology:

- affected animals are acidotic with increased pyruvic and lactic acid concentrations in blood (Weiss *et al.* 1986)
- necropsy findings undescribed

Diagnosis:

- access & syndrome
- assay feed for imidazoles; qualitative by GC-MS (available in only some laboratories)

Therapy: remove the ammoniated fodder from the ration

Prevention & control: no clear guidelines available

References:

VM8/1524

Johns JT, LaBore D, Evans JK (1984) Ammoniated forages and bovine hysteria. *J. Am. Vet. Med. Assoc.* **185**:215.

Kirstensen VF, Enevoldsen C, Witt N, Nielsen P, Kraul I, Friis C, Nielsen TK, Wolstrup C (1991) [Toxicity of ammoniated roughages.] *Beretning fra Faellesudvalget for Statens Planteavls-og Husdyrbrugforsøg* No.17, 41 pp. [Abstract 4337 (1992) *Vet Bull.* **62**:711]

Sivertsen T, Muller L (1999) Ammoniated forage poisoning: acute toxicity of newly identified dialkylimidazoles to inbred mice. *Vet. Human Toxicol.* **41**:363-368.

Weiss WP, Conrad HR, Martin CM, Cross RF, Shockey WL (1986) Etiology of ammoniated hay toxicosis. *J. Anim. Sci.* **63**:525-532.

Calcium (dogs)

Decreased bone modelling (enostosis with lameness and intramedullary calcification foci) and osteochondrosis in young growing dogs of large breeds (e.g. Great Dane) can be associated with chronic excess dietary intake of Ca, with or without a concomitant rise in P intake.

References:

Schoenmakers I, Nap RC, Mol JA, Hazewinkel HAW (1999) Calcium metabolism: an overview of its hormonal regulations and interrelation with skeletal integrity. *Vet. Quart.* **21**:147-153.

*Nitrate-nitrite (***q.v.***)*

See notes under phytotoxins above. Water and meat preservatives can be sources of nitrate-nitrite.

10: Other household, farm or industrial chemicals [Industrial-origin toxins]

ANTIFREEZE

Ethylene glycol

Core data

Common source: motor vehicle antifreeze
Animals affected: cat, dog (cattle)
Poisoning circumstances:
- approaching winter
- radiator fluid attractive to dogs, cats

Main effects:
- hypocalcaemia
- acidosis
- dehydration
- nephrosis + calcium oxalate crystals

Diagnosis: history + clinical pathology
Therapy:
- < 4 hr after ingestion or prognosis poor;
- emetic, activated charcoal + saline cathartic
- vigorous fluid therapy
- ethanol or 4-methylpyrazole (dog) + sodium bicarbonate

Sources:
- motor vehicle radiator **anti-freeze** (95% EG)
- minor sources include
  - de-icers
  - detergents
  - colour film processor kits (Thrall *et al.* 1984)

Toxicity:
- **cats** (minimum toxic dose = 1.5 ml/kg with mortality up to 100%), **dogs** (minimum toxic dose = 4.2-6.6 ml/kg with mortality of 60-70%) (Khan *et al.* 1999)
- calves (2.0 ml/kg), adult cattle (5-10 ml/kg), goats, pigs
- poultry (Hutchison & Dykeman 1997)

Mode of action:
- EG metabolised through several steps to
  - oxalic acid → nephrotoxicity, hypocalcaemia; combination of acids → acidosis

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Ethylene glycol → glycoaldehyde → glycolic acid → glyoxylic acid → **oxalic acid** → Ca oxalate

Hepatic alcohol dehydrogenase-dependant oxygenation

↓ ↓
↓ formic acid + CO_2
glycine + benzoic acid → hippuric acid
& glycine + serine

Conditions of poisoning:
- "winterising" vehicles → radiator fluid attractive to dogs, cats
- rapid absorption in absence of food → signs in < 1 hr
- peak EG concentrations: blood 1-4 hr, urine 6 hr

Clinical signs (dogs, cats):

12-24 hr after ingestion

- CNS effects → depression, stupor, hypothermia, ataxia, weakness
- GI effects → vomiting, anorexia
- ↑plasma osmolality → polydipsia (thirst centre stimulus) → polyuria (also ethylene glycol-induced diuresis)
- dehydration
- acidosis → tachycardia, hyperpnoea
- abdominal pain (particularly in renal area)

- occasional transient recovery, then rapid deterioration
- large EG doses → coma and death in 12-36 hours (with a distinct bias toward 12 hrs!)
- vomiting, if frequent & complete, usually prevents coma & death, but fatal doses usually retained

24-72 hr after ingestion

- renal insufficiency → uraemia
- further depression
- vomiting, oral ulcers
- oliguria, anuria
- convulsions

Pathology:

- clinical pathology
  - dehydration → ↑PCV, total protein
  - **renal azotaemia** → ↑urea, creatinine, inorganic P, K, ↓ Cl
  - **hypocalcaemia** (precipitation by oxalic acid; secondary to acidosis)
  - ↓ blood pH
  - hyperglycaemia (adrenalin, corticosteroid, insulin inhibition)
  - neutrophilia, lymphopaenia (from endogenous corticosteroid release &/or uraemia)
- urinalysis
  - ↓ pH & SG
  - proteinuria , glucosuria, haematuria
  - crystalluria (calcium oxalate, hippurate)
    - calcium oxalate dihydrate crystals (Maltese cross or envelope forms) seen in <20% of dogs and cats (Thrall *et al.* 1984)
    - hippuric acid crystals seen in 44% of dogs and 18% of cats (Thrall *et al.* 1984)
    - hippuric acid crystals reported as more easily recognised than oxalate crystals in microurine preparations (Kramer *et al.*1984); clear, variable in size, 6-sided with rounded corners, polarise light (birefringent), about 10% have a 4-sided daughter crystal "flaking" from the parent crystal with one end open where it emerges from the parent.
  - casts, leucocytes, renal epithelial cells
- necropsy
  → GI mucosal hyperaemia, pale swollen (acute cases) or mottled (chronic cases) kidneys
- histopathology → **nephrosis + calcium oxalate crystals in tubules**

Diagnosis:

combination of time of year with blood biochemistry & urinalysis
assay serum, stomach contents (vomitus) or suspected source for ethylene glycol and its metabolite glycolic acid by isocratic HPLC in a rapid test (10 min turn-around time) available only in some laboratories (Smith & Lang 2000).

Therapy:

- fairly successful if risk recognised before significant metabolism of the ingested ethylene glycol has occurred (< 4 hrs after ingestion)
- prognosis poor if
  - very low blood pH, severe base deficit, high venous oxygen concentration
  - 30 hr post exposure: blood urea, creatinine & P continue to rise, persisting hypocalcaemia & hypothermia

within 3-4 hrs of EG ingestion

- **reduce EG absorption**

→ emetic, then activated charcoal + saline cathartic

- **rehydrate, promote EG excretion**

→ vigorous fluid therapy (→ rehydrate, alleviate acidosis, promote renal EG excretion)

- after rehydration or if oliguria may → osmotic diuretics (e.g. dextrose, mannitol) → promote EG excretion

- **reduce hepatic EG metabolism to oxalic acid, correct acidosis, retard crystal formation**

→ pyridoxine & thiamine

- cofactors in glyoxylic acid metabolism along paths not ending in oxalic acid

→ compounds that compete with EG for hepatic alcohol dehydrogenase → ↑ excretion of unmodified ethylene glycol - **ethanol**, alkyldiols (**4-methylpyrazole** (fomepizole; Antizol-Vet®), 1,3-butanediol, propylene glycol)

→ **sodium bicarbonate** to control acidosis, promote renal excretion of toxin & inhibit renal precipitation of oxalate crystals

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Ethanol + sodium bicarbonate protocol (dogs & cats)

→ infuse 20% ethanol in saline @ 5.5 ml/kg IV (dog), 5.0 ml/kg i/p (cat)

→ infuse 5% sodium bicarbonate solution IP @ 8.0 ml/kg (dog), 6.0 ml/kg (cat)

treatment frequency: every 4 hrs (dog) or 6 hrs (cat) for 5 treatments, then four times daily for 5 treatments

side effects: ↑ CNS depression, diuresis → further dehydration

4-methylpyrazole (4-MP) protocol (**dogs only**)

→ infuse 5% 4-MP in 50% polyethylene glycol IV initially @ 20 mg/kg, then at 12 & 24 hrs @ 15 mg/kg then at 36 hrs @ 5 mg/kg

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- prognosis guarded if significant metabolism has occurred

→ symptomatic for renal failure (haemodialysis, peritoneal dialysis)

Prevention & control:

- prevent access
- 10 ppm denatonium benzoate (Bitrex®) bittering agent is added to some ethylene glycol products for automotive use to try to prevent consumption by children (and pets). [Caltex Anti-Freeze Anti-Boil Coolant, Caltex Extended Life Coolant, Penzoil Anti-freeze and Summer Coolant]
- new de-icing / anti-freeze compounds are under development

References: Os317, Se329, VM8/1530

Connally HE, Thrall MA, Forney SD, Grauer GF, Hamar DW (1996) Treatment of ethylene glycol poisoning in dogs. *J. Am. Vet. Med. Assoc.* **209**:1880

Hutchison TWS, Dykeman JC (1997) Presumptive ethylene glycol poisoning in chickens. *Can. Vet. J.* **38**:647.

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GASES & VAPOURS

Professor Dewar
Is a better man than you are.
None of you asses
Can condense gases.

Edmund Clerihew Bentley

☑ *Polytetrafluoroethylene (PTFE, polytef) - birds*

Core data

Common sources:

- empty overheated non-stick cookware
- heat lamps coated with PTFE

Animals affected:

- caged birds (small parrots such as budgerigars)
- poultry

Mode of action: pyrolysis products directly damage lung cells
Poisoning circumstances: inhalation of fumes
Main effects: sudden death, dyspnoea
Diagnosis: access + pathology
Therapy: nil
Prevention: avoid exposure

Sources:

- non-stick fluorocarbon polymer coatings [Teflon®, Silverstone®] on
  - cookware, cooking utensils (Blandford *et al.* 1975, Holt 1978)
  - baking sheets (Forbes & Jones 1997)
  - some heat lamps (Richardson 1991, Forbes & Jones 1997, Boucher *et al.* 2000)

Circumstances of poisoning:

- exposure of **caged birds** to fumes from **empty over-heated non-stick cookware**
- exposure of **poultry** (chickens & ducklings) (Boucher *et al.* 2000), raptors (Forbes & Jones 1997), birds in a zoological collection (Richardson 1991) to **heat lamps** coated with Teflon® [surface temperatures measured as 202 ^{o}C (Boucher *et al.* 2000)]
- exposure of free-flying birds to emissions from industrial plants using PTFE (Pennycott & Middleton 1997)
- coatings heated to > 260^{o}C → pyrolysis → polymer fumes [conventional electric stove will heat empty cookware to 400^{o}C in 8 min; cooking oils or butter will flame and other food will smoke & burn @ 280^{o}C]

Toxicity:

- transient "polymer fume fever" recognised in humans exposed to polymer fumes
- susceptibility: small parrots (**budgerigars**, cockatiels, love birds), other birds >>> humans
- pyrolysis products of PTFE include particulates of respirable size (< 1μm); particulates are toxic and contain or act as vehicles for other toxic compounds (including hydrogen fluoride, carbonyl fluoride, perfluoroisobutylene)
- fumes are acidic → direct damage to lung epithelium

Clinical signs:

- onset within 1 hr of exposure
- high fume concentrations → **sudden death**
- lower concentrations → dyspnoea, weakness, ataxia
- ± vomiting (Blandford *et al.* 1975)

Pathology:

- lung congestion, oedema, haemorrhage & necrosis

- air sacculitis

Diagnosis: history & pathology

Therapy: nil

Prevention/Control: avoid exposure

References:

Humphreys 84

Anon. (1969) *Cosmet. Toxicol.* **7**:368.

Blandford TB, Seamon PJ, Hughes R, Pattison M, Wilderspin MP (1975) A case of polytetrafluoroethylene poisoning in cockatiels accompanied by polymer fume fever in the owner. *Vet. Rec.* **96**:175-176.

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Wells RE (1983) Fatal toxicosis in pet birds caused by an overheated cooking pan lined with polytetrafluoroethylene. *J. Am. Vet. Med. Assoc.* **182**:1248-1250.

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Vapours from cooking fats/oils (birds)

Overheated fats and oils. Similar circumstances and effects to PTFE intoxications (above). Caged birds particularly susceptible.

References:

Humphreys 81

Duff P (1997) Acute inhalant toxicoses of cage birds. *Vet. Rec.* **141**:107.

Carbon monoxide

Chemical structure: CO

Sources:

- exhaust gas from internal combustion engines (diesel, petrol)
-

Circumstances of poisoning:

- caged birds (poultry, canaries) in buildings near parked vehicles with their engines running (Reece *et al.* 1985)

Clinical signs: dyspnoea, sudden death

Pathology: blood bright red (carboxy-haemoglobin)

References: Os177, Hu81, GM107

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.

Hydrogen sulphide (H_2S, manure gas)

See notes on sulphur (*q.v.*)

Sources:

manure pits

petroleum, sour gas and geothermal wells (Raisbeck 1999)

Toxicity & Clinical signs:

H_2S concentrations in air of

< 1 ppm – odour detectable and should provide warning to protect animals and people from acute poisoning, but high concentrations negate this (see below) (Raisbeck 1999).

> 50 ppm – conjunctivitis (lachrymation, photophobia) progressing to **keratitis** and blindness if exposure is prolonged; **dyspnoea** from oedema progressing to permanent scarring in the terminal bronchioles with inhibition of alveolar macrophage function predisposing to respiratory infections if exposure is prolonged (Raisbeck 1999)

>100-200 ppm – paralysis of olfactory epithelium, thus negating odour as a warning stimulus (Raisbeck 1999)

> 500 ppm – acutely lethal (**sudden death**) (Raisbeck 1999)
1000-2000 ppm - respiratory paralysis and death in minutes (Hooser *et al.* 2000). Convulsion may occur (Raisbeck 1999)
>2000 - H_2S directly paralyses the respiratory centre; 1-2 breaths lead to respiratory paralysis, generalised convulsions and death (Hooser *et al.* 2000)

Mode of action:

H_2S blocks oxidative metabolism in virtually all tissues, with the most profound effect on the CNS. Inhibition of the carotid body produces hyperpnoea followed by acarbia, apnoea and asphyxiation (Raisbeck 1999)

Circumstances of poisoning:

Inhalation of manure gas: agitation of manure in pits beneath animal confinement facilities → release of gas bubbles trapped in the manure (Hooser *et al.* 2000)

Pathology: polioencephalomalacia, vacuolation of sub-cortical white matter (Hooser *et al.* 2000)

Diagnosis:

syndrome + history of exposure
measurement of H_2S concentration in ambient air. **Warning**: extreme care is required during investigation of these cases. Protective breathing apparatus may be required.

Therapy:

usually not a practical option
theoretically possible through ventilation of affected animals with clean air if treatment starts immediately (Raisbeck 1999).

References:

Review literature

VM8:1531
Nordstrom GA, McQuirty JB (1976) *Manure Gases in the Environment. A Literature Review (with particular reference to cattle housing).* Department of Agricultural Engineering, Faculty of Agriculture & Forestry, University of Alberta, Edmonton, Canada.

General literature

Hooser SB, van Alstine W, Kiupel M, Sojka J (2000) Acute pit gas (hydrogen sulphide) poisoning in confinement cattle. *J. Vet. Diagn. Invest.* **12**:272-275.
Raisbeck MF (1999) Polioencephalomalacia and other forms of sulfur intoxication in ruminants. *Proc. Aust. Soc. Vet. Pathol. Conf.* pp.5-8.

Nitrogen dioxide (silage gases)

Syndrome names: "silo fillers disease" (humans)
Chemical structure: NO_2
Sources:

- **first few days of silage fermentation** → large quantities of gas, mainly CO_2 (0.2 – 9.1%) as well as a mixture of oxides of nitrogen (up to 400-500 ppm)
- oxides of N: nitrous oxide (N_2O), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4)
- in first hours of ensiling, indigenous bacteria begin → reduction of forage nitrate via nitrite to ammonia or NO or N_2O
- NO (colourless gas, the main oxide of N produced), exposed to air → spontaneous oxidation → **NO_2** (reddish-brown, heavy gas with irritating odour)

Toxicity:

- cattle, pigs, humans

Mode of action:

- NO & NO_2 react readily with water → nitrous acid (HNO_2) and nitric acid (HNO_3)
- these reactions occur in the water film lining the respiratory tract → severe respiratory irritation

Conditions of poisoning:

- silage made from high-nitrate content plant material (Wlikinson 1999)
- animals confined to pens or buildings and exposed to gas flowing from a silage container

Clinical signs:

- coughing
- dyspnoea (tongue extended, salivation)
- in humans, despite only mild irritation initially, death may occur up to a month later from serious lung injury (bronchitis fibrosa obliterans)

Pathology:

- pulmonary oedema, haemorrhage, emphysema

- fibrin in alveoli
- hyperplasia of respiratory epithelium
- obliterative bronchiolitis (chronic sequel to acute toxicity)
- nephrosis, skeletal muscle necrosis

Diagnosis: access to fermenting silage container, presence of red-brown heavy gas, syndrome
Therapy: supportive (antibiotics, anti-inflammatories)
Prevention & control: deny/prevent access, improve ventilation of silos
References:

Humphreys 84
Brightwell AH (1972) "Silo gas" poisoning in cattle. *Can. Vet. J.* **13**:224-225.
Cutlip RC (1966) Experimental nitrogen dioxide poisoning in cattle. *Path. Vet.* **3**:474-485.
Giddens WE, Whitehair CK, Sleight SD (1970) Nitrogen dioxide (silo gas) poisoning in pigs. *Am. J. Vet. Res.* **31**:1779-1786.
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O'Kiely P, Turley T, Rogers PAM (1999) Exposure of calves to nitrogen dioxide in silage gas. *Vet. Rec.* **144**:352-353.
Wilkinson JM (1999) Silage and animal health. *Nat. Toxins* **7**:221-232.

Gaseous chemical warfare agents used in World War 1

The trench warfare stalemate on the western front in France during 1914-1918 stimulated a search for weapons to break the deadlock. Poisonous gases were one avenue explored, unsuccessfully, by both sides. They were either released from cylinders in the front-line trenches and drifted onto the enemy lines with the wind, or were fired into enemy positions in artillery shells. Directed at soldiers, they also affected draft animals (horses) employed by the armies and livestock in the vicinity of the front. (Anon 1970)

Agent	**Date of first use**	**Approximate incapacitating concentration after a few seconds (parts per 10 million)**	**Approximate lethal concentration if breathed for > 1-2 min (parts per 10 million)**	**Combatants employing the agent B = British F = French G = German A = Austrian**
Acute lung irritants				
Chlorine	1915	1000	1000	B, F, G
Phosgene	1915	100	200	B, F, G
Chlormethyl-chloroformate	1915	100	1000	B, G
Trichlormethyl-chloroformate	1916	50	200	B, G
Chloropicrin	1916	50	200 cumulative	B, F, G
Stannic chloride	1916	-	1000	B
Phenyl-carbylamine-chloride	1917	50	1000	G
Cyanogen bromide	1918	-	300	A
Dichlor-methyl-ether	1918	1000	1000	G
Lachrymators (tear-producers)				
Benzyl bromide	1915	5	-	G
Xylyl bromide	1915	5	-	G
Ethyl-iodoacteate	1916	2-5	200	B
Bromacetone	1916	5	1000	B, A
Monobrom-methyl-ethyl-ketone	1916	2	2000	G, A
Dibrom-methyl-ethyl-ketone	1916	2	2000	G, A
Acrolein	1916	-	-	B
Methyl-chlorsulphonate	1915	-	-	G

Agent	Date of first use	Approximate incapacitating concentration after a few seconds (parts per 10 million)	Approximate lethal concentration if breathed for > 1-2 min (parts per 10 million)	Combatants employing the agent B = British F = French G = German A = Austrian
Paralysants				
Hydrocyanic acid (HCN)	1916	5000 rapidly fatal	5000	B, F
Sulphuretted hydrogen (H_2S, rotten-egg gas)	1916	10000 rapidly fatal	1000 affects eyes & lungs	B
Sternutators (sensory irritants of eyes, nose & chest)				
Diphenyl-chlorarsine	1917	1	200	G
Diphenyl-cynarsine	1918	1	200	G
Ethyl-dichlor-arsine	1918	20	500	G
Ethyl-dibrom-arsine	1918	-	-	G
N-ethyl carbazol	1918	-	-	G
Vesicants (blister producers)				
Dichloroethylsulphide (Mustard gas)	1917	-	10 (60 min exposure)	B, F, G, A

References

Anon. (1970) Gas. The odour of death. *History of the First World War* (Purnell:BPC Publishing Ltd., London). Volume 8, pp.3266-3267.

FERTILISERS

Nitrogenous fertilisers

See Nitrate-nitrite under Phytotoxins

Superphosphate

See fluorine

Gypsum

Gypsum = $CaSO_4 . 2H_2O$

See notes under S-associated polioencephalomalacia

Sheep with access to dumps of gypsum fertiliser used on *Brassica napus* (canola) crops because of their high demand for S. Ingestion in quantity → ruminal acidosis / metabolic acidosis (Dent 1997)

Possible chronic toxicity in cattle has been reported (Bourke & Ottway 1998)

References:

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

Dent CHR (1997) Sheep deaths after accidental ingestion of gypsum fertiliser. *Aust. Vet. J.* **75**:26-27.

ABSORBANTS

Bentonite (cats)

Chemistry:

Bentonite = Wilkinite. A colloidal native hydrated aluminium silicate (clay).

Cat; chronic ingestion of cat litter containing bentonite

Lethargy, muscle weakness

Hypokalaemia + hypochromic anaemia (iron deficiency)

Reference:

Hornfeldt CS, Westfall ML (1996) Suspected bentonite toxicosis in a cat from ingestion of clay cat litter. *Vet. Human Toxicol.* **38**:365-366.

WOOD PRESERVATIVES

Chlorinated phenols

Sources & Chemical structure:

creosote, pentachlorophenol (PCP) are wood preservatives (now replaced by the copper arsenates)

Toxicity:

- uncouple oxidative phosphorylation
- rare
- moderately toxic - acute lethal dose 50-150mg/kg for most domesticated animals

Conditions of poisoning:

- skin contact with freshly-treated timber
- in wood shavings used for poultry litter (N America) → egg taint
- wood shavings used as bedding for cats (Peet *et al.* 1977)

Clinical signs:

- mild poisoning → signs occur & regress in 24 hr
- severe poisoning → death in 24-36 hr
- rapid absorption from intact skin or alimentary tract →
  - incoordination, muscle tremor
  - depression → coma → terminal respiratory failure
- slow absorption →
  - ± haemolysis
  - progressive jaundice → death
- concentrated solutions corrosive to mucosae

Pathology: congestion, jaundice, hepatocyte degeneration, nephrosis, coagulation necrosis of epithelia

Diagnosis:

- urine tests (both positive → presumptive diagnosis)
  - 10 ml urine + 1 ml 20% aqueous ferric chloride → purple if positive
  - 10 ml urine boiled with 1-2 mls Millon's reagent [10 g Hg in 20 ml nitric acid, dilute with equal volume dist.H_2O, stand 2 hr, decant excess H_2O] → red if positive

Therapy: No specific therapy.

References: Os273, Se240, VM8/1521

Peet RL, MacDonald G, Keefe A (1977) Possible pentachlorophenol poisoning in cats. *Aust. Vet. J.* **53**:602.

TCDD (dioxin) & polychlorinated biphenyls (PCBs)

Chemical structure:

TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin

Sources:

- heat exchanger fluid
- electrical transformer fluid
- herbicides (contaminated with dioxins in manufacture)
- waste oil sludge
- open household rubbish fires (Lemieux *et al.* 2000, Hecht 2000)

- PCB manufacture was banned in Japan in 1972 and in USA in 1976, but environmental release has not stopped (Finklea *et al.* 2000).

Toxicity:

- no toxicity recorded in mammals in Australia to date
- USA: horses, dogs, cats, birds, humans
- low acute toxicity
- persistent in environment
- residues in animal products from contaminated livestock
- residues detected in Tasmanian platypuses (Munday *et al.* 1998), cetaceans (Finklea *et al.* 2000)
- act as thyroid antagonists/agonists with effects on spatial learning in rats (Schrantz *et al.* 1997); suspected of causing cognitive deficits in children (Jacobson & Jacobson 1996)

Conditions of poisoning:

- TCDD contaminated waste oil sludge sprayed on horse exercise ground to lay dust (USA)
- contaminated fats included in poultry diets

Clinical signs:

TCDD, horse: chronic **emaciation** with rapid weight loss**, hair loss**, dermatosis → **ulcerative dermatitis** extending to oral & nasal mucosae, dependent oedema, colic, haematuria, conjunctivitis, joint stiffness, laminitis

TCDD, dog, cat: hair loss, emaciation, chronic respiratory, oral & nasal lesions

Dioxins, PCBs, poultry: "Chicken oedema disease" or "toxic fat disease" - dyspnoea, depression, high mortality within 3-9 weeks of feeding

Pathology:

TCDD, horse: cerebrocortical oedema, adrenal cortex focal necrosis, diffuse portal cirrhosis, biliary ductular dilation, marked spleen & lymph node atrophy

Dioxins, PCBs, poultry: "Chicken oedema disease" or "toxic fat disease" - anasarca, ascites, hydropericardium, cardiac dilation, hepatomegaly, swollen pale kidneys; endothelial proliferation in small arteries, myocardial degeneration, glomerular endothelial proliferation

References: Os 218,224, Se243,247, VM8/1527,1528

Finklea B, Miller G, Busbee D (2000) Polychlorinated biphenyl residues in blubber of male Atlantic bottlenose dolphins (*Tursiops truncatus*) that stranded and died at Matagorda Bay. *Bull. Environ. Contam. Toxicol.* **64**:323-332.

Hecht J (2000) Definitely not in your backyard. *New Scientist* **165**(2221):8.

Jacobson JL, Jabobson SW (1996) Intellectual impairment in children exposed to polychlorinated biphenyls *in utero*. *New Engl. Med. J.* **335**:783-789.

Lemieux PM, Lutes CC, Abbott JA, Aldous KM (2000) Emissions of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans from the open burning of household waste in barrels. *Environ. Sci. Technol.* **34**:377-384.

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.

Schrantz SL, Seo BW, Moshtaghian J, Amin S (1997) Developmental exposure to polychlorinated biphenyls or dioxin: Do changes in thyroid function mediate effects on spatial learning? *Amer. Zoologist* **37**:399-408.

See also Arsenic, Copper, Chromium

DISINFECTANTS & CLEANING PRODUCTS

Chlorates

Strongly oxidising compounds → haemolysis, Heinz body formation, methaemoglobinaemia, disseminated intravascular coagulation
Irritant to alimentary tract (vomiting, diarrhoea)
Nephrotoxic → acute renal failure
Toxicity reported in humans, horses, cattle, sheep, fowls, pigs, dogs
Toxicity from careless disposal or accidental inclusion in feed
References: Os172,174

Gregory DG, Miller S, Whaley MW (1993) Chlorate toxicosis in a group of swine. *J. Vet. Diagn. Invest.* **5**:494-496.

Dichloromethane

Dog, UK, ingestion of paint stripper
Dichloromethane is metabolised to yield carbon monoxide and carbon dioxide which precipitate the clinical syndrome
Clinical signs: hyperexcitability, persistent convulsions (Harcourt-Brown *et al.* 2000)
Therapy: anaesthesia to suppress convulsions + pure oxygen
Reference:

Harcourt-Brown NH, Dawson MT, Judd AT (2000) Dichloromethane poisoning in a dog: a case report. *Vet. Rec.* **146**:48-49.

Hexachlorophene

Chemical structure:
A chlorinated phenol
Sources: antiseptic skin preparations
Toxicity:
- dogs, cats, calves, sheep
- uncouples oxidative phosphorylation
- young animals particularly susceptible (premature human infants)

Conditions of poisoning:
- ingestion
- skin application of 3% emulsion to areas of dermatitis for 7 days (dogs)

Clinical signs:
- severe **tremors** (dog, calf)
- weakness, **ataxia → flaccid paralysis** (cat, sheep)
- opisthotonus, nystagmus, stiffness (calf)
- diarrhoea (sheep)
- **blindness** in recovered sheep

Pathology:
- status spongiosis of CNS white matter (reversible lesion)
- permanent optic nerve degeneration (sheep) - Sheep recovered from acute poisoning have permanent damage to the optic nerves.

Diagnosis:
- history of exposure, clinical syndrome, pathology

Therapy:
- remove source
- supportive measures

Prevention & Control:
- avoid application to inflamed skin (?)

References: Os144, Se250

Finnie JW, Abbott DP, Allan ETB (1978) Hexachlorophene poisoning in a dog. *Aust. Vet. J.* **54**:365.

HUMAN FOODS & BEVERAGES

☑ Chocolate (theobromine)

Core data

Common sources: cocoa powder, chocolate
Animals affected: dogs
Mode of action: interference with the electrical activity of cardiac myocytes
Poisoning circumstances: rapid consumption of large amounts of cocoa powder or confectionary dominated by chocolate
Main effects:

- sudden death, myocardial necrosis
- pancreatitis

Diagnosis: syndrome + possible assay of stomach contents
Therapy: decontamination + antiarrhythmic drugs
Prevention: deny access

Chemical structure:

Theobromine = 3,7-dimethylxanthine

Sources:

- Plant source: *Theobroma cacao* → **cocoa**, **chocolate**
- Immediate sources:

cocoa powder (250 g packet lethal for a dog)
confectionary consisting entirely of or containing a large proportion of cocoa or chocolate

Organ systems affected: heart

Toxicity:

Animal species affected: Dogs

- Theobromine content of various sources in descending order of toxic risk (calculated from data in Gfeller & Messonnier 1998)

Source	Theobromine (g/kg)
Cocoa powder	5.3 – 21.0
Cooking chocolate (unsweetened)	15.8
Semisweet or dark chocolate	4.6 – 6.5
Milk chocolate	1.6 – 2.1

- Comparative toxicity of theobromine with other methylxanthines (Gans *et al.* 1980, Bruneton 1999a)

Methylxanthine	Oral LD_{50} (mg/kg) – single dose	
	Dog	Cat
Caffeine (1,3,7-trimethylxanthine)	140	100
Theobromine (3,7-dimethylxanthine)	Undetermined*	200
Theophylline (1,3-dimethylxanthine)	290	800

* single oral doses of 300, 500 and 1000 mg/kg each resulted in death of 1 dog from groups of 4, 8 and 2 respectively (Gans *et al.* 1980)

Mode of action:

Proposed mechanisms of physiological and pharmacological effects of methylxanthines have included (Serafin 1996):

- inhibition of phosphodiesterases, thus increasing intracellular cyclic AMP
- direct effects on intracellular calcium concentrations
- indirect effects on intracellular calcium concentration through cell membrane hyperpolarisation

- uncoupling of intracellular calcium increases with muscle contractile elements
- antagonism of adenosine receptors

Conditions of poisoning:

rapid consumption of large amounts of cocoa powder (250 g packet lethal for a dog) or confectionary dominated by chocolate

Clinical signs:

- Sudden death during exercise, cyanosis, tachycardia, terminal convulsions
- Pancreatitis can follow a large chocolate ingestion episode in dogs within a few days in some cases due to the high fat content (Plumlee K (2000) personal communication, VETTOX Discussion List)

Pathology:

- Necropsy → pulmonary oedema suggesting heart failure or no gross lesions
- Focal cardiomyopathy
- ± pancreatitis

Diagnosis:

history of consumption of large amount of chocolate/cocoa powder + syndrome + assay of stomach contents for theobromine

Therapy:

prompt decontamination measures (*q.v.*)
antiarrhythmic drugs

Prevention & control: deny access to large amounts of chocolate or cocoa powder to dogs

References (theobromine):

Bell H (1972) Suspected chocolate poisoning in calves (Correspondence). *Vet. Rec.* **90**:409. [reported poultry deaths associated with feeding cocoa shell]

Black DJG, Barron NS (1943) Observations on the feeding of a cacao waste product to poultry. *Vet. Rec.* **55**:166-167.

Blakemore F, Shearer GD (1943) The poisoning of livestock by cacao products. *Vet. Rec.* **55**:165.

Bruneton J (1999a) p.497-498.

Clough GW (1942) Theobromine poisoning in the dog. *Vet. J.* **98**:196-197.

Curtis PE, Griffiths JE (1972) Suspected chocolate poisoning of calves. *Vet. Rec.* **90**:313-314.

Decker RA, Meyers GH (1972) Theobromine poisoning in a dog. *J. Am. Vet. Med. Assoc.* **161**:198-199.

Drolet R, Arendt TD, Stowe CM (1984) Cacao bean shell poisoning in a dog. *J. Am. Vet. Med. Assoc.* **185**:902.

Gans JH, Korson R, Cater MR, Ackerly CC (1980) Effects of short-term and long-term theobromine administration to male dogs. *Toxicol. Appl. Pharmacol.* **53**:481-496.

Gfeller & Messonnier (1998) pp.109-113.

Glauberg A, Blumenthal HP (1983) Chocolate poisoning in the dog. *J. Am. Anim. Hosp. Assoc.* **19**:246-248.

Gunning OV (1950) Theobromine poisoning in ducks due to the feeding of cacao waste products. *Br. Vet. J.* **106**:31-32.

Hornfeldt CS (1987) Chocolate toxicity in dogs. *Mod. Vet. Pract.* pp.552-554.

Horskam EG, Haagsma J (1974) [Chocolate poisoning terminating in the death of two Dachshunds] *Tijdschr. Diergeneesk.* **99**:523-525.

Hovda LR, Kingston RL (1994) Cacoa bean mulch poisoning in dogs. *Vet. Human Toxicol.* **36**:357.

Serafin WE (1996) Drugs used in the treatment of asthma. Chapter 28 in *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 9th edition. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (eds.) McGraw-Hill, New York. p.673.

Sobamiwa O, Longe OG (1994) Utilization of cocoa-pod pericarp fractions in broiler chick diets. *Anim. Feed Sci. Technol.* **47**:237-244.

Soffietti MG, Nebbia C, Valenza F, Amedeo S, Re G (1989) Toxic effects of theobromine on mature and immature male rabbits. *J. Comp. Path.* **100**:47-58.

Strachan ER, Bennett A (1994) Theobromine poisoning in dogs. *Vet. Rec.* **134**:284.

Sutton RH (1981) Cocoa poisoning in a dog. *Vet. Rec.* **109**:563-564.

Water

Cattle (particularly calves) given access to large volumes of water after previous restrictions; dehydration may predispose

Failure of kidneys to handle overload → ↓ osmolality of blood → intravascular haemolysis → transient haemoglobinuria

Clinical signs:

- hyperaesthesia, muscle tremors, nystagmus, lethargy
- haemoglobinuria

Pathology:

- hyponatraemia (< 110 mEq Na / L), hyopchloraemia, anaemia
- cerebral oedema

Therapy: IV hypertonic saline, mannitol/other diuretics, corticosteroids

References:

Gilchrist F (1996) Water intoxication in weaned beef calves. *Can. Vet. J.* **37**:490-491.

Njoroge EM, Maribei JM, Mbugua PN (1997) Pathological changes in calves that died from experimental water intoxication. *Onderstepoort J. Vet. Res.* **64**:111-114.

Ethanol

see notes under yeasts

MISCELLANEOUS

Coal tar products – liver necrosis

Sources:

- **clay pigeons** (composed of pitch) used for trap shooting as contaminants of pastures
- **linoleum**

Toxicity: pigs/clay pigeons - estimated lethal dose 1 g/kg

Conditions of poisoning:

- pigs, cattle ingestion of fragments of clay pigeons in pasture
- dogs ingesting linoleum (anecdotal: EM Bailey, personal communication VETTOX 1997)

Clinical signs: sudden death

Pathology: massive centrilobular hepatocyte necrosis

Reference: Os321, VM8/1530

Crude oil, petroleum, diesel and associated products

Aspiration pneumonia is a common outcome of ingestion of toxic quantities of these substances.

Cattle are more frequently affected than sheep and goats

Goats experimentally dosed with kerosene (paraffin – North America) (Aslani *et al.* 2000):

@ 10 ml kerosene/kg developed depression, weakness and reluctance to move about lasting 5 days; transient increased body temperatures and respiratory rates; depressed rumen motility for 3 days with dry faeces, blackish in colour and smelling of kerosene from 5-9 days after dosing

@ 20 ml kerosene/kg developed the above plus mild to moderate bloat persisting for 2 days; transient coughing and increased plasma fibrinogen

@ 40 ml kerosene/kg developed severe bloat, frequent coughing, retching and regurgitation of fluid from mouth and nose, depression, star-gazing followed by death in 4 hrs or more gradual onset of severe bloat, coughing, regurgitation, weakness, depression, dyspnoea, tachypnoea, tachycardia and death in 36-48 hrs. Necropsy and histopathology: strong smell of kerosene from the carcase, congestion of trachea and lungs, hydrothorax, fibrinous pleurisy, fibrinopurulent pneumonia with areas of coagulation necrosis, nephrosis, hepatic fatty change, cerebral oedema.

References:

Review literature

Hu125, 193; VM8:1528; VM9:1628

Edwards WC (1989) Toxicology of oil field wastes. Hazards to livestock associated with the petroleum industry. *Vet. Clin. North Am.: Food Anim. Pract.* **5**(2):363-374.

Edwards WC, Gregory DG (1991)Livestock poisoning from oil field drilling fluids, muds and additives. *Vet. Human Toxicol.* **33**:502-504.

General literature

Aslani MR, Movassaghi AR, Mohri M, Vojdani M (2000) Experimental kerosene poisoning in goats. *Vet. Human Toxicol.* **42**:354-355.

Barber DM, Cousin DAH, Seawright D (1987) An episode of kerosene poisoning in dairy heifers. *Vet. Rec.* **120**:462-463.

Coppock RW, Mostrom MS, Khan AA, Semalulu SS (1995) Toxicology of oil field pollutants in cattle: a review. *Vet. Human Toxicol.* **37**:569-576.

Coppock RW, Mostrom MS, Stair EL, Semalulu SS (1996) Toxicopathology of oilfield poisoning in cattle: a review. *Vet. Human Toxicol.* **38**:36-42.

Kahn AA *et al.* (1996) Biochemical effects of pembina cardium crude oil exposure in cattle. *Arch. Environ. Contamin. Toxicol.* **30**:349.

Leighton FA (1986) Clinical, gross, and histological findings in herring gulls and Atlantic puffins that ingested Prudhoe Bay crude oil. *Vet. Pathol.* **23**:254-263.

Pahl G (1988) Dieseline poisoning in a steer. *Post-Grad. Committee in Vet Science, University of Sydney: Control & Therapy Series*. Mailing 143, No.2591.

Row LD, Dollahite JW, Camp BJ (1973) Toxicity of two crude oils and of kerosene to cattle. *J. Am. Vet. Med. Assoc.* **162**:61-66.

Toofanian F, Aliakbari S, Ivoghli B (1979) Acute diesel fuel poisoning in goats. *Trop. Anim. Hlth. Prod.* **11**:98-101.

TCDD (dioxin)

See notes under wood preservatives

11: Pharmaceuticals (human & veterinary) [Industrial-origin toxins]

ANALGAESICS & ANAESTHETICS

Paracetamol (cats)

Core data

Common source: human medication
Animals affected: cats >> other species; cat toxic dose 50-100 mg/kg (1 tablet/capsule)
Mode of action: cats deficient in hepatic glucuronidation (Phase II) enzymes
→ high doses metabolised in Phase I → active metabolites which:

- oxidise Hb to methaemoglobin
- Heinz bodies in erythrocytes → haemolysis
- bind to macromolecules → liver necrosis

Poisoning circumstances:

- accidental access by pets
- owner dosing for minor illness

Main effects:
Cats:

- Methaemoglobinaemia
- Heinz body haemolytic anaemia (haemoglobinuria)
- liver necrosis

Other species: liver necrosis
Diagnosis: cats: access history + brown blood, Heinz bodies/haemoglobinuria
Therapy:

- N-acetlycysteine (SH group donor)
- methylene blue/ascorbic acid

Q: Why is there no aspirin in the jungle?
A: Parrots eat 'em all

Chemical structure:
paracetamol = 4'-hydroxyacetanilide or *N*-acetyl-*p*-aminophenol
a para-amino phenol derivative

Sources:
- human analgesic medication; North America = **acetaminophen**
- numerous proprietary names for pharmaceutical preparations, often in 300-500 mg capsules/tablets [Trade names in Australia include: Capadex, Codalgin, Codapane, Codral, Di-Gesic, Dymadon, Fiorinal, Mersyndol, Norgesic, Panadeine, Panadol, Panalgesic, Panamax, Paradex, Paralgin, Setamol, Tempra, Tylenol]

Toxicity:
- toxicity in most species → liver necrosis; in cats → early methaemoglobinaemia dominates syndrome, then hepatic damage occurs
- cat toxic dose 50-100 mg/kg (= 1 tablet/capsule); males more susceptible
- dog toxic dose 600 mg/kg; oral 500 mg/kg → > 50% methaemoglobin; 3 doses in 24 hr totalling > 1000 mg/kg → hepatic failure (manifest in 36 hr); hepatotoxicity dominates syndrome
- paracetamol → glutathione depletion in RBC & liver
- methaemoglobinaemia produced by oxidising (electrophilic) metabolites - cat Hb has 8 SH groups/molecule (4 in other species) → specially sensitive to oxidation when glutathione levels fall
- Heinz body formation from irreversible oxidation of Hb SH groups → intravenous haemolysis

- hepatotoxicity: most species metabolise paracetamol in the liver, mainly by glucuronidation (Phase II biotransformation), but also by sulphation (Phase II); cats are deficient in glucuronidation enzymes (glucuronyl transferase) → low paracetamol doses sulphated, but high doses saturate sulphation → ↑ metabolism by cytochrome P450 (Phase I) → activated (electrophilic) metabolic products (e.g. N-acetyl-p-benzoquinone) → covalent binding to macromolecules → hepatic necrosis

Conditions of poisoning:
- accidental access by pets
- owner medication for minor illnesses

Clinical signs:
- depression, anorexia, ± vomiting, ± salivation, ± vocalisation
- **cyanosis**, **dyspnoea**, ↑ heart rate (4-12 hr after ingestion; from methaemoglobinaemia & anaemia)
- **haemoglobinuria** (blood methaemoglobin > 20%), haematuria
- oedema of face & paws + lacrimation, pruritus
- **jaundice** (in 2-7 days)

Pathology:
- methaemoglobin → **brown blood**
- **Heinz bodies** in erythrocytes; ↓ PCV, ↓ haemoglobin concentration
- ↑ serum hepatic enzymes, ↑ bilirubin
- mottled liver; periacinar hepatocyte degeneration/necrosis

Diagnosis: history of access, clinical signs, metheamoglobinaemia (brown blood)

Therapy:
- early therapy (within 4 hr of exposure) → favourable prognosis
- ↑ liver damage → ↓ prognosis
- **stabilise** (fluid therapy, etc.)
- **reduce further absorption** → emesis, activated charcoal, saline cathartic (→ ↑ survival rate)
- **antidote = N-acetylcysteine** [Parvolex®, Mucomyst®] - sulphydryl group (SH) donor → restores depleted hepatic and RBC reduced glutathione (reduces methaemoglobin to haemoglobin), acts as alternative substrate for toxic paracetamol metabolites
- alternative/additional glutathione & sulphate precursors: sodium sulphate, DL-methionine
- possible alternative/additional antagonist of hepatotoxicity: cimetidine [Tagamet®] → inhibition of cytochrome P450 activity

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Acetylcysteine therapy protocol
- 20% (200 mg/mL) solution
- oral dosing should be at least 2 hr **after** activated charcoal to avoid inactivation of antidote
- loading dose 280 mg/kg orally (or IV)
- 70 mg/kg every 4-6 hr for up to 3 days

- **counter methaemoglobinaemia & anaemia**
  - → oxygen and/or blood transfusion
  - antioxidants - ascorbic acid or methylene blue (MB more beneficial in female cats; may antagonise effects of N-acetylcysteine)
- **monitor haematology** for 1 week after therapy
- contraindications: corticosteroids, antihistamines

Supportive & alternative/additional therapy protocols
- sodium sulphate 1.6% solution IV @ 50 mg/kg every 4 hr
- ascorbic acid 40 mg/kg orally every 4 hr
- methylene blue in 10% sterile saline IV @ 1.5 mg/kg; may be repeated 2-3 times if needed (**Caution:** itself a cause of haemolysis in cats)

- DL-methionine [only give **before** extensive liver damage is apparent, otherwise may produce hepatoencephalopathy] @ 70 mg/kg every 8 hr

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Prevention & Control:
- owner education
- health warnings to pet cat owners on packaging?

References: Os303

Review literature

Taylor NS, Dhupa N (2000) Acetaminophen toxicity in cats and dogs. *Compendium on Continuing Education for the Practicing Veterinarian* **22**:160-171.

Bessems JGM, Vermeulen NPE (2001) Paracetamol (Acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. *Critical Reviews in Toxicology* **31**(1):55-138

General literature

Aronson LR, Drobatz K (1996) Acetaminophen toxicosis in 17 cats. *J. Vet. Emergency & Critical Care* **6**:65-69.

Ilkiw JE & Ratcliffe RC (1987) Paracetamol toxicity in a cat. *Aust. Vet. J.* **64**:245-247

Rumbeiha WK *et al.* (1995) Comparison of N-acetylcysteine and methylene blue, alone or in combination, for treatment of acetaminophen toxicosis in cats. *Am. J. Vet. Res.* **56**:1529-1533

☑ Aspirin (acetylsalicylic acid)

Core data

Common sources: human analgesic
Animals affected: cat, dog
Mode of action:
- uncouples oxidative phosphorylation
- inhibits platelet aggregation
- inhibits glycolysis → accumulation of lactic acid & metabolic acidosis
- restricts blood flow to gastric mucosa

Poisoning circumstances: overdose - iatrogenic, owner-administered or rapid consumption from accidental access
Main effects:
- thrombocytopaenia, anaemia
- gastric ulceration

Diagnosis: history, signs & lesions
Therapy:
- decontaminate (within 4 hr of acute dose): emesis, gastric lavage, activated charcoal, osmotic cathartics
- supportive therapy
  - counter metabolic acidosis (IV fluids containing sodium bicarbonate)
  - reduce fever (cooling baths)
  - reverse anaemia if required (transfusion)
  - treat gastric ulcers (sucralfate)
  - control gastric acid-secretion with histamine-receptor antagonists (cimetidine, ranitidine)

Source: commercial human analgesic; 300 & 500 mg tablets
Toxicity:
- cat: therapeutic dose 25 mg/kg/day; toxic dose 80-120 mg/kg for 10-12 days
- dog: therapeutic dose 25-35 mg/kg 3 times daily; toxic dose (acute) 50 mg/kg twice daily, (chronic) 100-300 mg/kg/day for 1-4 weeks [3-8 weeks fatal]
- uncouples oxidative phosphorylation, inhibits platelet aggregation, inhibits glycolysis → accumulation of lactic acid & metabolic acidosis; restricts blood flow to gastric mucosa
- conjugated in liver & excreted in urine → cats at greater risk of toxicity

Conditions of poisoning: overdosing

- medication prescribed by veterinarian
- administered by owner
- accidental access → consumption of large dose

Clinical signs:
- anorexia, depression
- vomiting (± haematemesis)
- melena
- hyperventilation (possibly related to acidosis)
- fever
- ± subacute hepatic failure (including jaundice, coagulopathy)

Pathology:
- thrombocytopaenia, anaemia, Heinz bodies (particularly cats)
- gastric ulcers

Diagnosis: history, signs & lesions

Therapy:
- decontamination (within 4 hr of acute dose): emesis, gastric lavage, activated charcoal, osmotic cathartics
- supportive therapy
  - counter metabolic acidosis (IV fluids containing sodium bicarbonate 1-3 mEq/L)
  - reduce fever (cooling baths)
  - reverse anaemia if required (transfusion)
  - treat gastric ulcers (sucralfate - Carafate®, SCF®, Ulcyte®)
  - control gastric acid-secretion with histamine-receptor antagonists (cimetidine - Magicul®, Sigmetadine®, Tagamet®; ranitidine - Zantac®)

Reference: Os304

💣☑ Other NSAIDs (ibuprofen, naproxen, phenylbutazone)

Core data

Common sources: commercial human analgesics or prescription drugs
Animals affected: cats, dogs, horses
Mode of action: As for aspirin (*q.v.*)
Poisoning circumstances: As for aspirin (*q.v.*)
Main effects: As for aspirin (*q.v.*) + renal necrosis + colic (horses)
Diagnosis: As for aspirin (*q.v.*)
Therapy: As for aspirin (*q.v.*). Aggressive early decontamination indicated.

NSAID = non-steroidal anti-inflammatory drug

Sources: commercial human analgesics or prescription drugs
- ibuprofen = ±2-(4-isobutylphenyl) propionic acid [ACT-3®, Brufen®, Codral Period Pain®, Nurofen®, Rafen®]
- naproxen = (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid [Inza®, Naprosyn®, Proxen®, Anaprox®, Naprogesic®, Synflex®]

Toxicity:

Ibuprofen (dogs; cats are susceptible to doses half those that affect dogs)
- 50 mg/kg repeatedly administered → anorexia, mild gastric irritation
- 100 mg/kg → moderate-severe poisoning **similar to aspirin** (above)
- 300 mg/kg → acute **renal necrosis**
- the above outcomes may be observed at lower doses in practice (Poortinga & Hungerford 1998)
- dogs: significant breed differences in susceptibility – German Shepherd more susceptible, Labrador less susceptible (Poortinga & Hungerford 1998)
- aggressive early decontamination of most dogs accidentally ingesting doses of ibuprofen is recommended; seriously consider advising owners on emetic use before delivering patient to clinic (Poortinga & Hungerford 1998)
- ferret: fatal poisoning recorded (Cathers *et al.* 2000)

Naproxen (dogs)

- 5 mg/kg daily → significant gastrointestinal damage similar to aspirin (above)
- 15 mg/kg is toxic

Phenylbutazone

- dogs:
  100 mg/kg twice daily for > 10 days have caused poisoning
  5 g (1 teaspoon of powder for horses) daily for 7 days (Linnett 2001)
- cats: 44 mg/kg daily for 2 weeks has been lethal
- horses: > 8.8 mg/kg/day; colic, diarrhoea, melena, weight loss, ventral oedema, petechiae of mucous membranes, oral & gastrointestinal erosions & ulcers, renal papillary necrosis (Collins & Tyler 1984)
- horses: ulceration of the right dorsal colon; acute cases have fever, anorexia, depression, colic and/or profuse watery diarrhoea; more chronic cases (some with stricture) present as intermittent fever and low-grade colic, weight loss, hypoalbuminaemia and ventral oedema ± diarrhoea; microvascular endothelial damage and thrombosis → infarction of colonic mucosa; moderate overdose is sufficient to cause lesions in horses; ponies and foals are more susceptible (Hough *et al.* 1999)
- horses (foals): 10 mg/kg/day for 12-42 days has caused gastric and buccal ulcers (Traub *et al.* 1983)
- stimulates respiratory centre, may → respiratory alkalosis

Conditions of poisoning, clinical signs, pathology, diagnosis, therapy: see aspirin (above)

- formulation intended for different animal species used (e.g. phenylbutazone powder for horses used for dogs) (Linnett 2001)

Reference:

Os306

Cathers TE, Isaza R, Oehme F (2000) Acute ibuprofen toxicosis in a ferret. *J. Am. Vet. Med. Assoc.* **216**:1426-1428.

Collins LG, Tyler DE (1984) Phenylbutazone toxicosis in the horse: a clinical study. *J. Am. Vet. Med. Assoc.* **184**:699-703.

Hough ME, Steel CM, Bolton JR, Yovich JV (1999) Ulceration and stricture of the right dorsal colon after phenylbutazone administration in four horses. *Aust. Vet. J.* **77**:785-788.

Isaacs JP (1996) Adverse effects of non-steroidal anti-inflammatory drugs in the dog and cat. *Aust. Vet. Practit.* **26**:180-186.

Linnett P (2001) Acute phenylbutazone toxicity in a dog. *Control & Therapy Series, Post Grad Foundation in Vet. Sci., Uni. Sydney* No.4377, Mailing 222, p.1302.

Poortinga EW, Hungerford LL (1998) A case-control study of acute ibuprofen toxicity in dogs. *Prev. Vet. Med.* **35**:115-124.

Traub JL, Gallina AM, Grant BD, Reed SM, Gavin PR, Paulsen LM (1983) Phenylbutazone toxicosis in the foal. *Am. J. Vet. Res.* **44**:1410-1418.

☑ Barbiturates

Core data

Common sources:

- carcases of animals killed with pentobarbitone euthanasia solution
- human medication

Animals affected:

- dogs
- raptors/scavengers

Mode of action: anaesthesia

Poisoning circumstances:

- access to carcases
- dogs will dig up carcases
- barbiturates persist in carcases for several months

Main effects: somnolence, hypothermia, hypotension, coma

Diagnosis:

- history of access
- assay blood for barbiturates

Therapy: basic decontamination & support measures

Prevention:

- effective carcase disposal (cremation)

Sources:
- **carcases** of animals killed with pentobarbitone or other barbiturate **euthanasia solution**
- human medication

Toxicity:
- **dogs**, **raptors** [bald eagles - North America] and other scavengers
- anecdotal evidence suggests raptors (eagles) are more susceptible than dogs (larger intake of material per unit body mass)
- barbiturates in toxic quantities will **persist for several months** (6-8) in carcases (buried or otherwise)
- livers of carcases contain larger concentrations than skeletal muscle

Mode of action:
- γ-aminobutyric acid (GABA)-like action → inhibition of neurotransmission

Conditions of poisoning:
- access to euthanased carcase
- dogs will dig up buried carcases

Clinical signs:
- somnolence, slowed respiratory rate, tachycardia, hypothermia, hypotension, coma, death

Pathology:
- engorged spleen

Diagnosis:
- history of access
- assay for barbiturates in blood

Therapy:
- oral decontamination (emetic, gastric lavage, activated charcoal, cathartic)
- artificial ventilation, oxygen
- fluid therapy to combat shock

Prevention & control: (Anon 1999)
- never assume that your clients will dispose of carcases safely; you may be sued if their dogs scavenge the carcase and are affected or die as a consequence
- advise clients that carcases of animals killed with barbiturates are toxic
- advise clients on effective disposal of carcases (**deep** burial; ultimate = cremation)

References:
Os 300
Anon. (1999) Take special care of euthanasia cases – both before and after the event. *Aust. Vet. J.* **77**:335.

Gaseous anaesthetic agents - dogs

Sources:
- chloroform ($CHCl_3$)
- methoxyflurane ($C_3H_4Cl_2F_2O$) (Ndiritu & Weigel 1977)
- halothane (Gaunt *et al.* 1984)

Toxicity:
- dogs, humans
- cases are rare

Conditions of poisoning:
- repeated exposure predisposes

Pathology:
- periacinar hepatocyte necrosis

References:
Gaunt PS, Meuten DJ, Pecquet-Goad ME (1984) Hepatic necrosis associated with use of halothane in a dog. *J. Am. Vet. Med. Assoc.* **184**:478-480.
Ndiritu CG, Weigel JW (1977) Hepatorenal injury in a dog associated with methoxyflurane. *Vet. Med. Small Anim. Clin.* **72**:545-550.

Benzocaine

Methaemoglobinaemia

Cats, dogs, humans

References:
Harvey JW, Sameck JH, Burgard FJ (1979) Benzocaine-induced methemoglobinemia in dogs. *J. Am. Vet. Med. Assoc.* **175**:1171-1175.

Krake AC, Arendt TD, Teachout DJ *et al.* (1985) Cetacaine-induced methemoglobinemia in domestic cats. *J. Am. Anim. Hosp. Assoc.* **21**:527-534.
Wilkie DA, Kirby R (1988) Methemoglobinemia associated with dermal application of benzocaine cream in a cat. *J. Am. Vet. Med. Assoc.* **192**:85-86.

Carprofen – dogs, idiosyncratic hepatotoxicity

Source:
- a propionic acid derivative NSAID
- Australian brand name = Zenecarp®; USA = Rimadyl®

Toxicity:
- dogs
- idiosyncratic, cytotoxic drug-induced hepatopathy recognised in USA
- both recommended doses (2.2 mg/kg PO every 12 hrs) and above recommended doses toxic
- less likely to cause GI tract bleeding than other NSAIDs (compare with aspirin and other NSAIDs: see notes under gastrointestinal disorders)

Drug-induced hepatotoxicoses are classified by suspected mechanism and character of injury.

Mechanisms
- *intrinsic*: dose-related, predictable, reproducible (e.g. paracetamol)
- *idiosyncratic*: random, unrelated to duration of administration or dose, difficult to reproduce experimentally

Injury type
- *cytotoxic*: hepatocyte degeneration/necrosis
- *cholestatic*: inflammation, proliferation of bile ductules, canalicular obstruction
- *mixed*

Mode of action: undefined

Conditions of poisoning:
- dogs being treated for musculoskeletal pain (osteoarthritis, hip dysplasia soft tissue injury)

Clinical signs:
- predominant signs = **anorexia, vomiting, jaundice**
- less commonly: lethargy, diarrhoea, polydipsia, polyuria, melena

Pathology:
- ↑ serum/plasma ALT, AST, ALP, bilirubin
- multifocal to extensive **hepatocyte necrosis**
- affected hepatocytes: vacuolation, lysis, apoptosis
- fibrosis, biliary ductular hyperplasia
- ± nephrosis

Diagnosis:
- exposure history + clinical signs & clinical pathology (+ liver biopsy)

Therapy:
- discontinue carprofen
- supportive therapy (fluids, anti-emetics, GI tract protectants)
- > 80% recovery rate

Reference:
MacPhail CM, Lappin MR, Meyer DJ, Smith SG, Webster CRL, Armstrong PJ (1998) Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. *J. Am. Vet. Med. Assoc.* **212**:1895-1901.

ANTHELMINTICS, ANTI-PROTOZOALS, INSECTICIDES & ACARICIDES

☑ Synthetic pyrethroids & phenylpyrazoles

Core data

Common sources: insecticides, acaricides
Animals affected: cats
Mode of action:

- interfere with Na channels in nervous tissue
- interfere with GABA & glutamic acid binding at receptor sites

Poisoning circumstances: cats treated topically for flea infestations
Main effects:

- tremors
- excessive salivation
- incoordination - seizures

Diagnosis: history of exposure + syndrome
Therapy:

- bathe with detergent
- activated charcoal PO
- muscle relaxants (methocarbamol, diazepam, mephenesin)
- monitor body temperature closely

Prevention: avoid excessive application to cats

Sources & Chemical structure:

Natural pyrethrins are products of *Tanacetum cinerariifolium* [= *Chrysanthemum cinerariifolium, Pyrethrum cinerariifolium*] (pyrethrum) flowers

Modified pyrethrins → synthetic esters (more stable than natural compounds, retain high insecticidal & low mammalian/avian toxicity). Type 1 pyrethroids contain no α-cyano moiety, Type 2 pyrethroids do.

Insecticides, acaricides e.g.
permethrin (numerous formulations for use on dogs, cats; Permoxin®),
cypermethrin (Barricade S®, Bastion®, Blaze®, Blockade-S®, Cypafly®, Cypercare®, Cypon®, Di-Flea®, Kleenklip®, Outflank®, Spurt®),
flumethrin (Bayticol®, Bay-O-Pet Kiltix®),
deltamethrin (Arrest®, Clout®, Coopafly®, Tixafly®),
fenvalerate (Sumifly®),
fipronil (Frontline®, Regent®) [fipronil = a phenylpyrazole insecticide]

Some acaricide formulations include OPs to combat organochlorine-resistant ticks (OCs share toxic mechanism of action on nerve conduction with pyrethroids) e.g. Barricade S® = cypermethrin + chlorfenvinphos

Type 1 pyrethroid:
Permethrin
Type 2 pyrethroids:
Cypermethrin
Flumethrin
Deltamethrin
Fenvalerate
Phenylpyrazole:
Fipronil

Toxicity:

susceptibility insects, crustaceans, fish >>> birds, mammals (cats > dogs)

aquatic invertebrates: synthetic pyrethroid toxicity = > 100 x OP toxicity; incautious disposal of sheep dip fluids in Scotland has → deaths of invertebrate species (insect larvae, crustaceans) in local rivers; cypermethrin may be more toxic than previous formulations (Pearce 1997) (House *et al* 2000)

mammalian hepatic detoxification is by ester hydrolysis or oxidation followed by hydroxylation or conjugation to either glucuronides or sulphates; cats are deficient in the ability to eliminate compounds through hepatic glucuronidation, making them potentially more susceptible than other domestic mammals (Meyer 1999)

There can be interaction between OPs and pyrethroids potentiating the toxicity of pyrethroids because OPs inhibit carboxylesterases and these enzymes are involved in the ester hydrolysis of pyrethroids (Kao *et al.* 1985, Ray & Forshaw 2000, Ramesh Gupta, personal communication VETTOX 14 June 2002)

Mode of action:

pyrethrins (natural compounds) decrease Na inflow and block K outflow at Na channels in axonal membranes

type 2 pyrethroids (contain an α-cyano moiety) interfere with GABA & glutamic acid binding at receptor sites

phenylpyrazole insecticides (including fipronil) are also GABA receptor inhibitors

Conditions of poisoning:

cats exposed to concentrated preparations applied topically; commonly female juvenile (< 9 months old) (Dorman *et al.* 1990, Hautekeete & Nicholson 1997)

cats treated with dog-only spot-on preparations containing permethrin (Meyer 1999)

cats having contact with / rubbing up against treated dogs (P.A. Volmer, personal communication VETTOX 1998, Meyer 1999)

dog drinking (!) deltamethrin preparation → salivation, tremors (J. McNally, veterinarian, Moree NSW, pers. comm. 1999)

55 cattle (estimated weight mean 300 kg) drenched by mistake with 20 ml deltamethrin pour-on preparation (15 g deltamethrin/L) did not develop clinical signs (TP Brennan, veterinarian, Roma Qld, pers. comm. 2000)

Clinical signs:

Laboratory animal studies

2 syndromes described

Type I or T (= tremor) → whole body tremor, aggression, hypersensitivity

Type II or CS (= choreoathetosis/salivation) → profuse salivation (no lachrymation), coarse tremors, clonic convulsions, writhing

Cats (signs in descending order of frequency - Dorman *et al.* 1990)

onset within hours of topical exposure
tremor
excess salivation
ataxia/incoordination
vomiting
depression
seizures
hyperaesthesia, irritation (may shake feet when walking, even when dry)
hypothermia
mydriasis
death in some (*ca.* 10% of cases)

Diagnosis: history of exposure + syndrome

Therapy:

Cats (Volmer *et al.* 1998)

bathe with mild detergent solution (e.g. hand dish-washing liquid) to remove remaining compound from skin/hair

activated charcoal PO to adsorb any ingested compound (cats self grooming)

IV fluids + nutritional support

control tremors/seizures

methocarbamol (Robaxin®) as a muscle relaxant for treatment of tremors/seizures@ 55-220 mg/kg IV, giving ½ rapidly (but not exceeding 2 ml/min), pause until the cat begins to relax, then continue to effect; maximum dose 330 mg/kg/day should not be exceeded

diazepam, mephenesin may control mild tremors, but may not control seizures (P.A. Volmer, personal communication VETTOX 1998)

pentobarbitone or mask induction with isoflurane may be required if the above do not control seizures

atropine vs. salivation (?); not usually required

monitor body temperature closely: hyperthermia can rapidly become hypothermia once tremors/seizures are controlled and the cat is bathed; N.B. hypothermia exacerbates clinical signs and prolongs recovery

early aggressive therapy leads to most cats recovering in 24-72 hrs

References:

Os241, Se286

Dorman DC, Buck WB, Trammel HL, Jones RD, Beasley VR (1990) Fenvalerate/*N,N*-diethyl-*m*-toluamide (Deet) toxicosis in two cats. *J. Am. Vet. Med. Assoc.* **196**:100-102

Hautekeete L, Nicholson S (1997) Treatment of permethrin toxicosis [cats]. *VETTOX Internet Postings*

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Kao LR, Motoyama N, Dauterman WC (1985) Multiple forms of esterases in mouse, rat and rabbit liver, and their role in hydrolysis of organophosphorus and pyrethroid insecticides. *Pestic. Biochem. Physiol.* **23**:66-73.

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Ray DE, Forshaw PJ (2000) Pyrethroid insecticides: Poisoning syndromes, synergies, and therapy. *Clinical Toxicology* **38**(2) 95-101.

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💣☑ *Macrocyclic lactone anthelmintics/insecticides (avermectins, milbemycin endectosides; macrolide endectosides)*

Core data

Common sources:

anthelmintic & insecticide/acaricide preparations

- abamectin (Avomec®)
- ivermectin (Ivomec®, Equimec®, Heartgard®)
- moxidectin (Cydectin®, Equest®, Proheart®)
- doramectin
- eprinomectin
- selemectin (Revolution® Pfizer)

Animals affected: cattle, horses, dogs, cats

Mode of action: GABA agonists: interfere with neurotransmission by γ-aminobutyric acid (GABA)

Poisoning circumstances:

- overdose (cattle, horses, dogs, cats)
  - ➢ use of farm animal formulations to treat dogs, cats
  - ➢ accidental consumption of livestock formulations by dog
- young calves, kittens, pups treated

Main effects: increasing severity → drooling saliva, ataxia, recumbency, slow pupillary reflex, mydriasis or miosis, tremors, death

Diagnosis: access + syndrome

Therapy: decontaminate, no specific antidote available

Sources:

- anthelmintic & insecticide/acaricide preparations e.g. abamectin (Avomec®), ivermectin (Ivomec®, Equimec®, Heartgard®), moxidectin (Cydectin®, Equest®, Proheart®), doramectin, eprinomectin and selemectin (Revolution® Pfizer)
- avermectins = disaccharide macrolide lactone metabolites of *Streptomyces avermitilis* (Burkhart 2000)
- milbemectin was isolated from *Streptomyces hygroscopicus* (Copping & Menn 2000).

Toxicity:

- cattle, horses, dogs, cats

- degree of sensitivity related to permeability of blood-brain barrier?
    - young >> adults; contra-indicated in calves, foals < 16 weeks old; kittens (Lewis DT *et al.* 1994)
    - increased sensitivity to avermectins in some dogs (Collies, Old English sheepdogs) & cattle (Murray Grey)
- doses reported to cause clinical signs (Roder & Stair 1998):
    - cattle 4-8 mg/kg (20-40 x therapeutic dose [TD])
    - horses 2 mg/kg (10 x TD)
    - pigs 30 mg/kg (100 x TD)
    - dogs: Collies 0.1-0.2 mg/kg (15-30 x TD); Beagles 2.5-4.0 mg/kg (>200 x TD)
    - cats: one report in kitten 0.3 mg/kg SC (adults less sensitive)
    - chelonians (red-footed and leopard tortoises) 0.1-0.4 mg/kg
    - amphibians (leopard frogs) 2.0 mg/kg IM was lethal; 20 mg/kg topically had no effect
- most of a dose is excreted in faeces; only slight hepatic metabolism
- concerns about toxic effects on invertebrates exposed to excreta from treated livestock (Edwards *et al.* 2001)
    - Australia: dung beetles: controlled-release formulations of ivermectin given to sheep caused significant mortality of larvae and reduced fecundity of adults; similar formulations given to cattle are believed capable of producing similar effects (Wardhaugh *et al.* 2001)
    - Scotland: farmed salmon – crustaceans, lugworms (Edwards 1996, Thain *et al.* 1997)

Mode of action:

- GABA agonists: interfere with neurotransmission by γ-aminobutyric acid (GABA) (Campbell 1981). Binding of avermectins to neuronal membranes → ↑ release of GABA which binds to the GABA-receptor chloride-channel complex of postsynaptic neuronal membranes → influx of Cl ions → hyperpolarise the neuronal membrane making them less excitatory → ↓ nerve transmission / paralysis (maintains neurones in resting state) → depression, stupor
- blood-brain barrier → toxicity invertebrates >> vertebrates. In vertebrates, GABA inhibitory neurotransmitter only in CNS, in invertebrates in PNS.

Conditions of poisoning:

- overdose (cattle, horses, dogs, cats)
    - use of farm animal formulations to treat dogs, cats
    - accidental consumption of livestock formulations by dog (Beal *et al.*1999)
- cattle toxic dose = therapeutic dose x 5 (lethal dose = x 10)
- young calves, kittens, pups (Parkes 2000) treated

Clinical signs:

- within 2 days of dosing; recovery in 4-5 days with care for recumbent animals
- mild ataxia in slightly-affected cattle
- increasing severity → depression, drooling saliva, anorexia, severe ataxia, recumbency, slow pupillary reflex, mydriasis or miosis, tremors, death
- ± colic, diarrhoea, muscle fasciculation, blindness (reversible), excess salivation, tongue paralysis
- seizures are uncommon

Pathology: no specific lesions (± pulmonary oedema)

Diagnosis:

- exposure history & clinical signs usually sufficient
- HPLC and ELISA assays available in some laboratories; sample liver, body fat, GI tract contents & faeces

Therapy:

- no safe specific antidote
- use oral activated charcoal + saline cathartic + supportive treatments
- possible additional therapies
    - physostigmine – an uncharged reversible inhibitor of acetylcholinesterase; has some effect on the comatose animal, possibly through increased ACh concentrations in affected neurones
    - picrotoxin – a CNS stimulant and GABA antagonist and thus suggested as an antidote; generally titrated to effect; narrow safety margin → convulsions controllable with diazepam or barbiturates; not effective in calves (Button *et al.* 1988)

References:

Review literature
Os 144, Se288
Edwards CA, Atiyeh RM, Römbke J (2001) Environmental impact of avermectins. *Rev. Environ. Contam. Toxicol.* **171**:111-137.

General literature
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Burkhart CN (2000) Ivermectin: an assessment of its pharmacology, microbiology and safety. *Vet. Human Toxicol.* **42**:30-35. [human therapy]
Button C, Barton R, Honey P, Rickford P (1988) Avermectin toxicity in calves and an evaluation of picrotoxin as an antidote. *Aust. Vet. J.* **65**:157-158.
Campbell WC (1981) An introduction to the avermectins. *N. Z. Vet. J.* **29**:174-178.
Copping LG, Menn JJ (2000) Biopesticides: a review of their action, application and efficacy. *Pest Management Sci.* **56**:651-676.
Edwards R (1996) Salmon farmers win licence to kill. *New Scientist* **151** (2046):4.
Godber LM, Derksen FJ, Williams JF, Mahmoud B (1995) Ivermectin toxicosis in a neonatal foal. *Aust. Vet. J.* **72**:191-192
Houston DM, Parent J, Matushek KJ (1987) Ivermectin toxicosis in a dog. *J. Am. Vet. Med. Assoc.* **191**:78-80.
Lewis DT, Merchant SR, Neer TM (1994) Ivermectin toxicosis in a kitten. *J. Am. Vet. Med. Assoc.* **205**:584
Parkes H (2000) Ivermectin toxicity in dogs. *Vet. Pathol. Report (Newsletter ASVP)* No.54, p.8.
Roder JD, Stair EL (1998) An overview of ivermectin toxicosis. *Vet. Human Toxicol.* **40**:369-370.
Seaman JT, Eagleson JS, Carrigan MJ, Webb RF (1987) Avermectin B_1 toxicity in a herd of Murray Grey cattle. *Aust. Vet. J.* **64**:284-285.
Thain JE, Davies IM, Rae GH, Allen YT (1997) Acute toxicity of ivermectin to the lugworm *Arenicola marina*. *Aquaculture* **159**:47-52.
Wardhaugh KG, Holter P, Longstaff B (2001) The development and survival of three species of coprophagous insect after feeding on the faeces of sheep treated with controlled-release formulations of ivermectin or albendazole. *Aust. Vet. J.* **79**:125-132.

☑ *Halogenated salicylanilide anthelmintics*

Core data

Common sources: closantel (anthelmintic)
Animals affected: goats, sheep
Mode of action: undescribed
Poisoning circumstances: overdose
Main effects:
- optic nerve & CNS white matter degeneration
- retinal degeneration

Diagnosis: history + eye & optic nerve histopathology
Therapy: nil
Prevention: care with dose rates

Sources:
- anthelmintics, anti-*Fasciola hepatica*
  - **closantel** (Seponver®, Razar®, Closal®)
  - rafoxanide (Ranide®), clioxanide (Tremerad®) - currently not on Australian market

Toxicity:
- goats, sheep, dogs (experimentally)
- closantel therapeutic dose 7.5 mg/kg; toxicity in goats @ 4-13 times therapeutic
- Australia: drug registered for use in sheep, not in goats

Mode of action: undetermined

Conditions of poisoning:
- overdosing (2-5 times recommended therapeutic doses)

Clinical signs:
- **blindness**
  - often within 2-3 days of dosing, but detection has taken 6-9 days or longer in some cases
  - some recovery in 3-4 weeks, remainder permanent
  - dilated pupils, ± walking in circles
- recumbency, death in severe cases

Pathology:
- necropsy: narrowing of intercanalicular segments of optic nerves

- **vacuolation** (myelinic oedema, status spongiosis) of **white matter** throughout **CNS + optic nerves** progressing to Wallerian degeneration and astrogliosis
  - particularly affected: optic tracts, lateral geniculate bodies, optic fasciculi
  - focal myelinic oedema in early cases: brain stem, cerebellar peduncles
  - pathogenesis: myelinic oedema → acute swelling of optic nerves → compression within bony optic canals of the cranium → necrosis, fibrosis of optic nerves, tracts → ± loss of neurones in retinal ganglion cell layer
- **retinal degeneration**
  - retina directly damaged, not a sequel to optic nerve damage
  - acute degeneration of the outer retina (mainly non-tapetal retina): degeneration of photoreceptor layer, pyknosis & loss of cells in outer nuclear layer → outer nuclear layer reduced to a row of cells or effaced + pigment-laden macrophages in the subretinal space and infiltrating the overlying retinal layers
  - initial acute degenerative change in outer retinal layers
  - ± neuronal loss in retinal ganglion cell layer (closantel)
  - complete absence of ganglion cells in chronic cases (rafoxanide)

Diagnosis: history, pathology of eyes, optic nerves & brain

Therapy: nil

Prevention & Control: close attention to dose rates of these drugs

References:

Se331

Barlow AM, Sharpe JAE, Kincaid EA (2002) Blindness in lambs due to inadvertent closantel overdose. *Vet. Rec.* **151**:25-26.

Button C, Jerrett I, Alexander P, Mizon W (1987) Blindness in kids associated with overdose of closantel. *Aust. Vet. J.* **64**:226.

Gill PA, Cook RW, Boulton JG, Kelly WR, Vanselow B, Reddacliff LA (1999) Optic neuropathy and retinopathy in closantel toxicosis of sheep and goats. *Aust. Vet. J.* **77**:259-261.

Prozesky L, Pienaar JG (1977) Amaurosis in sheep resulting from treatment with rafoxanide. *Onderstepoort J. Vet Res.* **42**:257-260.

Phenothiazine

Historical; compound used as an anthelmintic

Rumen flora → phenothiazine sulphoxide. Sheep liver → phenothiazone. Calf liver conversion inefficient → circulating phenothiazine sulphoxide → aqueous humour → corneal oedema/keratitis from photosensitisation

Reference: Se9, VM8/1508

Whitten LK, Filmer DB (1947) A photosensitized keratitis in young cattle following the use of phenothiazine as an anthelmintic I. A clinical description with a note on its widespread occurrence in New Zealand. *Aust. Vet. J.* **23**:336-340.

Clare NT (1947) A photosensitized keratitis in young cattle following the use of phenothiazine as an anthelmintic II. The metabolism of phenothiazine in ruminants. *Aust. Vet. J.* **23**:340-344.

Clare NT, Whitten LK, Filmer DB (1947) A photosensitized keratitis in young cattle following the use of phenothiazine as an anthelmintic III. Identification of the photosensitizing agent. *Aust. Vet. J.* **23**:344-348.

Gordon HMcL, Green RJ (1951) Phenothiazine photosensitisation in sheep. *Aust. Vet. J.* **27**:51-52.

Imidocarb

Source: Imizol® (imidocarb dipropionate) antiprotozoal for therapy & prophylaxis of bovine babesiosis and anaplasmosis and canine babesiosis

Toxicity:

- a rapidly reversible cholinesterase inhibitor (Todorovic *et al.* 1973, Mitchell *et al.* 1986)
- recommended highest treatment/prophylactic dose for cattle **SC** 2.5 mL (300 mg)/100 kg
- occasional transient anticholinesterase-type toxicity syndrome at therapeutic doses
- higher doses → nephrotoxic, hepatotoxic; poisonings: cattle, goats, dog

Conditions of poisoning:

- intravenous dosing
- **overdose** or **repeat doses** in attempts to treat tick fevers by lay persons

Clinical signs:

Cattle transient anticholinesterase effects may include excessive salivation, muscle fasciculation, ↑urination, ↑defaecation, diarrhoea, incoordination

Dog transient anticholinesterase effects may include vomiting, tachycardia, lacrimation
More serious signs are dyspnoea, severe depression, collapse → rapid death

Pathology:

- ↑ blood urea, creatinine
- nephrosis (acute tubular necrosis)
- hepatic necrosis (periacinar, paracentral)

Diagnosis: history, clinical syndrome, pathology

References:

Adams LG, Corrier DE, Williams JD (1980) A study of the toxicity of imidocarb dipropionate in cattle. *Res. Vet. Sci.* **28**:172-177.

Kock N, Kelly P (1991) Massive hepatic necrosis associated with accidental imidocarb dipropionate toxicosis in a dog. *J. Comp. Path.* **104**:113-116.

McHardy N, Woollon RM, Clampitt RB, James JA, Crawley RJ (1986) Efficacy, toxicity and metabolism of imidocarb dipropionate in the treatment of *Babesia ovis* infection in sheep. *Res. Vet. Sci.* **41**:14-20.

Mitchell AR, White DG, Higgins AJ, Moss P, Lees P (1986) Effect of induced hypomagnesaemia on the toxicity of imidocarb in calves. *Res. Vet. Sci.* **40**:264-270.

Todorovic RA, Vizcaino OG, Gonzalez EF, Adams LG (1973) Chemoprophylaxis (imidocarb) against *Babesia bigemina* and *Babesia argentina* infections. *Am. J. Vet. Res.* **34**:1153-1161.

Levamisole

Suspected as causing haemolytic anaemia in dogs treated for dirofilariasis.

Overdosing of sheep may lead to deaths. In December 1989, 5 Merino rams and wethers in a group of 25 in a flock at Roma, Queensland, died within 3 hours of being dosed at 2.5-3.0 times the recommended rate. Trembling and stiffness were reported. Necropsy revealed congestion of trachea, kidneys, liver, and abomasal mucosa and petechial haemorrhages beneath epi- and endocardium. No additional histological lesions were detected. (R.A.McKenzie & R.D.Newman, unpublished data 1989).

The safety factor for levamisole in sheep is reported as 4-12 times the therapeutic dose.

Reference:

Atwell RB, Johnstone I, Read R, Reilly J, Wilkins S (1979) Haemolytic anaemia in two dogs suspected to have been induced by levamisole. *Aust. Vet. J.* **55**:292-294.

Mebendazole – dogs, idiosyncratic hepatotoxicity

References:

Polzin DJ, Stowe CM, O'Leary TP *et al.* (1981) Acute hepatic necrosis associated with the administration of mebendazole to dogs. *J. Am. Vet. Med. Assoc.* **179**:1013-1016.

Swanson JF, Breider MA (1982) Hepatic failure following mebendazole administration to a dog. *J. Am. Vet. Med. Assoc.* **181**:72-73.

van Cauteren H, Marsboom R, Vandenberghe J *et al.* (1983) Safety studies evaluating the effect of mebendazole on liver function in dogs. *J. Am. Vet. Med. Assoc.* **183**:93-98.

Diethylcarbamazine (DEC) interactions – dogs, idiosyncratic hepatotoxicity

DEC + cyromazine (Decaflea®) produces rare cases (about 1 in 1000 dogs) of hepatotoxicity in dogs within the first month of administration. Hepatic lesions resemble those of aflatoxicosis. Most cases recover when the drug is removed (National Registration Authority for Agricultural & Veterinary Chemicals, personal communication, 7 October 1999).

DEC + oxibendazole produced chronic hepatopathy with periportal fibrosis, biliary ductule proliferation, lipid accummulation in hepatocytes, and hepatocyte regeneration nodules. Clinical improvement or recovery followed cessation of drug administration (Vaden *et al.* 1988).

References:

Vaden SL, Bunch SE, Duncan DE, Cullen JM (1988) Hepatotoxicosis associated with heartworm/hookworm preventative medication in a dog. *J. Am. Vet. Med. Assoc.* **192**:651-654.

Amitraz

Core data

Common sources: formamidine acaricide (Taktic® and others)

Animals affected:

- horses
- cattle (calves)

- dogs

Mode of action: α_2 adrenergic agonist

Poisoning circumstances:

- horses sprayed for tick control @ normal cattle dose rate
- dogs drinking cattle dip fluid or eating tick collars
- calves dipped in hot humid weather

Main effects:

- horses: progressive colonic impaction, necrotic colitis
- dogs, calves: transient tranquillisation to hyperexcitability

Diagnosis: syndrome + access history

Therapy:

- wash off residual compound
- α_2 antagonists e.g. atipamezole (Antisedan®), yohimbine (Reverzine®)
- horse: rehydrate, faecal softeners, analgesics

Prevention: avoid use on horses

Chemical structure:

Amitraz is a formamidine

Sources:

- acaricide/insecticide - dips, sprays, washes, tick collars
  - cattle - Taktic®, Amitik®, Amidaz®, Nu-Tic®
  - dogs - Ectodex®, Preventic 2 Month Tick Collar®
  - horses - Taktic® [ex-label use]

Toxicity:

Horses:

- amitraz (but not other formamidines) → incoordination of myoelectrical activity of the colon → persistent gut stasis
- experimentally reproduced with 1 mg amitraz / kg IV (Roberts & Seawright 1979)

Other species:

- susceptibility dogs, cats > cattle
- dog acute oral LD_{50} = 100 mg/kg
- dog: transient signs may occur at 20 mg/kg
- stable at high pH → breakdown in low pH stomach → rapid metabolism to harmless compound → urine excretion
- no tissue residues, no cumulative/chronic toxicity

Mode of action:

Horses:

α_2 adrenergic agonist and weak monoamine oxidase (MOA) inhibitor

Other species:

- believed to be α_2-adrenergic agonist + weak monoamine oxidase (MAO) inhibitor
- CNS and cardiovascular system main targets → cardiovascular collapse, respiratory depression

Conditions of poisoning:

Horses:

- **horses** sprayed with amitraz (Taktic®) for tick control at concentration recommended for cattle (0.025%)
- N.B. amitraz is *not* approved for use on horses
- only some horses adversely affected, predisposing factors unknown (possible correlation with degree of strongyle damage to mesenteric arteries)

Other species:

- dogs drinking cattle dipping fluid,
- dogs eating tick collars
- calves dipped in hot humid weather

Clinical signs:

Horses:

onset within 24 hr of spraying

- slight incoordination
- mild depression

- lack of normal gut sounds
- absence of faeces
- **progressive impaction of colon**
- colic
- mild dehydration + acidosis
- ± subcutaneous oedema of the face

Other species:

- transient tranquillisation → recumbency (may → mis-mothered calves)
- dogs (most recover in 48-72 hr)
  - sedation, ataxia, polyuria, hypothermia, bradycardia, anorexia, vomiting, hyperglycaemia
  - severe poisoning → mydriasis, hyperexcitability, hyperventilation

Pathology:

Horses (fatal cases):

- **necrosis of segments of colon wall**
- ± perforation → peritonitis

Other species:

no significant findings

Diagnosis:

syndrome + history of amitraz use

Therapy:

Horses:

Course of illness

- some spontaneously recover in 24 hr or recover with treatment over a longer period
- some die despite treatment or require euthanasia

Elements of therapy - may need to be continued for 6 + days

- wash off residual acaricide
- counter dehydration with fluid therapy IV, PO
- → analgesics repeated as required
- → enemas (with faecal softener [Coloxyl®]) + multiple doses of paraffin PO
- → corticosteroids

- yohimbine hydrochloride (Reverzine®), an α_2-adrenoreceptor antagonist with central action, reputedly used with success by one practitioner – unsubstantiated [D. Rossi, personal communication 1998]

Other species:

Dogs & cats - use α_2 antagonists e.g. atipamezole [Antisedan® Ciba-Geigy 50 μg/kg IM (Hugnet *et al.*1996)] or yohimbine [Reverzine SA® Parnell Labs or Antagonzil SA® Ilium]

Prevention & control: avoid use on horses

References:

Os245, Se283, VM8/1514 & 1517

Hugnet C, Buronfosse F, Pineau X, Cadore J-L, Lorgue G, Berny PJ (1996) Toxicity and kinetics of amitraz in dogs. *Am. J. Vet. Res.* **57**:1506-1510.

Roberts MC, Seawright AA (1979) Amitraz induced large intestinal impaction in the horse. *Aust. Vet. J.* **55**:553-554.

Dinitolmide (DOT) coccidiostat (pigeons, chickens)

Sources: commercial coccidiostat for poultry

Toxicity: susceptibility pigeons >> poultry

Conditions of poisoning:

- overdose in chickens
- commercial pigeons fed pelleted feed containing dinitolmide (accidental inclusion by feed manufacturer?) (Reece & Hooper 1984)

Clinical signs:

time from exposure to onset is about 2 weeks (Reece *et al.* 1999)

fine muscle tremors, rolling gait, incoordination (flying into walls, falling off perches, dysphagia)

Pathology:

necrosis of Purkinje cells of cerebellar cortex (pigeons, chickens)

vacuolation of neuropil in brainstem in severe prolonged cases (Reece *et al.* 1999)

Diagnosis: feed assay, clinical syndrome & pathology

Reference:

Reece RL, Hooper PT (1984) *Aust Vet J* **61**:259

Reece R, Ross T, Hum S, Glastonbury J, Walker K (1999) A wander through bird brains. *Proc. Aust. Soc. Vet. Pathol. Conf.* pp. 35-43.

Sodium fluoride

Chemical structure: FNa

Sources: Previously an anthelmintic (vs. ascarids) in pigs

Toxicity: 4-5% in ration toxic

Conditions of poisoning: overdose

Clinical signs:

Acute - vomiting, abdominal pain, diarrhoea, muscle weakness, collapse, death

Subacute → fluoride ion absorption → ↓ serum Ca → ↑ clotting time → fatal haemorrhage from surgery (castration)

Pathology: haemorrhagic gastroenteritis

Diagnosis: history, pathology

Therapy: nil

References: Os221, Se208

ANTIBIOTICS & ANTISEPTICS

Aminoglycoside antibiotics (gentamicin, paromomycin)

Dogs, cats, horses (foals), cattle, sheep, fish, humans
Nephrotoxicity & ototoxicity
References:

Fadel AA, Larkin HA (1996) Gentamicin-induced nephrotoxicosis in lambs. *Res. Vet. Sci.* **61**:187-192.

Frazier DL, Aucoin DP, Riviere JE (1988) Gentamicin pharmacokinetics and nephrotoxicity in naturally acquired and experimentally induced disease in dogs. *J. Am. Vet. Med. Assoc.* **192**:57-63.

Gookin JL, Riviere JE, Gilger BC, Papich MG (1999) Acute renal failure in four cats treated with paromomycin. *J. Am. Vet. Med. Assoc.* **215**:1821-1823.

Hinchcliff KW, Shaftoe S, Dubielzig RR (1988) Gentamicin-induced nephrotoxicosis in a cow. *J. Am. Vet. Med. Assoc.* **192**:923-925.

Reimschuessel R, Chamie SJ, Kinnel M (1996) Evaluation of gentamicin-induced nephrotoxicosis in toadfish. *J. Am. Vet. Med. Assoc.* **209**:137-139.

Cephalosporin antibiotics

Chemical structure:
Members of the β-lactam group of antibiotics (with penicillins)
Overdoses nephrotoxic; not as toxic as aminoglycosides
References:

Yilmaz O, Cabalar M, Ozbilgin S (1999) The *in vivo* and *in vitro* comparative nephrotoxicity of cefazolin and gentamicin. *Vet. Human Toxicol.* **41**:222-225.

Sulphonamide antibiotics

Sources:

Poultry:

- sulphaquinoxaline coccidiostat (Toltro®, Poultro®, Sulfa Quin®)

Organ systems affected:

Poultry: Blood clotting system
Dogs: Thyroid glands

Toxicity:

Poultry (sulphaquinoxaline):

- birds 4-7 weeks old most susceptible
- recommended therapeutic concentration in water = 80 mg/kg
- 200 mg/kg in water for 12 weeks → no effect
- 500-600 mg/kg in water for 4-5 days → intoxication
- >1000mg/kg in ration fed for 6 days → intoxication in 2-3 week-old chicks

Other species:

Dogs: Prolonged administration may rarely cause clinical hypothyroidism (Hall *et al.* 1993, Torres *et al.* 1996, Gookin *et al.* 1999). Experimentally, trimethoprim-sulfamethoxazole @ 60 mg/kg/day for 6 weeks interferes with thyroid function; doses in this range/duration are used for pyoderma in dogs (Hall *et al.* 1993)

Mode of action:

Poultry:

- interferes with vitamin K reduction after epoxidation during the final carboxylation step in synthesis of prothrombin and other vitamin K-dependant clotting factors
- inhibits platelet function

Other species:

Conditions of poisoning:

Poultry:

- overdose or prolonged dosing
- synergistic effect produced when dosed with ionophore coccidiostats

Other species:

Clinical signs:

Poultry:

- loss of appetite
- pallor

Other species:

Pathology:

Poultry:

- prolonged clotting time
- haemorrhages in muscles and alimentary tract

Other species:

Diagnosis:

Poultry:

assay water/feed for sulphaquinoxaline

Other species:

Therapy:

Poultry:

vitamin K

Other species:

Dogs: Thyroid hormone administration contra-indicated (suppresses pituitary TSH production, prolonging recovery time)

Prevention & control:

References:

Hu123, Os350

Gookin JL, Trepanier LA, Bunch SE (1999) Clinical hypothyroidism associated with trimethoprim-sulfadiazine administration in a dog. *J. Am. Vet. Med. Assoc.* **214**:1028-101031.

Hall IA *et al.* (1993) Effect of trimethoprim/sulfamethoxazole on thyroid function in dogs with pyoderma. *J. Am. Vet. Med. Assoc.* **202**:1959-1962.

Torres SMF, McKeever PJ, Johnston SD (1996) Hypothyroidism in a dog associated with trimethoprim-sulfadiazine therapy. *Vet. Derm.* **7**:105-108.

Nitrofuran antibiotics

Syndromes:

- acute neurological syndrome (calves and pigs)
- thrombocytopaenia (calves)
- chronic heart failure (poultry)
- infertility (poultry)

Sources: antibiotics

- furazolidone; commonly used in the commercial poultry industry
- nitrofurazone

Toxicity:

Acute neurological syndrome (calves and pigs):

- susceptibility: calves > pigs
- furazolidone → clinical signs @ 20-30 mg/kg/day (Taylor *et al.* 1991), 90 mg/kg for 2 days (Henning 1954)
- nitrofurazone → clinical signs @ 14 mg/kg for 3-5 weeks; 30 mg/kg for 4-14 days (Lister & Fisher 1970)
- cases in Europe, North America, Australia (Taylor *et al.* 1991)

Thrombocytopaenia (calves):

- calves fed furazolidone @ 4.0-8.5 mg/kg body weight for 7-20 weeks
- cases reported in Australia (Taylor *et al.* 1991, Finnie 1992), Europe, Japan

Chronic heart failure (poultry):

- turkeys (Jankus *et al.* 1972): natural case given either 330 or 660 mg furazolidone/kg in feed instead of the recommended 110-220 mg/kg.
- chickens (Feron & van Stratum 1966, Mustafa *et al.* 1984, Reed & van Vleet 1988, Khan *et al.* 1995); cases given 400 mg furazolidone/kg in feed for 6 weeks
- ducks
  - natural cases in ducklings (Reed *et al.* 1987); toxicity at 140-150 mg furazolidone/kg in feed
  - experimentally (van Vleet & Ferrans 1983a,b); toxicity @ 500 mg furazolidone/kg, deaths @ 750 mg furazolidone/kg in feed

Infertility (poultry):

- fowls, turkeys, ducks
- prolonged furazolidone use in feed results in toxicity problems including reduced fertility
- doses of 250-350 mg furazolidone/kg feed daily for 5 weeks in young male birds adversely affected sexual maturity (Andrabi *et al.* 1998)

Mode of action:

Nitrofurans inhibit enzymes of the tricarboxylic acid cycle, interfering with aerobic oxidation of glucose; metabolically active tissues are most susceptible (brain, heart, testes, kidney, liver).

Thrombocytopaenia (calves): suppression of bone marrow

Chronic heart failure (poultry): furazolidone reduces thiamine availability in chickens (Ali & Bartlet 1982)

Infertility (poultry): reduces circulating luteinising hormone; direct effects on the Leydig cells of the testis (site of testosterone production) are proposed (Andrabi *et al.* 1998)

Conditions of poisoning:

Acute neurological syndrome (calves and pigs):

calves fed high concentrations in milk-replacers

Thrombocytopaenia (calves):

prolonged administration of furazolidone to calves reared on milk substitutes

Chronic heart failure (poultry):

accidental overdose of furazolidone

Infertility (poultry):

prolonged use of high doses of furazolidone

Clinical signs:

Acute neurological syndrome (calves and pigs):

Calves

- anorexia
- hyperexcitability
- muscle twitching/tremors
- stilted gait, staggering
- tonic-clonic convulsions (opisthotonus)
- limb paralysis

Pigs (Borland 1979)

- signs initiated by handling
- ataxia, trailing of hind limbs
- hypermetria ("goose-stepping") or crouching, then leaping into the air
- lateral recumbency, paddling

Thrombocytopaenia (calves):

- depressed weight gains
- pyrexia (40-41^{o}C)
- pallor & petechiae in mucous membranes
- prolonged bleeding time
- progressing to widespread haemorrhage, blood in faeces, melena, haematuria, epistaxis
- disease duration 3-7 days

Chronic heart failure (poultry):

- increased mortality in flocks
- decreased growth rate
- abdominal distension (ascites)
- recumbency

Infertility (poultry):

- reduced fertility
- reduced hatchability of eggs
- delayed onset of egg production in hens / reproduction in cockerels

Pathology:

Acute neurological syndrome (calves and pigs):

no data

Thrombocytopaenia (calves):

- neutropaenia, thrombocytopaenia, anaemia
- widespread haemorrhage

Chronic heart failure (poultry):

- cardiac ventricular dilatation and thinning of ventricular walls without necrosis
- myocardial oedema
- hydropericardium
- ascites

Infertility (poultry):

- testicular degeneration (Webb & van Vleet 1991)
- ovarian and oviduct degeneration (Ullah *et al.* 1998)

Diagnosis:

Acute neurological syndrome (calves and pigs):

- history & clinical signs
- differential diagnoses include polioencephalomalacia, hypomagnesaemia

Thrombocytopaenia (calves):

- history + pathology (haematology, bone marrow histopathology)
- differential diagnosis included ptaquiloside poisoning (*q.v.*)

Chronic heart failure (poultry):

- history + pathology
- differentiate from "round-heart disease" which has myocardial necrosis and inflammation (van Vleet & Ferrans 1983a)

Infertility (poultry):

fertility rate and treatment history

Therapy:

Acute neurological syndrome (calves and pigs):

- nil
- spontaneous recovery in most cases when administration stops
- IM thiamine @ 100 mg/day may be helpful (Lister & Fisher 1970)

Thrombocytopaenia (calves): nil

Chronic heart failure (poultry):

- nil
- surviving affected birds slowly recover over several weeks (van Vleet & Ferrans 1983b)

Infertility (poultry):

- no specific therapy
- removal of furazolidone from ration can → reversal of testicular effects (Siddique *et al.* 1996) and ovarian/oviduct effects (Ullah *et al.* 1998)

Prevention & control:

Acute neurological syndrome (calves and pigs):

courses of therapy with nitrofurans should not exceed 3 days

Thrombocytopaenia (calves):

courses of therapy with nitrofurans should not exceed 3 days

Chronic heart failure (poultry):

- vitamin E, selenium or taurine supplements fail to prevent effects of intoxication (van Vleet & Ferrans 1983b)

References:

Os335; Beasely121

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Henning MW (1954) On the chemotherapy of calf paratyphoid. *J. Sth. Afr. Med. Assoc.* **25**:1.

Hofmann W (1972) [Haemorrhagic diathesis in calves caused by chronic poisoning by furazolidone] *Dtsch. Tierärztl. Wschr.* **79**:289-292.

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Siddique M, Khan MZ, Muhammad G, Islam N (1996) Reversibility of furazolidone-induced changes in testes and secondary sex characters of White Leghorn cockerels. *Vet. Human Toxicol.* **38**:413-417.
Taylor JD, Gibson JA, Yeates CEF (1991) Furazolidone toxicity in dairy calves. *Aust. Vet. J.* **68**:182-183.
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van Vleet JF, Ferrans VJ (1983b) Furazolidone-induced congestive cardiomyopathy in ducklings: regression of cardiac lesions after cessation of furazolidone ingestion. *Am. J. Vet. Res.* **44**:1007-1013.
Webb DM, van Vleet JF (1991) Ultrastructural alterations in furazolidone-induced cystic testicular degeneration in ducklings. *Avian Dis.* **35**:107-114.

Lincomycin - horses

Source: Pig or poultry feed containing the antibiotic (pigs 20-200 mg/kg [g/ton]; poultry 2-4 mg/kg)
Toxicity:
- horses (+ guinea pigs, hamsters, rabbits) very susceptible
- → toxins from proliferation of *Clostridium difficile*

Conditions of poisoning: accidental access to medicated feeds
Clinical signs: colic, diarrhoea, dehydration, shock
Pathology: **acute necrotising colitis**
Diagnosis: history, pathology
Therapy: non-specific supportive- very high case mortality rate
Reference: Os334

Griseofulvin

Source: Therapeutic drug for dermatomycoses
Toxicity:
- Placental transfer occurs; interferes with mitosis in fungal (and potentially mammalian) cells
- teratogenic effects reported in humans, lab animals, **dogs, cats, horses**

Mode of action: undescribed
Circumstances of poisoning: administration **early in pregnancy**
Clinical signs/Pathology: congenital defects reported have been
- **craniofacial anomalies** (including palatoschisis)
- **microphthalmia/anophthalmia** (retinal dysplasia?)
- cyclopia
- lack of eyelids
- skeletal abnormalities (spina bifida, fusion of phalanges of hind limbs)
- atresia ani, atresia coli

Diagnosis: congenital defect & history of administration early in pregnancy
Therapy: nil
Prevention & control: avoid administration to pregnant animals
References:

Schutte JG, van den Ingh TSGAM (1997) Microphthalmia, brachygnathia superior and palatocheiloschisis in a foal associated with griseofulvin administration to the mare during early pregnancy. *Vet. Quart.* **19**:58-60

Melaleuca oil

See notes under Plant toxins – lipids, oils, glycerides, fatty acids

ANTINEOPLASTIC DRUGS

Cisplatin (cats)

Source: antineoplastic drug (cis-dichlorodiammineplatinum) used successfully in humans and dogs
Toxicity:
in humans & dogs → emesis, myelosuppression, nephrotoxicity
in **cats → severe hydrothorax, pulmonary oedema** → acute death
Reference:
Knapp DW, Richardson RC, DeNicola DB *et al.* (1987) *J Vet Intern Med* **1**:29-35.

5-Fluorouracil

Chemical structure:
5-Fluorouracil is a pyrimidine analogue (a fluorinated pyrimidine).
Sources:
5-fluorouracil
Medicaments intended for treatment of human neoplasms, including use as injectable formulations and in creams and solutions for topical treatment of solar keratitis and skin neoplasia [Efudix® Derma Tech Laboratories; Fluoroplex® Allergan Australia Pty Ltd]. Dogs are most likely to have access to the topical formulations.
5-flucytosine
A fluorinated pyrimidine used as an antifungal agent [Ancotil® Derma Tech Laboratories] and converted to 5-fluorouracil by cytosine deaminase. Cytosine deaminase does not occur in mammalian cells, but ingestion of 5-flucytosine leads to conversion to 5-fluorouracil by cytosine deaminase in digestive tract microbes (Heit & Riviere 1995).
Organ systems affected:
alimentary tract
CNS
bone marrow
Toxicity:
dogs, cats
lowest dose to produce signs of toxicity in dogs is 8.6 mg/kg (Albretsen 2001)
lowest lethal dose is estimated as 20 mg/kg (Albretsen *et al.* 1998)
Mode of action:
Antimetabolite antimitotic action.
Inhibits RNA processing and function and DNA synthesis and repair, thus inhibiting cell division with maximal effects on rapidly-dividing cells.
Mechanism of action in dogs, particularly the generation of seizures, is not fully understood
Conditions of poisoning:
accidental ingestion through chewing containers of topical preparations for human use
anticancer chemotherapy IV doses (superseded) (Harvey *et al.* 1977)
Clinical signs:
time from ingestion to onset: 0.5 – 5.0 hr
vomiting (severe)
lethargy
tremors
seizures/hysteria/hyperexcitability (refractory to treatment)
cardiac arrhythmias
respiratory depression
blindness (cat) (Harvey *et al.* 1977)
death (common): as rapidly as 7 hr after ingestion; of 72 cases reported to ASPCA APCC in the period 1989-1998, 35 dogs died and 11 were humanely killed – 64% case fatality ratio (Albretsen 1998)
bone marrow suppression may occur in dogs surviving for more than 4 to 7 days and is manifest as leucopaenia, depression and hyperthermia (Albretsen 1998).
Pathology:
cat: focal malacic brain lesions (not further described) (Harvey *et al.* 1977)

myelosuppression: leucocyte counts as low as 750 cells/µl (normal 5000 – 14000 cells/µl)

Diagnosis: syndrome and history of access

Therapy:

No specific antidote is available.

Decontamination

- **before onset of signs**, early decontamination (induced vomiting + activated charcoal dose) provides the best prognosis
- **after onset of signs**, treatment *per os* must be postponed until vomiting, tremors and seizures are controlled and the patient's airway is protected to prevent aspiration of vomitus.
- Induced emesis is not helpful beyond 2-3 hr after ingestion.
- Activated charcoal is helpful up to 24 hr after ingestion.

Therapy for seizures & vomiting

- Gastrointestinal protection: give gastric acid secretion inhibitors such as
  - sucralfate [Carafate® Aventis Pharma Pty Ltd; Ulcyte® Alphapharm Pty Ltd]: 1g for large dogs, 0.5 g for small dogs PO t.i.d (if dog not vomiting).
  - misoprostol [Cytotec® Searle]: 2-5µg/kg PO t.i.d. to q.i.d (if dog not vomiting)
  - metoclopramide hydrochloride [Metomide® Delvet]: 0.1-0.3 mg/kg IV or PO t.i.d [Caution: could cause additional neurological signs (Dorman *et al.* 1990)]
- Seizure & tremor management: alternatives include (Dorman *et al.* 1990)
  - diazepam rarely controls seizures/tremors
  - pentobarbitone sodium [Nembutal® Merial]: 3-15 mg/kg IV slowly to effect
  - phenobarbitone [Phenobarbitone Injection]: 3-30 mg/kg IV slowly to effect
  - isoflurane [I.S.O. Inhalation Anaesthetic® Veterinary Companies of Australia Pty Ltd]
  - propofol [Rapinovet® Schering-Plough Animal Health]: 4-6 mg/kg IV or continuous rate infusion 0.6 mg/kg/min
- Supportive measures
  - IV fluids
  - thermoregulation
  - pain control : butorphanol tartrate [Dolorex® Intervet (Australia) Pty Ltd; Torbugesic® Fort Dodge Australia Pty Ltd] 0.2-0.4mg/kg every 2-5 hr SC, IM or IV
  - ± broad-spectrum antibiotics
- Bone marrow stimulation
  - filgrastim (a granulocyte colony-stimulating factor of human origin and stimulates bone marrow stem cell proliferation in dogs [Albretsen 1998]) [Neupogen® AMGEN Australia Pty Ltd]: 4.2-6.0µg/kg SC daily for 1-3 days

Prevention & control: secure storage of human medicaments beyond the reach of pets

References:

Review literature

Albretsen J (2001) 5-fluorouracil toxicosis in dogs. *Vet. Med.* **96** (4):270-274.

General literature

Albretsen J *et al.* (1998) Treatment of bone marrow suppression following toxic ingestion of 5-fluorouracil in dogs. [Abst.] *J. Vet. Intern. Med.* **12**:240.

Dorman DC *et al.* (1990) 5-fluorouracil toxicosis in the dog. *J. Vet. Intern. Med.* **4** (5):254-257.

Harvey HJ, MacEwan EG, Hayes AA (1977) Neurotoxicosis associated with the use of 5-fluorouracil in five dogs and one cat. *J. Am. Vet. Med. Assn.* **171** (3):277-278.

Heit MC, Riviere JE (1995) Antifungal and antiviral drugs. In *Veterinary Pharmacology and Therapeutics.* 7th edition. Adams HR (ed.). Iowa State University Press, Ames Iowa. p. 858.

NUTRITIONAL SUPPLEMENTS

Calcium formulations (bovine hypocalcaemia preventative/therapy)

Oral Ca salts may be irritant to the abomasal mucosa in certain formulations

- $CaCl_2$ in aqueous gel formulation (Jørgensen *et al.* 1990, Wentink & van den Ingh 1992, Furll *et al.* 1998)
- Ca formate ($C_2H_2CaO_4$) (Scott & van Wijk 1999)

Congestion, oedema of abomasal mucosa + necrotic foci

$CaCl_2$ in soya bean oil formulation has negligible toxic effect

References:

Furll M, Oetzel R, Schoon HA (1998) The influence of various calcium chloride formulations on blood calcium levels and calcium excretion in the urine, as well as the tolerance of cows to the formulations. *Proc. XX World Buiatrics Conf., Sydney.* pp. 143-146.

Jørgensen RJ, Basse A, Aslan V (1990) Sequelae to oral calcium chloride gel dosing of cows. *Proc. XVI World Buiatrics Congr., Brazil.* p.511.

Scott DJ, van Wijk N (1999) Comparison in dairy cattle of mucosal toxicity of calcium formate and calcium chloride in oil. *N. Z. Vet. J.* **48**:24-26.

Wentink GH, van den Ingh TSGAM (1992) Oral administration of calcium chloride-containing products: testing for deleterious side effects. *Vet. Quart.* **14**:76-80.

See also: Copper, Iodine, Iron, Selenium, Vitamin A

MISCELLANEOUS

Anticonvulsant drugs

Dogs
Associated with prolonged phenobarbital or primidone administration
Neutropaenia, thrombocytopaenia (reversible when drugs withdrawn)
References:

Jacobs G, Calvert C, Kaufman A (1998) Neutropenia and thrombocytopenia in three dogs treated with anticonvulsants. *J. Am. Vet. Med. Assoc.* **212**:681-684.

Methylene blue – cats, dogs

Induces Heinz bodies
References:

Schalm OW (1978) Methylene blue-induced Heinz body hemolytic anemia in a dog. *Canine Pract.* **5**:20-24.
Schechter RD, Schalm OW, Kaneko JJ (1973) Heinz body hemolytic anemia associated with the use of urinary antiseptics containing methylene blue in the cat. *J. Am. Vet. Med. Assoc.* **162**:37-44.

Vitamin K_3 (menadione sodium bisulphite) – horses

Nephrosis may be caused by administration of vitamin K_3 (menadione sodium bisulphite) @ 2.2-11 mg/kg IV or IM for prevention of or therapy for exercise-induced pulmonary haemorrhage or epistaxis in race-horses. Renal colic (slightly arched stance, rubbing of perineum and tailhead on surrounding objects, occasional looking at flank, lie down and get up intermittently, stranguria) and haematuria (microscopically evident, grossly evident in some) occur within 4-12 hr.
Reference:

Rebhun WC, Tennant BC, Dill SG, King JM (1984) Vitamin K_3-induced renal toxicosis in the horse. *J. Am. Vet. Med. Assoc.* **184**:1237-1239.

β_2 agonists

Sources (associated with toxicity in domestic animals or humans):

- salbutamol (albuterol) [Ventolin®] - human asthma medication available as inhalant ("puffer"), tablets, syrup, nebuliser solution (Mitten *et al.* 1999)
- metaproteranol (Rush & Keene 1990)
- clenbuterol (Ventipulmin®) – used as growth promotant in cattle; acts as repartitioning agent $\rightarrow\uparrow$ muscle, $\downarrow$fat in carcase by influencing protein synthesis and lipolysis; residues generally accumulate in liver; administration to farm animals and marketing of meat from such animals are prohibited in EU (Mersmann 1998, Smith 1998, Kuiper *et al.* 1998, Mitchell & Dunnavan 1998, Soporano *et al.* 1998)

Toxicity:

- full Ventolin® inhaler contains 20 g salbutamol base
- rat & mouse oral LD_{50} (salbutamol) = > 2 g/kg

Mode of toxic action:

- β_2 adrenergic receptor agonists (stimulant)
- at high dose, effective on cardiac β_1 receptors $\rightarrow$ tachycardia
- high IV doses in sheep $\rightarrow$ myocardial necrosis
- stimulation of a β_2 receptor linked to a membrane-bound Na^+/K^+ ATPase $\rightarrow$ hypokalaemia

Conditions of poisoning:

- dog chewing and puncturing a Ventolin® inhalant canister
- humans ingesting beef (veal) liver (Martinez Navarre 1990, Pulce *et al.* 1991) or meat (Sporano *et al.* 1998) from cattle injected with clenbuterol as a growth promoter; toxicity from meat usually when cattle (calves) overdosed illegally and die and meat is "salvaged" for human consumption on the black market (Sporano *et al.* 1998)

Clinical signs:

Dogs (salbutamol, metaproteranol):

- depression, panting, tachyarrhythmia, femoral pulse deficits
- ECG $\rightarrow$ paroxysmal ventricular tachycardia + multiple premature ventricular complexes

- ± vomiting (Emerton 1998)

Humans (clenbuterol residues):

- palpitations, tachycardia, nervousness, tremors, gastroenteric symptoms, vertigo, myalgia-arthralgia, cephalgia, and in some, astenia or mental cloudiness; ECG – sinus tachycardia, erratic superventricular extrasystoles ± atrial fibrillation (Sporano *et al.* 1998)

Pathology (dogs):

- hypokalaemia (2.47 mM K /L; normal 3.6-5.8; Mitten *et al.* 1999)
- possible myocardial damage (elevated CPK, AST) (Rush & Keene 1990)

Diagnosis: access + syndrome

Therapy: (Mitten *et al.* 1999)

- correct hypokalaemia (IV KCl @ 0.3 mEq/kg/hr in lactated Ringers)
- nasal O_2 @ 2L/min
- correct tachyarrhythmia (propranolol @ 6 µg/kg hourly for 4 hrs; if unsuccessful, lignocaine HCl @ 2mg/kg as slow IV bolus then infused @ 50 µg/kg/min); Note: hypokalaemia will interfere with lignocaine effectiveness and must be corrected first.
- monitor heart function and continue therapy to effect

Prevention & control:

References:

Emerton N (1998) Salbutamol poisoning. *Control & Therapy Series, Post Grad Foundation in Vet. Sci., Uni. Sydney* No.4016, Mailing202, p.1006.

Kuiper HA, Noordam MY, van Dooren-Flipsen MMH, Schilt R, Roos AH (1998) Illegal use of β-adrenergic agonists: European community. *J. Anim. Sci.* **76**:195-207.

Martinez Navarre JF (1990) Food poisoning related to consumption of illicit β-agonist in liver. *Lancet* **336**:1311.

Mersmann HJ (1998) Overview of the effects of β-adrenergic receptor agonists on animal growth including mechanisms of action. *J. Anim. Sci.* **76**:160-172.

Mitchell GA, Dunnavan G (1998) Illegal use of β-adrenergic agonists in the United States. *J. Anim. Sci.* **76**:208-211.

Mitten RW, Lucas AN, Warburton CJ (1999) Salbutamol (Albuterol) toxicity in a dog. *Aust. Vet. Practit.* **29**:10-14.

Pulce C, Lamaison D, Keck G *et al.* (1991) Collective human food poisonings by clenbuterol residues in veal liver. *Vet. Human Toxicol.* **33**:180-181.

Rush JE, Keene BW (1990) Metaproteranol intoxication in a dog. *J. Am. Vet. Med. Assoc* **197**:1351.

Smith (1998) The pharmacokinetics, metabolism, and tissue residues of β-adrenergic agonists in livestock. *J. Anim. Sci.* **76**:173-194.

Sporano V, Grasso L, Esposito M, Olivero G, Brambilla G, Loizzo A (1998) Clenbuterol residues in non-liver containing meat as a cause of collective food poisoning. *Vet. Human Toxicol.* **40**:141-143.

Stiles MS, Plumb DC (1993) Toxicity associated with β-agonist aerosol exposure in three dogs. *J. Am. Anim. Hosp. Assoc.* **29**:235.

Oestrogens (human hormone replacement medications) - dogs

Sources: Human hormone replacement medications prescribed for control of menopause symptoms and after ovariectomy.

Organ systems affected: bone marrow

Toxicity:

Dogs

Doses of oestrogen tolerated by dogs are 0.010-0.030 mg/kg (Sutton *et al.* 1997). Lethal doses reported have been 0.16-0.44 mg/kg (Legendre 1976, Weiss & Klausner 1990) and 1.0 mg/kg (Aranda *et al.* 1994).

Mode of action:

Conditions of poisoning: accidental ingestion of human medication

Clinical signs:

Pathology:

Pancytopaenia & aplastic anaemia:

- an initial rise in leucocyte count over 2-3 weeks followed by neutropaenia (Gaunt & Pierce 1986)
- thrombocytopaenia occurs after about 9 days (Aranda *et al.* 1994)
- progressive anaemia develops within 2-5 weeks (Aranda *et al.* 1994)

Diagnosis: history of exposure + syndrome

Therapy:

lithium (Hall 1992)

Filgrastim, a granulocyte colony-stimulating factor (Suttorp *et al.* 2002)

Prevention & control:

References:

Review literature

General literature

Aranda E, Pizarro M, Pereira j, Mezzano D (1994) Accumulation of 5-hydroxytryptamine by aging platelets: studies in a model of suppressed thrombopoiesis in dogs. *Thrombosis and Haemostasis* **71**:488-492.

Farris GM, Benjamin SA (1993) Inhibition of myelopoiesis by serum from dogs exposed to estrogen. *Am. J. Vet. Res.* **54**:1374-1379.

Gaunt SD, Pierce KR (1986) Effects of estradiol on hematopoietic and marrow adherent cells of dogs. *Am. J. Vet. Res.* **47**:906-909.

Hall EJ (1992) Use of lithium for treatment of estrogen-induced bone marrow hypoplasia in a dog. *J. Am. Vet. Med. Assoc.* **200**:814-816.

Legendre AM (1976) Estrogen-induced bone marrow hypoplasia in a dog. *J. Am. Anim. Hosp. Assoc.* **12**:525-527.

Sutton DJ, Geary MR, Bergman JG (1997) Prevention of pregnancy in bitches following unwanted mating: a clinical trial using low dose oestradiol benzoate. *J. Reprod. Fertil.* Suppl. **51**:239-243.

Suttorp M, Hoffmann B, Sippell WG (2002) Prevention of oestradiol-associated toxicosis in a Dalmatian by early intervention with granulocyte colony-stimulating factor. *Vet. Rec.* **151**:244-245.

Weiss DJ, Klausner JS (1990) Drug-associated aplastic anaemia in dogs: eight cases (1984-1988). *J. Am. Vet. Med. Assoc.* **196**:472-475.

12: Drugs of abuse [Industrial-origin toxins]

☑ *Cannabis sativa*

See notes under plant toxins

Amphetamine

Sources: illicit or prescription drug [USA]; metamphetamine = "speed"
Toxicity: approx. oral lethal dose 10-30 mg/kg [tablets 5 & 10 mg in USA]
Conditions of poisoning: accidental ingestion by pets
Clinical signs:

- onset 1-2 hr after ingestion
- hyperexcitability, agitation
- dilated pupils
- tetanic convulsions (degree of exaggeration of reflexes & hyperaesthesia less than seen in strychnine poisoning)
- severe tremor
- tachycardia, cardiac arrhythmia, hypertension

Pathology:

- lactic acidosis, hypoglycaemia
- possible rhabdomyolysis may cause myoglobinuric renal failure

Diagnosis: assay stomach contents, plasma, urine for amphetamine
Therapy:

- control hyperactivity and convulsions (see below)
- detoxification - emesis, activated charcoal, cathartic
- supportive therapy - acidify urine (enhances elimination - see strychnine above), reduce high body temperature from seizures if required

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Therapeutic protocol in amphetamine-induced seizures
Sedation: acetylpromazine (1 mg/kg) or diazepam or haloperidol (IV1mg/kg)
Use barbiturates only if other means fail.

References:

Os309
Bischoff K, Beier E, Edwards WC (1998) Metamphetamine poisoning in 3 Oklahoma dogs. *Vet. Hum. Toxicol.* **40**:19-20.

Cocaine

Sources:

- illicit drug (alkaloid) derived from *Erythroxylon coca* or *E. monogynum* (coca plant) in South America
- freebase = chemically-extracted pure cocaine alkaloid
- street cocaine = often "cut" (diluted, mixed) with amphetamine, caffeine, lidocaine, quinine, strychnine

Toxicity:

- dog (cat) oral LD_{50} estimated at 50 mg/kg
- lethal doses → cardiac or respiratory arrest
- rapid absorption from alimentary tract, mucous membranes and lungs
- plasma half-life < 3 hr

Conditions of poisoning: accidental access by pets to cocaine used illegally by owners
Clinical signs:

- alternate CNS stimulation & profound depression
- hyperaesthesia & seizures
- hyperthermia (associated with seizures + peripheral vasoconstriction)
- tachycardia, hypertension, cardiac arrhythmias

Pathology (Frazier *et al.* 1998):

- gross lesions absent or unreliable

mild erosive gastritis
pulmonary oedema
mild degeneration of myocardial fibres
moderate to marked vasoconstriction of coronary vasculature

Diagnosis:
assay plasma, urine for recent exposure (note short half-life)
assay stomach contents – detection can be made through TLC method for strychnine revealing another alkaloid-type compound visualised with potassium iodoplatinate spray; subsequent confirmation may be made with TLC, GC-MS or HPLC methods (Frazier *et al.* 1998).

Therapy:
detoxification relatively ineffective because of rapid absorption
possible respiratory support
control hyperthermia
chlorpromazine alleviates cardiovascular effects & may help control seizures
propranolol antiarrhythmic value uncertain

References: Os311

Frazier K, Colvin B, Hullinger G (1998) *Post mortem* diagnosis of accidental cocaine intoxication in a dog. *Vet. Human Toxicol.* **40**:154-155.

Phencyclidine (PCP)

Sources:
- illicit drug; common street names = PCP, angel dust, hog
- chemical analogue of ketamine

Toxicity:
- dogs (cats) oral toxic doses = 2.5-10 mg/kg; lethal dose 25 mg/kg
- rapidly absorbed from intestines, poorly from stomach
- → death from respiratory failure complicated by cardiovascular dysfunction

Conditions of poisoning: accidental ingestion to drug used by owner

Clinical signs:
- CNS signs: alternate depression & excitation, dilated pupils, tonic-clonic seizures, champing of jaws, salivation; dogs → hyperactivity & stereotypical circling
- cardiovascular signs: tachycardia, arrhythmias, hypertension

Pathology: ± pulmonary haemorrhage & congestion

Diagnosis: assay stomach contents, urine (only some laboratories)

Therapy:
- decontamination including repeated activated charcoal (interrupt enterohepatic circulation)
- keep patient cool, isolate from external stimuli
- control excitement, seizures with diazepam
- promote urinary excretion: IV fluids, acidify urine (see strychnine above), furosemide diuresis

References: Os312

Ethanol

See notes under yeasts