LIPIDS, OILS, GLYCERIDES, FATTY ACIDS

Definitions [adapted from Lewis' Dictionary of Toxicology 1998 and Blood & Studert's *Comprehensive Veterinary Dictionary* 1999]

Fatty acids (= Carboxylic acids): Organic compounds with the general formula RCOOH, where R = a hydrocarbon or other organic moiety. Examples are formic, acetic and trichloroacetic acids. Many occur in plants and as esters in fats and oils. Carboxylic acids are termed mono-, di-, or tri-basic depending on the number of carboxyl (COOH) groups on the molecule.
Glycerides: Organic acid esters of glycerine (glycerol). Glycerides are termed mono-, di-, or tri-glycerides depending on the number of ester linkages.
Lipids: Simple lipids are triglycerides, each composed of one molecule of glycerol joined by ester linkages to three fatty acid molecules.
Oil: An unctuous, combustible substance that is liquid at ambient temperature (or easily liquefiable on warming), is not miscible with water, but is soluble in ether. Oils are classified by origin as animal, vegetable or mineral.
Essential, ethereal or volatile oils: Oils that evaporate readily.

☑ *Unsaturated fatty acids, particularly crepenynic acid*

Core data

Common sources: Ixiolaena brevicompta seedheads
Animals affected: sheep
Mode of action: lipid peroxidation myopathy
Poisoning circumstances:

- grazing plants with mature seedheads
- floodplain of Darling River and tributaries

Main effects: skeletal & cardiac muscle degeneration & necrosis
Diagnosis: pathology + access + seeds in rumen contents
Therapy: nil
Prevention: deny access to mature seedheads

Sources:
Family Asteraceae (Compositae):
Ixiolaena brevicompta (flat billy-buttons, plains plover-daisy) [DM67]
Toxicity:
- sheep
- western New South Wales & Queensland
- toxins concentrated in **seeds**

Mode of action:
- lipid peroxidation-induced myopathy

Conditions of poisoning:
- **mature seed heads** grazed along the flood-plains of the Darling River & tributaries
- forced exercise precipitates/exacerbates signs

Clinical signs:
- sudden death
- reduced exercise tolerance, muscle weakness, recumbency
- cardiac arrhythmia

Pathology:
- skeletal muscle pallor
- **muscle fibre degeneration and necrosis** in skeletal muscle and heart

Diagnosis:
- pathology + access
- identify seeds in rumen contents

Therapy: nil
Prevention & control: deny access to mature plants carrying seed

References: Se66

Walker KH, Ford GL (1985) Toxicity in sheep due to *Ixiolaena brevicompta*. In *Plant Toxicology*, eds. Seawright AA, Hegarty MP, James LF, Keeler RF, Queensland Poisonous Plants Committee, Brisbane. pp. 401-407.

☑ Isocupressic acid (bicyclic labdane diterpene acids) and/or Vasoactive lipids

Core data

Syndrome name: pine needle abortion
Common sources:

- ***Pinus ponderosa*** (Ponderosa pine)
- ***Cupressus macrocarpa*** (Monterey cypress, macrocarpa)

Animals affected:

- cattle
- sheep

Mode of action: unclear
Poisoning circumstances:

- cattle; North America - snow on winter range → browse ponderosa pine needles
- sheep & cattle; NZ, Tasmania, Victoria → eat lopped or trimmed *Cupressus macrocarpa*

Main effects: premature birth; retained placenta, pyometra
Diagnosis: syndrome + access
Therapy: nil
Prevention: deny access to pregnant stock

Syndrome names: pine needle abortion
Chemical structure:

There is wide variation in the toxin content of the trees involved in this syndrome. There remains uncertainty about the toxin or toxins responsible for the abortion syndrome. Candidate toxins are:

- bicyclic labdane diterpene acid (**isocupressic acid**) reproduced the toxicity when dosed to pregnant cows (Gardner *et al.* 1994, 1996, 1997), but not to pregnant guinea pigs (Ford *et al.* 1999)

  Ester derivatives of isocupressic acid, acetylisocupressic acid and succinylisocupressic acid, also induce abortions in cattle (Gardner *et al.* 1994). These compounds are both metabolised in the bovine rumen to isocupressic acid, with half-lives in rumen fluid of 2 and 4 hrs respectively.

  Other bicyclic diterpene acids from *Pinus ponderosa*, imbricataloic, imbricatoloic and dihydroagathic acids have not been tested for abortifacient activity. Imbricataloic acid occurs at similar concentrations to isocupressic acid in *Pinus ponderosa* (Gardner *et al.* 1998b)

- ruminal metabolites of isocupressic acid, agathic and dihydroagathic acid, increase in blood after ponderosa pine feeding (Lin *et al.* 1998), but their abortifacient capacity has yet to be tested.

- **vasoactive lipids** (myristate and laurate esters of 1,14-tetradecanidiol and 1,12-dodecanediol), in particular the most potent member of the class of compounds isolated, 1-12-dodecanedioyl-1,12-dimyristate (**14-12-14**), cause vasoconstriction of the caruncular artery of isolated perfused bovine placentomes (Al-Mahmoud *et al.* 1995,), and abortion in guinea pigs (Ford *et al.* 1999), but not in cattle (Short *et al.* 1996).

Tricyclic labdane diterpene acids also occur in source plants, but have not produced abortion (Gardner *et al.* 1994). Instead, when cattle were fed large doses of these or of new growth pine tips (containing a relatively large concentration of tricyclic compounds compared with pine needles) they developed anorexia, mild ruminal acidosis, dyspnoea, paresis progressing to paralysis and death (Stegelmeier *et al.* 1996).

Sources:

Gymnosperms (cone-bearing plants)

Family Pinaceae:

Pinus ponderosa (Ponderosa pine) [Australia; Hill 1998a]

Pinus radiata (radiata pine) [Australia; Hill 1998a]

Pinus contorta (lodgepole pine) (Gardner *et al.* 1998a)

Pinus jeffreyi (Gardner *et al.* 1998b)

Family Cupressaceae

Cupressus macrocarpa (Monterey cypress, macrocarpa) [Australia, New Zealand; MacDonald 1956, Hill 1998b, Parton *et al.* 1996]

Cupressus sempervirens (European cypress) (Gardner *et al.* 1998b)

Cupressocyparis leylandii (Leyland cypress) (Hutton *et al.* 1999)

Juniperus communis (common juniper) (Gardner *et al.* 1998a)

Juniperus scopulorum (Rocky Mountain juniper) (Gardner *et al.* 1998b)

Toxicity:

North America, New Zealand, southern Australia

cattle, sheep

horses unaffected (Kip Panter, personal communication VETTOX discussion group, 1999)

one experimental study indicated that cattle and bison were susceptible to *P. ponderosa* toxicity, but sheep and goats were not (Short *et al.* 1992)

Mode of action:

The pathogenesis of abortions is not fully understood but is apparently linked to a progressive decrease in uterine blood flow through **vasoconstriction of the caruncular arterial bed**. The consequently reduced delivery of oxygen and nutrients to the rapidly-growing foetus in late pregnancy causes foetal distress, elevations in circulating foetal ACTH and cortisol concentrations and thus foetal-initiated early parturition through the effects of these hormones on the uterus (Christenson *et al.* 1992a,b; Ford *et al.* 1999)

Conditions of poisoning:

cattle in western North America. Snow on winter range → browse ponderosa pine needles

sheep & cattle in New Zealand, cows in Tasmania & Victoria → eat lopped or trimmed *Cupressus macrocarpa*

Clinical signs:

cows in last trimester → **premature birth** → live calf dies from results of prematurity

abortion 8-10 days after ingestion of toxic dose of plant

subsequent complications - **retained placenta**, pyometra, toxaemia, death

affected cows may "bag up" (begin lactation) and have swollen vulvas with mucus discharge indicative of impending parturition (K. Panter, personal communication, VETTOX 1998)

Pathology:

serosal haemorrhages, oedema and flaccidity of uterus; no gross lesions in the foetus (Bicknell 1990)

histologically, a profound constriction of the caruncular arterial bed in the uterus (Stuart *et al.* 1989)

± cerebral leucoencephalomalacia in bovine foetus - ? anoxia

Diagnosis: syndrome + access

Therapy: nil

Prevention & control: deny access to pregnant stock

References:

Se41; Cheeke 415

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☑ Persin

Core data

Common sources:

- avocado (*Persea americana*)
- Guatemalan & Guatemalan x Mexican hybrid cultivars (not pure Mexican)

Animals affected:

- horses
- goats
- ostriches
- caged birds

Mode of action:

- cardiotoxicity pathogenesis undescribed
- affects vasculature of mammary gland

Poisoning circumstances: consumption of any part of the plant

Main effects:

- heart failure: severe oedema of head (horse), neck (ostrich)
- cardiac muscle necrosis
- agalactia from sterile mastitis

Diagnosis: syndrome + access

Therapy: non-specific

Prevention: deny access

Syndrome names: **avocado poisoning**

Chemical structure:

Persin, (Z,Z)-1-(acetyloxy)-2-hydroxy-12,15-heneicosadien-4-one, appears to be mainly responsible for all manifestations of avocado poisoning in vertebrates, and is a monoglyceride (Bull & Carman 1994) or a biologically-active aliphatic acetogenin (Ruprecht *et al.* 1990) with some similarities of structure with polyether ionophore antibiotics (Oelrichs *et al.* 1995). It was first isolated from avocado leaves as a growth inhibitor of silk-worm larvae (Chang *et al.* 1975)

and subsequently shown to have antifungal properties (Prusky *et al.* 1992). Oelrichs *et al.* (1995) termed the compound, a colourless oil, "persin" and obtained a yield of 0.9-1.0% from avocado leaf. The compound exists in nature as the *R* isomer, with the *S* isomer being non-toxic (Oelrichs *et al.*1995). The ester group on the molecule is thought to be essential for toxicity (Oelrichs *et al.* 1995).

Sources:

Persea americana (avocado)

Three horticultural races are recognised: Guatemalan, Mexican and West Indian (Whiley 1984) **Guatemalan cultivars and their hybrids are toxic** (e.g. Hass, Fuerte); **Mexican cultivars are non-toxic** (crushed leaves of Mexican cultivars smell of aniseed [AA Seawright, personal communication]). All major varieties grown in Australia are hybrids, mostly between Guatemalan and Mexican cultivars, namely Hass [G], Fuerte [MxG], Sharwil [GxM], Rincon [MxG], Wurtz [G], Edranol [G], Hazzard [G], Zutano [MxG], Bacon [MxG], Reed [G], Pinkerton [GxM], Jim [MxG], Santana [MxG] (Whiley 1984)

Toxicity:

horses, goats, ostriches, caged birds, dogs (Buoro *et al.* 1994)

goat leaf toxic dose 9 g/kg

budgerigars ripe fruit lethal dose 50-100 g/kg (Hass & Fuerte)

canary ripe fruit lethal dose 100 g/kg (Hass)

mouse mammary gland damage is caused by a single dose of 60-100 mg persin/kg PO and doses above 100 mg/kg cause myocardial damage (Oelrichs *et al.* 1995).

silkworm larvae (Chang *et al.* 1975)

persin is antifungal for ripe avocado fruit (Prusky *et al.* 1992)

Mode of action:

The pathogenesis of the cardiotoxic syndrome is undetermined, but the affinity of the structure of persin with polyether ionophore antibiotics suggests a similar mode of action (Ruprecht *et al.* 1990, Oelrichs *et al.* 1995).

The agalactic effect is on the vasculature of the mammary gland, not on the secretory epithelium.

Conditions of poisoning:

- Consumption of any part of the plant (usually leaves). Persin appears absent from mature avocado seeds (Oelrichs *et al.*1995)
- Ripe fruit is toxic to caged birds (budgerigars, canaries) and dogs

Clinical signs:

Cardiotoxic syndrome:

sudden death ± dyspnoea (budgerigars, canaries)

anasarca of head and neck (particularly neck in ostriches)

fluid line detected on chest wall

brisket oedema

dyspnoea, coughing

Mammary gland syndrome:

agalactia

Other effects:

± swollen masseter muscles, tongue paresis (horse)

colic (foals)

± laminitis - 2 cases have been seen in horses after avocado consumption (CC Pollitt, personal communication 26 Oct 2001)

Pathology:

Cardiotoxic syndrome:

cardiac muscle necrosis

hydrothorax

pulmonary oedema

Mammary gland syndrome:

sterile mastitis with necrosis of the acinar epithelium of the mammary gland

Other effects:

± masseter muscle necrosis (horses)

Diagnosis:

syndrome + access

significant differential diagnoses in **horses with head oedema** = Hendra virus infection (equine morbillivirus; Australian bat paramyxovirus), African horse sickness; others include *Atalaya hemiglauca* (whitewood) poisoning

Therapy:

remove from source

specific therapy not reported; anti-inflammatory drugs and diuretics have been used

prognosis is fair-good for affected horses without masseter muscle or tongue involvement

Prevention & control:

deny access, particularly to lactating females and cage birds

References:

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Urushiols

Chemical structure:

3-n-alkenyl-catechols

Sources:

Toxicodendron radicans (poison ivy) (El Sohley *et al.* 1982)

Anacardium occidentale (Brazil cashew) (Tyman *et al.* 1989)

Semecarpus australiensis (Australian native cashew) (fruit - Oelrichs *et al.* 1997)

Toxicity:

humans

cashew fruit (Brazil & Australian) toxic – irritant on contact

Clinical signs: contact dermatitis on handling fresh cashew fruit

References:

El Sohley MA, Adawadkar PD, Cheng-Yu MA, Turner CE (1982) Separation and characterisation of poison ivy and poison oak urushiol components. *J. Nat. Prod.* **45**:532-538.

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Pulegone [pennyroyal oil]

Chemical structure:

Pulegone is a monoterpenoid ketone: 5-methyl-2-(1-methyl-ethylidene) cyclohexanone and constitutes 85% of pennyroyal oil

Sources:

Pennyroyal oil is used as a topical treatment for flea infestations

Plant sources from which the oil is distilled [Note: *pulex* (Latin) = flea]: Family Lamiaceae - leaves and flowering tops of *Mentha pulegium* (pennyroyal), *Hedeoma pulegoides* (American pennyroyal)

Toxicity:

known hepatotoxic and abortifacient properties

humans: hepatic damage detected after 500 mg pennyroyal oil (425 mg pulegone)/kg

dog: natural case – topical exposure of 2000 mg pennyroyal oil (1600 mg pulegone) /kg (Sudekum *et al.* 1992)

Conditions of poisoning:

excessive application rate [60 ml pennyroyal oil on a 30 kg dog (Sudekum *et al.* 1992)]

Clinical signs:

vomiting
diarrhoea
coagulopathy – haemoptysis, epistaxis, gastrointestinal bleeding
DIC
seizures, coma

Pathology:

massive hepatic necrosis
diffuse pulmonary "damage"
widespread haemorrhage
vacuolation of cerebellar white matter

Diagnosis: history of exposure and syndrome

Therapy:

topical overdose: wash repeatedly in mild detergent, monitor body temperature
ingestion: activated charcoal PO

Reference:

Sudekum M, Poppenga RH, Raju N, Braselton WE Jr (1992) Pennyroyal oil toxicosis in a dog. *J. Am. Vet. Med. Assoc.* **200**:817-818.

*Tea-tree (*Melaleuca*) oil*

Chemical structure:

Terpenes (*Melaleuca* oil contains 50-60% terpenes & 6-8% cineole). According to Bruneton (1999b), the major constituents are usually terpin-1-en-4-ol and hydrocarbons (terpinenes), but some clones produce an essential oil in which the cineole content reaches 60%.

Sources:

antiseptic skin preparations

The oil is obtained by steam distillation of freshly-harvested *Melaleuca alternifolia* leaves (called Australian tea-tree oil in overseas literature).

Toxicity:

dogs, cats (+ fruit bat)
human (infant) (del Beccaro 1995)

Conditions of poisoning:

ingestion (self-grooming of skin)
excessive skin application or application to inflamed skin

Clinical signs:

tremors
weakness, ataxia
behavioural disorders, depression

diarrhoea, buccal irritation (ingestion)
possible vomiting, seizures from large doses

Pathology: no data

Diagnosis:
history of exposure, clinical syndrome

Therapy:
remove source
supportive measures

Prevention & Control:
avoid application to inflamed skin

Reference:
Bischoff K, Guale F (1998) Australian tea tree (*Melaleuca alternifolia*) oil poisoning in three purebred cats. *J. Vet. Diagn. Invest.* **10**:208-210.
del Beccaro MA (1995) *Melaleuca* oil poisoning in a 17-month-old. *Vet. Human Toxicol.* **37**:557-558.
Villar D, Knight MJ, Hansen SR, Buck WB (1994) Toxicity of *Melaleuca* oil and related essential oils applied topically on dogs and cats. *Vet. Human Toxicol.* **36**:139-142.

Protoanemonin

Chemical structure:
The volatile oily irritant protoanemonin, the lactone of γ-hydroxyvinylacrylic acid (Bonora *et al.* 1987) and a "hemiterpenoid" lactone, is the hydrolysis product of the glycoside ranunculin, is unstable and readily dimerizes to the non-toxic crystalline anemonin on drying (Bruneton 1999b).

Sources:
Family Ranunculaceae

***Ranunculus* spp.** (buttercups and crowfoots) in Australia associated with actual/potential poisoning [*exotic naturalised species]:
- *Ranunculus repens** (creeping buttercup) (Morales 1989)
- *Ranunculus sceleratus** (celery-leaved buttercup, poison buttercup, celery-leaved crowfoot, cursed crowfoot)
- *Ranunculus colonorum* (referred to by Hurst 1942 and Gardner & Bennetts 1956 as *R. lappaceus*) - WA
- *Ranunculus inundatus* (river buttercup) - identity of the species reported as toxic to cattle in NSW by Hurst (1942) is uncertain, but was probably *R. inundatus, R. undosus* or *R. rivularis*
- *Ranunculus undosus* (river buttercup) – associated with colic and gastroenteritis in calves near Jandowae (Darling Downs, Qld) (DPI Poisonous Plants Files, unpublished data 1957)

Ranunculus species in Europe associated with actual/potential poisoning:
- *Ranunculus acris* (meadow buttercup, common buttercup, field buttercup, tall buttercup, crowfoot); UK, Norway (Heggstad 1989)
- *Ranunculus bulbosus* (bulbous buttercup, St.Anthony's turnip); UK
- *Ranunculus sceleratus* [see above]; UK

Anemone spp. (anemones). Cultivated as garden plants in Australia; no poisoning cases on record. Poisoning recorded from Europe (Cooper & Johnson 1998)
- *Anemone nemorosa* (wood anemone); UK
- *Anemone pavonina* (*hortensis*); Italy; poisoning reproduced experimentally (Milillo *et al.* 1991, Colella *et al.* 1991)
- *Anemone pulsatilla* (pasque flower); Europe (Mirkovic 1936)

Clematis spp.
- *Clematis aristata* ; Australia (Q, NSW, Vic, SA); suspected toxicity to cattle, horses in NSW; dullness, anorexia, severe diarrhoea (Hurst 1942)
- *Clematis glycinoides* (headache vine, traveller's joy); Australia (NT, Q, NSW, Vic); suspected of poisoning cattle in Qld but unpalatable; crushed young leaves or mature leaves in sappy growth irritate the nose and eyes and relieve headache; prolonged rubbing → blistering of skin (Everist 1981)

Clematis microphylla (small-leaved clematis); Australia (all states); similar irritant and analgesic effect to *C. glycinoides* (Everist 1981)
Clematis vitabla (traveller's joy, old man's beard) UK (Moore 1971); cultivated in Australia

Helleborus spp.
Helleborus foetidus (stinking hellebore, bear's foot) UK
Helleborus niger (Christmas rose, Easter or Lent rose, black hellebore) UK
Helleborus viridis (green hellebore, bear's foot) UK

Toxicity:
- cattle, sheep, goats, humans
- rare cases: dog, *Ranunculus acris* (Winters 1976); pig, *Ranunculus acris* (Tehon *et al.* 1946); horse (Piekarz 1981)
- toxicity of fresh growing leaves of *Anemone pavonina* in November > plants at start of flowering in January (Milillo *et al.* 1991)
- protoanemonin concentration increases with growth, peaking during flowering (Shearer 1938)
- protoanemonin content:

Family Ranunculaceae member	Protoanemonin content µg/g (wet weight) (other workers' data cited by Bonora *et al.* 1987)	Protoanemonin content µg/g (wet weight) (Bonora *et al.* 1987) HPLC method
Anemone nemorosa	586-5172	333
Anemone trifolia albida		169
Clematis flammula		494
Clematis montana	897-931	418
Clematis jubata		626
Clematis recta		96
Clematis vitalba	931-3138	150
Helleborus foetidus	4827-5827	672
Helleborus niger	10137-11758	5820
Helleborus odorus		5
Helleborus viridis		28
Ranunculus aconitifolius	414	19
Ranunculus acris	4482-5724	1372
Ranunculus arvensis		1646
Ranunculus bulbosus	8965-10931	7766
Ranunculus illyricus		5128
Ranunculus nemorosus		75
Ranunculus repens	207-276	126
Ranunculus serbicus		3066
Ranunculus velutinus		787

Ranunculus sceleratus contained 2.5% protoanemonin in dry matter (Shearer 1938)

Conditions of poisoning:
- poisoning is **rare** because plants in this group are unpalatable; to humans, they have an acrid taste
- ingestion of fresh (flowering) plants when other feed is scarce
- ingestion of herbicide-treated *Ranunculus* sp.; plant palatability increased by herbicide (Blaszyk 1969)
- ingestion of *Helleborus* spp. in garden refuse (Johnson & Routledge 1971, Holliman & Milton 1990)
- dermal application of herbal preparations of *Helleborus* spp. for lice control in cattle (Burselli 1936)
- **dried** plants (e.g. as contaminants of hay) are **non-toxic** (protoanemonin polymerised to anemonin during drying)

Clinical signs (Cooper & Johnson 1998):

- excessive salivation
- stomatitis and glossitis sometimes progressing to ulceration
- signs of abdominal pain
- dyspnoea
- nasal mucosa congestion, muzzle oedema (Milillo *et al.* 1991)
- ± diarrhoea (faeces dark)
- ± dark or blood-stained urine
- ± blindness
- ± hepatogenous photosensitisation (one case noted – Kelch *et al.* 1992)
- fatal cases are rare; convulsions may precede death
- ± abortion (cattle; *Ranunculus repens*; Morales 1989)
- humans: blistering of the skin on close contact

Pathology:

- inflammation of the alimentary tract, sometimes with ulceration

Diagnosis:

- access + syndrome
- detection of plants in rumen

Control:

- *Ranunculus*: hormone herbicides e.g.2,4-D; do not graze treated pasture for 14 days after treatment (increased palatability → increased risk of poisoning)

References:

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Nepetalactone

Chemical structure:

Nepetalactone constitutes 70-99% of the essential oil of *Nepeta cataria*. The main attractant is the trans, cis-isomer of the unsaturated lactone, nepetalactone. This compound is metabolised to nepetalic acid.

Sources:

Family Lamiaceae

Nepeta cataria (**catnip**, catnep, catmint, catrup, catwort, nip, nep, field balm)

available as the fresh or dried herb or incorporated in toys for pets

Toxicity:

plant highly attractive to cats (wild and domestic) > 3 months old, and other mammals

cats' attraction reaction is inherited (autosomal dominant trait) and not all cats respond; no correlation with breed or coat colour

N. cataria has been used as a herbal remedy and hallucinogenic drug by humans

Mode of action: undescribed

Conditions of poisoning:

exposure to growing, green or dried plant

affected cats will return repeatedly to eat and roll in the foliage

Clinical signs:

altered behaviour: cats' response to the presence of the plant appears to be pleasurable (euphoric), may in part be the result of hallucination and is characterised by sniffing, then licking and chewing with head-shaking, followed by chin and cheek rubbing and then a head-over roll and body rubbing; spontaneous vocalisation occurs occasionally (Grognet 1990).

overdoses/adverse reactions (Means, C [ASPCA NAPCC] 2000, personal communication, VETTOX Discussion Group):

common signs: depression, vomiting, excessive salivation and mydriasis

in fewer cases: ataxia, aggression, hyperactivity, muscle fasciculations, seizures

mortality has not been reported from the effects

Pathology: Nil

Diagnosis: access + syndrome

Therapy: symptomatic including activated charcoal + tranquillisers

References:

Grognet J (1990) Catnip: its uses and effects, past and present. *Can. Vet. J.* **31**:455-456.

Furans - Perilla frutescens *(perilla mint, wild coleus)*

Source:

Perilla frutescens (perilla mint, wild coleus) [Family Lamiaceae] – North America

Cases reported in cattle in North America

→ at least 3 lung oedemagenic compounds (perilla ketone, egomaketone, isoegomaketone) with similar structure to mouldy *Ipomoea batatus* furans (*q.v.*)

References:

Garst JE, Wilson WC (1991) Position of perilla ketone metabolism by lung cytochromes P450: evidence for the mechanism of bioactivation through design of an *in vivo* inhibitor of toxicity. Chapter 17 in Keeler RF, Tu AT (eds) *Handbook of Natural Toxins. Vol.6. Toxicology of Plant and Fungal Compounds.* Marcel Dekker, Inc., New York. pp. 353-368.

3-methoxy-2(5H)-furanone [Liliaceae nephrosis – cats, cattle, deer]

Chemical structure:

The **nephrotoxin** from *Narthecium ossifragum* and *N. asiaticum* is **3-methoxy-2(5H)-furanone** (Langseth *et al.* 1999, Flåøyen *et al.* 1999a). Stabursvik (1954) first isolated this compound from *Narthecium ossifragum* without perceiving it to be toxic (Langseth *et al.* 1999). Saponins isolated from *N. asiaticum* (Kobayashi *et al.* 1993, Inoue *et al.* 1995) are disputed as toxic principle responsible for nephrosis by Flåøyen *et al.* (1995b, 1999a), who subsequently detected 3-methoxy-2(5H)-furanone in the plant (Flåøyen *et al.* 1999a). The nephrotoxin responsible for poisoning by *Lilium* spp. and *Hemerocallis* spp. is yet to be determined, but is likely to be 3-methoxy-2(5H)-furanone or a similar compound.

Concentrations of 3-methoxy-2(5H)-furanone in 4 batches of *Narthecium ossifragum* flowering stems were 113-344 μg/g wet weight (Langseth *et al.* 1999). The toxin is water soluble (Flåøyen *et al.* 1997b)

Sources:

Family Liliaceae

***Narthecium* spp.**

Narthecium ossifragum (bog asphodel) – cases in Europe (Norway, UK) (Malone *et al.* 1992, Flåøyen *et al.* 1995)

Narthecium asiaticum – cases in Japan (Suzuki *et al.* 1985)

***Lilium* spp.**

Lilium longiflorum (Easter lily, Christmas lily, November lily)
Lilium tigrinum (tiger lily)
Lilium speciosum (Japanese show lily, rubrum lily)
Lilium lancifolium (Japanese show lily, rubrum lily)
Lilium sp. (Asiatic hybrid lily) (Brady & Janovitz 2000)

Hemerocallis spp. (day lilies)

Toxicity:

Narthecium spp. – cattle (sheep, goats); cervids (moose, red deer, reindeer, but not fallow deer) (Flåøyen *et al.* 1999b, Vikøren *et al.* 1999). Sheep appear capable of developing tolerance to toxicity (Flåøyen *et al.* 2001)
Nephrotoxicity of pure 3-methoxy-2(5H)-furanone for goats was demonstrated at doses PO of 15 mg/kg and above. Nephrotoxicity was seen with smaller doses of less pure 3-methoxy-2(5H)-furanone, being 7 mg/kg at 98%, 5 mg/kg at 96% and 4 mg/kg at 95% purity, suggesting a possible co-agent in *Narthecium* spp. which enhances toxicity (Langseth *et al.* 1999).

Lilium -cats
cats only (reproduced experimentally – Hall 1992)
all vegetative parts including flowers are toxic
consumption of less than one leaf can produce severe intoxication

Mode of action: undescribed

Conditions of poisoning:

Narthecium ossifragum – cattle: grazing pastures in dry weather conditions in summer, possibly providing access to boggy ground not usually available for grazing; flowering stems more toxic than leaves (Flåøyen *et al.* 1997a)

Lilium – cats: exposure in gardens, as potted plants and as cut flowers

Clinical signs:

Narthecium ossifragum – cattle
depression, anorexia
dehydration
melena or fresh blood in faeces
rumen activity weak or absent
erosion of buccal mucosa (a few animals)
sternal recumbency common

Lilium -cats
Within 2 hr of ingestion: vomiting, anorexia, depression
vomiting may subside by 12 hrs
anorexia, depression continue and intensify 24-72 hrs after ingestion
± polyuria
± anuria
untreated cases die within 5 days

Pathology:

Narthecium ossifragum – cattle
↑↑ plasma creatinine & urea
± erosions of buccal & oesophageal mucosa
perirenal oedema
ascites
kidneys pale and swollen
necrosis of renal cortical tubular epithelium

Lilium -cats
↑↑ plasma creatinine (up to 44 mg/dl), urea, P during 24-72 hrs after ingestion
epithelial cats & glucose in urine within 18 hrs of ingestion
necrosis of renal tubular epithelial cells (basement membrane remains intact)

Diagnosis:

history of access/ingestion + clinical pathology (+ histopathology if fatal)

Therapy:

Lilium –cats (Volmer 1999)
renal tubular epithelium can regenerate if therapy is prompt and aggressive
postponing therapy for longer than 18 hrs after ingestion can lead to irreversible renal failure and death

anuria indicates a poor prognosis

decontaminate: **emetic** followed after vomiting by **activated charcoal + cathartic** (sorbitol, magnesium or sodium sulphate)

fluid diuresis: lactated Ringer's solution at x2 maintenance rate (130 ml/kg/day) for at least 48 hrs required to maintain urine flow; urine production should be maintained at 2 ml/kg/hr or more

renal function has been restored in some cases after peritoneal dialysis

Prevention & control:

Narthecium – ruminants

cattle develop an aversion to experimentally-fed plant suggesting that feeding of sub-toxic doses of plant to cattle before their release to pasture may induce an aversion and prevent intoxication (Flåøyen 1998)

Lilium -cats

deny access to cats/dogs likely to chew plants

References:

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