ALKALOIDS

Definition [adapted from Lewis' Dictionary of Toxicology 1998]

Alkaloid: Any of a large heterogeneous group of alkaline, bitter-tasting, biologically-active, usually water-insoluble, nitrogenous organic compounds produced mostly by dicotyledonous plants. Most are crystalline solids (a few liquids or gums) and are derivatives of heterocyclic and/or aromatic nitrogen ring compounds. Their trivial names usually end in –ine, e.g. atropine, strychnine.

Alkaloids are most commonly associated with the flowering plants, but there are other natural sources in cyanobacteria (*q.v.*), macrofungi (*q.v.*), amphibians (*q.v.*) and ants.

☑ *Pyrrolizidine alkaloids*

Core data

Common sources:
- *Senecio* spp. (groundsels, fireweeds)
- *Heliotropium* spp. (common & blue heliotropes)
- *Echium* spp. (Paterson's curse, viper's bugloss)
- *Crotalaria* spp. (rattlepods)

Animals affected: pigs > poultry > cattle, horses > sheep & goats

Mode of action: oxidation in liver (± lungs, kidney) → highly reactive pyrrolic metabolites
→ bind to macromolecules (DNA) →
- cell necrosis
- halt mitosis → megalocytosis
- damage blood vessels

Poisoning circumstances:
PAs unpalatable; intake because
- inadequate pasture
- contaminated hay
- feed grains contain weed seeds

Main effects:
- delayed onset; doses cumulative
- chronic hepatopathy with megalocytosis (except pigs - nephrosis)
- hepatoencephalopathy (horses)
- lung damage (some alkaloids)

Diagnosis:
- access history (± difficult)
- + liver pathology (pigs - kidney)
- + detect pyrrolic metabolites

Therapy: nil

Prevention:
- deny access,
- graze plants with sheep/goats,
- herbicides,
- biological control,
- stock feed regulations (weed seeds)

Pyrrolizidine alkaloids (PAs) are among the most important natural toxins affecting livestock in Australia and the world. Their properties impact directly on human and domestic animal health and consequently they impact indirectly on national and international trade in grain and livestock products.

Pyrrolizidine alkaloidosis was first reproduced experimentally when John Anderson Gilruth fed *Senecio jacobaea* (ragwort) to cattle in New Zealand in 1902 during investigation of the cause of Winton disease (Gilruth 1902a,b cited by Connor 1977; Gilruth 1903, 1905 cited by Bull *et al.* 1968). The first isolation of

a pyrrolizidine alkaloid was from *Senecio vulgaris* (Grandval & Lajoux 1895). Their association with disease was first established with 'senecifoline' and 'senecifolidine' (probably mixtures including seneciphylline) isolated from *S. latifolius* by Watt (1909) and tested in experimental animals by Cushny (1911). See Bull *et al.* (1968) for a thorough account of early research.

In Australia, Gilruth (1911) noted the close similarity between Winton disease in New Zealand and descriptions given to him of Kimberley horse disease. Legg (1923) (together with C.T.White) investigated a similar syndrome (Gilbert River horse disease) in Queensland. Murnane & Ewart (1928), distracted by Ewart's preconception that saponins were the responsible toxin, declared *Atalaya hemiglauca* (whitewood) (*q.v.*) the cause of Kimberley horse disease after investigations and experiments in the Kimberley region confounded by using local horses, probably with pre-existing PA lesions, as experimental subjects (Bull *et al.* 1968).

Syndrome names:

> **Pyrrolizidine alkaloidosis** (pyrrolizidinosis) is the general name for poisoning by this group of phytotoxins which generally causes chronic liver damage and may additionally involve other organs including the kidneys and lungs. This syndrome may also be called **seneciosis** if caused by *Senecio* spp. Crotalariosis has been used, but is less precise, as syndromes other than typical pyrrolizidine alkaloidosis are caused by the *Crotalaria* genus.

> Several local syndrome names are also used, including syndrome names employed for the disease of horses in Australia - **Kimberley horse disease** and **walkabout disease** known from north-western Australia since European settlement in the 1880s (Murnane & Ewart 1928) and Gilbert River horse disease in Queensland (Legg 1923). The disease in cattle and horses associated with *Senecio jacobaea* has been called Winton disease in New Zealand (Connor 1977) and Pictou disease in Canada (Bull *et al.* 1968). Poisoning of horses by *Senecio linearifolius* in Tasmania was called Waratah horse disease after the locality where it occurred (Dickinson 1930). Poisoning from *Senecio* spp. in southern Africa has been called Molteno cattle sickness (in cattle) and stomach staggers, dunsiekte (enzootic liver cirrhosis) or Molteno horse disease (in horses) (Bull *et al.* 1968). Poisoning by species of *Crotalaria* in north America has been called Missouri bottom disease and walking disease (Bull *et al.* 1968).

> **Veno-occlusive disease** is a syndrome in humans with chronic liver damage from pyrrolizidine alkaloids. Similar lesions may occur in other species.

> **Jaagsiekte** (an Afrikaans name meaning `driving disease') or *Crotalariosis equorum* is a kind of pyrrolizidine alkaloidosis with lesions principally in the lungs and affecting horses & mules in South Africa (now largely historical) (Theiler 1918, Marais 1944, Steyn & van der Walt 1945), and has been described in horses in Australia in the 1960s in the Kimberley region of Western Australia and recently (2001) in north Queensland.

> **Acute pneumotoxicity** occurs from ingestion of certain *Crotalaria* spp. by ruminants and has been reproduced in experimental animals.

Chemical structure:

Several hundred PAs have been identified and characterised, but **not all are toxic** (see below). Of the toxic PAs, most are **hepatotoxic**, with a few being **pneumotoxic** or **nephrotoxic**. Most toxic PAs are esters of the bases retronecine and heliotridine which are amino alcohols and diastereomers with opposite configuration at C7. PAs based on heliotridine are more toxic than those based on retronecine.

Structural features necessary for toxicity include
- a 1,2 double bond in the pyrrolizidine nucleus. PAs based on saturated necine bases (without this double bond) cannot be oxidised to pyrrolic metabolites.
- a branch in the ester group – this hinders hydrolysis and thus promotes greater pyrrole production

PAs often occur in plants in the water-soluble N-oxide form as well as in the free base alkaloid form. N-oxides are, in general, less toxic than the corresponding alkaloid. They can be reduced to the corresponding

free bases in the digestive tract and thus contribute to the toxicity of plants containing them. Evaluation of plant sources of toxic PAs should take into account both their free base and *N*-oxide contents.

Toxic PAs are of three types in **increasing order of toxicity**: monoesters, noncyclic (open) diesters and cyclic diesters. Diesters produce more pyrroles than monoesters.

Sources:

Hepatotoxicity

Major plant sources of hepatotoxic PAs in Australia (most important species in bold) occur in 3 plant families: Asteraceae (= Compositae), Boraginaceae and Fabaceae (= Leguminosae in part)

- Family Asteraceae (Compositae): Genera **Senecio,** *Ageratum*
    - Genus **Senecio** - about 50 species in Australia; about 8 species (3 exotic naturalised*) associated with poisoning, namely
        *__Senecio jacobaea__ (ragwort, tansy ragwort [USA], stinking Willie [Scotland – so named after HRH Prince William, Duke of Cumberland, commander of the victorious Hanoverian forces at the battle of Culloden on 16 April 1746, because of the subsequent massacre and persecution of Jacobite adherents and others in the Scottish highlands])
        *__Senecio madagascariensis__ (fireweed, Madagascan fireweed) [cattle - Walker & Kirkland 1981; horses - Seawright *et al.* 1991b; horses - Small *et al.* 1993]
        Senecio lautus (fireweed, variable groundsel) [cattle - Noble *et al.* 1994]
        Senecio cunninghamii
        Senecio linearifolius (fireweed) [= *Senecio australis* (Dickinson 1930)]
        Senecio magnificus (tall yellowtop)
        *__Senecio pterophorus__ (African daisy, South African daisy, winged groundsel, perdegifbos [South Africa])
        Senecio quadridentatus (cotton fireweed)

Senecio jacobaea (ragwort) plants in natural habitat as pasture weeds. [RAM Photo]

Whole flowering plant of *Senecio lautus* (fireweed) in natural habitat. [RAM Photo]

Flowering *Senecio madagascariensis* (Madagascan fireweed) plant. [RAM Photo]

- Genus *Ageratum*

      Ageratum conyzoides (billygoat weed [Australia], babadotan [Indonesia]) in Indonesia) has been associated with cattle poisoning in Sumatra (Murdiati & Stoltz 1987)and is experimentally toxic to rats (Sani & Stoltz 1993, Sani & Bahri 1994, Sani *et al.* 1998). PAs have been isolated from plants in Kenya (Wiedenfeld & Röder 1991)/

      Ageratum houstonianum (blue billygoat weed [Australia]). PAs have been isolated from plants in Mexico (Wiedenfeld & Andrade-Cetto 2001) and it has produced sporadic photosensitisation (*q.v.*) in Cuba and Australia.

- Family Boraginaceae: Genera **Heliotropium, Echium**

    - Genus **Heliotropeum** - 81 species of *Heliotropium* in Australia and about 300 worldwide (Craven 1996), 5 species (4 exotic naturalised*) associated with poisoning, namely

      ***Heliotropium europaeum** L. (common heliotrope, potato weed) (Jones *et al.* 1981)

      ***Heliotropium amplexicaule** Vahl (blue heliotrope) [DM98] (Ketterer *et al.* 1987)

      **Heliotropium supinum* L. (prostrate heliotrope)

      **Heliotropium indicum* L. (Indian heliotrope) (L.Laws, unpublished data 1961; van Weeren *et al.* 1999)

      Heliotropium ovalifolium Forsskål (Creeper *et al.* 1999)

Flowering *Heliotropium europaeum* (common heliotrope). [RAM Photo]

Flowering *Heliotropium amplexicaule* (blue heliotrope). [RAM Photo]

Flowering twig of *Heliotropium amplexicaule* (blue heliotrope). Note the structure of the uncurling inflorescence with flowers on the exterior of the curve. [RAM Photo]

- Genus **Echium** - 4 species of *Echium* naturalised in Australia, only 1 associated with poisoning
Echium plantagineum (Patterson's curse, Salvation jane) [DM87; Dellow & Seaman (1985)]

Flowering and immature (rosette) stages of *Echium plantagineum* (Patterson's curse, salvation Jane). [RAM Photos]

- Family Fabaceae (Leguminosae): Genus ***Crotalaria***
    - Genus ***Crotalaria*** - There are 36 native and naturalised* *Crotalaria* species in Australia including 23 subspecies and varieties (Lee 1978; Holland 2002). Some additional exotic species are cultivated. Worldwide, there are about 600 species in the tropics and subtropics, mostly in Africa (Polhill 1982).
    13 species in Australia have been associated with PA poisoning of domestic animals, namely
        Crotalaria crispata F.Muell. (Kimberley horse poison) – see also jaagsiekte (below) [horses - Gardiner *et al.* 1965]
        Crotalaria eremea F.Muell. (bluebush pea) [DM122] (Lee 1978) [sheep - Laws 1965]
        Crotalaria novae-hollandiae DC. (New Holland rattlepod) [DM75] (Lee 1978)
        ****Crotalaria retusa*** L. (wedge-leaf rattlepod) [DM76] native of SE Asia
        ****Crotalaria spectabilis*** Roth (showy rattlepod) [DM77] native of Asia [horses - Seawright *et al.* 1991a]

Crotalaria pallida Aiton (streaked rattlepod) [DM75] native of tropical Africa [sheep - Laws 1968]
Crotalaria dissitiflora Benth. (grey rattlepod) (Lee 1978)
Crotalaria goreensis Guill. et Perr. (Gambia pea) native of tropical Africa
Crotalaria incana L. (woolly rattlepod) native of the Americas
Crotalaria juncea L. (sunn hemp) native of India - see also jaagsiekte (below)
Crotalaria laburnifolia L. (bird flower) native of SE Asia & eastern Africa
Crotalaria mitchellii Benth. (yellow rattlepod) (Lee 1978) – see also jaagsiekte (below) [horses - PM Summers unpublished data 2001]
Crotalaria montana Heyne ex Roth [= *Crotalaria linifolia*] [cattle - Pinch 1999]

2 native species have been associated with equine oesophageal ulceration (*q.v.*) from unknown toxin(s), namely
Crotalaria aridicola Domin (Chillagoe horse poison)
Crotalaria medicaginea Lamk. (trefoil rattlepod) (Lee 1978)

Other native or naturalised species in Australia should be regarded as potentially toxic until proven otherwise, namely
Crotalaria agatiflora Schweinf.
Crotalaria alata Ham. ex D.Don
Crotalaria brevis Domin
Crotalaria calycina Schrank
Crotalaria cunninghamii R.Br. (bird flower)
Crotalaria distans Benth.
Crotalaria grahamiana Wight & Arn.
Crotalaria humifusa Graham ex Benth.
Crotalaria lanceolata E.Meyer
Crotalaria lunata Beddome ex Polhill
Crotalaria micans Link
Crotalaria mysorensis Roth
Crotalaria ochroleuca G.Don
Crotalaria prostrata Rottl.
Crotalaria quinquifolia L.
Crotalaria ramosissima Roxb.
Crotalaria sessiliflora L.
Crotalaria smithiana A.T.Lee (Lee 1978)
Crotalaria verrucosa L.
Crotalaria virgulata Klotzsh
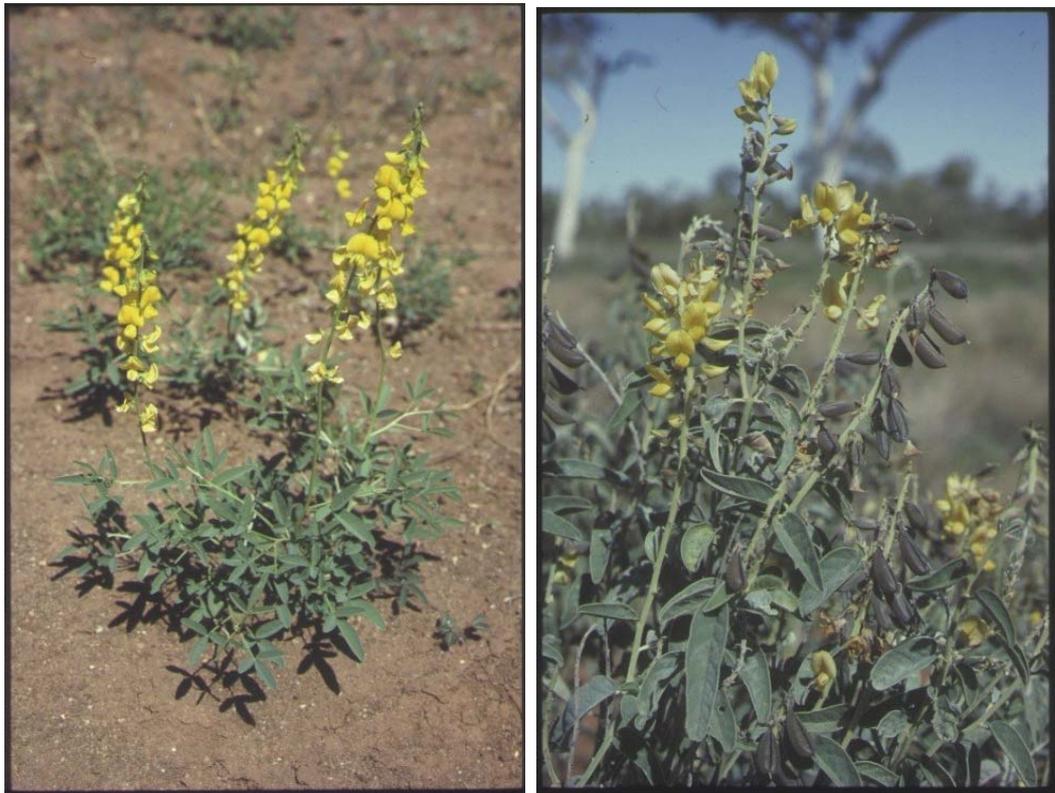*Crotalaria zanzibarica* Benth.

Flowering *Crotalaria crispata* (Kimberley horse poison) [RAM Photo]

Crotalaria crispata (Kimberley horse poison) - whole plant with flower buds [RAM Photo]

Crotalaria retusa (wedge-leaf rattlepod) flowers (left) and seed pods (right) [RAM Photos]

Crotalaria dissitiflora (grey rattlepod) (left); *Crotalaria novae-hollandiae* (New Holland rattlepod) (right) [RAM Photos]

Crotalaria pallida (streaked rattlepod) (left); *Crotalaria spectabilis* (showy rattlepod) (right). [RAM Photo]

Minor plant sources of hepatotoxic PAs in Australia occur in :
Family Apocynaceae: Genus *Parsonsia*
Family Boraginaceae: Genera *Amsinckia* (ironweeds), *Borago* (borage)*, Buglossoides, Cynoglossum* (hound's tongues), *Symphytum* (comfreys), *Trichodesma* (camel bush)
Family Asteraceae: Genera *Echinacea, Emilia*

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Numerous plant species of these and some other genera are associated with PA intoxication of domestic animals in Europe, North & South America, Africa and Asia, including [N.B. This list is under construction and very incomplete]:
Asia
Heliotropium dolosum - seeds recorded as toxic to poultry in Turkey (Eröksüz *et al.* 2001)

Europe
Cynoglossum officinale (houndstongue) – recorded as toxic to grazing horses in Germany (Zentek *et al.* 1999)
Senecio subalpinus – cattle, Albania (Smith & Panariti 1995)

North America
Cynoglossum officinale (houndstongue) – recorded as toxic when dried in hay fed to horses (Knight *et al.* 1984; Stegelmeier *et al.* 1996), cattle (Baker *et al.* 1989, 1991); PAs measured (Pfister *et al.* 1992)

South America
Senecio erraticus – the only one of 300 *Senecio* species in Chile recorded as toxic (Araya & Fuentealba 1990)
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Jaagsiekte

All cases of jaagsiekte in both southern Africa and Australia have been associated with consumption of plants in the genus *Crotalaria*.

Sources of pneumotoxic PAs in Southern Africa (Kellerman *et al.* 1988):

Crotalaria dura Wood & Evans (wild lucerne, wilde lusern, jaagsiektebossie) contains dicrotaline (Marais 1944)

Crotalaria globifera E.Mey (wild lucerne, wilde lusern, jaagsiektebossie) contains dicrotaline (Marais 1944)

Crotalaria juncea L. (sunn-hemp, sunn-hennep)

Crotalaria spartioides DC. (dune bush, duinebos, besembossie, Januariebos)

Sources of pneumotoxic PAs in Australia:

Crotalaria crispata (Kimberley horse poison) (Gardiner *et al.* 1965) contains fulvine, crispatine and monocrotaline

Crotalaria juncea L. (sunn hemp) – no clinical cases on record in Australia

Crotalaria mitchellii (yellow rattlepod) (PM Summers *et al.* unpublished data 2001) contains monocrotaline and retusamine

Acute pneumotoxicity
Associated with *Crotalaria* spp.

Crotalaria pallida [= *Crotalaria mucronata*] (streaked rattlepod) (Laws 1968)

Crotalaria spectabilis (showy rattlepod)

Crotalaria eremea (blue-bush pea) contains monocrotaline (Culvenor 1967) and has poisoned sheep (Laws 1965)

Toxicity:

The details of syndromes resulting from PA ingestion by vertebrates vary due to
- **animal species** because of the different rates at which incoming PAs are metabolised to active compounds by the livers of different species and
- the **individual PAs** in the ingested plants influencing the speed with which their metabolites escape being bound in the liver and then enter the general circulation to impact on extra-hepatic target organs. For example, active metabolites of monocrotaline and fulvine from certain *Crotalaria* spp. escape very rapidly (almost entirely), while metabolites of PAs from boraginaceous plants, such as *Heliotropium* spp. and *Echium* spp., do not escape at all.

Syndromes include
- **hepatotoxicity in horses** sometimes combined with a variety of less common effects
- **hepatotoxicity in ruminants** sometimes combined with a variety of less common effects
- acute pneumotoxicity in ruminants
- jaagsiekte (pneumotoxicity) in horses
- nephrotoxicity in pigs

Hepatotoxicity – domestic animals
About half the known PAs (*ca.* 250) are hepatotoxic. PAs are **cumulative** in tissues, resulting in chronic disease. Syndromes may commence **weeks to months after ingestion ceases** and run a course of up to about 4 weeks. Or more than one season's exposure may elapse before clinical signs appear, particularly in the more resistant species like sheep. **Delayed clinical manifestation** of hepatotoxicity can occur. Molyneux *et al.* (1988) reported that a lag of 18 months was possible between dosing and onset of signs in cattle.

Animal species susceptibility in order of increasing resistance (with relative rating in parentheses) is pigs (1) > poultry (5) > cattle & horses (14) > rats (50) > mice, sheep & goats (150). Sheep & goats appear to be the most resistant ruminants because their ruminal floras contain more active PA-degrading bacteria and their hepatic drug-metabolising enzymes detoxify PAs more efficiently than cattle. Consequently, sheep or goats have been used to control PA-containing plants in pasture for cattle & horses.

Hepatotoxicity - humans

Veno-occlusive disease of humans has resulted from *Heliotropium, Trichodesma, Senecio* and *Crotalaria* seed contamination of cereal grains in Asia and Africa, and from ingestion of herbal remedies containing *Crotalaria* species in the West Indies and, rarely, *Symphytum* species (comfrey) and others elsewhere. PAs are regarded as carcinogens (Schoental 1968)

Hepatotoxicity - Australian native animals
There is concern that intoxication may occur in the rare and endangered orange-bellied parrot (*Neophema chrysogaster*) through feeding on the seeds of *Heliotropium europaeum* and *Echium plantagineum* while wintering in southern Australia (South Australia, Victoria) after migration from breeding grounds in Tasmania, but evidence of actual cases is unrecorded.

Jaagsiekte
Jaagsiekte (Afrikaans = `driving disease') of horses & mules in South Africa (not to be confused with the viral disease of sheep) is caused by dicrotaline in *Crotalaria dura* (wild lucerne), *C. globifera* (wild lucerne) and *C. juncea* (sunn hemp) (Kellerman *et al.* 1988). Very similar lung lesions of cattle in South Africa are caused by *C. spartioides* (dune bush) (Kellerman *et al.* 1988). Fulvine in *Crotalaria crispata* (Kimberley horse poison) in Australia also causes lung lesions in Kimberley Horse Disease (Gardiner *et al.* 1965). Monocrotaline in *Crotalaria mitchellii* is believed to have caused cases in horses in northern Queensland (PM Summers *et al.* unpublished data 2001).

Acute pneumotoxicity - ruminants
Natural cases are recorded in sheep (Laws 1965, Laws 1968). Experimentally, both sheep (Laws 1965, 1968) and cattle (Tokarnia & Döbereiner 1982) are susceptible.
Crotalaria eremea: 566g of plant collected 2 days previously at Quilpie was fatal to a sheep within 24 hours of oral dosing (Laws 1965).
Crotalaria pallida: 57-85 g of flowering plant from the Darwin area of the Northern Territory fed immediately after cutting killed goats in 8-24 hours, but dried plants were not toxic (Lewis 1912). Fresh or wilted leaves from the Brisbane area dosed at 11.1-13.5 g wet weight/kg within 2 hours of harvest killed 5 sheep within 15-23 hours (Laws 1968). In Brazil, fresh recently-collected leaf dosed at 25-80 g/kg killed calves within 16-68 hours (Tokarnia & Döbereiner 1982).

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Insect utilisation of pyrrolizidine alkaloids
PAs are used as defense chemicals by a number of insects that feed on the source plants. The bitter-tasting PAs deter predation by birds, spiders and other insects. In some insects (e.g. moths, butterflies), PAs accumulated by the larval male insect while feeding on its host plant (*Crotalaria* spp.) are transferred to the female in sperm "packages" and this, in addition to PAs accumulated by the female herself, protects the fertilised eggs and the female (Gonzales *et al.* 1999).

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Mode of action:
> Pyrrolizidine alkaloids themselves are not significantly toxic. Their oxidation in tissues (liver mostly, but some in lungs or kidney) in normal xenobiotic biotransformation reactions creates **pyrrolic metabolites** (dehydroalkaloids) - highly reactive electrophilic alkylating agents - which bind to DNA and other cell macromolecular components. The main **target organs** (in descending order of general importance) are **liver**, **lung** and **kidney**.

> The direct effects of pyrrolic metabolites are
> - **cell necrosis** (particularly of hepatocytes)
> - **halting mitosis** of cells in target organs, thus producing **megalocytes** (giant cells e.g. hepatocytes)
> - damage to blood vessels leading to **veno-occlusive disease** (fibrosis around hepatic lobule central veins leading to their obliteration)
> - cross-linking of DNA which may lead to mutagenesis and carcinogenesis (neither effect has been observed clinically in domestic animals)

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PAs & human health
PAs are not proven human carcinogens, but are genotoxic and mutagenic and cause cancer in rats. They may act in synergy with aflatoxins and hepatitis viruses to cause human hepatic carcinoma. [WHO Task Group on Pyrrolizidine Alkaloids (1988), Prakash *et al.* (1999), Newberne & Rogers (1973)]

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Conditions of poisoning:
PA-containing plants are bitter and **unpalatable**. The N-oxides of the alkaloids, and which commonly occur in the same plant material, are not bitter and are normally excreted in urine. N-oxides may be reduced to their parent alkaloids in the gut and thus lead to toxicity.

Critical predisposing factors for the consumption of PA-containing plant material
- low availability or unavailability of wholesome pasture.
- hay or bedding straw contaminated with PA-containing plants
- silage contaminated with PA-containing plants. Alkaloids as a group are not destroyed by the ensiling process (Borsberry 1999).
- feed grains contaminated with PA-containing seeds

PAs may be excreted in milk. PAs may (rarely) pass the placenta and affect the foetus *in utero* (Small *et al.* 1993).

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Sources of human exposure to pyrrolizidine alkaloids or pyrrolic metabolites
- medicinal preparations containing source plants ("bush" teas, herbal remedies)
- plant-origin foodstuffs contaminated by source plants (weed seeds in cereal grains)
- animal-origin foodstuffs from animals exposed to source plants (honey, milk, eggs, liver) (Edgar *et al.* 2002)

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Clinical signs:
Horses - hepatotoxicity
Hepatotoxicity commonly results in **hepatoencephalopathy**, manifest as the syndromes called "walkabout disease" and "Kimberley horse disease" [Literature includes Rose *et al.* 1957a,b; Pearson 1991; McGorum *et al.* 1999]. **Note well!** Affected horses may present with a dummy syndrome, but suddenly become manic and highly aggressive when restrained or handled. These animals are dangerous to anyone attempting to examine them closely or to obtain blood samples from them. ***Exercise extreme caution***.

The most **common** syndrome consists of
- weight loss → emaciation
- ± slight jaundice
- lethargy, repeated yawning
- muscle tremor, incoordination
- irritability
- compulsive walking or galloping → skin abrasions of the chest, forelimbs, neck and face
- blindness, head pressing

A variety of **uncommon** signs reported in horses include
- sudden death (anorexia, depression, jaundice)
- oedema of underline and legs
- colic
- diarrhoea

- ❖ constipation, tenesmus
- ❖ photosensitisation
- ❖ haemolysis, haemoglobinuria
- ❖ paralysis (full or part) of larynx, tongue → roaring
- ❖ dyspnoea (lung lesions from fulvine in *C. crispata*) – see jaagsiekte (below)
- ❖ gastric impaction

Horses - jaagsiekte
The syndrome consists of fever (intermittent and not present in all cases), cough, hyperpnoea (sudden increase of respiratory rates to 100-120/min), dyspnoea, rales, stridor, tachycardia and sometimes subcutaneous emphysema (Kellerman *et al.* 1988).

Cattle - hepatotoxicity
- Main syndrome
  - weight loss → emaciation
  - persistent diarrhoea with tenesmus
  - ± jaundice
  - anorexia, lethargy
- Uncommon signs
  - rectal prolapse (Wiltjer & Walker 1974)
  - photosensitisation
  - nervous derangement (↑aggression, aimless walking, blindness, head-pressing)
  - haemolysis

Sheep - hepatotoxicity
- British breeds and cross-breeds graze *H. europaeum* more readily than Merinos
- *H. europaeum* grazing → 1-7% deaths in season 1 → 50-90% deaths in season 2.
- *H. europaeum* may → widespread losses in lambs in western Victoria in some years (Harris & Nowara 1995)
- Main syndrome
  - weight loss → emaciation
  - jaundice (PA poisoning predisposes to increased Cu uptake into ovine hepatocytes, promoting chronic copper poisoning → haemolysis)
  - photosensitisation
  - ascites

Pigs - nephrotoxicity (Hooper & Scanlan 1977)
- *Crotalaria retusa* seeds in feed @ > 0.01% → death in 2-4 months
- *C. retusa* seeds @ 0.1-0.5% →
  - inappetence, ↓ weight gain
  - severe **nephrosis** with megalocytosis → uraemia, anaemia, perirenal oedema
  - interstitial pneumonia with megalocytosis
  - hepatic megalocytosis (not clinically significant)

Poultry - hepatotoxicity
- *Crotalaria* spp. or *H. europaeum* seeds in feed
- Main syndrome
  - inappetence, ↓ weight gain or weight loss
  - depression → coma
- acute poisoning → diffuse hepatocyte necrosis, ascites
- chronic poisoning → liver fibrosis, megalocytosis, ascites; kidney megalocytosis
  - decreased production can result from poisoning without characteristic lesions developing in livers (Pass 1982)

Ruminants - acute pneumotoxicity
Affected sheep and goats collapse die rapidly (Lewis 1912, Laws 1968). Dyspnoea and cyanosis were seen in sheep, with collapse and death within 15 minutes of onset of clinical signs (Laws 1968).

Dogs
PA toxicity is practically unknown in this species. A suspected toxicity from chronic idiosyncratic consumption of *Senecio* sp. (fireweed) with liver failure (uninvestigated histologically) has been reported in suburban Perth, WA (Lamond 2000)

Pathology:

Hepatotoxic syndrome
Clinical pathology findings are variable. There may be increased plasma concentrations of bilirubin and liver-associated enzymes and decreased plasma concentrations of albumin and urea. **The most consistent finding is hyopalbuminaemia**. Anaemia may be found also. Pyrrolic metabolites can be detected on haemoglobin by TLC techniques.

The major lesion is a **chronic hepatopathy** characterised by atrophy of hepatic parenchyma (reduced numbers of hepatocytes) with **megalocytosis** of the survivors, bile ductule proliferation and fibrosis (usually periportal, less commonly centrilobular) (Bull 1955). Multiple regeneration nodules of hepatocytes may occur. Pyrrolic metabolites can be detected in liver by TLC techniques.

Secondary and minor lesions may include ascites, status spongiosis of cerebral white matter (sometimes also grey matter), pulmonary emphysema and interstitial fibrosis, and megalocytosis of renal or pulmonary epithelium. Oedema and infarction of the caecum and colon are reported in experimental *Cynoglossum officinale* poisoning of a horse (Stegelmeier *et al.* 1996).

Jaagsiekte
Major lesions seen at necropsy are pulmonary emphysema (lungs fail to collapse), patchy atelectasis and consolidation, thickened oedematous inerlobular septa. Interstitial emphysema extending to the subcutis, hydrothorax and hydropericardium sometimes occur. Histologically, the major lung lesions are a mixed inflammatory infiltrate, interstitial fibrosis, oedema and hypertrophy of the tunica media of pulmonary blood vessel walls and multifocal hyperplasia of bronchiolar epithelium (regarded by Theiler 1918 as pathognomonic) in addition in some cases to a chronic hepatopathy with megalocytosis (Kellerman *et al.* 1988).

Acute pneumotoxicity - ruminants
Pulmonary oedema with tracheobronchial foam and distension of interlobular septa with fluid is the main lesion. Hydrothorax, hydropericardium and sub-pleural haemorrhages are also seen. Fibrin is present in the thoracic fluid and it coagulates on exposure to air. Histologically, there is proteinaceous fluid and some haemorrhage in alveoli. No significant hepatic lesions are seen. [Laws 1965, 1968; Tokarnia & Döbereiner 1982]

Diagnosis:

Field tests are available to detect PAs and PA N-oxides in plants (Mattocks & Jukes 1987). Results obtained should be confirmed by laboratory assays.

Plant access by affected animals can be difficult to establish due to the lag between ingestion and the onset of signs weeks to months later.

Hepatotoxicity

Liver histopathology: **megalocytosis**, biliary ductular hyperplasia, fibrosis (note differential diagnosis includes aflatoxicosis)

Serum γGT may be used as a screening test for subclinical liver damage in horses (Curran *et al.* 1996).

Pyrrolic metabolites (PM) bound to tissue macromolecules may be detected in liver or blood using TLC (thin layer chromatography), but only in specialised laboratories (Mattocks & Jukes 1990; Seawright *et al.* 1991a).

Conditions for successful PM detection by this means include

- large sample sizes (at least 10 g liver or 20 ml whole blood in EDTA) are required to detect the small concentrations involved, so liver samples obtained by biopsy are unsuitable for testing.

- blood sample collection during or within about 2 weeks of access to the PA source so that sufficient PMs remain bound to haemoglobin of circulating erythrocytes for detection. As erythrocytes turn over (normal 120 day lifespan), dilution of the PM concentration occurs.

- liver samples fixed in formalin are suitable for PM detection

Ultrasound has been used in cattle to assess the abdominal viscera (Braun *et al.* 1999).

Jaagsiekte

Lung histopathology is characteristic.

Acute pneumotoxicity - ruminants

Plant access & pathology. Differential diagnoses should include poisoning by galegine (*q.v.*).

Therapy:

No useful therapy is recognised for any form of pyrrolizidine alkaloidosis. Horses that develop non-lethal poisoning and recover often have a permanently reduced capacity to work.

Prevention & control:

Plant-oriented

- graze PA-containing plants with relatively resistant species (sheep, goats), but only for a limited time (1 season).
- fence-off hazardous concentrations of plants or remove susceptible animals
- apply herbicides
- introduce biological control agents for naturalised weeds. Agents need to attack young seedlings, thus reducing seed production.
  - ❖ *Heliotropeum europaeum* - introduced beetle *Longitarsus albineus* not very successful; rust fungus *Uromyces heliotropii* (released 1991 in NSW & WA; kills seedlings & → ↓ seed in mature plants); fungus *Cercospora heliotropii-bocconii* (under study in Europe; reduces plant growth, infects seeds → ↓viability); combination of these fungi may be effective.
  - ❖ *Echium plantagineum* - leaf-mining moth *Dialectica scalariella* (released 1988-90 in Victoria & WA; summer damage caused but seed production not reduced); winter-feeding root crown-boring weevils *Mogulones (Ceutorhynchus) larvatus* & *M. geographicus* (released NSW 1989 &1993; attacks rosette stage); 6 more agents scheduled for release.
  - ❖ *Senecio jacobaea* - crown-boring moths, ragwort flea beetles and cinnabar moths released in Victoria & Tasmania 1995-1998. Control to date is good in Tasmania, less so in Victoria (DRDC 1998).
- promulgate stock feed regulations intended to prevent the sale of feed grains contaminated by hazardous quantities of toxic weed seeds, but these can fail e.g. *H. europaeum* seed poisoning of poultry and pigs in Victoria and South Australia in 1993 (Gaul *et al.* 1994).

Animal-oriented

Immunisation, manipulation of rumen flora, manipulation of hepatic metabolism, protection with thiol compounds and genetic selection for resistance have all been **unsuccessful** for decades. The transfer into cattle of ovine rumen fluid from sheep resistant to toxicity from *Senecio jacobaea* resulted in resistance of inoculated cattle to poisoning by this plant (Johnston *et al.* 1998), suggesting an avenue of possible future control.

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✹✱ ☑ *Strychnine & brucine [indole alkaloids]*

Core data - Strychnine

Common sources: vertebrate pesticide
Animals affected: all species, mainly dogs
Mode of action:

- antagonises post-synaptic inhibition in spinal cord & medulla
- → uncontrolled, diffuse reflex activity involving all striated muscles

Poisoning circumstances:

- malicious poisoning of dogs
- secondary poisoning of carnivores (pets, raptors) during rodent baiting

Main effects: tetanic seizures induced by external stimuli
Diagnosis:

- syndrome
- assay stomach contents, urine

Therapy:

- first control spasms (muscle relaxant or barbiturate)
- reduce absorption (emetic if conscious, gastric lavage ± retrograde enema)
- activated charcoal + saline cathartic
- forced diuresis + acidify urine
- provide warm quiet environment

> Somebody sent Dean Swift
> An ounce of strychnine as a gift.
> He took about thirty-five minims
> While writing about the Houyhnhms.
>
> Edmund Clerihew Bentley

Chemical structure:

Strychnine is an indole alkaloid

Sources:

Strychnine is from seeds and bark of members of the Family Loganiaceae
nux vomica (seeds of *Strychnos nux-vomica*) from SE Asia
ignatius beans (pods/seeds of *Strychnos ignatii*) from SE Asia
Strychnos icaja bark is the richest source, yielding 6.6% strychnine in dry weight (Harborne & Baxter 1996)

The genus *Strychnos* contains about 170 species in the tropics and subtropics, with the greatest number in Africa, America and Malesia. Four species of *Strychnos* occur in northern Australia (*S. minor, S. lucida, S. arborea* and *S. psilosperma*), the latter 2 of which are endemic (Conn & Brown 1996). No case of poisoning from these plants is on record.

Brucine (10,11-dimethoxystrychnine) is a structurally similar, less potent, alkaloid with similar physiological effects from bark, wood and seeds of several *Strychnos* spp. including *S. nux-vomica, S. ignatii* and *S. aculeata* (Harborne & Baxter 1996).
Strychnine is available as a **vertebrate pesticide** (rodents, canids [dingo, coyote])
→ used for malicious poisoning of pets, doping of greyhounds, race horses
- legal possession in Qld is restricted to permit-holders under the Health (Drugs and Poisons) Regulations 1996 administered by Queensland Health

It was formerly used in human and veterinary medicine in stimulants / tonics

Toxicity:

- susceptibility: cattle, horse, pig > dog > cat > rat > fowl
- LD_{50} for domestic animals = 0.5-3.0 mg/kg. Dogs = 0.75 mg/kg
- readily absorbed from small intestine $\rightarrow$ 10% excreted in urine, 90% metabolised (liver)
    - relatively resistant to degradation in the environment; strongly adsorbed to soil particles; poorly water soluble; microbial breakdown is required for its removal and a lag period with little breakdown may extend to 20 days depending on soil type, followed by a period of rapid breakdown with 90% degraded in soil over 40 days exposure (Anon. 1998)

Bufo marinus (cane toads) are reported to have died in convulsions after eating petals fallen from flowers of *Strychnos nux-vomica* trees in Hawaii. One toad was reported to have eaten 10 flowers before dying. Petals contained 1.023% strychnine. [Brock 1948, Arnold 1968]

Mode of Action:
- CNS action: **antagonises** glycine-mediated post-synaptic **inhibition in spinal cord & medulla**, particularly that mediated by the Renshaw cells [= interneurones (cells between the primary afferent neurone and the final motor neurone) in CNS providing regulatory feedback to control the excitability of motor neurones] $\rightarrow$ uncontrolled, diffuse reflex activity involving all striated muscles $\rightarrow$ symmetrical generalised rigidity & **tetanic convulsions**
- action reversible; no lesions of nerves or muscles

Conditions of poisoning:
- secondary poisoning of carnivores (pets, birds of prey) during rodent-baiting operations
- malicious poisoning of pets

Clinical signs:
- onset: 10-30 min after ingestion; untreated $\rightarrow$ death in *ca.* 1 hr
- early signs - apprehension, nervousness, tenseness $\rightarrow$ gradually developing stiffness
- muscle rigidity
- violent **tetanic spasms**
    - spontaneous or **induced** by various stimuli (touch, sound, sudden bright light) (cf. metaldehyde)
    - initially intermittent $\rightarrow$ more frequent $\rightarrow$ death from diaphragmatic spasm & asphyxia
- pupil dilation
- cyanosis

Pathology:-
- *rigor mortis* rapid onset, short duration (muscular activity exhausts muscles' reserves of glycogen & ATP)
    ["Normal" onset of *rigor mortis* is around 1-6 hours and termination is around 24-48 hours, depending on ambient temperature and the physiological state of the animal, but is highly variable (Thompson 1978). Dogs dying of strychnine poisoning may be in *rigor* virtually from the time of death - WR Kelly & RD Sutton 1996, personal communication]
- stomach contents in place (strychnine does not $\rightarrow$ vomiting)
- ± haemorrhages in organs poorly supported by connective tissues (thymus, pancreas)
- ± intramuscular haemorrhages

Diagnosis:
- clinical syndrome, exposure history
- assay **stomach contents**, urine, liver, kidney (highest concentration in stomach contents followed by liver, then kidney – Blakley 1984)
- N.B. differential diagnosis includes metaldehyde poisoning, roquefortine poisoning (see below), penitrem A poisoning (see below), tetanus (*Clostridium tetani* wound infection $\rightarrow$ intoxication)

Therapy:
Elimination time of strychnine = 24-48 hrs $\rightarrow$ muscle spasm control may need maintenance for this period. *Prompt aggressive measures to remove/neutralise strychnine will shorten this period.*
Contraindications

- morphine (respiratory depression, potential stimulation of spinal cord)
- ketamine (brain motor stimulant effects)

Suggested protocol:

Immediately control spasms

→ muscle relaxant (see box) OR anaesthetise & intubate trachea

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Alternative muscle relaxants suggested in strychnine poisoning
- Diazepam: 1 mg/kg IV followed by 1 mg/kg IM; repeat frequently to effect
- Glycerol guiacolate ether: 110 mg/kg IV (→ control for10-60 min); may require 2-5 doses or more at 20 min - 6 hr intervals depending on response
- Methocarbamol (Robaxin®): 150 mg/kg IV (→ control for 30-120 min); subsequent 90 mg/kg doses for maintenance
- Xylazine: IV to effect (care to prevent aspiration of vomitus induced by this drug)

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Reduce/eliminate further strychnine absorption from GI tract

If conscious and spasms controlled → emetic - apomorphine 0.03 mg/kg SC

If anaesthetised → gastric lavage and consider retrograde enema with continued anal fluid administration and gastric lavage tube in place until clear fluid flows from the oesophageal tube.

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Lavage fluids suggested in strychnine poisoning
- Saline OR
- 1-2% tannic acid OR
- 1:2000 potassium permanganate solution

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Then → activated charcoal + Na or Mg sulphate cathartic

Promote urinary excretion of absorbed strychnine

→ forced diuresis - 5% mannitol in 0.9% NaCl solution @ 6.6 ml/kg/hr

Acidify urine → oral ammonium chloride 100-200 mg/kg/day in 3-4 divided doses

Provide warm quiet environment with facilities for O_2 administration & positive pressure pulmonary ventilation

Prevention & Control: Replace strychnine with other means of rodent control (preferably non-toxic)

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Os284, Se341

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Alstonine, alstonidine and other indole alkaloids of Alstonia constricta

Core data

Common sources: Alstonia constricta (bitter bark, quinine bush)
Animals affected: ruminants
Mode of action: probably similar to strychnine
Poisoning circumstances: trees browsed during periods with poor pasture production

Main effects: tetanic spasms
Diagnosis: access + syndrome
Therapy: as for strychnine poisoning
Prevention: prevent access or supplementary feed to reduce browsing; herbicide control of plants

Sources:

>   ***Alstonia constricta*** F. Muell. (bitter bark, quinine tree, quinine bush, quinine bark, Peruvian bark, native cinchona, native quinine, lacambie or lecambil [Clarence River aboriginal people]) (Family Apocynaceae) is a tree (to 15 m tall) widespread in coastal and inland southern Queensland and north-eastern New South Wales. Occurs in vine thickets and vine forests or in open forests and woodlands. It suckers freely (particularly if roots are damaged such as by cultivation), flowers from August to January and fruits from July to December. *Alstonia* is a genus of 40-45 species in Africa, Asia, Malesia, Melanesia and Australia with 6 species in Australia, 3 of which are endemic. (Forster 1996)

Toxicity:

>   **Ruminants** have been reported as susceptible to poisoning.
>   Leaves, fruit and twigs are toxic (Copeland & Seddon 1931).
>   Alstonine, alstonidine and reserpine have been identified in bark (Boaz *et al.* 1957, Svoboda 1957, van Camp & Rose 1957, Bisset 1958).
>   Sheep have been experimentally intoxicated. Three of 4 sheep fed 1.5 kg green leaf and young fruit daily for between 11 and 21 days developed clinical signs (Hurst 1942).

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Medical uses

Alstonia constricta stem bark has been used as a febrifuge and tonic. In the 19th century, it was proposed as an anti-malarial, hence some of the common names applied to the plant, but it actually has very little if any anti-malarial activity. The reserpine in root bark could be used as a hypotensive, but is not in commercially useful amounts. (Cribb & Cribb 1981; Lassak & McCarthy 1983; Collins *et al.* 1990)

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Organ systems affected: CNS
Mode of action: Undescribed, but probably similar to that of strychnine and brucine (*q.v.*)
Conditions of poisoning:

>   Many cases of poisoning have been reported in Qld and NSW in cattle and sheep grazing quietly in the paddock in seasons when grass was dry and scarce (Everist 1981). Experimental sheep appeared to prefer eating the fruits of the plant (Hurst 1942).
>   Dogs fed meat from experimentally-poisoned sheep developed nervous signs consistent with poisoning of ruminants by the plant, recovering in 24 hr (Hurst 1942).

Clinical signs:

>   Hurst (1942) described natural cases in sheep as developing diarrhoea, muscle tremors ("shivers"), ataxia ("staggers") and stiffness of limbs with loss of condition and death in a few days. The syndrome was reported to resemble strychnine poisoning. Experimentally-fed sheep (Hurst 1942) developed tetanic spasms of limbs and neck - the limbs were held rigidly and the body stiffly with the head thrown back. There was heightened excitability and an exaggerated response to sound or touch. Affected animals fell easily.

Pathology: No lesions have been reported at necropsy.
Diagnosis:

>   Access + syndrome
>   Examination of rumen samples collected at necropsy for the presence of the plant may be useful in some cases.

Therapy:

>   Field cases have been reported to recover when denied access to the plants (Hurst 1942).
>   Application of treatment regimens used for strychnine (*q.v.*) should be useful in serious cases.

Prevention & control:

Grazing animals at risk of eating the plant under dry pasture conditions should be either denied access to them or given adequate supplementary feed to reduce the probability of significant browsing of shrubs and trees.

Effective mechanical removal of the plant is hindered by its capacity to produce root suckers readily. Picloram + triclopyr (Access®) is registered for use on bitterbark as a basal bark or cut stump application using diesel as a carrier. Long-term control of root suckers in fallowed cultivation (> 3 years) is by applying picloram + triclopyr (Grazon® DS) as a 1:4 concentration in water using a blanket wiper in autumn. Adding glyphosate provides no advantage. Use 2% Grazon® DS (100 ml concentrate in 5 L water) to spot spray individual plants, thoroughly wetting all leaves and stem. Treated areas should not be cultivated for 6 months. These are registered uses of these herbicides. [Osten & McCosker 2002]

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Indole (pyrrolidinoindoline) alkaloids - calycanthine, chimonanthine, idiospermuline

Chemical structure:

The known toxic pyrrolidinoindoline alkaloids are

- calycanthine [CA] (Hamor *et al* 1960, Woodward *et al.* 1960)
- chimonanthine [CH]
- idiospermuline [ID] (Duke *et al.* 1995)

Sources:

Plants

Australia

Idiospermum australiense (Diels) S.T.Blake [= *Calycanthus australiensis* Diels] (ribbonwood) is a rare lowland rainforest tree of northern Queensland in the monotypic Family Idiospermaceae (Blake 1972). Its "seeds" are 3-6 cm in diameter and comprise naked embryos each with 3-4 massive fleshy cotyledons (Blake 1972). The "seeds" contain CA, CH, ID (Duke *et al.* 1995).

New Guinea

Bhesa archboldiana (Merr. & Perry) Ding Hou [= *Kurrimia archboldiana* Merr. & Perry] is a large rainforest tree of New Guinea in the Family Celastraceae. Its bark contains CA (Culvenor *et al.* 1970).

North America

Calycanthus L. (2 species - Mabberley) are shrubs in the Family Calycanthaceae distributed in southern USA

Calycanthus fertilis Walt. ("bubby" or strawberry bush; Carolina, hairy or smooth allspice; sweet or pale sweet shrub; Indian toothpick) There is field evidence of its toxicity in Tennessee USA (Beasley *et al.* 1997).