GLYCOSIDES

Definition [adapted from Lewis' Dictionary of Toxicology 1998]

Glycoside: A compound yielding a sugar (most often a pentose or hexose) and a non-sugar (aglycone) on hydrolysis. They are produced naturally in plants by combining diverse hydroxy compounds with sugars, occurring more widely and abundantly than alkaloids.

The biologically-active part of glycosides is often the aglycone. The sugar moiety may often be important for absorption and penetration of biological membranes.

References:

Review literature

Majak W (1992) Mammalian metabolism of toxic glycosides from plants. *J. Toxicol. – Toxin Reviews* **11**:1-40.

☑ Cyanogenic glycosides [→ Cyanide, HCN or Prussic acid]

Core data

Syndromes:

- Acute cyanide poisoning (sudden death)
- Chronic cyanide poisoning
  - Posterior ataxia & urinary incontinence
  - Foetal arthrogryposis
  - Goitre
  - Sulphur-responsive reduced production

Common sources:

- Acute
  - HCN released when plant tissue damaged
  - *Sorghum* spp. (sorghum)
  - Numerous other plants
- Chronic
  - *Sorghum* spp.
  - *Cynodon* spp. – congenital goitre, sheep
  - *Sorghum sudanense* and hybrids – foetal arthrogryposis

Animals affected:

- Acute: ruminants >>> monogastrics
- Chronic:
  - cattle, horses - posterior ataxia & urinary incontinence + foetal arthrogryposis
  - sheep – congenital goitre
  - ruminants – sulphur-responsive decreased production

Poisoning circumstances:

- Acute
  - young leaf material
  - stressed plants (grasshoppers, wilting)
  - sorghum hay retains toxicity
- Chronic
  - pregnant stock grazing Sudan grass hybrids

Main effects:

- acute:
  - blocks cellular respiration
  - rapid death, bright red blood (O_2 unabsorbed)
- chronic:
  - spinal cord white matter degeneration
  - ataxia, urinary incontinence
  - foetal arthrogryposis
  - congenital goitre

Diagnosis:

- Pathology + access to sources
- picric acid spot test on plant → red if positive

Therapy:
Acute: sodium thiosulphate IV + PO
Prevention:

- graze sorghum > 75 cm tall
- ensile hazardous sorghum

Cyanide (as HCN) was first recognised as toxic when Scheele, a famous synthetic chemist, accidentally poisoned himself in 1786 by inhaling cyanide vapours that he had just synthesised (Graham *et al.* 1977).
Sodium cyanide (NaCN) and potassium cyanide (KCN) are industrial products used for ore extraction (e.g. gold), electroplating and other manufacturing processes. They are highly toxic.

Syndromes:

Acute cyanide poisoning (sudden death) is the most common and important outcome of ingestion of plants containing cyanogenic glycosides.

Chronic effects attributed to cyanide poisoning are rarely reported. These are

- posterior ataxia & urinary incontinence
- congenital goitre
- foetal arthrogryposis
- Sulphur-responsive reduced production

A syndrome of abortion (early foetal loss) or stillbirth (late foetal loss) in mares in Kentucky during April-May 2001 called Mare Reproductive Loss Syndrome (MRLS) has been tentatively attributed to ingestion of cyanide from faeces of Eastern Tent caterpillars feeding on black cherry trees (presumed to be *Prunus serotina* [Kingsbury365]) in pastures grazed by pregnant mares (Anon. 2001, Hood 2001).

Chemical structure:

Cyanogenic glycosides or **cyanogens** are composed of a cyanide-containing aglycone linked to a sugar or sugars (usually glucose). Cyanide can also occur in plants as cyanolipids in seed oils of some species of the Family Sapindaceae (Cheeke 1998).

Cyanogenic glycosides are derived by plants from the amino acids leucine, isoleucine, valine, tyrosine, phenylalanine and apparently from a glycine derivative (Moller & Siegler 1999).

Hydrolysis of cyanogenic glycosides releases hydrogen cyanide (HCN) (= prussic acid)

Major cyanogenic glycosides include amygdalin (laetrile), dhurrin, linamarin, lotaustralin, lucumin and prunasin

Function in plants: Cyanogenic glycosides act as deterrents of herbivory by such animals as molluscs (snails, slugs) and insects. (Jones *et al.* 1999)

Sources:
Acute poisoning (sudden death):

Plant sources of HCN in Australia

Those included by Everist (1981) are indicated below. Significant species are given in **bold**. Plant families with significant cyanogenic plants of importance for animal health are Poaceae (grasses), Euphorbiaceae (spurges), Fabaceae (peas), Linaceae (linseed), Myoporaceae (native fuchsias), Myrtaceae (gums), Rosaceae (plums) and Sapindaceae.

Family Poaceae (Grasses)

Brachiaria mutica (para grass) - reported cyanogenic (as *Panicum muticum*) (Petrie 1913) (Ev891)

Brachyachne spp. (native couch grasses) (Ev891)

Brachyachne ciliaris (Benth.) C.E.Hubbard (hairy native couch). No cases of poisoning are recorded, but Everist (1981) believed that this species was potentially toxic.

Brachyachne convergens (F.Muell.) Stapf. (native couch, Downs couch, Kimberley couch, gulf star grass, spider grass) [N.B. Differs from *Cynodon dactylon* (common couch, green couch, Indian couch, Bermuda grass) in being annual not perennial, not rooting at joints and having the lower glumes as long as or longer than the lemmas (Everist 1981)] [DM50]; has yielded 60-670 mg/kg (0.006 - 0.067%) HCN on green weight basis (highest = 1150 mg/kg (0.115%) on dry weight basis) (Anon. 1940, Francis 1940); numerous hungry sheep (several days without feed) with access to water have been poisoned on stock routes (Everist 1947).

Brachyachne tenella (R.Br.) C.E.Hubbard (slender native couch); specimens from Clermont yielded 430 mg/kg (0.043%) HCN in dry matter (Everist 1981 p.305); no cases of poisoning are recorded.

Chloris spp. (Ev893)

Chloris distichophylla Lag. (evergreen chloris, winter-growing Rhodes grass, frost-resistant Rhodes grass); native of South America; 160-750 mg/kg (0.016 - 0.075%) HCN recorded in NSW in February & May (Hurst 1942) and also detected in Qld samples (Anon 1937, Everist 1937); no poisoning cases recorded (Everist 1981).

Chloris truncata R.Br. (windmill grass); strong positive qualitative test for HCN recorded (Petrie 1913), but no toxicity recorded.

Chloris ventricosa R.Br. (tall chloris, windmill grass); strong positive qualitative test for HCN recorded (Petrie 1913), but no toxicity recorded.

Cynodon spp. (couch grasses)

Cynodon dactylon Pers. (common couch, green couch, Indian couch, Bermuda grass) (Ev896); listed by McBarron (1972, 1976) as cyanogenic, but Everist (1981) doubted this conclusion.

Cynodon incompletus Nees (blue couch) (Ev896); HCN yields measured in New South Wales have varied from 250 to 1980 mg/kg of dry matter (0.025-0.198%) peaking in summer (Petrie 1913, Finnemore & Jaffray 1935, Hurst 1942). Numerous cases have occurred in sheep and cattle in New South Wales (Hurst 1942, Macadam 1966).

Cynodon nlemfuensis Vanderyst (African star grass, budgee grass, giant star grass) (Ev896); HCN yield of young green samples from south-eastern Queensland varied with season from 50 to 1380 mg/kg (0.05 - 0.138%) of dry matter (Everist 1981). In Africa, yields from irrigated and fertilised plants ranged from 410 to 4430 mg/kg (0.041-0.443%) (Rodel 1972). *Cynodon plectostachyus* (African star grass) has been confused with *C. nlemfuensis* and is not recorded reliably as cyanogenic (Everist 1981).

Cynodon aethiopicus

Danthonia spp (wallaby grasses) (Ev896). No field cases have been recorded associated with this genus (Everist 1981).

Danthonia semianularis tested faintly positive for HCN (Petrie 1913). The current identity of the plants tested by Petrie (1913) is uncertain (Vickery 1956, Everist 1981).

Danthonia racemosa tested faintly positive for HCN (Petrie 1913). The current identity of the plants tested by Petrie (1913) is uncertain (Vickery 1956, Everist 1981). McBarron (1972) recorded a strong positive reaction.

Danthonia caespitosa tested strongly positive (McBarron 1972).

Danthonia longifolia tested strongly positive (McBarron 1972).

Danthonia paradoxa tested strongly positive (McBarron 1972).

Danthonia setacea tested strongly positive (McBarron 1972).

Eleusine spp. (Ev897)

Eleusine indica (L.) Gaertn. (crow's-foot grass). Strong positive test results were reported for New South Wales plants by Petrie (1913), but whole plant from Queensland yielded 130 mg/kg (0.013%) (Smith & White 1914) and Gurney (1941) and McCray (1956) detected no HCN in leaves or stems. The yield from seeds ranged from 30 to 580 mg/kg with most yielding 150-190 mg/kg

HCN (Gurney 1941, McCray 1956). Documented cases of poisoning in sheep are rare (Everist 1981).

Eleusine tristachya (Lam.) Lam. (crow's-foot grass). Samples from New South Wales have yielded weak positive tests (McBarron 1972). No poisoning cases are recorded (Everist 1981).

Glyceria maxima (Hartm.) Holmb. [= *Glyceria aquatica* (L.) Wahlenb.; *Poa aquatica* L.] (reed sweet-grass, swamp grass, water meadow grass). A semi-aquatic weed of farm dams and waterways in temperate parts of Australia (Parsons & Cuthbertson 2001). Toxicity in cattle is recorded from New Zealand (Sharman 1967) and Victoria (Barton *et al.* 1983). HCN yield has been recorded at 1520 mg/kg in New Zealand (Sharman 1967).

Panicum spp. (Ev909)

Panicum coloratum L. (coolah grass). Plants in Africa yielded 170-1700 mg HCN /kg (Rodel 1972).

Panicum maximum Jacq. (guinea grass). Yielded HCN from New South Wales samples (Petrie 1913, McBarron 1972).

Paspalum dilatatum Poir. (paspalum, Dallis grass) (Ev910). African samples yielded 4-86 mg/kg (Rodel 1972). No poisoning cases are recorded.

***Sorghum* spp.** (grain, forage & silk sorghums, Johnson grass, Sudan grass) [DM55] (Ev917). Dhurrin is commonly present.

Sorghum* x *almum Parodi (Columbus grass, sorghum almum). HCN yield of plants from Queensland is reported as 600-810 mg/kg (Everist 1981).

Sorghum bicolor (L.) Moench [= *Sorghum "vulgare"* complex and includes various taxa such as *Sorghum arundinaceum* (Willd.) Stapf, *Sorghum dochna* (Forsk.) Snowden, *Sorghum drummondii* (Steud.) Millspaugh & Chase] (grain, forage & silk sorghums, milo, broom millet) - cultivated in summer-rainfall areas of Australia. Toxicity is recorded, particularly from regrowth on grain sorghum stubbles.

Sorghum halepense (L.) Pers. (Johnson grass). A weed of roadsides and cultivation. HCN yield of a plant from the Darling Downs (Qld) was 290 mg/kg (Everist 1981).

Sorghum sudanense (Piper) Stapf (Sudan grass). Numerous poisoning cases are recorded, for example by Hurst (1942).

Sorghum verticilliflorum (Steud.) Stapf (wild sorghum). HCN yields have been reported as ranging from 250 to 1790 mg/kgin whole plants, 630 to 2090 mg/kg in new shoots from old plants and 900 to 5230 mg/kg in new shoots from plants with aerial parts removed (Winks 1940)

Triraphis mollis R.Br. (purple plume grass) [DM58] (Ev918). HCN yield recorded at 350 mg/kg 4 days after sampling from a locality in which rams had died after being forced by flood waters onto sand hills carrying the grass (SL Everist, unpublished data 1955 cited by Everist 1981).

Zea mays (corn) (Family Poaceae) regrowth [sheep poisoned in Israel (A. Shlosberg, personal communication 1999)]

Sorghum halepense (Johnson grass); whole plant (left), inflorescence (right). [RAM Photos]

Herbs, shrubs & trees:

Family Araceae
- *Colocasia esculenta* (taro) (Ev894)

Family Asteraceae
- *Osteospermum* spp. (South African daisies) (Ev909)
  - *Osteospermum ecklonis*
  - *Osteospermum jucundum*

Family Chenopodiaceae
- *Chenopodium* spp. (Ev893)
  - *Chenopodium carinatum*
  - *Chenopodium cristatum*
  - *Chenopodium melanocarpum*
  - *Chenopodium pumilio* (?)
  - *Chenopodium rhadinostachyum*
- *Dysphania* spp. (Ev897)
  - *Dysphania littoralis*
  - *Dysphania myriocephala*

Family Davidsoniaceae
- *Davidsonia pruriens* (Davidson's plum) (Ev896)

Family Droseraceae
- *Drosera* spp. (sundews) (Ev897)
  - *Drosera auriculata*
  - *Drosera bulbosa*
  - *Drosera macrophylla*
  - *Drosera peltata*
  - *Drosera spathulata*
  - *Drosera whittakeri*

Family Euphorbiaceae

Breynia oblongifolia (Ev891)
Bridelia spp. (Ev891)
Bridelia exaltata
Bridelia leichhardtii
Euphorbia spp. (Ev898)
Euphorbia boophthona (Gascoyne spurge) (?)
Euphorbia dallachyana (?)
Euphorbia drummondii (mat spurge, red soldier) – syndromes described are inconsistent with the effects of cyanide
Euphorbia prostrata - syndromes described are inconsistent with the effects of cyanide
Leptopus decaisnei [= *Andrachne decaisnei*] (Ev889)
Manihot spp. (Ev906)
Manihot esculenta (cassava)
Manihot palmata
Phyllanthus spp. (Ev911)
Phyllanthus gasstroemii
Phyllanthus lacunaris (?)
Poranthera spp. (Ev912)
Poranthera corymbosa
Poranthera microphylla

Family Fabaceae
Canavalia spp. (Ev892)
Canavalia ensiformis
Canavalia gladiata
Canavalia maritima
Entada phaseoloides (Ev898)
Goodia spp. (Ev901)
Goodia lotifolia (golden tip, clover tree)
Goodia medicaginea
Indigofera australis (Ev902)
***Lotus* spp.** (birdsfoot trefoils) (Ev905)
Lotus angustissimus
Lotus australis
Lotus corniculatus
Lotus cruentus
Lotus hispidus
Lotus major
Lotus pedunculatus
Trifolium repens (white clover) produces cyanogenic glycosides (Ev918), but has never induced acute toxicity for a number of reasons including its relatively high S content (Vickery *et al.* 1987, Stochmal & Oleszek 1997). It may contribute to goitrogenesis in lambs under certain conditions (Vickery *et al.* 1987) and may contribute to Se deficiency in grazing livestock (Crush & Caradus 1995).
Vicia sativa (common vetch) (Suter 2002)

Family Flagellariaceae
Flagellaria indica (Ev899)

Family Goodeniaceae
Dampiera brownii (Ev896)

Family Haloragidaceae
Glishrocaryon spp. (Ev905)
Glishrocaryon aureum [= *Loudonia aureum*] (pop flower)
Glishrocaryon roei [= *Loudonia roei*]
Haloragis heterophylla (Ev901)

Family Icacinaceae
Pennantia cunninghamii (Ev910)

Family Juncaceae
Juncus spp. (Ev903)
Juncus holoschoenus (joint-leaf rush) (Albiston 1937, Barton *et al.* 1983)
Juncus prismatocarpus (Ev903)

Family Juncaginaceae

Triglochin spp. (water ribbons). Members of the genus are recognised as cyanogenic and toxic in North America (Burrows & Tyrl 2001).

Triglochin procera. Suspected of toxicity in Tasmania (Munday & Morris 1978).

Family Lecythidaceae

Barringtonia asiatica (Ev890)

Family Linaceae

Linum spp. (Ev904)

Linum marginale

Linum usitatissimum (linseed) (Family Linaceae)

Family Mimosaceae

Acacia spp. (wattles) (Ev888)

The *Acacia cheelii* Group of eastern Australia (distinguished by spikes arranged in short racemes, phyllodes with numerous closely-spaced non-anastomosing longitudinal nerves, and linear pods slightly constricted between seeds) (Tindale & Kodela 2001a) includes the following potentially toxic taxa:

Acacia binervia (J.C.Wendl.) J.F.Macbr. [= *Acacia glaucescens* (L.) Willd.] (coast myall, sally wattle) - contains sambunigrin; yielded 0.155-0.41% HCN in dry matter (Hurst 1942); toxicity confirmed experimentally for sheep and cattle (Seddon & White 1929)

Acacia burrowii Maiden (Burrow's wattle) - flowers yielded 0.051% HCN (Hurst 1942); trees are lopped for forage in some districts (Tindale & Kodela 2001b)

Acacia cheelii Blakely (motherumbah) - contains sambunigrin (Hurst 1942)

Acacia deanei ssp. *paucijuga* (F.Muell. ex N.A.Wakef.) Tindale - prunasin detected (Secor *et al.* 1976)

Acacia farnesiana (L.) Willd. (cassie, cassy, dead finish, farnese wattle, mimosa, mimosa wattle, mimosa bush, prickly mimosa bush, prickly moses, needle bush, north-west curara, sheep's briar, sponge wattle, sweet acacia, thorny acacia, thorny feather-wattle, wild briar) - unidentified glycoside detected (Secor *et al.* 1976)

Acacia longifolia (Andrews) Willd. (Sydney golden wattle, sallow wattle) - suspected of poisoning a goat & positive for HCN (Hurst 1942); subspecies (*longifolia* and *sophorae* (Labill.) Court) are recognised (Court 2001)

Acacia oswaldii Muell. (nelia, midget, middia, miljee, ram's horn tree, umbrella wattle, umbrella bush, curly yarran, whyacka and other names) - a widespread transcontinental species in all mainland states south of 19°S (Cowan & Maslin 2001); specimen from Moree, NSW, tested positive for HCN (Hurst 1942)

Acacia parramattensis Tindale (Sydney green wattle, Parramatta wattle) - mandelonitrile glycosides detected (Secor *et al.* 1976)

Acacia pulchella R.Br. (prickly moses) - mandelonitrile glycosides detected (Secor *et al.* 1976)

The 4 following *Acacia* species (members of the often confused poorly-defined "*Acacia cunninghamii*" Group) have all previously been included within the taxon *Acacia cunninghamii* Hooker (Pedley 1999) from which sambunigrin has been reported (Secor *et al.* 1976), but reports of toxicity in cattle and goats in New South Wales and Queensland cannot now be assigned to particular taxa within this group (Everist 1981).

Acacia concurrens Pedley (curracabah, late-flowering black wattle)

Acacia crassa Pedley

Acacia longispicata Benth.

Acacia leiocalyx (Domin) Pedley (black wattle, early-flowering black wattle, curracabah)

Family Myoporaceae

***Eremophila* spp.** (Ev898)

Eremophila maculata (spotted native fuchsia) (Brunnich & Smith 1910)

Eremophila bignoniiflora (?)

Family Myrtaceae

***Eucalyptus* spp.** (Ev898)

Eucalyptus cladocalyx (sugar gum) (Finnemore *et al.* 1935, Hurst 1942, Ev898, Webber *et al.*1985)
Eucalyptus viminalis (manna gum) (Finnemore *et al.* 1935, Ev898)

Family Olacaceae
Olax benthamiana (Ev909)
Ximenia americana L. (yellow plum, hog or monkey plum, tallow nut) (Ev920)

Family Passifloraceae
Passiflora spp. (passion vines) (Ev910) [larvae of the South American butterfly *Heliconius sara* feeding on *Passiflora auriculata* can metabolise cyanogenic compounds without releasing HCN (Engler *et al.* 2000)]
Passiflora aurantia
Passiflora cinnabarina
Passiflora foetida (stinking passion vine)
Passiflora herbertiana
Passiflora suberosa
Passiflora subpeltata

Family Proteaceae
Grevillea spp. (Ev901)
Grevillea banksii - only flowers contain cyanogenic glycosides
Grevillea robusta (silky oak) - only flowers contain cyanogenic glycosides
Hakea spp. (Ev901)
Hakea dactyloides
Hakes saligna
Hicksbeachia pinnatifolia (Ev902)
Lambertia formosa (mountain devil) (Ev903)
Lomatia silaifolia (crinkle bush) (Ev905) - only flowers contain cyanogenic glycosides
Macadamia spp. (Ev905)
Macadamia integrifolia (Queensland nut, bopple nut)
Macadamia ternifolia
Macadamia tetraphylla
Macadamia whelanii
Xylomelum spp. (woody pears) (Ev920)
Xylomelum angustifolium
Xylomelum pyriforme

Family Rosaceae
Cotoneaster spp. (Ev894)
Crataegus spp. (haws [hawthorns], medlars, azarole, manzanilla) (Ev894)
Cydonia oblonga (quince) (Ev895)
Eriobotyra japonica (loquat, Japanese medlar, nispero) (Ev898)
Malus sylvestris (apple) (Ev906)
Prunus spp. (Ev606,912)
Prunus amygdalus (almond)
Prunus armeniaca (apricot)
Prunus cerasus (cherry)
Prunus domestica (plum)
Prunus laurocerasus (cherry laurel)
Prunus persica (peach)

Family Rubiaceae
Canthium vaccinifolium (Ev892)
Pomax umbellata (Ev912)

Family Rutaceae
Zieria spp. (Ev921)
Zieria laevigata
Zieria smithii

Family Sapindcaeae
Alectryon oleifolius [= *Heterodendron oleifolium*] (booneree) (Ev902)

Family Winteraceae
Drimys spp. (Ev897)

Ferns:

Family Aspleniaceae (Ferns)
Asplenium flabellifolium (Ev890)
Family Davalliaceae (Ferns)
Davallia spp. (hare's foot ferns) (Ev896)
Family Dennstaedtiaceae (Ferns)
Lindsaea spp. (Ev904)
Pteridium spp. (brackens) (?) (Ev913): Some populations of bracken ferns (*Pteridium aquilinum*) contain the cyanogenic glycoside prunasin and a ß glucosidase and this combination deters consumption of these plants by herbivores such as sheep, deer and locusts (Cooper-Driver & Swain 1976), however bracken is *not* recorded as causing cyanide poisoning of livestock.
Pteridium esculentum (?)
Pteridium revolutum (?)
Family Gleicheniaceae (Ferns)
Gleichenia spp. (Ev901)

Eremophila maculata (spotted native fuchsia). Whole plant in natural habitat. [RAM Photo]

Eremophila maculata (spotted native fuchsia) fruiting and flowering branches. Note the S-shaped stalk on fruit and flower and the spotting in the throat of the flower. [RAM Photos]

Posterior ataxia & urinary incontinence:

***Sorghum* spp.** (grain & forage sorghums)

Goitre:

Plant sources associated with congenital goitre are *Cynodon nlemfuensis* (African star grass), *Panicum coloratum* (coolah grass) (Rodel 1972) and possibly *Trifolium repens* in sheep, and *Manihot esculenta* (cassava) in humans

Foetal arthrogryposis:

Sources associated with congenital arthrogryposis are ***Sorghum sudanense* hybrids** (Sudan grass hybrids), *Cynodon nlemfuensis* (African star grass) and *Panicum coloratum* (coolah grass) (Rodel 1972).

Toxicity:

Acute poisoning (sudden death):

All species can be affected, but toxicity is much more likely in **ruminants** than in monogastrics because the low stomach pH of monogastrics inhibits ß glucosidase and ruminal microbial ß glucosidase releases HCN rapidly. However, cases are recorded in monogastrics e.g. in donkeys eating *Prunus virginiana* (Jackson 1995).

The minimum lethal dose of potassium cyanide PO is about 2.0 mg/kg in most species. Lethal blood cyanide concentrations of 3-5 µmol/dl may occur within 5 min of ingestion of cyanide salts or cyanogenic plants (Burrows 1981).

Posterior ataxia & urinary incontinence:

Cases have been reported in cattle (McKenzie & McMicking 1977), sheep and horses. In humans, the syndrome of tropical ataxic neuropathy has been linked with eating insufficiently-processed *Manihot esculenta* (cassava) roots (Mlingi *et al.* 1998).

Foetal arthrogryposis:

Cases have been reported in horses in North America and cattle in Australia (NSW). The toxins responsible were probably cyanogenic glycosides. The syndrome may be associated with the ataxia/urinary incontinence syndrome

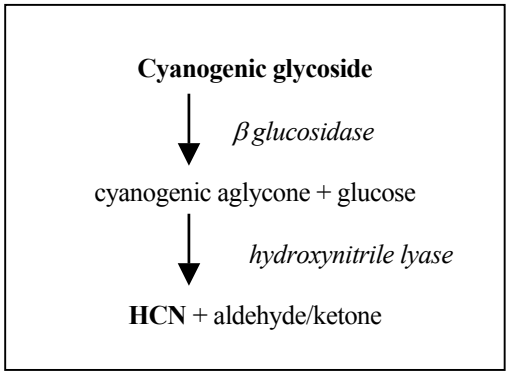
Sulphur-responsive reduced production:

Chronic cyanide intake may interfere with selenium metabolism (Stochmal & Oleszek 1997)

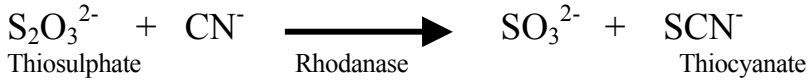
Mode of action:

Acute poisoning (sudden death):

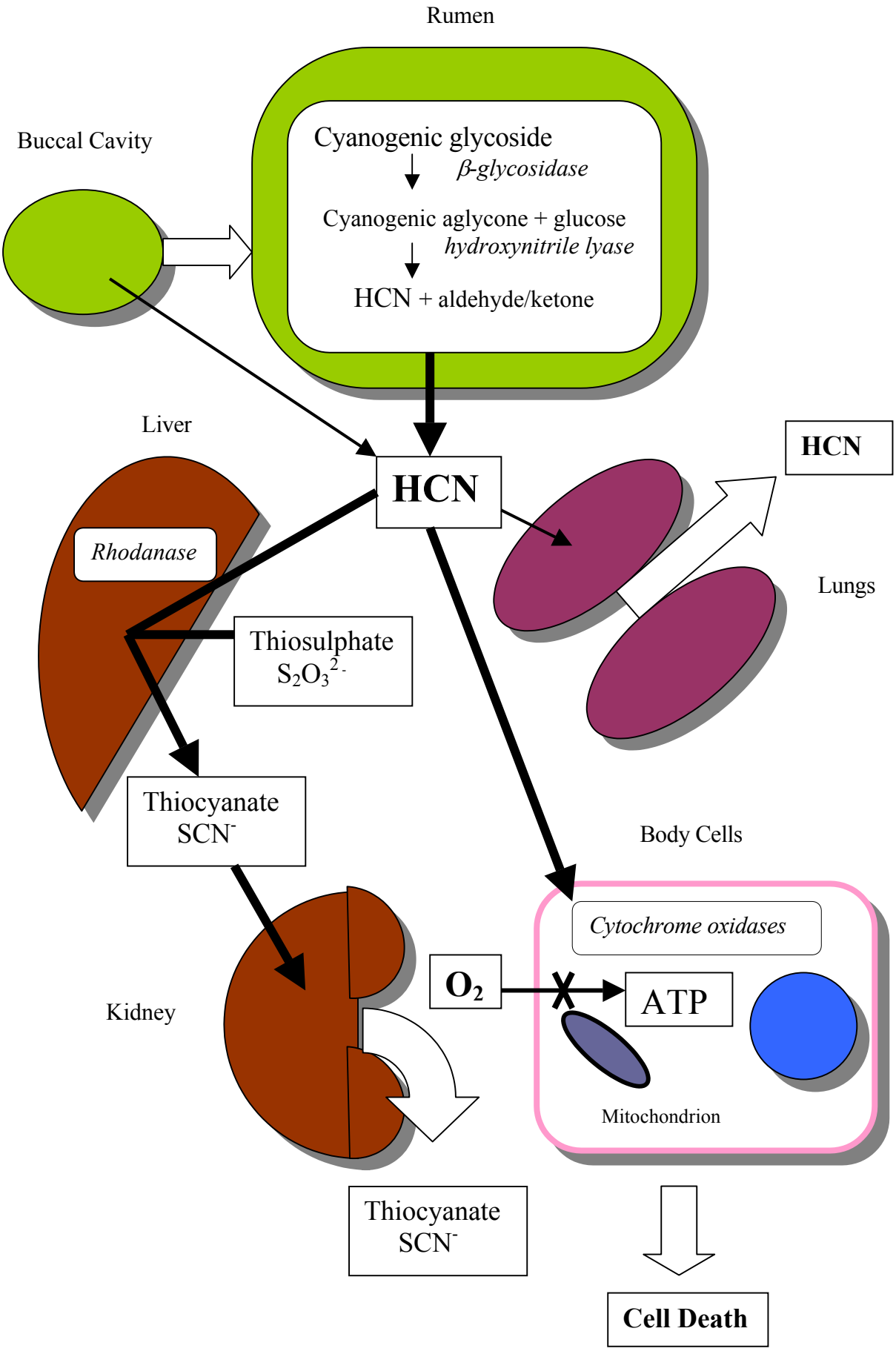
Cyanogenic glycosides, ß glucosidase and lyase are stored separately in plant tissues; glycosides in vacuoles, enzymes in the cytosol. Damage to plant tissues ruptures the vacuoles, leading to mixing of glycosides with enzymes and the release of HCN (hydrogen cyanide).



- excretion/detoxication of absorbed HCN
  - excreted through lungs in expired air
  - converted to thiocyanate by hepatic **rhodanase** (thiosulphate sulphurtransferase) → renal excretion; species differences in tissue rhodanase activity may mediate differences in susceptibility to HCN poisoning between animal species (Aminlari & Gilanpour 1991, Aminlari & Shahbazi 1994). Alimentary tract mucosa, liver and kidney have the highest activities of rhodanase.



- intoxication when HCN intake exceeds excretion capacity
- HCN inhibits cytochrome oxidases (binds to ferrocytochrome a_3 [Jones *et al.* 1984]), the terminal step in electron transport → blocks electron transport, mitochondrial oxygen utilisation and production of ATP and thus cellular aerobic respiration (Borron & Baud 1996)
- oxygen-dependant tissues such as heart, brain, liver are most affected by acute poisoning (Borron & Baud 1996) → death from respiratory failure (Greer & Jo 1995)


Rumen
Buccal Cavity
Cyanogenic glycoside
β-glycosidase
Cyanogenic aglycone + glucose
hydroxynitrile lyase
HCN + aldehyde/ketone
Liver
HCN
HCN
Rhodanase
Lungs
Thiosulphate
$S_2O_3^{2-}$
Thiocyanate
SCN^-
Body Cells
Cytochrome oxidases
O_2
ATP
Kidney
Mitochondrion
Thiocyanate
SCN^-
Cell Death

Posterior ataxia & urinary incontinence:
It has been suggested that this syndrome may result from absorption of the intact glycosides.
Goitre:
The goitrogen affecting the thyroid gland is thiocyanate.
Foetal arthrogryposis:
Unknown

Conditions of poisoning:
Acute poisoning (sudden death):
- most cyanogenic glycosides occur in **young leaf**
- factors influencing HCN poisoning
  - plant genetic variation (sorghums)
  - active growth, young plants → more toxic
  - plant nutrition - fertilizer → ↑HCN, sulphur → ↓HCN
  - diurnal/seasonal variation
  - plant stress → ↑HCN
    - drought
    - grasshopper attack
    - light frost
  - animal exposure history -
  - animal feed intake - hungry stock → ↑intake

Foetal arthrogryposis:
pregnant females grazing Sudan grass hybrids

Clinical signs:
Acute poisoning (sudden death):
- all species
- rapid deep breathing
- irregular weak pulse
- muscle weakness/spasms
- coma, **rapid death**
- **bright red blood** (O_2 not absorbed by tissues)

Posterior ataxia & urinary incontinence:
- cattle, sheep, horses
- **ataxia**
- **urinary incontinence**

Sheep grazing *Sorghum* are recorded with a syndrome of muscle tremors of head & neck, nystagmus, extension of forelimbs, aimless running and collapse (Bradley *et al.* 1995, Glastonbury & Maloney 1997, Creeper 2000).

Goitre:
congenital goitre in sheep, humans

Foetal arthrogryposis:
- dystocia
- arthrogryposis
- less severely-affected calves (probably affected later in gestation) may have opisthotonus, slow lateral nystagmus, clonic seizures progressing to tonic rigidity when stimulated, blindness (unable to stand or suckle) (Moloney 1995)

Sulphur-responsive reduced production

Pathology:
Acute poisoning (sudden death):
non-specific (agonal haemorrhage, congested organs)
bright red blood
± fleeting "bitter almond" odour immediately on opening stomach [Benzaldehyde, a break-down product of amygdalin (the cyanogenic glycoside in bitter almond (*Prunus amygdalus* var. *amara*) kernels and some other plants), is responsible for the odour (Lewis 1998). Benzaldehyde is readily oxidised in air to benzoic

acid, rendering the odour fleeting (Lewis 1998). About 40-60% of humans are allegedly genetically unable to detect the odour (Trestrail 2000)]

leucoencephalomalacia in some of the rare cases where animals (including humans) survive sufficiently long (Levine & Geib 1966)

Posterior ataxia & urinary incontinence:

- cystitis
- **spinal cord white matter degeneration**

Sheep grazing *Sorghum* that develop a variant neurological syndrome (see above) have pathology including axonal spheroids throughout the brain most numerous adjacent to the cerebellar roof nuclei + focal Wallerian degeneration in cerebellar white matter and spheroids in ventral grey matter of cervical cord (Bradley *et al.* 1995, Creeper 2000, Glastonbury & Maloney 1997).

Sot-Blanco *et al.* (2002) produced mild neurological damage in the brainstem, spinal cord and cerebellum (mild axonal swelling, gliosis, reduction in Purkinje cell numbers) by PO administration of 1.2 or 3.0 mg KCN/kg/day for 5 months.

Foetal arthrogryposis:

- fixation of foetal limb joints (arthrogryposis)
- Wallerian degeneration of foetal white matter of spinal cord, medulla, pons and cerebellum
- cerebral oedema

Diagnosis:

Acute poisoning (sudden death):

A rapid field spot test, the **picric acid test for free HCN** (Henrici test), can be used on **plants, rumen contents, liver or skeletal muscle**. The test papers are yellow, turning brown-red if positive (details are given below).

Muscle samples can be usefully analysed up to 20 hr after death, liver samples 4-5 hr and rumen samples < 1 hr (Terblanche *et al.* 1964a,b). The smallest concentration *in skeletal muscle* suggestive of toxicity is 0.63 μg HCN/g tissue.

Blood cyanide concentrations in a cow that survived poisoning have been reported as 60 – 173 μ*M* (Majak *et al.* 1980). Reference ranges for HCN in cattle determined by GC-MS method are: serum <0.7 to 35.0 μ*M*; rumen fluid < 0.7 to 28.1 μ*M* (Meiser *et al.* 2000). In humans, cyanide concentrations of > 40 μ*M* in blood are considered toxic and 100-200 μ*M* are considered lethal (Meiser *et al.* 2000).

The smallest concentration *in plants* to suggest toxicity is 200mg HCN/kg plant (0.02%). Plant material subjected to assay for HCN production **must be unwilted at the time of testing**. When submitting plants to a laboratory for testing, collect the whole plant with a clump of soil enclosing the roots; wrap the root ball and soil in damp paper and send the whole plant to arrive as soon as possible to try to prevent wilting.

Commercial test strips are available for semi-quantitative determination of cyanide ions in effluent from industrial processes (Merckoquant® 10044 Cyanide Test), but a method is not available for using these with plant or animal material at present.

Dalefield (2000) has compared commercial test papers (CYANTESMO® paper – impregnated with N,N,N',N'-tetramethyl-4,4'-diaminodiphenylmethane; manufactured by Macherey-Nagel, Duren, Germany), marketed for detecting cyanide in water and subsequently used to detect cyanide in the blood of poisoned humans (Fligner *et al.* 1992), with picric acid papers for testing standard KCN solutions and both cyanogenic and non-cyanogenic plant material. She found the CYANTESMO papers to produce a more rapid result and to be more convenient to use.

Assay methods: spectrophotometry (Lundquist *et al.* 1985). Meiser *et al.* (2000) have developed a GC-MS method for cyanide in serum and rumen fluid of cattle.

Picric acid spot test for cyanide (Henrici test) in rumen contents or plants

Test papers

0.5 g sodium bicarbonate + 0.5 g picric acid dissolved in 100 ml distilled water - solution keeps for 4 months if well-stoppered and kept cool. Saturate strips of filter paper in the solution and allow to almost dry before use.

Strips may be dried and stored in a stoppered container, but lose sensitivity in about 1 week. Moisten before use.

Procedure

Place rumen contents in a flask and add enough water to make contents slushy,

OR a couple of grams of moist shredded plant material in the flask and add 4 drops of chloroform.

Fix a picric acid filter paper strip above the sample by jamming it into the neck of the flask with a stopper - do not let the paper touch the sides of the flask or the sample. Run a negative control sample (a blank) simultaneously. Incubate in a warm place.

Positive test = red/brown to violet colour. Incubate test for at least 24 h before declaring it negative.

Foetal arthrogryposis:

- pathology + access
- differentiate from viral and genetic aetiologies

Therapy

Acute poisoning (sudden death) (Burrows 1981):

Give IV **sodium thiosulphate** ("hypo") @ 500 mg/kg or more **plus** oral or intraruminal doses. Repeated IV therapy may be required if HCN continues to be released from the alimentary tract. Sodium thiosulphate in high dose can be effective when given up to 30 minutes after ingestion of a toxic dose of cyanide; alternative therapies require earlier application for effectiveness.

Therapeutic protocols for acute cyanide poisoning of ruminants

Intravenous

• IV sodium thiosulphate ("hypo") @ 660 mg/kg [Previous recommendation 66 mg/kg]

- maximum cold water solubility of sodium thiosulphate = 50% (50 g/100 ml); therapeutic dose = 1 ml/kg (Cattle:150g hypo in 300 ml water; Sheep:30 g in 60 ml)

• OR Can combine hypo with

- sodium nitrite @ 22 mg/kg,

or - p-aminopropriophenone @ 1.5 mg/kg,

or – cobaltous chloride @ 10.6 mg/kg [**not** to be used in sheep]

[Probably do not improve effect of *high* dose of hypo alone]

• OR IV p-aminopropriophenone @ 1.0 – 1.5 mg/kg alone

[Less effective than hypo when HCN dose is large]

PLUS Oral or intraruminal

sodium thiosulphate (Cattle: 30 g; Sheep 5 g)

- repeat hourly
- dose in-contact `normal' animals also

- sodium thiosulphate is rapidly excreted through urine; repeated doses may be needed and given with very little risk of toxicity in contrast to repeat doses of sodium nitrite or p-aminopropriophenone
- alternative therapies may include
  - the classical nitrite-thiosulphate combination IV: amyl or sodium nitrite to produce methaemoglobin to compete with cytochrome oxidase for cyanide ions and sodium thiosulphate as a sulphur donor for rhodanase to enhance conversion of

cyanide to thiocyanate; the effective dose of nitrite is 40-50% of its LD_{50} in sheep

- cobalt salts: hydroxycobalamine (vitamin B_{12}), cobaltous EDTA chelate (= dicobalt edetate used IV in humans; Kelocyanor®), cobaltous histidine chelate and others appear to act by directly binding cyanide ions; too toxic for use in sheep
- oxygen in combination with nitrite-thiosulphate IV
- p-aminopropriophenone induces methaemoglobin more rapidly than nitrite

Prevention & control:

Acute poisoning (sudden death):

- avoid new growth, stressed plants, *Sorghum* forage < 75 cm (30 inches; 2.5 ft) tall
- hay from hazardous *Sorghum* forage will be hazardous
- ensilage → ↓HCN content of forage
- proposed safe upper limit for human food 10 mg HCN equivalent/kg dry matter (FAO/WHO 1991)
- supplement with sulphur when grazing forage *Sorghum*

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Cardiac glycosides

Core data

Common sources:

- Important Plants
  - *Nerium oleander* (oleander)
  - *Cascabela thevetia* [=*Thevetia peruviana*] (yellow oleander)
  - *Cryptostegia grandiflora* (rubber vine)
  - *Bryophyllum* spp. (mother-of-millions)
  - *Homeria* spp. (cape tulips)
  - *Adonis microcarpa* (pheasant's eye)
  - *Digitalis purpurea* (foxglove)
  - *Corchorus olitorius* (jute)
- Pharmaceuticals
  - Digoxin

Animals affected: cattle, horses

Poisoning circumstances:

- garden clippings (oleanders, foxglove)
- in hay or seeds in feed grain (cape tulips, pheasant's eye, jute)
- hunger or lack of other feed (mother-of-millions)
- overdose of digoxin

Main effects:

- sudden death
- cardiac arrhythmia
- diarrhoea with blood
- azotaemia
- focal myocardial necrosis

Diagnosis:

- access
- cardiac arrhythmia
- myocardial histopathology

Therapy:

- activated charcoal + electrolyte replacement fluid PO
- + atropine
- + propranolol

Syndrome names:

Two syndromes are associated with intoxication by cardiac glycosides:

- **acute cardiac glycoside poisoning** – discussed in this section
- cotyledonosis or krimpsiekte [Afrikaans = "twisted disease"] due to certain bufadienolides in particular plants and confined to southern Africa – discussed in the following separate section

Chemical structure:

A cardiac glycoside is any plant-derived steroid glycoside with cardiotonic activity. This activity depends on the presence in the aglycone of an unsaturated lactone ring and a hydroxyl group in a specific spatial relationship. Some 400 such compounds have been identified. [adapted from Lewis' Dictionary of Toxicology 1998]. There are some structural affinities with cucurbitacins (*q.v.*) and some similarities of pathological effect.