

Poisonous Plants and Residues

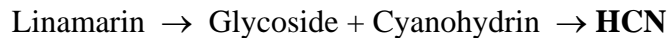
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POISONOUS PLANTS

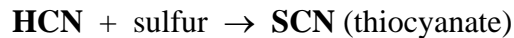
1. Cassava and Bitter Almond

- A perennial woody shrub that is grown as a root crop in the tropics, and considered the fourth most important source of calories for humans among crops produced in those areas.
- It is an important staple for about 800 million people worldwide. About 120 million tons of cassava produced annually worldwide — as measured from 1979 to 1981.
 - ◆ **Africa** produces 37% of the world cassava crop and contains over 50% of the earth's soil used for cassava growth (world cassava area).
 - ◆ **Asia** produces 37% of the world crop, and accounts for 27% of the world cassava area. India, Thailand, and Indonesia are major producers.
 - ◆ Brazil dominates the production of cassava in the **Western Hemisphere** approximating 20% of world crop. Colombia and Paraguay are also major producers.
 - ◆ Papua New Guinea and Fiji are important producers in the **Pacific**.
- Cassava is considered an important basic energy source for the human diet that can be produced on marginal agricultural lands. It has become an important food source in addressing growing food deficits especially in poverty-stricken areas in third world countries.
- The plant is used as animal feed and for industrial uses of starch.
- Sometimes cassava is considered as undesirable food that contains little besides carbohydrate. However, in many developing countries calories are the paramount nutritional shortage.
- The cyanide present in cassava is a drawback.
- Chronic cyanide toxicity occurs only in certain areas of Africa, and it appears to be associated with severely deficient diets combined with an under-processing of cassava for food preparation.
- Cassava (*Manihot esculenta* [Crantz]) is in the spurge family (Euphorbiaceae). It originated in South and Central America between the 30°N and 30°S latitude.
- Two distinct types of cassava exist — the sweet and the bitter.

- Commercially, cassava is grown by planting a cutting taken from the woody part of the stem. It grows well in low fertility soils and can tolerate long periods of drought. The roots begin to develop into starch storage bins at about three months of age. The plant can be harvested anytime after that or can be grown for 2–3 years before harvest.
- The plant is not harmed by locust swarms since the root is not damaged and provides nutrients for re-growth of the vegetative parts.
- Raw cassava contains two **cyanogenic glycosides**, linamarin and lotaustralin, which can release prussic acid (hydrogen cyanide; HCN). Generally, the cyanogenic glycosides are not considered toxic. Once ingested by a person, the following reactions occur:



- The HCN is the **toxic form** of cyanide. It targets the ferric iron (Fe^{+3}) of the "a"-**cytochromes** of the electron transport system in the mitochondria. As a result, electron transport to oxygen is inhibited and **energy production stops** (no ATP being produced) resulting in rapid cell death.
- The body is able to **detoxify** low levels of cyanide in the body through the action of an enzyme, rhodenase, by the following reaction:



This is an important reaction since the formation of **thiocyanate** contributes to the chronic toxicity problems of cyanide. It is excreted by the kidney.

- Health problems can result from cassava ingestion. Acute death has occurred from eating raw roots due to high levels of cyanide. Death is due to the lack of energy production in the brain and heart.
- Proper processing of the plant by drying, soaking in water, or cooking reduces the cyanide levels so that the roots are not acutely toxic.
- Chronic cyanide toxicity occurs within some localities in Africa. Areas of high cassava consumption, low meat diets, and low iodine intake lead to the development of a two syndromes known as tropical ataxic neuropathy and epidemic spastic paraparesis. The incidence is as high as 3% in some areas.

Tropical ataxia neuropathy is associated with damage to one specific spinal cord tract that results in difficulty walking due to ataxia (muscular in-coordination when voluntary muscular movements are attempted). It occurred with high incidence in adult males from Nigeria.

Epidemic spastic paraparesis is an acute disease mostly in women and children causing permanent crippling of victims from one day to the next by damaging nerve

tracts in the spinal cord necessary for movement resulting in a spastic paresis (partial or incomplete paralysis with tense muscles) of both legs. A period of food shortages in the 1980's affected 10,000 women and children in cassava-dominated areas. Families consumed new crops without proper processing due to starvation. The conditions are permanent.

- High cassava ingestion and low dietary protein are associated with these neurological disorders. Additionally, the body's pool of sulfur is lowered when cyanide is ingested at low levels due to the formation of thiocyanate (SCN) that is excreted from the body via the kidney. Thus, **sulfur-containing aminoacids** in the body become deficient. This deficiency may play a role in development of the syndromes. Also, the enzyme, thiocyanate oxidase, can convert thiocyanate to free cyanide that may affect neuronal cells. Experimental studies have demonstrated that **cyanide can induce demyelination** of nervous tissue. The exact mechanism of how this occurs is not well understood.
- Another plant that causes spastic paraparesis similar to cassava is *Lathyrus sativa*. This is also an important plant in areas of the world similar to cassava. It serves as a dietary staple in areas of drought. It contains lathrogens that are toxic amino acids and β -cyanoalanine (a nitrile). Consumption of seeds (peas) is the source of poisoning.
- **Goiter** and **goiter-cretinism** are other problems associated with cassava. **Goiter** is due to iodine deficiency resulting in enlargement of the thyroid gland. In areas where the dietary iodine is marginal, cassava consumption leads to an increase in the incidence of goiter in man and animals. The high production of thiocyanate by the body due to continual ingestion of cassava results in interference with iodine uptake by the thyroid gland. The resulting effect is iodine deficiency that leads to the development of goiter. **Goiter-cretinism** is an endocrine disorder involving the thyroid and the central nervous system. **Neurological cretinism** is associated with mental deficiency, hearing and speech problems, disorders of stance and gait, and stunted growth. **Myxedematous cretinism** has the same signs plus problems associated with hypo-function of the anterior pituitary gland. There are 2 hormones released by the thyroid gland: T₄ and T₃. Individuals with this disease have very low thyroid hormone (T₄), but paradoxically have elevated T₃ levels. This is thought to possibly be responsible for the neurological damage associated with cretinism that leads to myxedematous and neurological cretinism. Newborn children are affected with myxedematous cretinism at 2–7% in some African communities. This is a very rare disease condition. **Congenital hypothyroidism** in Africa is 15% of newborns

— 500 times the rate of industrialized nations. Thiocyanate (elevated in individuals) is believed to prevent the secretion of iodine from the mother to the developing child *in utero*. Similarly, it prevents the secretion of iodine into the milk of nursing mothers that continues the disease process. Again, the exact mechanism of goiter-cretinism is not well understood.

- A commercial woody tree that is grown for oil extraction of its fruit, *Amygdalus communis var amara*, is commonly known as Bitter Almond. It is well-known in Europe. The fruit (almond) of this plant contains **amygdalin**, a cyanogenic glycoside containing benzaldehyde. When cyanide is formed, benzaldehyde is released producing a characteristic odor referred to as the “bitter almond” smell. These fruits are grown for oil extraction of essential oils that are used in the perfume industry as well as in health foods. Raw fruit is added to specialized recipes to provide the “bitter” taste characteristic of these nuts. Ingestion of too much raw fruit can produce acute cyanide poisoning. Similarly, the remaining cake residue of bitter almond following extraction for oil, contains amygdalin that will produce fatal poisoning when fed to livestock.
- This is not to be confused with *Amygdalus communis var dulcis* which is the Sweet Almond. This almond is the confectionary nut common throughout the world and regarded as a good health food. It also contains essential oils that can be extracted for purposes similar to bitter almond. This nut does not contain any cyanogenic glycosides and the entire plant is considered safe. The almonds grown in California are from this plant.

2. Water Hemlock

- *Cicuta douglasii* and *C. maculata* (Western waterhemlock and Spotted waterhemlock, respectively) are two plants of concern in California belonging to the Parsley Family (Umbelliferae=Apiaceae).
- The plants are perennial herbs. The leaves are twice-compound and the segments are not divided. The roots are tuberous and show a series of cross-partitions containing the yellow liquid. The flowers are white and in large, open, compound umbels. The seeds are flat faced to concave.
- There are seven species of *Cicuta* in the US. The whole plant is toxic but especially the root that contains a readily visible yellow liquid. Leaves are also very toxic early in the spring.

- All domestic and wild animals are susceptible. Man is susceptible because of mistaken identification of the plant for **edible parsnip plants** (*Lomatium* sp, *Sium suave*).
- **Western waterhemlock** is found in northern and central California being able to grow at elevations to as high as 8000 ft. **Spotted hemlock** is found in central and southern California and also in Modoc county of California. In addition, this plant and its varieties are spread across the US. These plants are associated with fresh water streams, ditches, and marshes, and are the most poisonous plants in the Northern Hemisphere.
- These plants contain an unsaturated, long-chain aliphatic alcohol called **cicutoxin** — a neuropoison.
- Clinical signs include nausea, salivation, and emesis that can develop within 15–60 minutes of ingestion. Trismus (tetanic spasm of the jaw muscle) and toxic-clonic convulsions occur shortly thereafter leading to unconsciousness, cardiac arrest, and per-acute death.
- Diagnosis is by the history of eating naturally growing plants in the Umbelliferae family. Plant identification and chemical analysis of body fluids for cicutoxin will confirm the diagnosis. Treatment for the condition is invariably futile. Removal of the poison with gastric lavage and activated charcoal, oxygen-assisted ventilation, pentobarbital, epinephrine, atropine, sodium bicarbonate, and body warming are commonly attempted.

3. Poison Hemlock

- *Conium maculatum* (Spotted Hemlock) is a common weed in California and other states.
- There are two species of poison hemlock in the US.
- These plants, like waterhemlock, are in the Umbelliferae family.
- Poison hemlock is a tall, branching biennial herb, sometimes attaining 10 ft high. It has a long, white, often branched tap root. The stem is stout, smooth, and dotted with irregular purple marks. The herbage has a mouse-like odor. The leaves are twice-compound and the segments are toothed or deeply cut. The petiole is often purple colored. The flowers are white and in large, open, compound umbels. Fruits are oval, granular, and have prominent wavy ribs with the face grooved.
- The plant is **mistaken for wild carrot** (*Daucus carota*) by persons who desire to "live off the land."

- The roots and seeds are the most toxic, but all parts of the plant are poisonous since the poison accumulates with age in the seeds, roots, stems and leaves. The degree of toxicity varies.
- Several alkaloids are found in this plant and their content fluctuates. The major toxic principle is **coniine** and related alkaloids. One of the related alkaloids, β -coniceine, is 7–8 times more toxic and is present in higher concentrations during the growing season when fruits are green. Coniine is volatile and is slowly lost on drying.
- Exposure to pregnant animals causes congenital malformations particularly in cattle and pigs. Other animals can be affected too. In man, a woman with child would have to ingest the plant for several days to weeks at a dose not producing acute signs. Both coniine and β -coniceine are responsible. The malformations are related to decreased movement of the fetus at specific critical times of development.
- Poison hemlock has historic interest. It was used as a lethal agent during that time of history. It is the plant that Socrates was forced to drink and whose course of poisoning was recorded via Socrates himself.
- The **clinical signs** of acute poisoning are that of ascending paralysis. They develop in progressing order including nervousness, trembling, ataxia of rear legs, mydriasis, collapse, bradycardia, poor perfusion, coma and respiratory failure leading to death. A convulsive syndrome may occur particularly if ingestion of the roots or seeds occurs.
- Identification of the plant and the history of eating naturally growing plants in the Umbelliferae family will make diagnosis possible. A mousey odor is helpful in identifying the plant. Analysis of stomach contents or body fluids for the alkaloids can be performed if no history is available.
- Proper removal of the plant during acute poisoning often results in an uneventful recovery within several days, but the prognosis is guarded. Supportive care is important in moderately affected persons while ventilatory assistance is required for comatous individuals. Death can occur.

4. Death Camas

- *Zigadenus* sp (Death Camas) is a member of the lily family (Liliaceae).
- These plants are herbaceous perennial plants with onion-like bulbs (lacking the onion odor) and slender folded linear leaves. A single showy flowering raceme characterizes the plant with yellowish-white colors. The plants sprout very early in the spring.

- The whole plant is toxic including the flowers but the bulbs are most toxic. The **toxic principle** are alkaloids called zygacine and zygademine, iso- and neo-germidine, and protoveratridine.
- Both cattle and sheep are susceptible to poisoning under grazing conditions. One bulb can kill a sheep. Man is poisoned by **mistakenly eating the bulbs** of the plant that was believed to be an onion plant.
- Clinical signs are primarily that of vomiting, nausea and abdominal pain within one hour of ingestion. The heart rate characteristically slows down so that bradycardia is present. Generally, more serious signs do not develop in adults. The onset of severe illness may occur in children with the development of weakness, staggering, hypotension, and dyspnea (troubled breathing). Collapse, coma, and/or seizures may develop.
- Identification of the plant and the history of eating naturally growing plants in the Lily family will make diagnosis possible. Urine and stomach contents can be submitted for an alkaloid screen.
- Antiemetics are recommended for treatment of adults plus oral administration of activated charcoal. Treatment is aimed at correction of hypotension with fluids and vasopressors and with atropine to correct bradycardia in patients with more advanced signs. More serious signs would require artificial ventilation and drugs to control seizures. Patients respond favorably.

DRUG RESIDUES

Definition

- The concentrations of drugs or environmental chemicals that are detectable by analytical methods are defined as drug or chemical residues in tissues of food producing animals and other agricultural commodities for human consumption.
- Residues refer to the parent drugs or chemicals, their metabolites, and their decomposition products, if formed.
- The quantity of residue if detected is expressed by weight such as a mg of drug present in a kg of tissue, which is parts per million (ppm). If expressed as μg of drug present in a kg of tissue, then it is parts per billion (ppb). Fluids such as milk are expressed in 1-liter units instead of a kg.
- Residues are either intentional or unintentional. Intentional residues result from a desired usage of the drug in animals or food products. Unintentional residues are caused by events that exposed animals or food products to drugs or chemicals, not intended to be received by them.

Importance

- Federal law governs the amounts of residues allowed in human foods. The Delaney Amendment of the Food, Drug, and Cosmetic Act states that a known carcinogen is illegal in foods consumed by man. This is referred to as "Zero Tolerance" and infers that no residue of a carcinogen is allowed for edible foods. Analytical sensitivity determines the "Zero Tolerance." However, absurdity in certain cases has allowed exceptions to be applied to this Amendment.
- Drugs and chemicals that do have a finite "Tolerance Level" are allowable in foods as long as the quantity is within an established "Margin of Safety."
- A "Tolerance Level" is established which allows residues to be acceptable for sale that are equal to or below the tolerance limit. Residues that exceed the "Tolerance Level" are illegal and not saleable for human food.
- The largest source of drugs that can result in residues is the food-producing animals. Over 300 feed additives and antimicrobial agents are in use within the US for applications in livestock and poultry. New drugs are being added annually.
- Feed additives are drug, chemical, or biological substances added directly to animal feeds in small quantities for the purpose of increasing performance or production. Antimicrobial agents are drugs used to treat infectious diseases or other pathogenic agents that produce disease.
- Indiscriminate use of drugs is the cause of drug residues. Proper management of animals and following directions on drug usage will avoid residue problems in most cases.

Agencies Associated with Residues

In the US, four entities interact in the control of drug or chemical residues.

- **Food and Drug Administration (FDA)**—This is a federal organization that regulates the safety of drugs used in the United States. The agency is responsible for setting "Tolerance Limits" of drugs, and enforcing violations of "Tolerance Limits" established for milk.
- **United States Department of Agriculture (USDA)**—This is a federal organization that is responsible to enforce violations of "Tolerance Limits" set by FDA for drugs or for chemicals which are set by EPA in meat or poultry products.
- **Environmental Protection Agency (EPA)**—This is a federal organization that determines the safety of chemicals used within the environment. They are responsible for setting "Tolerance Limits" of chemicals used in the environment such

as various pesticides, fungicides, or industrial contaminants. They also enforce violations of these "Tolerance Limits".

- **Drug Companies**—These are privately owned enterprises. Every drug (or chemical) that comes upon the market must go through an extremely laborious study in order to determine its toxicological properties and its safe application in man, animals, or other agricultural commodities. Every drug must be qualified for review (by the FDA) by application from the drug company for a "New Drug Application" which entails proof performed by the drug company of the drug's toxic effects, efficacy, and safety.

Establishment of Tolerances

- Tolerances are determined for non-carcinogenic compounds (drugs or chemicals which do not induce cancer) by using the **no-effect drug concentration** in the **most sensitive species** used for study. Several factors are then applied to calculate the tolerance of drug based upon studies performed by drug companies and upon human biological estimates.
- The "Acceptable Daily Intake (**ADI**)" is the daily dose of a drug or chemical residue that a human would be exposed to throughout their lifetime so that no appreciable health risk would exist. The ADI is established to provide the estimate of the maximum quantity of which can be safely eaten in food without health risk concerns. Feeding trials in animals primarily are the basis for determining the ADI's. In order to determine the ADI, a **no-effect level** of the drug must be determined. It is determined by feeding trials in various laboratory rodents conducted over a 2-year period. Six-month or longer studies are performed in non-rodent species such as the dog or monkey. The species for which the drug is intended (**target species**) must also be studied. The maximum dose fed that produced no harmful, adverse effects in the most sensitive species is defined as the no-effect level (or no-adverse-effect level). Based then upon the body weight of the most sensitive species and the dosage of drug eaten per day, a "mg of drug/kg of body weight" is defined. Then, **this "mg/kg" amount** is divided by 100 (safety factor) to give the ADI for that drug. The formula for 200 g rats that eat 15 g/day and have a no-effect feed level of 100 ppm would have the following calculations:

$$\text{ADI} = \frac{(15 \text{ g} / 1000 \text{ g/kg}) \times 100 \text{ mg/kg}}{0.2 \text{ kg rat}} = 7.5 \text{ mg/kg}$$

$$\text{Add safety factor} = 7.5 \text{ mg/kg} / 100 = 7.5 \times 10^2$$

The tolerance level can now be calculated by using the ADI and a food factor constant. Consumption factors are based upon consumption of muscle being 0.33 of the total diet. The factor for muscle in all species (beef, pork, lamb, poultry) is one. This indicates that it is the most consumed and consisting of 0.33 of the total daily diet. Other organs, such as liver, kidney, skin, and fat, have higher whole numbers (two to five) depending upon which species. The higher the number, the less this tissue is eaten relative to muscle since 0.33 is multiplied by the number.

The formula to calculate tolerance is given below:

$$\text{Tolerance} = \frac{\text{ADI mg/kg/day} \times 60 \text{ kg}}{\text{Food Factor} \times 1.5 \text{ kg/day}}$$

Sixty kg is the average human adult body weight. Man is estimated to consume 1.5 kg of food/day. The food factor is one for beef muscle. If the ADI of a non-carcinogenic drug in beef muscle is determined to be 8.25×10^{-4} , the tolerance would be as follows:

$$T = \frac{8.25 \times 10^{-4} \times 60}{(0.33 \times 1) \times 1.5} = 0.1 \text{ mg/kg which is } 0.1 \text{ ppm}$$

Hence the tolerance set for the drug in beef muscle would be 0.1 ppm.

Carcinogenic, Mutagenic, and Teratogenic Drugs

- Carcinogenic drugs or chemicals are initiators or promoters of cancer. These drugs bind irreversibly with DNA, proteins, and other cellular components to form adducts. Adducts are damaged cellular machinery. It is estimated that 1×10^5 adducts can be removed/cell/12 hr by DNA repair systems which implies accumulation may not occur as rapidly. However, there are many natural and environmental carcinogens which also invade the body that add to the adduct load. The goal, then, is to minimize this adduct load.
- Drugs are tested for carcinogenicity, and those found to be so are eliminated from development, since no carcinogenic compounds are to be present in human foods. Aflatoxin is an exception. It is an unintentional carcinogen that does have a tolerance limit in peanuts (20 ppb) and milk (0.5 ppb).

- Mutagenic drugs or chemicals damage the genetic engineering of a cell or organism. Basically, damage occurs to DNA by point mutation, gene elimination, or chromosomal breakage. Evaluation of mutagenic effects by drug companies is performed by three-generation reproductive studies in various species and other specialized tests. A natural mutagen believed responsible for colon cancer is (S)-3-(1,3,5,7-dodecapentaenyloxy)-1,2-propanediol, which is produced in the bowel of humans by five species of bacteria.
- Teratogenic drugs or chemicals produce damage to the developing embryo or fetus during a critical phase of gestation (pregnancy). Congenital malformations affect the structure and bodily functions of the animal tested. An excellent example of this was the tragic results from the thalidomide incident that occurred in Europe. It was used to control morning sickness in pregnant women. Several years after its usage, it was found responsible for inducing phocomelia (seal limbs) in children. The FDA did not allow thalidomide to be used in the US because they were not convinced by the data provided by the drug company that it was safe. That is a real tribute to the FDA. Drug companies must perform the three-generation reproductive studies in various species along with other specialized tests to demonstrate if the drug is teratogenic or not.
- Finite tolerances can be made for mutagenic and teratogenic compounds, but the safety factor used in determining the ADI is 1000. When the tolerance is calculated, it will be 10-fold lower than a non-carcinogenic drug's finite tolerance, which is not mutagenic or teratogenic.

Margin of Safety

The above calculations are providing a "Margin of Safety" for all drugs. To do this, at least two species require lifetime or chronic toxicity testing. One species must be a non-rodent. Once the ADI is calculated, the safety factor is incorporated. If the ADI is run in the target species, only a safety factor of 10 is required. Interspecies ADIs require another 10 factor resulting in $10 \times 10 = 100$ as the safety factor. Drugs known to be mutagenic or teratogenic have a safety factor of 1000. The average daily intake of the drug by the species studied is then divided by the safety factor.

Withdrawal Times

Withdrawal time is the time required for the drug to reach a safe concentration, as determined by tolerance. As a result, a time interval is established from the time of drug removal to the time of slaughter that allows for the drug to deplete from the body in order

to be within tolerance. In 1958, the Food Additives Amendment made it mandatory for drug manufacturers to submit tissue residue and depletion data along with methodology to detect the residues. This amendment involves drugs used for food producing animals only. The depletion data are extremely important, since the FDA determines the tolerances. Therefore, calculation of the time interval can be made based upon such data.

The half-life of the drug is determined in these instances. The residue amount in the tissue(s) of study will decrease at each successive measurement. The drug amounts are plotted against the time of measurement following drug removal. When plotted on a semi-log graph, a relatively straight line results. Using this, the half-life of the drug can be determined. Calculation of the half-life will then allow the withdrawal time to be established since the time at which the tolerance limit is passed can be realized. Each tissue in the body has differing depletion rates of the drug which means the half-life is different between tissues.

Some Drugs and Chemicals Assayed for Residues in Edible Foods

Antibiotics — These are antimicrobial agents of various types. They are used primarily for treatment of acute disease, but some are used prophylactically (preventatively) and fed for long periods of time. Measurement of residues is to prevent antibody resistance in microorganisms due to out-of-control residue levels being found in foods, protect against hypersensitivity (allergies), and avoidance of potential chronic diseases induced by certain antibiotics (such as chloramphenicol).

- a. Tetracyclines
- b. Chloramphenicol
- c. Penicillin and related drugs
- d. Dihydrostreptomycin
- e. Novobiocin
- f. Neomycin
- g. Gentamycin
- h. Cefoperazone (cephalosporin-3rd generation)
- I. Sulfonamides

Environmental Chemicals

- | | |
|------------------------------|---------------------------|
| a. Polychlorinated Biphenyls | e. Dioxins |
| b. Hexachlorobenzene | f. Pentchloronitrobenzene |

- c. Polybrominated Biphenyls
- d. Pentachlorophenol
- g. Toxaphene and others

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