Industrial and household toxicology

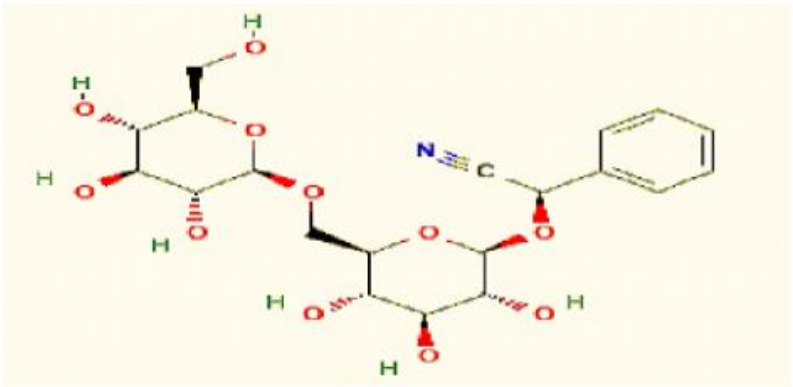
CYANIDE TOXICITY

Sources

1. Natural sources of cyanide:

- Certain plants contain high quantities of AMYGDALIN (glycoside)….is converted to cyanide in the small intestine by an enzyme (emulsin)

- Plants?? Apple, Peach, Plum, Apricot, Bitter Almond, Black Cherry



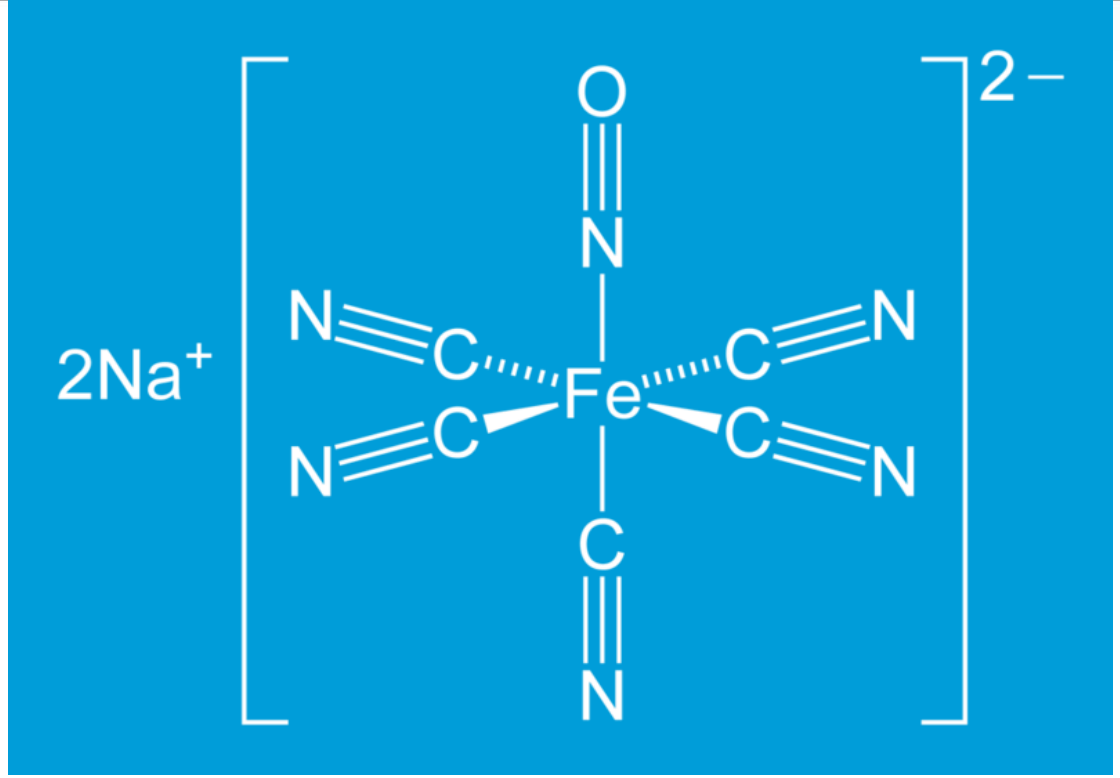
Molecular formula: $C_{20}H_{27}O_{11}$
Synonyms: (R)-Amygdalin; D-Amygdalin; (R)-Laenitrile

- Natural sources of cyanide

Sources

2. Other sources:

- The vasodilator drug **nitroprusside** releases cyanide upon exposure to light or through metabolism
- **Aliphatic Nitriles** used **in plastic manufacturing** are absorbed by skin and liberate hydrogen cyanide gas….
- **Acetonitrile**: a **solvent component of some artificial nail glue removers**……caused several pediatric death
- Cyanide solution is **rapidly absorbed** through the skin



Sodium nitroprusside

- It is **rapidly metabolized by uptake into red blood cells with liberation of cyanide.** Cyanide in turn **is metabolized by the mitochondrial enzyme rhodanase**, in the **presence of a sulfur donor**, to the **less toxic thiocyanate**

Cyanide toxicity

- Deliberate cyanide exposure (through **cyanide salts**) remains an important instrument of homicide and suicide
- ……***highly soluble in water****, and thus readily dissolve to form free cyanide (most toxic form,* CN^{--} *or HCN)*
- **Halogenated cyanide: irritating gases,** cause pulmonary edema and excessive salivation

Sources

2. Other sources:

- **Hydrogen cyanide**……is a gas easily generated by mixing acid with cyanide salts
- Is a common combustion by-product of burning plastics, wool, and many other natural and synthetic products……poisoning is an **important cause of death from structural fires**
- It is common on autopsy to find CN and CO in blood of those who have succumbed to smoke inhalation

Toxic dose

- Exposure to **hydrogen cyanide gas** (HCN), even at low levels **(150–200 ppm), can be fatal**
- The air level considered immediately dangerous to life or health (IDLH) is 50 ppm
- The recommended workplace ceiling limit (TLV) is 4.7 ppm
- **Acute cyanide poisoning with nitroprusside infusion (at normal infusion rates) or after ingestion of amygdalin-containing seeds is relatively rare**

FATAL DOSE

Name	Commercial use	Fatal dose
Acetonitrile	Solvent	120mg/kg
Cyanogen bromide	Fumigant	13mg/kg
Potassium cyanide	Electroplating	2mg/kg
Hydrocyanic acid	Fumigant	0.5mg/kg

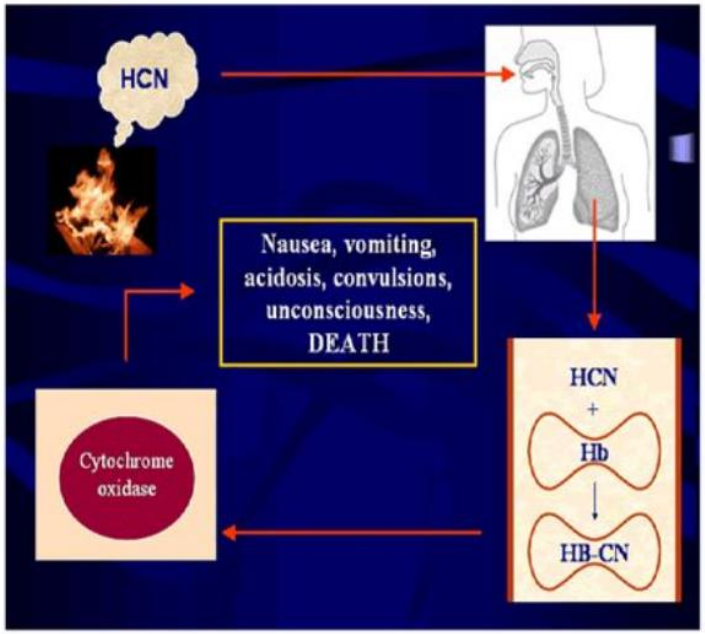
- **Solutions of cyanide salts can be absorbed through intact skin**

Mechanism of Action

- CN is a chemical asphyxiant……inhibits **CYTOCHROME OXIDASE SYSTEM**
- …….**Blocks the aerobic utilization** of oxygen
- Cellular anoxia….CNS, cardiac arrest, and respiratory arrest
- Cyanide readily binds to many enzymes having a metallic component…**binds avidly to heme Fe^{+3}** causing cellular hypoxia.

Cyanide Poisoning
Mechanism of Action

- **Cyanide** inhibits mitochondrial cytochrome oxidase , thus blocks electron transport, resulting in decreased oxidative metabolism and oxygen utilization
- Lactic acidosis occurs as a consequence of anaerobic metabolism (accumulation of Lactic acid).
- Most affected cells are at the **heart & CNS**



Routes of exposure....absorption

- **INGESTION**: oral absorption is rapid.
- Ingestion of **cyanogenic plants** or nitriles need **hours** before development of symptoms…conversion of amygdalin to cyanide & nitriles metabolized to cyanide after absorption

Routes of exposure....absorption

- **INHALATION**: respiratory absorption is almost **immediate**....the patient become unresponsiveness within seconds and succumb rapidly without supportive care

- **DERMAL**: dermal exposure is **rare** but reported with large surface area exposures. Nitriles are readily absorbed by the skin....delayed effect

Routes of exposure....elimination

- Cyanide is **eliminated** from the body by **different mechanisms**
- Most imp mechanism of elimination **(80%)** is by **irreversible conversion to thiocyanate** by rhodanese enzyme....
- .....Requires sulfur donor (thiosulfate) and then eliminated by kidneys
- Excreted in small amounts in urine
- also **incorporated into cobalamin (Vit B12)**

Clinical presentation

- Abrupt onset of profound toxic effects shortly after exposure is the hallmark of cyanide poisoning:

1. 15 seconds after inhalation of a high conc. of cyanide vapor there is a transient **dyspnea**…..**metabolic acidosis**…increase lactate coz anaerobic respiration
2. Followed in 15-30 seconds by the onset of **convulsions**
3. **Respiratory activity stops** two to three minutes later
4. **Cardiac activity ceases** several minutes later still

- **Onset of acute cyanide poisoning** depends on the route of adm., cyanide dose, and whether itself or precursor is administered (delayed onset if ingested or need metabolism)

CN level (mg/l)	Degree of poisoning	Signs and symptoms
0.5-1.0	Mild	Conscious, nausea, headache, flushed
1.0-2.5	Moderate	Stuporous but responsive to stimuli, tachycardia, dyspnea
≥ 2.5	Severe	Comatose, seizures, cyanosis, CV collapse, death

- Whole-blood levels higher than 0.5–1 mg/L are considered toxic

Diagnosis

- Diagnosis is primarily made by the index of suspicion and clinical judgement
- • Case history, suspicion of exposure, Clinical presentation, metabolic acidosis, multisystem involvement

odor of bitter almonds.

- Laboratory diagnosis
- • blood cyanide levels can be drawn, but empiric treatment is almost always required before lab results are available
- • arterial pO2 may be elevated

Management

- **GENERAL MEASURES:**
  - DECONTAMINATE & PROTECT YOURSELF
  - ABCs EVALUATION (O2 100%, intubation, maintain blood pressure)
  - TREAT COMA AND HYPOTENSION
  - DIAZEPAM or PHANYTOIN TO CONTROL SEIZURES
  - Immediately place a gastric tube and administer ACTIVATED CHARCOAL*, then perform GASTRIC LAVAGE
  - Give additional activated charcoal and a cathartic

Management

CYANIDE KIT

- Cyanide has higher affinity for the iron in methemoglobin than for the iron in cytochrome oxidase

- Nitrites convert the ferrous iron in hemoglobin to the ferric form, yielding methemoglobin

Management

- **CYANIDE ANTIDOTE KIT (NITRATE-THIOSULFATE KIT)**

1. **AMYL NITRITE** for rapid inhalation
   - 5% methemoglobinemia
2. **SODIUM NITRITE** solution for i.v injection (300 mg; 6 mg/kg for children)
   - 10%-12% methemoglobinemia
3. **SODIUM THIOSULFATE** solution for i.v injection, 12.5 g

- If ineffective, half of the dose can be repeated
- The dose must be corrected for weight

CYANIDE KIT

- **3-STEP PROCEDURE:**

1. Break a pearl of **amyl nitrite** under the nose of the victim followed by….
2. I.V administration of **sodium nitrite**, which rapidly increases the methemoglobin level to the degree necessary to remove a significant amount of cyanide from cytochrome oxidase followed by…
3. I.V sodium **thiosulfate**…converts cyanomethemoglobin to thiocyanate & methemoglobin
4. Thiocyanate is much less toxic than cyanide and is excreted by the kidney

Hb + Amyl nitrite/ sod nitrite ⟶ Meth Hb

Cyanide-Cyt Oxidase complex + Meth Hb ⟶ Cyanomethemoglobin + Cyt oxidase

Cyanomethemoglobin + Thiosulfate ⟶ Thiocyanate + Sulfite + Meth Hb

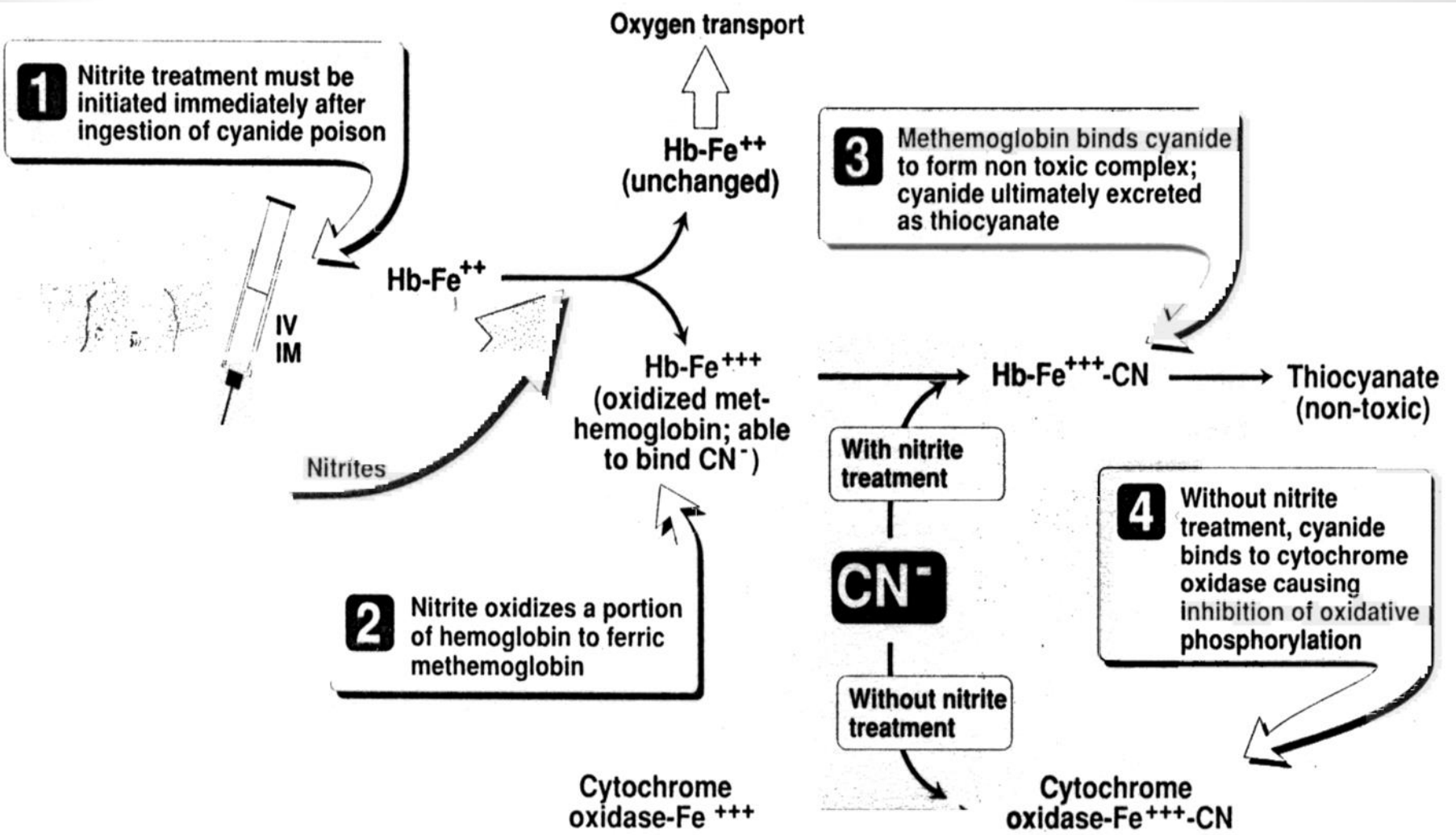


Figure 18.3
Treatment of cyanide poisoning with nitrites.

CYANIDE KIT

- **PROBLEMS WITH THE KIT:**
  - Hypotension with nitrites
  - Excessive methemoglobinemia is fatal because methemoglobin is a very poor oxygen carrier…***Caution!!!***
  - Thiosulfate is relatively benign
  - Methemoglobinemia not tolerated well in children

CYANIDE KIT

- Recently, the FDA approved a concentrated form of **hydroxocobalamin**, one form of Vit B_{12}…….**Cyanokit**)
- ……..combines rapidly with CN^- to form cyanocobalamin (another form of vitamin B_{12})
  - If CO & CN poisoning
  - If renal failure or children
- In acute poisoning, give 5 g of hydroxocobalamin (children: 70 mg/kg) by IV infusion over 15 minutes
- A second administration may be considered
- Also used for prophylaxis of cyanide toxicity from nitroprusside (25 mg/h by IV infusion)
- Well tolerated; allergic reactions are rarely reported

Management

- **Enhanced elimination:**
- Thiocyanate may accumulate in patients with renal insufficiency who do not excrete thiocyanate at a normal rate
- Thiocyanate toxicity is manifested as weakness, disorientation, and convulsions
- Hemodialysis may be indicated in patients who develop high thiocyanate levels while on extended nitroprusside therapy

- **Hyperbaric oxygen** has no proven role in cyanide poisoning treatment.