

# Chemistry and Biology of Cyanides: A Literature Review

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## ABSTRACT

The term cyanide is used to describe compounds that contain the cyano,  $\text{-C}\equiv\text{N}$ , group. The cyanides exist in nature as inorganic as well as organic compounds in the forms of gas or liquid such as HCN, CNCl and acetonitrile, or solids such as NaCN, KCN, and  $\text{Ca}(\text{CN})_2$ . Cyanide compounds are also found in addible plants as cyanogenic glycosides. Compounds that can release cyanide are known as cyanogenic compounds. HCN has a low boiling point (25.63 °C) and is as weakly acidic with a pKa 9.2. It partially ionizes in water to give the cyanide anion,  $\text{CN}^-$ . Cyanide ion from salt reacts with acid to give HCN, but at high pH (8-10), it remains as cyanide ion even if the temperature of the water is 80.0-100.0 °C. Cyanide is one of the deadliest poisons,  $\text{LC}_{50}$  is 1.1 and  $<5.0$  mg/kg for HCN and NaCN, which can cause death to those who come into contact within a few minutes or hours of exposure, depending on the level and route of exposure. It is a rapidly acting, potentially deadly chemical that interferes with the body's ability to use oxygen. Due to its toxicity, cyanide has many roles in industry such as pesticides and medicines as nitrile-containing pharmaceuticals. Organic compounds that have a  $\text{-C}\equiv\text{N}$  functional group are called nitriles. Over 30 nitrile-containing pharmaceuticals are currently marketed for a diverse variety of medicinal indications with more than 20 additional nitrile-containing leads in clinical development. In addition, over 120 naturally occurring nitriles have been isolated from terrestrial and marine sources. In plants, cyanides are usually bound to sugar molecules in the form of cyanogenic glycosides. Hydrogen cyanide can be released from hydrolysis of cyanogenic glycosides which are commonly present in edible plants. Because it is a relatively common toxin in the environment, the body can detoxify a small amount of cyanide. The major route of metabolism for cyanides is detoxification in the liver by the mitochondrial enzyme rhodanese, which catalyzes the transfer of the sulfane sulfur of thiosulfate to the cyanide ion to form thiocyanate. Ingested cyanide may be countered by administering antidotes, such as natural vitamin B<sub>12</sub> and sodium thiosulfate, that detoxify cyanide or bind to it.

**Keyword:** chemistry, biology, cyanide, toxicity

## 1. INTRODUCTION

The term cyanide refers to any chemical containing a carbon-nitrogen ( $\text{C}\equiv\text{N}$ ) bond. It is a primitive compound that existed on earth before the beginning of life and it was the basis for the formation of amino acids, which are the precursors in the evolution of life forms on earth (Das et al. 2019). Many substances contain cyanide, but not all of them are deadly poisons. Sodium cyanide

(NaCN), potassium cyanide (KCN), hydrogen cyanide (HCN), and cyanogen chloride (CNCl) are lethal, but thousands of compounds called nitriles contain the cyanide group yet are not as toxic. In fact, we can find cyanide in nitriles used as pharmaceuticals, such as citalopram (Celexa) and cimetidine (Tagamet). Nitriles are not as dangerous because they do not readily release the CN<sup>-</sup> ion, which is the group that acts as a metabolic poison.

Cyanide can be a colorless gas or liquid, such as hydrogen cyanide (HCN) or cyanogen chloride (CNCl). Cyanide can also be a crystal solid form such as sodium cyanide (NaCN), potassium cyanide (KCN) or calcium cyanide (Ca(CN)<sub>2</sub>). Cyanide is one of the deadliest poisons, which can cause death to those who come into contact within a few minutes or hours of exposure, depending on the level and route of exposure. Cyanide is a rapidly acting, potentially deadly chemical that interferes with the body's ability to use oxygen. However, the human body has the natural ability to detoxify small amounts of cyanide (Zottola, 2009).

Cyanide is a naturally occurring chemical, found in many plants, that has been used in conventional warfare and poisoning for more than two millennia (Baskin & Brewer, 2001). It is highly lethal, whether inhaled as a gas, ingested in solid form, or absorbed through topical exposure. Three notable incidents in recent history include the Jonestown Massacre in 1978, the Tylenol poisonings in 1982, and the controversial Jessica-Mirna Ice Cold Coffee in 2016, which highlight the lethality of this poison. More than 900 people died in the Jonestown massacre, including some 300 who were age 17 or under. It is one of the largest mass deaths in American history (Eldridge, 2023). The Chicago Tylenol murders were a series of poisoning deaths resulting from drug tampering in the Chicago metropolitan area in 1982. The victims consumed Tylenol-branded acetaminophen capsules that had been laced with potassium cyanide. Seven people died in the original poisonings, and there were several more deaths in subsequent copycat crimes (Wikipedia, 2023a). On January 6, 2016, Wayan Mirna Salihin, 27 years old, died after drinking Vietnamese iced coffee at Olivier Cafe, Grand Indonesia, Jakarta (Wikipedia, 2023b). Based on the results of the crime scene investigation and examination of witnesses, the police named Jessica Kumala Wongso as a suspect and through a lengthy court process, Jessica was finally sentenced to 20 years jail. The pros and cons of Mirna's death emerged again to the public after the Netflix's film entitled *Ice Cold: Murder, Coffee, and Jessica Wongso* (Wikipedia, 2023c). Despite its historical use as a chemical warfare agent, the most common cause of cyanide poisoning is smoke inhalation from fires.

First isolated in 1782, cyanide is a compound composed of carbon atom triple-bonded to a nitrogen atom (C≡N). Cyanide is a naturally occurring chemical can be produced by certain types of bacteria, fungi, and algae and found in several types of plants, seeds, and fruit stones, including bamboo, cassava, bitter almonds, apples, and peaches. Despite its toxicity, cyanide has many roles in industry and medicine. In industry, it is used in manufacturing, pesticides, and can be found in several industrial chemicals (CDC, 2018; Holstege & Kirk, 2019). In medicine, cyanide can be found in the widely used antihypertensive sodium nitroprusside, each molecule of which contains 5 ions of cyanide.

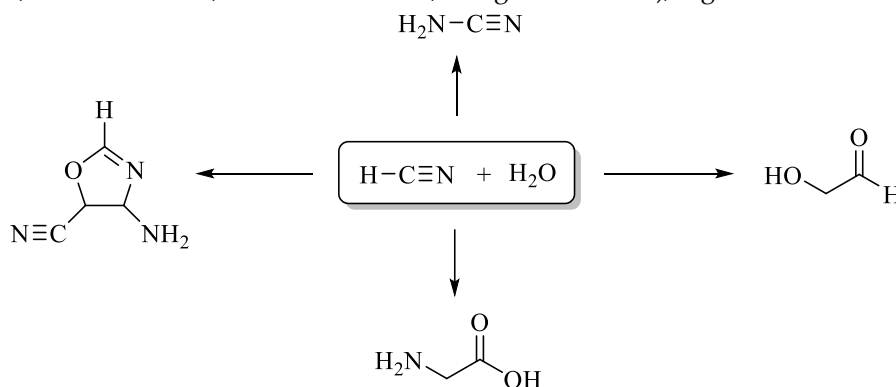
In this review, we would like to give a comprehensive knowledge, the chemistry and biology, regarding to the cyanide compounds, so, people can understand and act when face with cyanide compounds.

## 2. OCCURRENCE OF CYANIDE COMPOUNDS

### 2.1 Cyanide in Interstellar Medium

Molecules containing a cyanide group are of key importance in the physical chemistry of the interstellar medium. The cyanide active radical ( $\bullet\text{CN}$ ) has been identified in interstellar space (Pieniasek et al. 2005) and cyanogen (NC-CN) is used to measure the temperature of interstellar gas clouds (Roth et al. 1993). In addition, many complex organic molecules such as CH<sub>2</sub>-CN, CH<sub>3</sub>-CN or CH<sub>2</sub>=CH-CN contain the cyanide group and play a crucial role in the chemical evolution of molecular

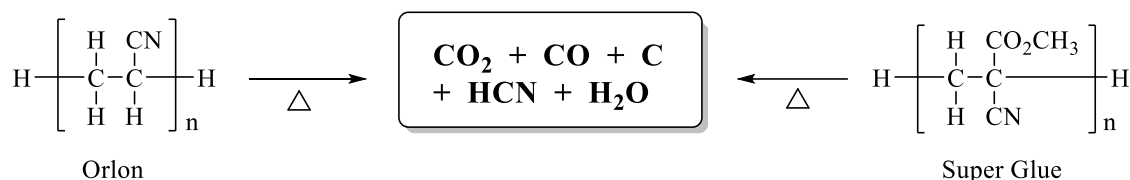
clouds (Vera et al. 2013). The cyano radical ( $\bullet\text{CN}$ ) can react to electrophilic sites such as formaldehyde ( $\text{HCHO}$ ) to lead the formation of compounds containing the CN moiety such as formyl cyanide,  $\text{HCOCN}$ , in interstellar medium. In the fact that there are relative abundances of CN, formaldehyde, and acetaldehyde in the Sagittarius B2 region, where also formyl cyanide was detected. They can be key intermediates in the synthesis of amino acids, the building blocks of proteins, and/or nucleobases, the essential components of nucleic acids (Das et al. 2019; Puzzarini & Barone, 2020; Salta et al. 2020; Tonolo et al. 2020; Danger et al. 2012), Figure 1.



**Figure 1.** The formation of key intermediate amino acids, the building block of protein, and nucleobases (Das et al. 2019).

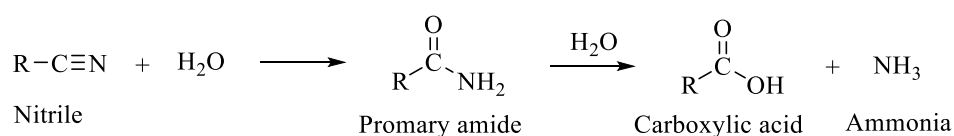
## 2.2 Cyanide from Pyrolysis and Combustion Products

Hydrogen cyanide is produced by the combustion or pyrolysis of certain materials under oxygen-deficient conditions or incomplete combustion. For example, it can be detected in the exhaust of internal combustion engines and tobacco smoke. Certain plastics, especially those derived from acrylonitrile (Orlon®) and methyl  $\alpha$ -cyanoacrylate (Super Glue), release hydrogen cyanide when heated or burnt (CDC, 2013).



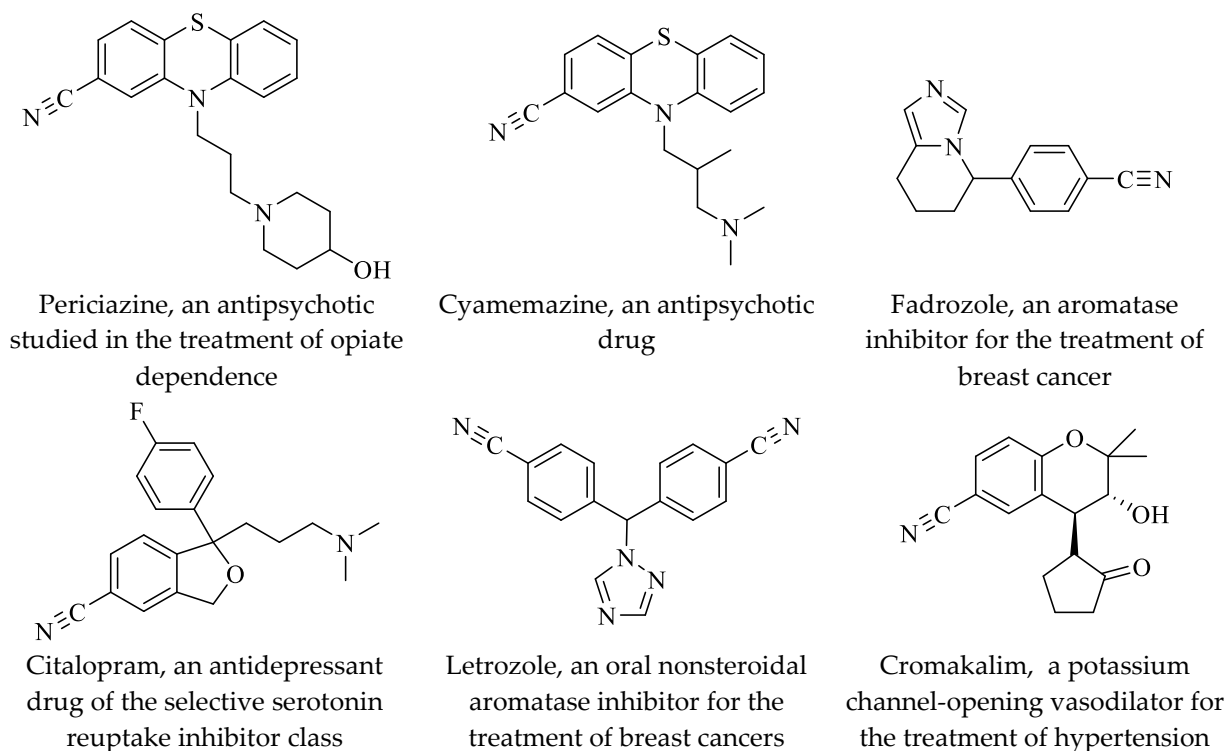
## 2.3 Cyanide as Organic Derivatives

In IUPAC nomenclature, organic compounds that have a  $-\text{C}\equiv\text{N}$  functional group are called nitriles (IUPAC, 1997; Wade, 2006a). In nitriles, the  $-\text{C}\equiv\text{N}$  group is linked by a single covalent bond to carbon. An example of a nitrile is acetonitrile,  $\text{CH}_3-\text{C}\equiv\text{N}$ , and phenylacetonitrile,  $\text{C}_6\text{H}_5\text{CH}_2-\text{C}\equiv\text{N}$ . Nitriles usually do not release cyanide ions, but give carboxylic acid under acidic or basic hydrolysis.



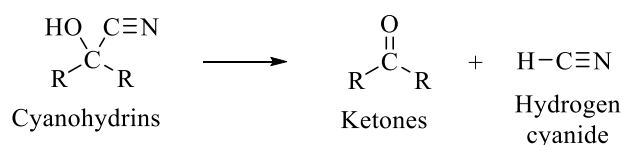
Over 30 nitrile-containing pharmaceuticals are currently marketed for a diverse variety of medicinal indications with more than 20 additional nitrile-containing leads in clinical development. The types of pharmaceuticals containing nitriles are diverse, from vildagliptin, an antidiabetic drug, to anastrozole, which is the gold standard in treating breast cancer. In many instances the nitrile mimics functionality presence in substrates for enzymes, whereas in other cases the nitrile increases

water solubility or decreases susceptibility to oxidative metabolism in the liver (Fleming et al. 2010). Figure 2 shows the nitrile functional group found in several drugs (Wang et al. 2021).



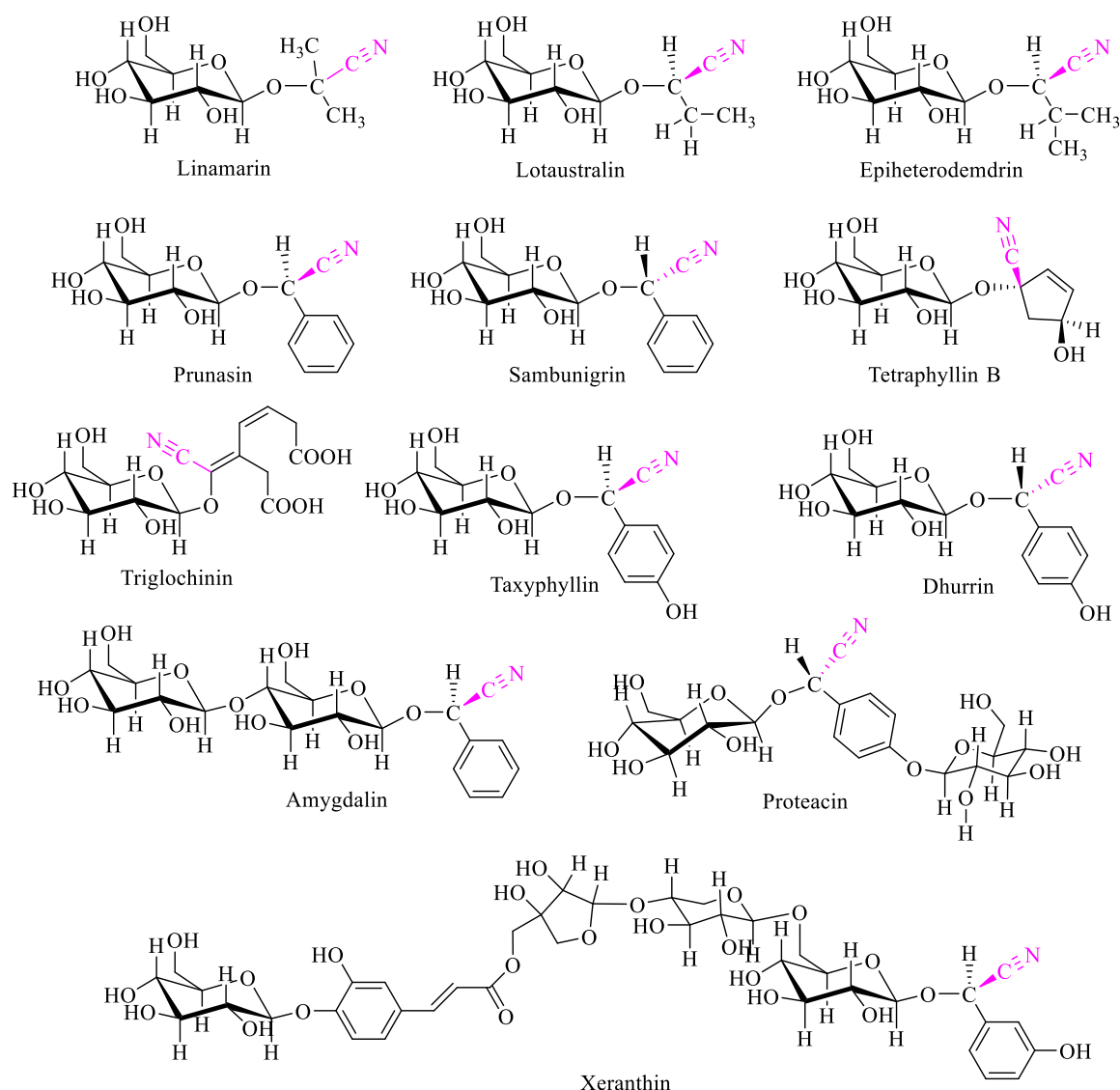
**Figure 2.** Molecular structure of some nitrile-containing pharmaceutical compounds (Wang et al. 2021).

Organic compound containing a functional group with a hydroxyl  $-OH$  and cyanide  $-CN$  bonded to the same carbon atom is called cyanohydrin ( $R_2C(OH)CN$ ). Unlike nitriles, cyanohydrins do release poisonous hydrogen cyanide.



## 2.4 Cyanide in Nature

Nitriles occur naturally in a diverse set of plant and animal sources. Cyanides are produced by certain bacteria, fungi, and algae. It is an antifeedant in a number of plants. Cyanides are found in substantial amounts in certain seeds and fruits, such as those of bitter almonds, apricots, apples, and peaches (Graham & Traylor, 2019). Chemical compounds that can release cyanide are known as cyanogenic compounds. In plants, cyanides are usually bound to sugar molecules in the form of cyanogenic glucosides and defend the plant against herbivores (Fleming, 1999). Cassava roots, also called manioc, an important potato-like food grown in tropical countries and the base from which tapioca is made, also contain cyanogenic glycosides (NIOSH, 2011; Ewa et al. 2017). All cassava tissues, but not for seeds, contain the cyanogenic glycosides linamarin (>90% total cyanogen) and lotaustralin (<10% total cyanogen). Leaves have the highest cyanogenic glycoside levels (5.0 g linamarin/kg fresh weight), whereas roots have approximately 20-fold lower linamarin levels (McMahon et al., 1995). Figure 3 shows molecular structure of some cyanogenic glycosides found in major edible plants and Table 1 presents cyanide concentration in food products.



**Figure 3.** Molecular structure of some cyanogenic glycosides found in major edible plants.

Over 120 naturally occurring nitriles have been isolated from terrestrial and marine sources. Nitriles are commonly encountered in fruit pits, especially almonds, and during cooking of *Brassica* crops such as cabbage, Brussels sprouts, and cauliflower, which release nitriles through hydrolysis. Madelonitrile, a cyanohydrin produced by ingesting almonds or some fruit pits, releases hydrogen cyanide and is responsible for the toxicity of cyanogenic glycosides (Fleming, 1999).

The hydrogenase enzymes contain cyanide ligands attached to iron in their active sites. The biosynthesis of cyanide in the NiFe hydrogenases proceeds from carbonyl phosphate, which converts to cysteinyl thiocyanate, the  $\cdot\text{CN}$  donor (Reissmann et al. 2003).

Amygdalin (D-Mandelonitrile 6-O- $\beta$ -D-glucosido- $\beta$ -D-glucoside) is naturally the most abundant cyanogenic glycosides which found in the seeds and kernels of some fruits, that is, apricot, almond, apple, cherry, plum, lemon, peach, and nectarine (Bolarinwa et al. 2014). Some of the seeds of mentioned fruit are not eaten directly as a food. Table 2 gives amygdalin contents in seeds of some fruit species and processed fruits. Amygdalin is a medically interesting but controversial compound as it has anticancer activity on one hand and can be toxic via enzymatic degradation and production of hydrogen cyanide on the other hand (Jaszczak-Wilke et al. 2021).

**Table 1.** Cyanide concentrations in food products (Jaszczak-Wilke et al. 2021; Aranguri-Llerena & Siche, 2020).

Type of product	Cyanide concentration (mg/L)
Cereal grains and their products	0.001–0.45
Soy protein products	0.07–0.3
Soybean hulls	1.24
Apricot pits, wet weight	89–2170
Home-made cherry juice from pitted fruits	5.1
Home-made cherry juice containing 100% crushed pits	23
<b>Commercial fruit juice</b>	
Cherry	4.6
Apricot	2.2
Prune	1.9
<b>Tropical Foodstuffs</b>	
Cassava (bitter) / dried root cortex	2360
Cassava (bitter) / leaves	300
Cassava (bitter) / whole tubers	380
Cassava (sweet) / leaves	451
Cassava (sweet) / whole tubers	445
Gari flour (Nigeria)	10.6–22.1
Sorghum / whole immature plant	2400
Bamboo / immature shoot tip	7700
Lima beans from Java (coloured)	3000
Lima beans from Puerto Rico (black)	2900
Lima beans from Burma (white)	2000

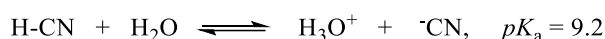
**Table 2.** Amygdalin contents in seeds of some fruit species and processed fruits (Bolarinwa et al. 2014; Aranguri-Llerena & Siche, 2020).

Sources	Amygdalin content (mg/g)	Sources	Amygdalin content (mg/g)
<b>Fruit Seeds</b>		<b>Processed Fruits</b>	
Apricot	14.37 ± 0.28	Toasted almond	0.12 ± 0.06
Cherry (Black)	2.68 ± 0.02	Almond milk (toasted)	0.05 ± 0.01
Cherry (Red)	3.89 ± 0.31	Almond cocoa dessert	0.04 ± 0.02
Peach	6.81 ± 0.02	Almond flour	0.03 ± 0.01
Plum (Green)	17.49 ± 0.26	Apple juice (pressed)	0.09 ± 0.03
Plum (Black)	10.00 ± 0.14	UHT apple juice	0.004 ± 0.01
Plum (Red)	0.44 ± 0.04	Apple puree	0.02 ± 0.01
Apple	2.96 ± 0.02	Apricot slices	0.05 ± 0.07
		Peach drink	0.04 ± 0.05
		Peach slices	0.06 ± 0.01

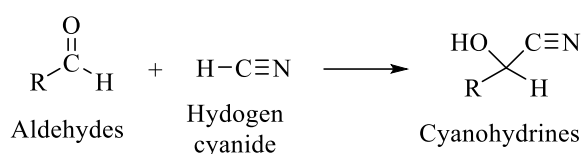
### 3. CHEMISTRY OF CYANIDES

In chemistry, a cyanide is a chemical compound that contains a C≡N functional group and structurally, CN is defined as a triple bond molecule with a negative charge. This group, known as the cyano group, consists of a carbon atom triple-bonded to a nitrogen atom (IUPAC, 1977), where a carbon atom in the oxidation state +2 and a nitrogen atom in the oxidation state -3. In inorganic cyanides, the cyanide group is present as the cyanide anion  $\text{C}\equiv\text{N}^-$ . This anion is extremely poisonous.

Soluble salts such as sodium cyanide (NaCN) and potassium cyanide (KCN) are highly toxic (Jaszczak et al. 2017). Hydrocyanic acid, also known as hydrogen cyanide, or HCN, is a highly volatile liquid that is produced on a large scale industrially. It is obtained by acidification of cyanide salts. Hydrogen cyanide, HCN, is a toxic, a colourless or light blue liquid or gas, and extremely flammable that boils at 25.63°C (Wade 2006b). Hydrogen cyanide is a potent oral poison producing symptoms in minutes and death in minutes to hours. It has a faint bitter almond odour, though not everyone is able to detect this. Because of it is mildly acidic, HCN is sometimes called hydrocyanic acid. Hydrogen cyanide is an acid which is soluble in water.



The conjugate base of hydrogen cyanide is the cyanide ion ( $:\text{C}\equiv\text{N}^-$ ), Cyanide ion is strong base and a strong nucleophile. It attacks ketones and aldehydes to give addition products called cyanohydrins (Wade 2006b).



Many other cyanide salts and compounds exist, which generally may share similar properties, effects, and decontamination methods, although some salts can vary significantly. Inorganic cyanide compounds such as sodium, potassium, and calcium cyanide salts are widely commercially available as white powders, crystals, granules, flakes, lumps, or egg-shaped pellets with a faint, almond-like odor. They are toxic and deadly human poison by ingestion. The cyanide compounds are soluble in water to give a clear colorless solution. Table 3 provides some properties of cyanide compounds (PubChem, 2023).

**Table 3.** The properties of cyanide compounds (PubChem, 2023a-f).

Compound	Formula	Mr (g/mol)	mp (°C)	Density (g/ml, 20°C)	Solubility in water (g/L)	Toxicity (LC <sub>50</sub> )
Hydrogen cyanide	HCN	27.02	-13.28	0.6875	Miscible	1.10 mg/kg
Sodium cyanide	NaCN	49.00	563.0	1.596	520.0	<5 mg/kg
Potassium cyanide	KCN	65.11	634.0	1.550	716.0	<5 mg/kg
Magnesium cyanide	Mg(CN) <sub>2</sub>	76.24	500 (dec)	NA	Slightly	NA
Calcium cyanide	Ca(CN) <sub>2</sub>	92.12	350 (dec)	1.850	500.0	39 mg/kg (rat, oral)
Acetonitrile	CH <sub>3</sub> CN	41.05	-(46-44)	0.786	miscible	2.46 g/kg (rat, oral)

Cyanide compounds can interfere with the body's use of oxygen causing asphyxiation. They are most toxic when ingested, but also pose an inhalation hazard if they convert to toxic hydrogen cyanide gas (HCN) following the addition of water or acid. The amount and rate of HCN release is dependent on the acidity and moisture content, but when salt is present, always consider that HCN may be present. Cyanide salts are not volatile and hence, odorless, but atmospheric moisture may cause salts to release HCN. Around 60-70% of the population can detect a bitter, almond odor if HCN is released; however, olfactory fatigue onsets rapidly, diminishing this limited safeguard. Solutions of cyanide salts, depending on concentration, are reported to have a bitter, burning taste;

lower doses may be mostly tasteless. If HCN is formed from cyanide salts, HCN is flammable with a flash point of  $-18^{\circ}\text{C}$ , explosive potential is severe in the presence of heat, flame or alkaline agents. Isolated cyanide salts are stable and persistent. Cyanide salts will persist in water and on moist surfaces as cyanide ions. The cyanide ion ( $\text{CN}^-$ ) may form cyanide compounds by reaction with other substances in the water or, depending on pH, may be converted to HCN, which is considered “non-persistent” because it can readily volatilize from surfaces and open water vessels. Persistence will depend upon amount and purity of the cyanide salt, method of release, environmental conditions, and the types of surfaces and materials impacted.

HCN is a colorless, extremely poisonous, and flammable liquid that boils slightly above room temperature, at  $25.63^{\circ}\text{C}$ . Acute Exposure Guideline Level (AEGL) values for hydrogen cyanide (HCN) are used to obtain the conservative AEGL values for the cyanide salts (NRT, 2017). Hydrogen cyanide is used as a surrogate for data on the cyanide salts because the cyanide moiety is responsible for the acute toxicity of the cyanide salts. The AEGL values for the cyanide salts are the concentrations of those salts required to produce the equivalent AEGL concentration of hydrogen cyanide after complete hydrolysis. Table 4 gives AEGL values of cyanides salts at various exposure duration (NRT, 2017).

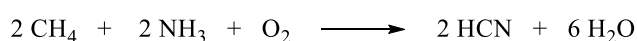
**Table 4.** AEGL levels of cyanide salts at various of exposure durations (NRT, 2017).

AEGL Level in $\text{mg}/\text{m}^3$ , at various exposure durations	10 min.	30 min.	1 hour	4 hours	8 hours
AEGL 1: Threshold mild effects	5.0, 6.6, 4.7, 13	5.0, 6.6, 4.7, 13	4.0, 5.3, 3.8, 13	2.6, 3.5, 2.4, 13	2.0, 2.7, 1.9, NR
AEGL 2: Potentially irreversible effects or impaired ability to escape	34, 45, 32, 80	20, 27, 19, 80	14, 19, 13, 50	7.0, 9.3, 6.6, 21	5.0, 6.6, 4.7, 14
AEGL 3: Threshold for severe effects/medical needs/increasing potential for lethality	54, 72, 51, 240	42, 56, 39, 240	30, 40, 28, 150	17, 23, 16, 64	13, 18, 12, 42

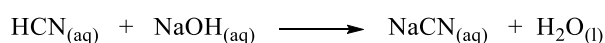
Note: AEGLs and Exposure Guidelines are listed in this order NaCN, KCN,  $\text{Ca}(\text{CN})_2$  and  $\text{CH}_3\text{CN}$

### 3.1 Preparation Cyanide Compounds

The principal process used to manufacture cyanides is the Andrussow process in which gaseous hydrogen cyanide is produced from methane and ammonia in the presence of oxygen and a platinum catalyst (Andrussow, 1927; Andrussow, 1935).

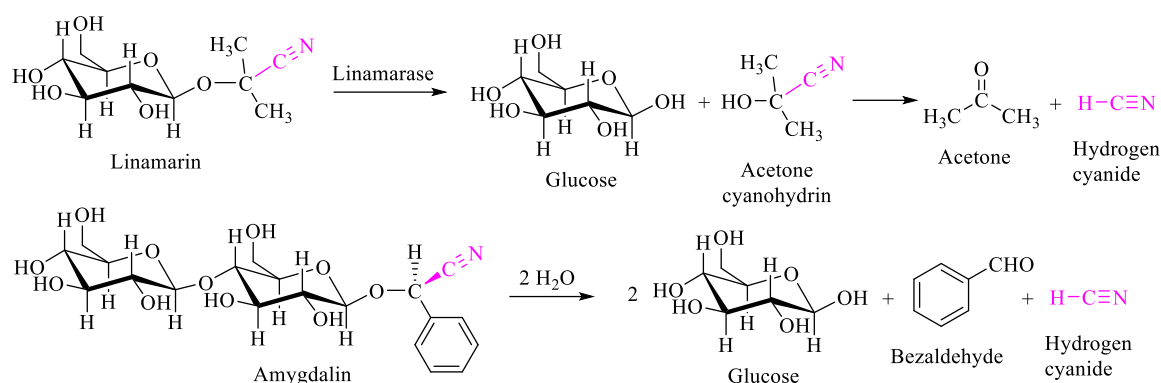


Sodium cyanide, the precursor to most cyanides, is produced by treating hydrogen cyanide with sodium hydroxide (Rubo et al. 2006).



In nature, hydrogen cyanide can be released from hydrolysis of cyanogenic glycosides which are commonly present in edible plants. For example, linamarin in cassava are rapidly hydrolyzed by linamarase to glucose, acetone, and hydrogen cyanide (Kwok, 2008), Figure 4. Similarly, amygdalin, which is also present in cassava, bitter almonds, and peach stones, is converted to glucose, benzaldehyde, and hydrogen cyanide, Figure 4. Hydrogen cyanide release can occur during maceration, which activates intracellular *beta*-glucosidases. This reaction can also result from chewing, which causes the enzyme and the cyanogenic glycosides stored in different compartments to combine. The reaction occurs rapidly in an alkaline environment, and the hydrolysis is complete in 10 min. Hydrolysis is possible in an acid solution and takes place slowly.





**Figure 4.** Hydrolysis of linamarin and amygdalin to produce hydrogen cyanide.

### 3.2 Reactions of Cyanides

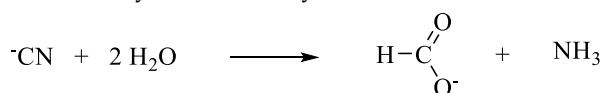
#### (1) Protonation

Cyanide is basic. The  $pK_a$  of hydrogen cyanide is 9.21. Thus, addition of acids stronger than hydrogen cyanide to solutions of cyanide salts releases hydrogen cyanide, but at high pH (8-10), it is possible for it to exist in aqueous solution, even if the temperature of the water is 80.0–100.0 °C (Das et al. 2019).



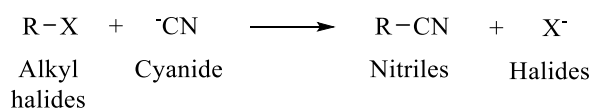
#### (2) Hydrolysis

Cyanide is unstable in water, but the reaction is slow until about 170 °C. It undergoes hydrolysis to give ammonia and formate, which are far less toxic than cyanide (Kwok, 2008). Cyanide hydrolase is an enzyme that catalyzes this reaction.



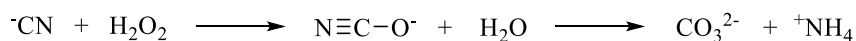
#### (3) Alkylation

Because of the cyanide anion's high nucleophilicity, cyano groups are readily introduced into organic molecules by displacement of a halide group, such as the chloride on methyl chloride. In general, organic cyanides are called nitriles. In organic synthesis, cyanide is a C-1 synthon, i.e., it can be used to lengthen a carbon chain by one, while retaining the ability to be functionalize (Pollak et al. 2000).



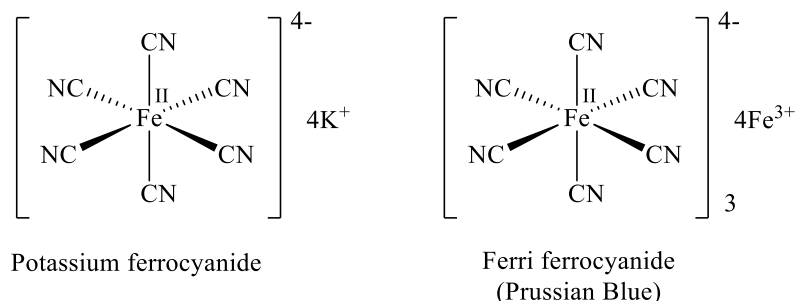
#### (4) Redox

The cyanide ion is a reductor and is oxidized by strong oxidizing agents such as molecular chlorine ( $\text{Cl}_2$ ), hypochlorite ( $\text{ClO}^-$ ), and hydrogen peroxide ( $\text{H}_2\text{O}_2$ ). These oxidizers are used to destroy cyanides in effluents from gold mining (Young & Jordan, 1995; Yermakov, 2023; Botz, 2023). For example, hydrogen peroxide oxidizes cyanides into cyanates ( $\text{N}\equiv\text{C}-\text{O}^-$ ), which is considered much less toxic, or into carbonates ( $\text{CO}_3^{2-}$ ).



#### (5) Metal complexation

The cyanide anion reacts with transition metals to form M-CN bonds known as coordination compounds. This reaction is the basis of cyanide's toxicity (Sharpe, 1976). The high affinities of metals for this anion can be attributed to its negative charge, compactness, and ability to engage in  $\pi$ -bonding.



**Figure 5.** Potassium ferrocyanide complex and Prussian Blue.

Among the most important cyanide coordination compounds are the potassium ferrocyanide,  $\text{K}_4[\text{Fe}(\text{CN})_6] \cdot 3\text{H}_2\text{O}$  and the pigment Prussian blue,  $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$ , Figure 5, which are both essentially nontoxic due to the tight binding of the cyanides to a central iron atom (Parker-Cote et al. 2018). Prussian blue was first accidentally made around 1706, by heating substances containing iron and carbon and nitrogen, and other cyanides made subsequently and named after it. Among its many uses, Prussian blue gives the blue color to blueprints, bluing, and cyanotypes.

## 4. BIOLOGY OF CYANIDES

### 4.1 Symptoms of Cyanide Poisoning

People can be exposed through touching, drinking, or eating food contaminated with cyanide and skin contact, eye contact, or inhaling the cyanide gas. Breathing in cyanide gas causes symptoms to appear the quickest but swallowing solid or liquid cyanide can be toxic also. Following a release of cyanide into water, people can be exposed by touching or drinking water. Solid cyanide released into water can also produce hydrogen cyanide gas (HCN) resulting in possibly inhaling the gas. Contamination of food or drink is more likely with solid forms. Cyanide gas is most dangerous in enclosed places where gas will be trapped. Cyanide gas can disperse quickly in open spaces depending on the weather, making it less harmful outdoors. Hydrogen cyanide (HCN) gas is lighter than air, so the gas will rise. Cyanogen Chloride (CNCl) is heavier and will sink to low-lying areas and increase the risk of exposure there.

Inhaling a high dose of cyanide gas rapidly causes unconsciousness and often death. Lower doses may be survivable, especially if immediate aid is provided. The symptoms of cyanide poisoning are similar to those displayed by other conditions or exposure to any of a number of chemicals, so do not assume cyanide is the cause (Parker-Cote et al. 2018). In any event, do remove yourself from the cause of exposure and seek immediate medical attention.

#### (1) Immediate symptoms

The immediate symptoms include headache, dizziness, weakness, confusion, fatigue, and lack of coordination.<sup>51</sup>

#### (2) Symptoms from larger doses or longer exposure

The symptoms for larger doses or longer exposure include low blood pressure, unconsciousness, convulsions, slow heart rate, lung damage, respiratory failure, and coma. Death from poisoning usually results from respiratory or heart failure (Parker-Cote et al. 2018). A person exposed to cyanide may have cherry-red skin from high oxygen levels or dark or blue coloring, from

Prussian blue (iron-binding to the cyanide ion). Also, skin and body fluids may give off an odor of almonds.

#### 4.2 Toxicity of Cyanides

Many cyanides are highly toxic, Table 5. Cyanide is a potent oral poison producing symptoms in minutes and death in minutes to hours. The cyanide anion is an inhibitor of the enzyme cytochrome c oxidase, the fourth complex of the electron transport chain found in the inner membrane of the mitochondria of eukaryotic cells. It attaches to the iron within this protein. The binding of cyanide to this enzyme prevents transport of electrons from cytochrome c to oxygen. As a result, the electron transport chain is disrupted, meaning that the cell can no longer aerobically produce ATP for energy (Nelson & Cox, 2000). Tissues that depend highly on aerobic respiration, such as the central nervous system and the heart, are particularly affected. This is an example of histotoxic hypoxia (Parker-Cote et al. 2018).

**Table 5.** Cyanide toxicity in terms of LC<sub>50</sub> and LD<sub>50</sub> (Jaszczak et al. 2017; Aranguri-Llerena & Siche, 2020).

Organism	Cyanide Compound	Toxicity/Exposure Time	Concentration
Fish			
<i>Oncorhynchus mykiss</i>	K <sub>3</sub> Co(CN) <sub>6</sub>	LC <sub>50</sub> /96 h	112.9 mg/L
<i>Cyprinus carpio</i>	NaCN	LC <sub>50</sub> /96 h	1.0 mg/L
<i>Carassius auratus</i>	NaCN	LC <sub>50</sub> /96 h	318 µg/L
<i>Pimephales promelas</i>	NaCN	LC <sub>50</sub> /8 days	114 µg/L
Invertebrate			
<i>Daphnia magna</i>	NaCN	LC <sub>50</sub> /24 h	0.171 mg/L
	NaCN	LC <sub>50</sub> /48 h	0.12 mg/L
	NaCN	LC <sub>50</sub> /72 h	0.07 mg/L
	NaCN	LC <sub>50</sub> /96 h	0.019 mg/L
<i>Daphnia magna</i>	K <sub>3</sub> Co(CN) <sub>6</sub>	LC <sub>50</sub> /96 h	0.502 mg/L
Higher organism			
Mouse	KCN	LD <sub>50</sub> /24 h	8.4 mg/kg
Mouse	KCN	LD <sub>50</sub> /24 h	8.87 mg/kg
Rat	CH <sub>3</sub> CN	LD <sub>50</sub> /24 h	>500 mg/kg
	CH <sub>2</sub> CHCN	LD <sub>50</sub> /24 h	95.1 mg/kg
	CH <sub>2</sub> (CN) <sub>2</sub>	LD <sub>50</sub> /24 h	66.4 mg/kg
	CH <sub>3</sub> CH <sub>2</sub> CN	LD <sub>50</sub> /24 h	83.6 mg/kg
	C <sub>2</sub> H <sub>4</sub> (CN) <sub>2</sub>	LD <sub>50</sub> /24 h	378.5 mg/kg

LD<sub>50</sub>: Amount of a given substance (mg/100 g or mg/kg of body weight) that causes the death of 50% of a group of animals under test (dermal or oral).

LC<sub>50</sub>: Concentration of a chemical in the air or in water (mg/L), which kills 50% of the test animals, in each time (usually 4 hours).

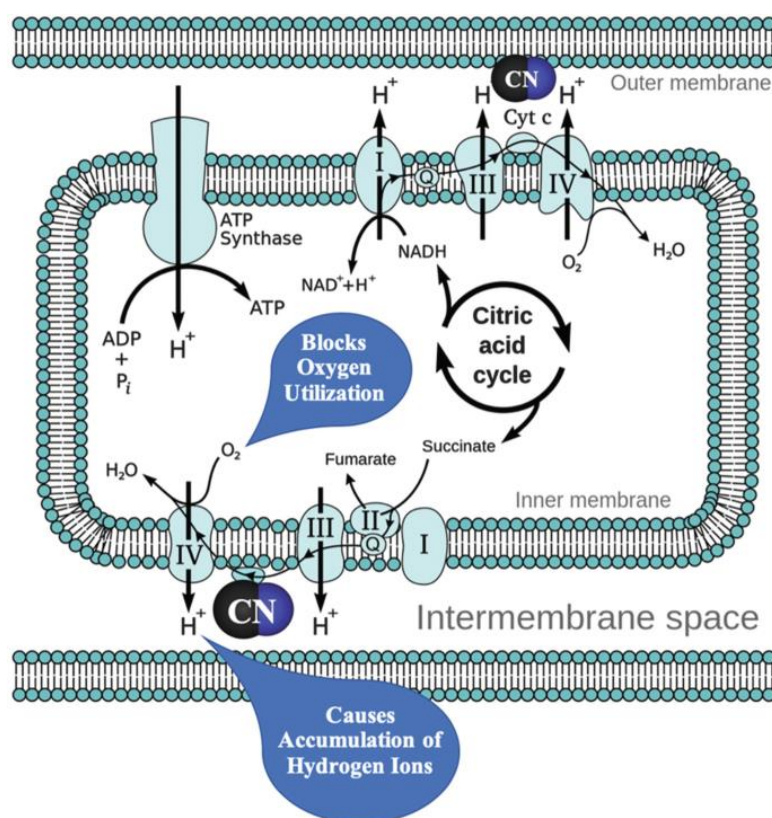
The most hazardous compound is hydrogen cyanide, which is a gas and kills by inhalation. For this reason, an air respirator supplied by an external oxygen source must be worn when working with hydrogen cyanide (CDC, 2023). Hydrogen cyanide is produced by adding acid to a solution containing a cyanide salt. Alkaline solutions of cyanide are safer to use because they do not evolve hydrogen cyanide gas. Hydrogen cyanide may be produced in the combustion of polyurethanes, for this reason, polyurethanes are not recommended for use in domestic and aircraft furniture. Oral ingestion of a small quantity of solid cyanide or a cyanide solution of as little as 200 mg, or exposure to airborne cyanide of 270 ppm, is sufficient to cause death within minutes (Biller, 2007).

Organic nitriles do not readily release cyanide ions, and so have low toxicities. By contrast, compounds such as trimethyl cyanide ( $(\text{CH}_3)_3\text{SiCN}$ ) readily release HCN or the cyanide ion upon contact with water (MSDS, 2022).

Cyanide as hydrogen cyanide is rapidly absorbed following inhalation exposure. Humans retained 58% of hydrogen cyanide in the lungs after inhaling the gas through normal breathing. Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body. Tissue levels of hydrogen cyanide were 0.75, 0.42, 0.41, 0.33, and 0.32 mg/100 g of tissue in the lung, heart, blood, kidney, and brain, respectively, in a man who died following inhalation exposure to hydrogen cyanide gas. In another case, tissue cyanide levels from a man who died from inhalation of hydrogen cyanide were reported as 0.5 mg per 100 mL of blood and 0.11, 0.07, and 0.03 mg/100 g in the kidney, brain, and liver, respectively. Urinary cyanide levels were reported as 0.2 mg/100 mL, and 0.03 mg/100 g were found in the gastric contents (DHSA, 2006a).

#### 4.3 Mechanism of Action

Cyanide as hydrogen cyanide, originating in vivo by dissociation of sodium cyanide, potassium cyanide, and other cyanogenic compounds or arising from catabolism of cyanogenic glycosides, exerts its acute toxic effects by complexing with the ferric iron atom in metalloenzymes, resulting in histotoxic anoxia through inhibition of cytochrome c oxidase, metalloenzymes that function as the terminal oxidase of the inner mitochondrial membrane respiratory chain (Everett et al. 2020; Isom & Borowitz, 2016), Figure 6.



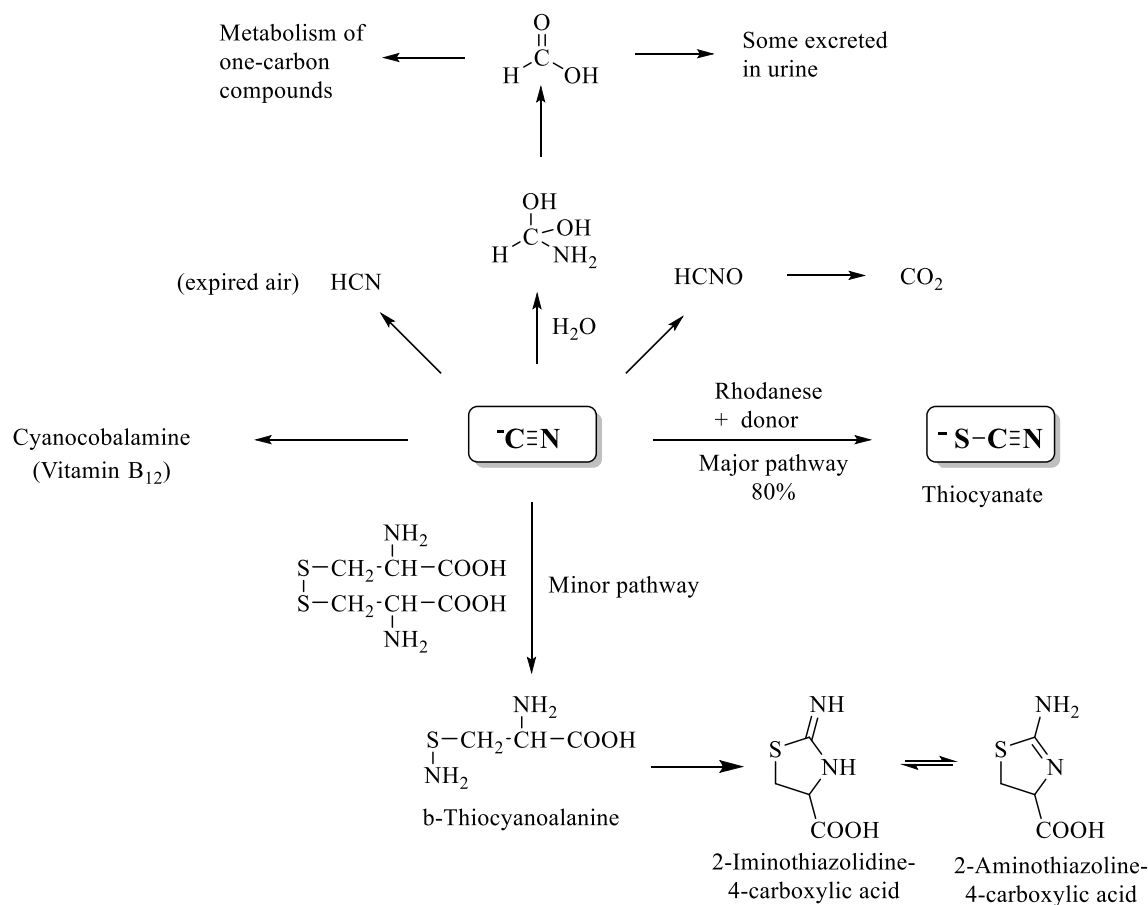
**Figure 6.** Mechanism of cyanide poisoning (Everett et al. 2020).

A two-step process has been proposed: cyanide as hydrogen cyanide first penetrates a protein crevice of cytochrome c oxidase and binds to the protein in the mitochondria of cells. Hydrogen cyanide then binds to the trivalent iron ion of the enzyme, forming a relatively stable (but reversible) coordination complex. One mole of hydrogen cyanide is bound to one mole of cytochrome c oxidase. As a result, the enzyme becomes unable to catalyze the reactions in which

electrons would be transferred from reduced cytochrome to oxygen. Cellular oxygen utilization is thus impaired, with resultant reduction in or cessation of aerobic metabolism. Glucose catabolism then shifts from the aerobic pathway to anaerobic metabolism including the pentose phosphate pathway, resulting in increased blood glucose, pyruvic acid, lactic acid, and nicotinamide adenine dinucleotide (NADPH) level, and a decrease in the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio (Bortey-Sam et al. 2020). Some investigators suggest that it is the binding of cyanide to oxidized  $Cu_B$ , the copper ion that is part of the dioxygen binding-site that leads to the inhibition of cytochrome c oxidase. The inhibition of oxygen use by cells (termed histoxic hypoxia) causes oxygen tensions to rise in peripheral tissues. This results in a decrease in the unloading gradient for oxyhemoglobin; thus, oxyhemoglobin is carried in the venous blood. Inhibition of oxygen utilization is thought to occur rapidly after cyanide exposure. In addition to binding to cytochrome c oxidase, cyanide also binds to catalase, peroxidase, methemoglobin, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthin oxidase, and succinic dehydrogenase. These reactions may also contribute to the classic signs of cyanide toxicity (DHHSA, 2006b).

The mitochondrial electron transport system may also be seriously disturbed by cyanide through the inhibition of succinate dehydrogenase, which is a nonheme flavin-containing iron-sulfur protein which passes electrons to the cytochrome system. The peculiarity of this enzyme is its sulfur linkages which are of the persulfide or sulfane type, favoring a "labile sulfur" condition that is essential for activity. Cyanide is a strong thiophile reacting with the "labile" sulfur thus breaking the persulfide bond (Bortey-Sam et al. 2020; NRCC, 1982).

#### 4.4 Metabolism of Cyanide



**Figure 7.** Basic processes involved in the metabolism of cyanide.

Reports of ingestion of cyanides by humans and reports of occupational exposure indicate that cyanide is transformed into thiocyanate. Conversion of cyanide into thiocyanate is enhanced when cyanide poisoning is treated by intravenous administration of a sulfur donor. The sulfur donor must have a sulfane sulfur, a sulfur bonded to another sulfur, e.g., sodium thiosulfate. During conversion by rhodanese, a sulfur atom is transferred from the donor to the enzyme, forming a persulfide intermediate. The persulfide sulfur is then transferred from the enzyme to cyanide, yielding thiocyanate. Once thiocyanate is formed, it is not converted back to cyanide. Thiocyanate is then readily excreted in the urine as the major metabolite.

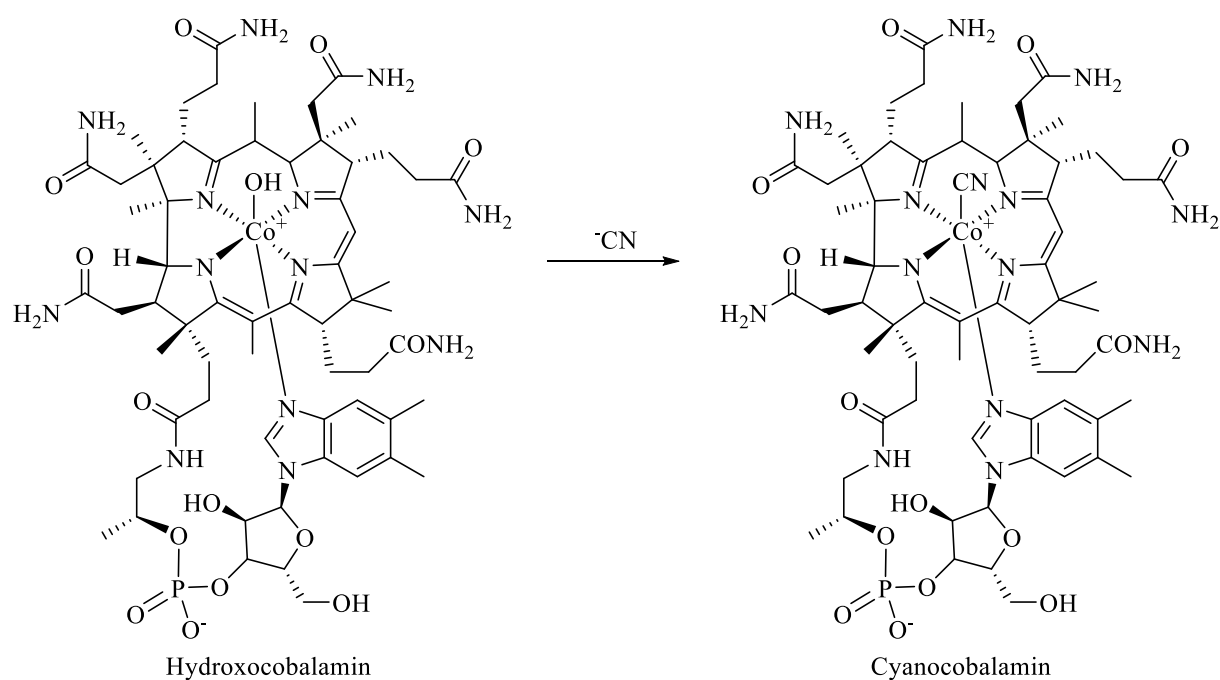
Figure 7 shows the pathway involved in the metabolism of cyanide. The proposed metabolic pathways are (1) the major pathway, conversion to thiocyanate by either rhodanese or 3-mercaptopyruvate sulfur transferase; (2) conversion to 2-aminothiazoline-4-carboxylic acid; (3) incorporation into a 1-carbon metabolic pool; or (4) combining with hydroxocobalamin to form cyanocobalamin (vitamin B<sub>12</sub>). Thiocyanate has been shown to account for 60 to 80% of an administered cyanide dose while 2-aminothiazoline-4-carboxylic acid accounts for about 15% of the dose (DHHSA, 2006c; Gyamfi et al. 2019).

While absorbed cyanide is principally excreted as thiocyanate in the urine, traces of free hydrogen cyanide may also be excreted unchanged in the lungs, saliva, sweat, or urine, as carbon dioxide in expired air, or as  $\beta$ -thiocyanoalanine in saliva and sweat.

Organic nitriles are converted into cyanide ions through the action of cytochrome P450 enzymes in the liver. Cyanide is rapidly absorbed and distributed throughout the body. Cyanide is mainly metabolized into thiocyanate by either rhodanese or 3-mercaptopyruvate sulfur transferase. Cyanide metabolites are excreted in the urine (DHHSA, 2006c).

#### 4.5 Treatment for Cyanide Poisoning

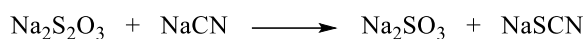
Because it is a relatively common toxin in the environment, the body can detoxify a small amount of cyanide. For example, you can eat the seeds of an apple or withstand cyanide from cigarette smoke without dying (Ewa et al. 2017).



**Figure 7.** Binding cyanide ion by hydroxocobalamin to form cyanocobalamin.

When cyanide is used as a poison or a chemical weapon, treatment depends on the dose. A high dose of inhaled cyanide is lethal too quickly for any treatment to take effect. Initial first aid for inhaled cyanide requires getting the victim to fresh air. Ingested cyanide or lower doses of inhaled cyanide may be countered by administering antidotes that detoxify cyanide or bind to it. For example, natural vitamin B<sub>12</sub> or hydroxocobalamin reacts with cyanide to form cyanocobalamin, which is excreted in urine (Meillier & Heller, 2015; Thompson & Marrs, 2012). The cobalt ion in hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin. Each hydroxocobalamin molecule can bind one cyanide ion by substituting it for the hydroxo ligand linked to the trivalent cobalt ion, to form cyanocobalamin (Meillier & Heller, 2015; Thompson & Marrs, 2012), Figure 7.

Another antidote that detoxifies cyanide is sodium thiosulfate (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>) (Anseeuw et al. 2013). Sodium thiosulfate is considered one of the most important medicines in the health system because of its ability to treat rare diseases, like pityriasis versicolor, calciphylaxis, and most famous cyanide poisoning. Sodium thiosulfate reacts with sodium cyanide to produce sodium sulfite and sodium thiocyanate (Ewa et al. 2017), a substance that is 200 times less toxic than cyanide.



Cyanide antidote kits are commercially available kits that included three different chemical components: amyl nitrite, sodium nitrite, and sodium thiosulfate. However, amyl nitrite is no longer included in cyanide antidote kits and is not currently approved by the FDA as an initial antidote. Sodium nitrite and sodium thiosulfate given by intramuscular injection are effective against severe cyanide poisoning in three clinically relevant animal models of prehospital emergency care (Bebarta et al., 2017). For nonmilitary use, sodium nitrite and sodium thiosulfate are issued in separate bottles as a formulation called Nithiodote (Multum, 2023).

## 5. CONCLUSION

There are many cyanide compounds in nature, including inorganic forms and organic derivatives. In inorganic cyanides, the cyanide group is present as the cyanide anion,  $\text{C}\equiv\text{N}^-$ . This anion is extremely poisonous. Soluble salts such as sodium cyanide (NaCN) and potassium cyanide (KCN) are highly toxic. Hydrogen cyanide (HCN) is a highly volatile liquid that is produced on a large scale industrially. It is obtained by acidification of cyanide salts. Organic cyanides are usually called nitriles. In nitriles, the  $\text{C}\equiv\text{N}$  group is linked by a single covalent to carbon. Nitriles occur naturally in a diverse set of plant and animal sources. Chemical compounds that can release cyanide are known as cyanogenic compounds. In plants, cyanides are usually bound to sugar molecules in the form of cyanogenic glycosides and defend the plant against herbivores. A functional group with a hydroxyl  $\text{-OH}$  and cyanide  $\text{-CN}$  bonded to the same carbon atom is called cyanohydrin ( $\text{R}_2\text{C}(\text{OH})\text{CN}$ ). Nitriles generally do not release cyanide ions, the cyanohydrins do and are thus toxic.

Cyanide is one of the deadliest poisons, which can cause death to those who come into contact within a few minutes or hours of exposure, depending on the level and route of exposure. Cyanide is a multifaceted poison - toxicant in fire smoke; agent of suicide, murder, and terrorism; and industrial and occupational hazard. As it exists in gas, liquid, and solid forms, it can cause human toxicity via multiple routes including inhalation, ingestion, parenteral administration, and dermal or conjunctival contact. One of the most rapidly acting and deadly of poisons, cyanide can kill within seconds or minutes to hours of exposure depending on the route and length of exposure as well as the dose received.

The mechanism of cyanide intoxication has been attributed to the inhibition of cytochrome oxidase, thereby decreasing the tissue utilization of oxygen. The major route of metabolism for hydrogen cyanide and cyanides is detoxification in the liver by the mitochondrial enzyme rhodanese, which catalyses the transfer of the sulfane sulfur of thiosulfate to the cyanide ion to form thiocyanate. About 80% of cyanide is detoxified by this route. Cyanide and thiocyanate can also be metabolized by several minor routes, including the combination of cyanide with

hydroxycobalamin (vitamin B<sub>12a</sub>) to yield cyanocobalamin (vitamin B<sub>12</sub>) and the non-enzymatic combination of cyanide with cystine, forming 2-iminothiazoline-4-carboxylic acid, which appears to be excreted without further change. Ingested cyanide or lower doses of inhaled cyanide may be countered by administering antidotes that detoxify cyanide or bind to it. Natural vitamin B<sub>12</sub> or hydroxocobalamin reacts with cyanide to form cyanocobalamin, which is excreted in urine. Other antidotes that detoxify cyanide are sodium nitrite and sodium thiosulfate.

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