Hydrogen Cyanide

Toxicological Overview

Key Points

Kinetics and metabolism

- hydrogen cyanide is rapidly absorbed and distributed following inhalation, oral or dermal exposure
- the cyanide ion blocks oxidative respiration; this causes failure of oxygen usage, leading to hypoxia and metabolic acidosis
- metabolism of hydrogen cyanide occurs primarily through conversion to thiocyanate, which is readily excreted in the urine

Health effects of acute exposure

- hydrogen cyanide may be fatal following exposure by all routes
- onset of signs and symptoms following exposure is rapid
- features of toxicity include non-specific CNS symptoms, muscular and neurological effects, tachypnea and tachycardia
- severe features include seizures, a rapid loss of consciousness, cardiorespiratory depression and collapse, pulmonary oedema and death
- lactic acidosis is a key feature and correlates with the severity of intoxication
- on survival of severe intoxication, profound neurological impairment may develop

Health effects of chronic exposure

- long-term exposure to low levels may lead to non-specific neurological symptoms, effects on the thyroid, and optic neuropathy
- hydrogen cyanide has no mutagenic properties and is not considered to be a carcinogen
Summary of Health Effects

Hydrogen cyanide is highly toxic, with rapid onset of symptoms noted following acute exposure. Symptoms may occur within seconds following inhalation and minutes following ingestion or dermal contact.

The cyanide ion blocks oxidative respiration, causing tissue hypoxia; tissues with high metabolic demand such as the central nervous system (CNS) are therefore key targets for toxicity. Early features of systemic toxicity include non-specific CNS symptoms, muscular and neurological effects, tachypnea and tachycardia. Late effects or those following larger exposures may include seizures, a rapid loss of consciousness, cardiorespiratory depression and collapse, pulmonary oedema and death. Lactate acidosis may also be noted.

After a single, brief exposure to a low concentration of hydrogen cyanide from which an individual recovers quickly, no long-term health effects are anticipated. However, survivors of larger exposures may suffer long-term CNS damage; observed sequelae include intellectual deterioration, confusion, personality changes, memory deficits and Parkinsonism. Chronic exposure to hydrogen cyanide has been linked to a range of non-specific neurological effects, thyroid effects, optic neuropathy and effects on the skin and the gastrointestinal (GI) system.

Hydrogen cyanide has no structural alerts for DNA reactivity. Hydrogen cyanide has not been classified as a human carcinogen and there is no evidence to suggest that it has mutagenic potential.

There is limited data on reproductive and developmental toxicity for hydrogen cyanide.
Kinetics and Metabolism

The cyanide ion (CN⁻) is the toxic moiety in hydrogen cyanide. This is also true of simple cyanide salts such as potassium and sodium cyanide; therefore their toxicology is similar to that of hydrogen cyanide [1]. For more information on these compounds please refer to the incident management and general information compendium entries for sodium and potassium cyanide.

Owing to its small size and moderate lipid solubility, hydrogen cyanide is readily absorbed following inhalation, ingestion and dermal contact [2, 3]. Data on absorption by inhalation in humans is limited; results from a volunteer study measuring pulmonary retention of a 3-minute dose of 0.5–20 mg/m³ in 10 individuals led to an estimated absorption of 58–77% [4]. Ingested simple cyanide salts (i.e. sodium and potassium cyanide) are rapidly and completely converted into hydrogen cyanide in the stomach; the free cyanide ion is bound to the hydrogen ion in the acidic environment [1]. Liquid hydrogen cyanide is rapidly absorbed through the skin [5]. Absorption of hydrogen cyanide across abraded skin may be enhanced [6].

The distribution of hydrogen cyanide following absorption is rapid and widespread [4]. Following ingestion, cyanide is found in the stomach, with lesser amounts found in the spleen, blood, liver, brain and kidney; it is found in the lung, blood, brain and kidneys following inhalation [3, 4]. The majority of hydrogen cyanide in blood is sequestered in erythrocytes and a small proportion is transported in the plasma to target organs [4, 7]. Cyanide is unlikely to accumulate in human tissues after chronic oral exposure [2, 7].

Metabolism of hydrogen cyanide primarily involves its conversion to soluble and less acutely toxic thiocyanate (SCN⁻) by the enzyme rhodanese, with about 80% of hydrogen cyanide metabolised by this route [1, 4, 7]. This requires sulphane-sulphur as a co-factor, i.e. one sulphur atom bonded to another sulphur atom such as in a thiosulphate salt (e.g. sodium thiosulphate). This conversion is irreversible; the thiocyanate ion may then be readily excreted in the urine. The process is typically rapid, with the supply of sulphur-containing donor molecules being rate limiting [4]. Rhodanese is widely distributed in the mitochondria of all tissues, with the highest concentrations found typically in the liver, kidney, brain and muscle [4, 7]. Hydrogen cyanide may also be metabolised by lesser pathways, including the complexing of cyanide with cobalt in hydroxo-cobalamin to form cyanocobalamin (vitamin B₁₂) and metabolism by other sulphur transferases [7, 8]. The rate of spontaneous detoxification of cyanide in humans has been estimated to be about 1 µg/kg per minute, which is far slower than that in rodents [7].

The majority of absorbed cyanide is excreted in the urine as thiocyanate. Small amounts may also be excreted unchanged in the lungs, saliva, sweat or urine or converted to carbon dioxide in expired air [1, 4]. A plasma half-life of 20 minutes to 1 hour has been estimated for cyanides in humans [2].
Sources and Route of Human Exposure

Hydrogen cyanide is an important industrial reagent; it is used in the production of nylon, acrylates and acetonitrile [5]. It is also used as a fumigant and pesticide, in metal cleaning, gardening, ore extraction, electroplating, dying, printing and photography [5].

A number of edible plants contain low concentrations of hydrogen cyanide in the form of cyanogenic glycosides [7, 9]. Notable examples are the kernels of wild (bitter) almonds, apricots and black cherries, bamboo shoots, lima beans and cassava [7]. Cyanogenic glycosides within plants may liberate hydrogen cyanide when the plant is damaged (eg ground or chewed) or enzymatically hydrolysed within the body [7].

Industrial use is the origin of most cyanide in the environment, although some will be present by natural processes such as biomass combustion [4]. Hydrogen cyanide may be released from a range of combustion process, particularly those that involve nitrogen-containing materials such as polyurethane and PVC. The half-life of hydrogen cyanide in the atmosphere is 1–3 years [10]. Hydrogen cyanide does not generally enter soils [10]. It has a tendency to volatilise from water, where it has a half-life of hours to a few days [11].

People may be exposed to hydrogen cyanide released as a combustion product during house fires [9]. Hydrogen cyanide intoxication is a contributing factor to morbidity and mortality arising from smoke inhalation, together with other toxicants such as carbon monoxide [12, 13].

For the general population (excluding those exposed to high levels of cyanogenic glycosides in food), cigarette smoke is considered to be the greatest source of exposure to hydrogen cyanide [7]. Mainstream smoke from one filter cigarette contains about 100 μg of hydrogen cyanide, while the amount from non-filter cigarettes may be five times that amount [1]. Human exposure may also occur in industrial settings or from accidents during storage or transportation. Ambient levels of cyanide in the atmosphere and in drinking water are low and are considered not to be sources of significant exposure in the UK.

A workplace exposure limit (WEL) for hydrogen cyanide has been set in the UK, to protect workers from its harmful effects. The short-term WEL (15-minute reference period) for hydrogen cyanide is 11 mg/m³ [14].
Health Effects of Acute/Single Exposure

Human data

Mechanism

Hydrogen cyanide has a high affinity for the ferric moiety of cytochrome c oxidase in mitochondria, forming a stable but reversible complex [5]. Binding of cyanide to cytochrome a-a₃ complex blocks the last stage in the electron transfer chain and thus blocks ATP production [5]. This results in cellular hypoxia and a shift of aerobic to anaerobic respiration, leading to cellular ATP depletion, lactic acidosis, and cell and tissue death [2, 8, 15]. Anaerobic respiration increases to compensate, with a concomitant increase in plasma lactate levels [5, 12, 16]. Tissue damage (histotoxic hypoxia) throughout the body results from the reduced cellular utilisation of oxygen, the most sensitive tissues being those with high oxygen demand or low detoxifying capacity [2]. The central nervous system (CNS) is particularly vulnerable to the effects on hydrogen cyanide intoxication, owing to its high oxygen demand and limited capacity for anaerobic oxidation [7]. Cyanide may also inhibit other metalloenzymes [3].

General toxicity

Hydrogen cyanide is highly toxic by all routes [5]. Its acute toxicity is characterised by a steep dose-response curve, with lethality occurring by any route [4].

Features of poisoning include anxiety, excitement, nausea, faintness, headache, dizziness, weakness, confusion, lethargy, vomiting, constricting sensation in the chest, incontinence, ataxia, convulsions, tachypnea and tachycardia [4, 7]. Later features of severe poisoning may include seizures, deep coma, fixed unreactive pupils, pulmonary oedema, cardiovascular collapse, respiratory depression and arrest, and death [4, 9]. Haemodynamic status may become unstable; the affected individual may develop ventricular arrhythmias, bradycardia, heart block and cardiac arrest [17]. Cyanosis may be a late sign and does not always occur [5].

Following lower level acute exposures, individuals may display symptoms of hypoxia, including flushing, light-headedness, dizziness and headache [4].

Inhalation

Exposure to a massive concentration of hydrogen cyanide gas may render an individual unconscious within seconds and may lead to coma and death within minutes [18, 19]. Some estimates of lethal concentrations are reported in Table 1.
Table 1: Time to death following hydrogen cyanide inhalation in humans

<table>
<thead>
<tr>
<th>Dose</th>
<th>ppm</th>
<th>Time to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/m³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120–150</td>
<td>110–135</td>
<td>30 min – 1 h or later</td>
</tr>
<tr>
<td>200</td>
<td>180</td>
<td>10 min</td>
</tr>
<tr>
<td>300</td>
<td>270</td>
<td>Immediate</td>
</tr>
</tbody>
</table>

Reference

Only mild effects may occur after exposure to 20–40 mg/m³ for several hours [7, 20]; 50–60 mg/m³ may be tolerated for 20 minutes to 1 hour without immediate or late effects [7]. Features following inhalation exposure are typical of those following other routes (see the general toxicology section above).

Hydrogen cyanide is reported to have a characteristic odour of almonds or bitter almonds [5]. However, not all individuals can detect this, so odour is not to be considered to be a reliable indicator of exposure [5].

Ingestion
Ingestion of hydrogen cyanide, or compounds that may liberate hydrogen cyanide within the body, may rapidly lead to an onset of systemic toxicity (see the general toxicity section) [6].

Features noted after deliberate ingestion of cyanide compounds may include nausea, retching and collapse [21]. Patients may be unresponsive to painful stimuli and have restless, non-purposeful movements with intermediate decorticate posturing of upper and lower extremities, together with severe anion gap metabolic acidosis [21, 22].

The acute lethal oral dose for hydrogen cyanide has been reported at between 50 and 90 mg; for potassium or sodium cyanide it has been reported at 200 mg (equivalent to 81 and 110 mg of hydrogen cyanide, respectively) [23].

Dermal/ocular exposure
Dermal exposure to hydrogen cyanide may cause dermatitis and rash [3]. Reportedly, death has occurred following dermal contact with hydrogen cyanide; a worker (wearing a gas mask) died following a 5-minute exposure to liquid hydrogen cyanide on the hand [3].

Ocular exposure to hydrogen cyanide may result in pain, swelling, blepharospasm, lacrimation, conjunctivitis, palpebral oedema and photophobia [5].
Delayed effects following acute exposure

After a single, brief exposure to a low concentration of hydrogen cyanide from which an individual recovers quickly, no long-term health effects are anticipated. However, there are rare reports of long-term sequelae in individuals who have survived a substantial exposure [5]. Survivors of larger exposures may suffer long-term CNS damage; observed sequelae include intellectual deterioration, confusion and Parkinsonism [5]. Magnetic resonance imaging investigations have revealed effects in the basal ganglia, including multiple areas of low signal intensity in the globus pallidus and posterior putamen [24–26]. These findings in CNS structures with a high metabolic demand such as the basal ganglia, cerebral cortex and sensorimotor cortex have been attributed to both direct toxicity of cyanide and a consequence of cerebral hypoxia secondary to the cyanide intoxication [27–29].

A slow recovery from severe dystonia syndromes arising from cyanide intoxication has been noted in some cases and has involved treatment with Parkinsonism therapies such as levodopa [24, 27, 28, 30].

The onset of toxicity from dermal exposure may be delayed for several hours [5].

Animal and in-vitro data

Inhalation

In a study of five cynomologus monkeys, incapacitation (defined in the study as semi-consciousness and loss of muscle tone) occurred within 8–19 minutes of exposure to 100–156 ppm (110–172 mg/m³) of hydrogen cyanide [31]. Early in the exposure period, marked hyperventilation developed and was associated with an increase in EEG delta wave activity. Respiration then slowed and a pattern of slow deep breaths occurred, with a pause at the end of expiration between each successive breath. Heart rate decreased over the exposure period. Exposure was terminated before the full 30-minute period in three out of five animals as a precautionary measure due to the severity of the signs noted. A rapid recovery to a conscious and fairly active state was noted in the first 10 minutes of a recovery period. Consciousness was regained in 3–7 minutes with the heart rate normal within 5 minutes of the start of the recovery period [31]. One animal was noted to have signs of convulsions after exposure for 28 minutes to 123 ppm (136 mg/m³) of hydrogen cyanide.

Maximal non-lethal concentrations in a number of species have been reported in an early study as approximately 100 mg/m³ (dogs and rats), 140 mg/m³ (mice), 180 mg/m³ (rabbits, monkeys and cats) and 400 mg/m³ (guinea pigs) [1].

The concentration of hydrogen cyanide inhaled markedly affects the acute toxicity and is illustrated below in the rat (Table 2). The total dose of hydrogen cyanide leading to death is disproportionately larger at low concentrations than at high concentrations; consequently the time to death is disproportionately longer [1]. This effect has been attributed to the proportionally greater detoxification of cyanide at the lower delivery levels [32].
Table 2: Acute inhalation toxicity of hydrogen cyanide in rats

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>Medium lethal toxicity as LC\textsubscript{50} (mg/m\textsuperscript{3})</th>
<th>as total dose (mg/m\textsuperscript{3} min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 s</td>
<td>3,778</td>
<td>631</td>
</tr>
<tr>
<td>1 min</td>
<td>1,471</td>
<td>1,471</td>
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<tr>
<td>5 min</td>
<td>493</td>
<td>2,463</td>
</tr>
<tr>
<td>30 min</td>
<td>173</td>
<td>5,070</td>
</tr>
<tr>
<td>60 min</td>
<td>158</td>
<td>9,441</td>
</tr>
</tbody>
</table>

References

Ingestion
Oral LD\textsubscript{50} values in the range 3–4 mg/kg have been reported in the rat (using hydrogen, potassium or sodium cyanide) and slightly lower values in the rabbit (2–3 mg/kg). Signs of toxicity occur within minutes of dosing [1].

Dermal/ocular exposure
Dermal LD\textsubscript{50} values in the range 7–10 mg/kg have been reported following application of cyanides in aqueous solutions to rabbit skin. Toxicity is markedly greater following application to abraded skin [1].
Health Effects of Chronic/Repeated Exposure

Human data

General toxicity

Chronic exposure to cyanide may result in a range of neurological effects (similar to those described in the section on delayed effects following acute exposure above) and effects on the thyroid [3].

Thyroid effects following chronic exposure to cyanide have been reported in a number of studies on workers; effects include enlargement (goitre), functional changes and altered thyroid hormone levels [4]. Thiocyanate is generated in the detoxification of cyanide (see the kinetics and metabolism section above) and is known to disrupt iodine uptake by the thyroid; the observed effects on the thyroid may then be a result of increased thiocyanate and not due to direct hydrogen cyanide toxicity [3, 7].

Optic neuropathy has been observed in some cases of chronic cyanide toxicity, including atrophy, ambylopia and colour deficits [5]. Respiratory tract irritation, breathlessness, hoarse voice, chronic rhinitis and deafness have also been reported [5]. Some gastrointestinal and skin effects have been observed, which are likely to be due to cyanide’s irritant effects [3]. There is some debate as to whether the effects observed on repeat exposure to cyanide are truly due to repeat dose toxicity or the result of acute intoxication [3].

Inhalation

Data on chronic inhalation exposure to hydrogen cyanide is limited. In one study, workers exposed chronically (duration not specified) to 15 ppm hydrogen cyanide reported a range of effects, including fatigue, dizziness, headache, disturbed sleep, tinnitus and paraesthesia of the extremities [2]. Similar findings have been reported in another study which also included delayed memory and/or visual impairment in 31.5% of workers. The concentrations of hydrogen cyanide were not, however, specified [2]. Neurological features have been reported to persist on cessation of chronic exposure [2].

Ingestion

Limited data was identified for chronic exposure to hydrogen cyanide by ingestion in humans. It is be expected that repeated small exposures to cyanide over time would result in less toxicity than a single acute exposure of the same dose, owing to first-pass metabolism by the liver [7].

Genotoxicity

There is no in-vivo human data on which to assess the genotoxicity of hydrogen cyanide. However, hydrogen cyanide has no structural alerts for DNA damage and, taking into account the in-vitro data, it can be concluded that hydrogen cyanide does not have significant mutagenic potential.
Carcinogenicity

There is insufficient evidence to classify hydrogen cyanide as a carcinogen in humans and it has not been classified by the International Agency for Research on Cancer. Hydrogen cyanide is considered not to be a carcinogen.

Reproductive and developmental toxicity

There are no epidemiological studies on hydrogen cyanide poisoning during pregnancy, only case reports on outcomes in poisonings by cyanogenic compounds [9]. The data is insufficient to assess the risk to the fetus following maternal exposure [9]. Limited data suggests that cyanide can cross the placenta [4].

Animal and in-vitro data

Inhalation

Dogs were repeatedly exposed to 50 mg/m³ hydrogen cyanide (enough to give signs of acute toxicity) for 12.5 minute periods, with a break in exposure that was sufficient for nine of twelve dogs to recover from acute effects (the remaining three died) [3]. Subsequent histology suggested that repeated toxic exposures had led to severe brain damage [3].

Histology on rabbits exposed to 0.5 mg/m³ hydrogen cyanide continuously for up to 4 weeks showed no effects on the heart, lung and adjacent arteries [3].

Ingestion

There is limited data on the chronic ingestion of hydrogen cyanide in experimental animals. In a 2-year feeding study, rats were provided with food fumigated with hydrogen cyanide, with customised jars used to limit loss through volatilisation. Intakes in treated animals were 4.3 and 10.8 mg/kg bw/day. No treatment-related effects on survival or growth rate, signs of toxicity, haematological or histopathological changes in examined organs were noted; a no observed adverse effect level of 10.8 mg/kg bw/day was established [1].

Genotoxicity

There are limited studies on which to assess the genotoxicity of hydrogen cyanide. When tested on *S. typhimurium* strains TA1535, TA1538, TA98, TA100, TA97, TA102, hydrogen cyanide only gave a positive result in one case, TA100, without metabolic activation [3, 33, 34]. The weight of evidence suggests that cyanide is not genotoxic [1].

Carcinogenicity

In a dietary study, rats were fed every 2 days for 2 years on feed which had been exposed to hydrogen cyanide gas (the highest dose being around 3.5 mg/kg bw/day). No effects (including cancer endpoints) were seen; however, the study size was small and the endpoints tested were restricted; therefore it is not possible to draw any definitive conclusions regarding carcinogenicity [3].
Reproductive and developmental toxicity

Insufficient data is available on the reproductive or developmental toxicity of hydrogen cyanide [35].

References


Toxicological Overview


