CYANIDE - TOXGUIDE™

CHEMICAL AND PHYSICAL INFORMATION

Cyanides (multiple CASRNs) are a diverse family of compounds containing the highly reactive cyanide anion (CN^-). They are produced from both anthropogenic and natural sources. The cyanide compounds most commonly found in the environment include hydrogen cyanide, a colorless gas, and sodium cyanide and potassium cyanide, which are white or colorless solids. Most cyanide compounds have a faint almond odor.

Anthropogenic sources include releases of cyanide into the environment during the course of industrial usage or from smoke or vehicle exhaust containing the incomplete combustion products of nitrogen-containing organic polymers. Natural sources include numerous plant species that contain cyanogenic glycosides that can release hydrogen cyanide upon biodegradation or ingestion. The most common sources are pits and seeds of common fruits (e.g., apple, apricot, peach) and the cassava root (tapioca).

ENVIRONMENTAL FATE AND DETECTED LEVELS

Air: Outdoor air concentrations range from 0.33 to 0.76 ppbv.

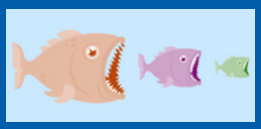
Hydrogen cyanide is a volatile compound that is released mainly to the atmosphere. It can potentially be transported over long distances before it is degraded by photochemically generated hydroxyl radicals. Precipitation is a negligible partitioning pathway.

Water: Cyanide is detected in only 22% of U.S. surface water samples; of these, <1% had cyanide concentrations >10 µg/L.

Cyanide in surface water is expected to be rapidly removed via volatilization. Cyanide in groundwater and less soluble cyanide compounds may persist longer and may also be removed via biodegradation. Treatment of water (chlorination) may result in formation of cyanogen chloride, which is less volatile than hydrogen cyanide.

Sediment and Soil: Levels near U.S. industrial sites ranged from 0.32 to 0.95 mg/kg.

At soil surfaces, volatilization as hydrogen cyanide is a significant loss mechanism for cyanides. In subsurface soil, sorption and aerobic or anerobic biodegradation are potential pathways.



Bioconcentration: Common forms of cyanide compounds are not expected to bioconcentrate.

GENERAL POPULATION EXPOSURE

General population exposure to cyanide is expected to be low.

Primary route of potential exposure: Oral

- Ingestion of contaminated water
- Ingestion of foods naturally high in cyanogenic compounds (e.g., cassava root)

Possible routes of potential exposure: Inhalation, Dermal

- Inhalation of contaminated ambient air and cigarette smoke
- Dermal and inhalation exposure may occur during household water use (e.g., showering, bathing, washing of dishes or clothes) if the water contains hydrogen cyanide

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POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

Workers involved in electroplating, metallurgy, pesticide application, firefighting, gas works operations, tanning, blacksmithing, metal cleaning, photoengraving, photography, cyanotype printing, or the manufacture of steel, adiponitrile/nitriles, methyl methacrylate, cyanuric acid, dyes, pharmaceuticals, or chelating agents may be exposed via:

- Inhalation of contaminated workplace air
- Direct skin contact with hydrogen cyanide vapor or liquid cyanide

Compared to the general population, the following groups may also have increased risk of exposure:

- Populations living near industrial releases or contaminated hazardous waste sites (via ambient air and/or groundwater contamination).
- Communities with high dietary consumption of non-processed foods high in cyanogenic compounds (e.g., tropical communities).

BIOMARKERS

Primary: Levels of cyanide and its metabolite, thiocyanite in blood and urine.

Alternatives:

2 Amino 2 thiazoline 4 carboxylic acid (ATCA), is a stable biomarker of cyanide in blood and urine. However, since it is produced via a minor metabolic pathway, it may not be a sensitive biomarker.

Exhaled levels of hydrogen cyanide are a proposed biomarker of inhalation exposure, particularly in fire victims.

Clinical: An almond like smell is often detectible in the breath of approximately 60% of poisoned individuals.

BIOMONITORING LEVELS

Geometric mean urinary thiocyanate levels (NHANES 2015 2016):

Non smoking adults:
0.817 mg/L (0.922 µg/g creatinine)

Smoking adults:
3.88 mg/L (3.91 µg/g creatinine)

TOXICOKINETICS

Absorption: Absorption is rapid through the lungs and gastrointestinal tract for gases and soluble salts. Absorption is slower through the skin.

Distribution: Cyanide is rapidly and widely distributed following inhalation exposure. Following oral exposure, the highest levels have been detected in the lungs and blood.

Metabolism: Cyanide is rapidly metabolized (plasma half-life of 20 minutes to 1 hour).

- Major pathway (~80%): The predominant metabolic pathway for cyanide is conversion to thiocyanate (SCN-) by a sulfur donor (e.g., rhodanese).

$$CN^- \longrightarrow SCN^-$$

- Minor pathways: Conversion to ACTA (or its tautomeric form 2-iminothiazolidine-4-carboxylic acid [ICTA]), incorporation into a 1-carbon metabolic pool, or combining with hydroxocobalamin to form cyanocobalamin (vitamin B12).

Excretion: Cyanide metabolites are excreted primarily in the urine (approximately 80% as thiocyanate), with small amounts excreted through the lungs.

Physiologically based pharmacokinetic (PBPK) models: Available to extrapolate internal cyanide doses to ingested or inhaled cyanide levels based on biomarker levels. PBPK models for interspecies and route-to-route dosimetry extrapolation have not been developed.

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HEALTH EFFECTS

It is well-established that death can occur following intentional or accidental cyanide poisoning via inhalation, oral, or dermal exposure.

Inhalation effects:
Occupational studies in humans suggest potential associations between low exposure levels and adverse respiratory, neurological, and thyroid effects.

In animals, data are limited. The only system affected at concentrations below lethal exposure levels was the respiratory system.

Oral effects:
A systematic review was conducted on sensitive effects following acute- (neurological) and intermediate-duration (thyroid, male reproductive) oral exposure in animals following drinking water or dietary exposure*.

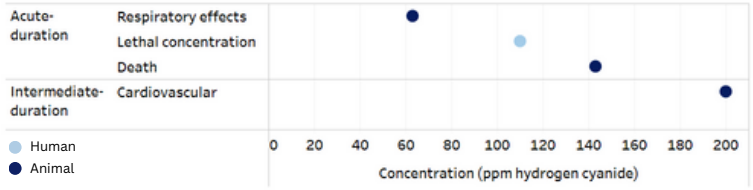
The nervous system is a known health effect of oral exposure to cyanide based on case reports and case series following high-level cyanide exposure, studies in human populations with high dietary cassava intake, and animal studies.

The thyroid is a presumed health effect of oral exposure cyanide based on studies in human populations with high dietary cassava intake, animal studies, and mechanistic data.

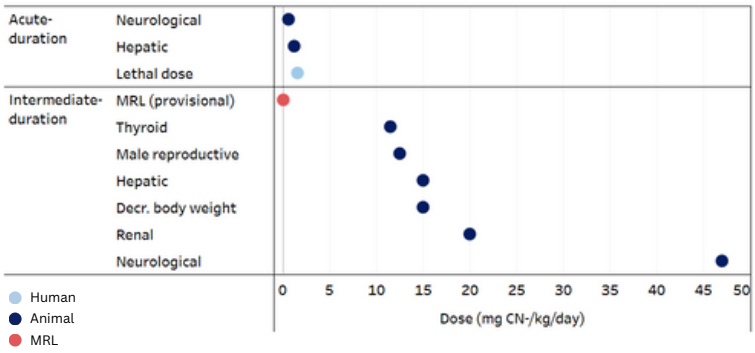
The male reproductive system is a suspected health effect of oral exposure to cyanide based on animal studies.

Health effects are determined by the dose (how much), the duration (how long), and the route of exposure.

Sensitive Effects of Inhalation Exposure to Cyanide**



Sensitive Effects of Oral Exposure to Cyanide**



*Animal studies considered for MRL development were limited to drinking water and dietary studies. Gavage studies were not considered for dose-response assessment because bolus administration may overwhelm detoxification processes in a manner not typical of the gradual exposures from dietary sources or drinking water expected for the general population (see toxicological profile for more details).

**Human studies in figures are limited to those with reliable exposure estimates.

MINIMAL RISK LEVELS (MRLs)

Acute: ≤14 days; Intermediate: 15 364 days; Chronic: ≥365 days

Inhalation: No inhalation MRLs were derived for any duration.

Oral:

- **Acute:** Not derived.
- **Intermediate:** A provisional intermediate duration oral MRL of 0.04 mg CN /kg/day was derived based on thyroid effects in rats.
- **Chronic:** Not derived.

CANCER

The U.S. Environmental Protection Agency has determined that there is inadequate information to assess the carcinogenic potential of hydrogen cyanide and cyanide salts. The U.S. Department of Health and Human Services and the International Agency for Research on Cancer have not evaluated the potential for cyanide or cyanide compounds to cause carcinogenicity in humans.

REFERENCE

Agency for Toxic Substances and Disease Registry (ATSDR). 2024. Toxicological profile for cyanide (draft for public comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Services. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=72&tid=19.