

Acetonitrile

Synonym: methyl cyanide

CAS: 75-05-8

MF: CH₃CN

MW: 41.05

Acetonitrile is a liquid at room temperature and has an ether-like odor.

Solubility: miscible with water, methanol, methyl acetate, acetone, ether, chloroform, and carbon tetrachloride [1].

Major use

Acetonitrile is used as a laboratory and industrial solvent; as a synthetic intermediate in the organic synthesis of acetophenone, alfa-naphtaleneacetic acid, thiamine, and acetamide. It is used to remove tars, phenols, and coloring matter from petroleum hydrocarbons that are insoluble in acetonitrile, and in the extraction of fatty acids from fish liver oils and other animal and vegetable oils. Acetonitrile is also used as an ingredient of acrylic nail remover [2].

Human toxicity

The major toxicity of acetonitrile is due to the *in vivo* formation of cyanide as a metabolite (see Metabolism and Toxicologic mechanisms).

Systemic cyanide toxicity has been reported following ingestion, inhalation and dermal exposure with acetonitrile. The onset of signs and symptoms depends on route, quantity, and duration of exposure, but is typically delayed over 2 to 13 h because of slow conversion to cyanide. Main signs and symptoms: a) cardiovascular: tachycardia, bradycardia, hypotension, cardiac arrhythmia, cardiac arrest, and death; b) respiratory: respiratory insufficiency, bronchial/chest tightness; c) neurologic: headache, dizziness, agitation, confusion, weakness, seizures, and coma; d) gastrointestinal: nausea and vomiting are common initial signs of poisoning [2].

Metabolic acidosis and lactic acidosis are common after ingestion of acetonitrile [2].

Ingestion of 1-2 g/kg of acetonitrile is lethal [2].

In the fatal case, the acetonitrile blood level on the third day following exposure was 11.8 mg/l [3]. In another study, post-mortem laboratory analysis revealed acetonitrile concentrations in blood samples of 310 and 560 mg/l, and 440 mg/l in the urine. The blood cyanide concentration was 4.4 mg/l [4]. Post-mortem blood acetonitrile concentrations averaged 710 mg/l (range, 560-800) in five individuals who died following either accidental ingestion (doses of 0.5-2.4 g/kg) or prolonged vapor inhalation (reviewed in [5]).

Threshold limit value (TLV) at workplace: 40 ppm (67 mg/m³) in the industrial atmosphere, which is approximately the odor threshold of the vapor [5].

Carcinogenicity: not classifiable as a human carcinogen [2].

Kinetic data

Kinetics: first order for acetonitrile (data from one case of poisoning) [6].

Absorption: acetonitrile and its metabolites are systemically absorbed.

In dog, absorption of cyanide was 95% [7].

Volume of distribution: 0.7 l/kg [5].

Distribution: in post-mortem cases acetonitrile was found in heart, liver, kidney, spleen and lungs (reviewed in [2]).

Passage of blood-brain barrier: restricted (AK*); acetonitrile was not found in the brain in post-mortem cases.

Plasma half-life: 36 h for acetonitrile and 44 h for cyanide (calculated from four concentrations in one case) [6].

Time to peak blood concentration: no data available.

Plasma protein binding: in dog plasma in vitro, cyanide is approximately 60% bound (reviewed in [8]). Human data are not available.

Elimination half-life: 32.4 h for acetonitrile and 15 h for cyanide, following an ingestion of 5 ml of 95% acetonitrile [8]. Acetonitrile and its metabolites thiocyanate and free cyanide (see below) are eliminated via kidney.

Metabolism and excretion

Acetonitrile is an organocyanide that is slowly metabolized to organic cyanide in a reaction forming hydrogen cyanide [9]. Acetonitrile undergoes a two-step activation reaction mediated by liver cytochrome P450. This reaction results in the formation of cyanohydrin which undergoes peroxidation releasing hydrogen cyanide, and then cyanide is liberated by catalase. Cyanide is also metabolized to thiocyanate by the specific enzyme rhodanase, which mediated oxidation of endogenous thiosulphate to thiocyanate, that is largely excreted in the urine (reviewed in [6, 7]). All metabolites of acetonitrile are toxic; when the level of serum thiocyanate exceeds 120 mg/l, the magnitude and severity of the toxic responses increased [10]. Thiocyanate is less toxic compared to cyanide [7].

Excretion: thiocyanate and partly cyanide are excreted via urine; a substantial portion of cyanide is exhaled unchanged in the breath [5].

Toxic metabolites of acetonitrile: cyanide, hydrogen cyanide, and thiocyanate.

Toxicological mechanisms

Metabolic release of cyanide following absorption of acetonitrile is most likely responsible for toxicity. Cyanide inhibits enzymes such as succinic dehydrogenase, superoxide dismutase, carbonic anhydrase, and cytochrome oxidase.

Toxic effect of cyanide on *cytochrome c oxidase* is best studied. Cytochrome c oxidase is an iron-containing respiratory enzyme essential for oxidative phosphorylation and aerobic energy production. Cyanide induces cellular hypoxia by inhibiting the aa₃ component of cytochrome oxidase, and by blocking the respiratory chain in mitochondria [11].

Lactate production is increased as the result of anaerobic energy production in an attempt to maintain ATP synthesis. Pyruvate can no longer enter the tricarboxylic acid cycle (the Krebs' cycle) from the glycolytic pathway and is converted to lactate.

Cyanide can produce nerve injury. Hypothetical mechanisms suggest that cyanide increases intraneuronal calcium levels and affects lipid peroxidation (reviewed in [7]).

Target organ: CNS (?).

References

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