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Cyanide Level in the Environment and Occupational Settings: A Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author MNA designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors MYA, MN and MYA managed the search strategy, literature searches and wrote the first draft of the manuscript. Authors KMA, TA, MSH, MAN, BF and MS read and approved the final manuscript.

Review Article

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ABSTRACT

Aims: To assess the safe level of cyanide in environment and occupational related activities.
Methodology: Systematic literature search of the related articles were carried out using the following databases: PubMed, Science Direct, Scopus, Cochrane Library, Science Citation Index Expanded, CINAHL and Ovid. Results were screened for duplicates and assessed for eligibility. Relevant data were extracted and assessment was conducted based on adverse events associated with cyanide exposure in the ambient air.
Results: A total of 8 related studies and 1 unpublished study from US EPA were identified for this review. Only 7 studies mentioned the hazardous level of cyanide with the symptoms in different occupational activity. The hazardous level varies from the lowest of 30µg/m^3 to 17 mg/m^3.
Conclusion: There is no adverse effects of exposure to the low concentrations of cyanide that are generally present in the general environment (<1 µg/m^3 in ambient air).

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However, exposure of HCN at a concentration of >1,000 μg/m^3 in ambient air for at least 5 years may show symptoms of toxicity and >7,000 μg/m^3 may show signs of thyroid enlargement. As for at least 8.5 months or 24-hour in a confined area of 27m^3 at a concentration of > 17,000 μg/m^3 or >8,000 μg/m^3 respectively may lead to death.

Keywords: Cyanide; hydrogen cyanide; environment; ambient air; occupational; exposure.

1. INTRODUCTION

Cyanide exists in several forms, including hydrogen cyanide (HCN), cyanogen, cyanogen halides, soluble potassium and sodium cyanide salts, and insoluble mercury, copper, gold, and silver salts [1]. Cyanide compound in the environment originate mainly from a variety of industrial processes, such as the electroplating industry, blast furnaces, coke-producing plant and gas works [2]. Cyanide is used for extraction of gold and silver from their ores, in electroplating, case-hardening of steel and in photographic processes [3]. The extraction of gold from low-grades ores, a solution of sodium cyanide is trickled over pads of crushed ores. During this operation, small quantities of hydrogen cyanide gas may escape to the ambient air. Cyanide has been used as a poison for thousands of years where the effects of high dose of cyanide are quick and death occurs within minutes [4].

Cyanide salts (for examples potassium or sodium cyanide) react readily with acid or water to form HCN, which is highly poisonous by all routes of administration.

Cyanide-containing substances also occur naturally in the fruits, seeds, roots, and leaves of numerous plants, and are released to the environment from natural biogenic processes from higher plants, bacteria, and fungi. Cyanide producing plants includes almonds, apricots, bamboo, bean sprouts, cassava, cashews, cherries, lentils, olives, potatoes, sorghum, and soybeans [5]. However, an estimate of the amount of cyanide released to the environment from natural biogenic processes is not available [6].

The cyanide ion is readily absorbed from the lungs, the gastro-intestinal tract, and even through the intact skin. Toxic cyanides are mostly metabolized approximately 80% in the body to non-toxic thiocyanates through sulfuration with thiosulfate by mitochondrial rhodanese and excreted in the urine. In the physiological condition, blood cyanide is mainly distributed in erythrocytes, tightly binding to met-haemoglobin.

Theoretically, 1 g of met-haemoglobin can bind approximately 60 μmol of HCN and that 1 L of erythrocytes should be able to bind approximately 50–200 μmol (1.4–5.4 mg) HCN at physiological levels of methemoglobin (0.25–1%) [7]. This readily reversible reaction is considered to be a naturally detoxification pathway for low levels of cyanide in the blood [8].

The first phase of treatment for acute cyanide poisoning consists of administering amyl nitrite or sodium nitrite to cyanide-poisoned individuals [9]. Amyl nitrite and sodium nitrite are oxidants that increase the conversion of hemoglobin to methemoglobin, thus providing a sink for cyanide to reduce interaction with tissue cytochrome c oxidase. Under this treatment approach, cyanide is then detoxified by slow release from cyanomethemoglobin and cytochrome c oxidase and subsequent conversion by the enzyme rhodanese to thiocyanate (SCN^-), which has much lower acute toxicity than cyanide. High levels of thiocyanate are also found in saliva, and the physiological role of salivary thiocyanate may be the antibacterial effect of hypothiocyanate which is produced by the action of salivary

peroxidases from thiocyanate. Plasma thiocyanate levels provide a more suitable index of the cyanide exposure than blood cyanide levels. The metabolic pathway for cyanide is described in Fig. 1. The regression relationship between thiocyanate in the urine and the concentration of cyanide in air is represented by the equation M = 0.65 C (where M = thiocyanates (mg) in total amount of urine excreted in 24 hours and C = concentration of cyanides in air (ppm)) [11].

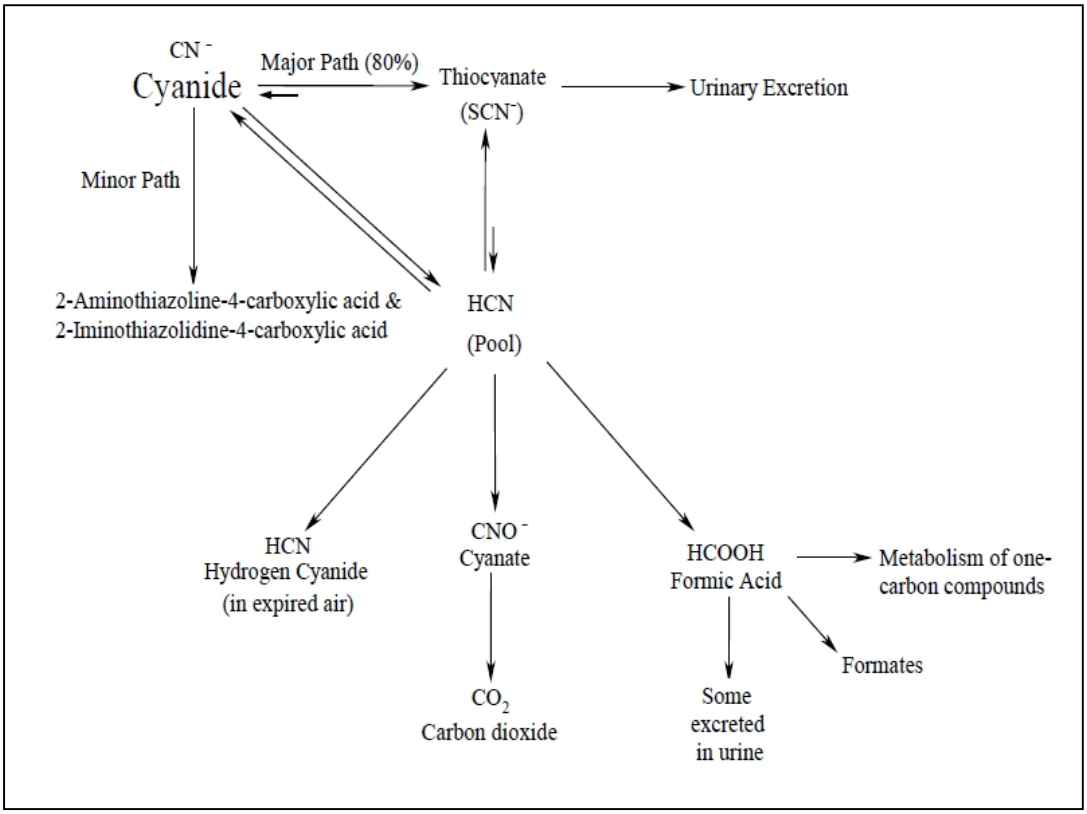

Fig. 1. Metabolic Pathway for Cyanide [10]

Sodium thiosulfate administered as the second phase of treatment for acute cyanide poisoning accelerates detoxification by supplying a sulfur substrate for the reaction. Other substances used to detoxify cyanide include hydroxycobalamin (vitamin B12a), an antidote used outside the United States that binds cyanide to form cyanocobalamin (vitamin B12), and cobalt edetate, which is used as an antidote in some countries due to the high affinity of cobalt for cyanide [9].

Levels of significant exposure of cyanide for each route and duration showing no-observed-adverse-effect levels (NOAELs) or lowest observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. However, according to ATSDR (2006), the agency has established guidelines and policies to classify these end points. This approach will help to distinguish between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered important because it helps to identify levels of exposure at which major health effects start to appear. LOAELs or

NOAELs also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health [7].

The toxic effects involve inhibition of several metals –containing enzymes. The critical interaction appears to be in the mitochondria where the inactivation of cytochrome C oxidase, an end-chain enzyme of cellular respiration, consequently causing cellular anoxia. The cardiovascular, respiratory, and central nervous systems are primarily affected. It also competes with iodine in the thyroid gland.

Workers with chronic exposure to hydrogen cyanide experienced subjective symptoms of central nervous system toxicity, such as headache, weakness and changes in taste and smell. Several of them had an enlarged thyroid gland. The US Environmental Protection Agency (US EPA) has established a reference concentration (RfC) of 3μg/m^3 (2.67 ppb) [12] in order to protect against the toxic effects of long term inhalation exposure to hydrogen cyanide in air. Cyanide poisoning is relatively uncommon in urbanized area, so high index of suspicion is important for early detection, diagnosis and treatment [13].

According to US Occupational Safety and Health Administration (OSHA) requires employers of workers who are occupationally exposed to cyanide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 10 ppm (11 mg/m^3) as cyanide. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls [14]. US National Institute of Occupational safety and Health (NIOSH) recommends a 10-minute ceiling of 5 mg/m^3 for cyanide in compounds such as sodium cyanide or potassium cyanide [15].

2. MATERIALS AND METHODS

2.1 Search Strategy

A comprehensive search strategy was developed to search PubMed, Science Direct, Scopus, Cochrane Library, Science Citation Index Expanded, CINAHL and Ovid databases. A search was conducted for articles in the English language published from 1970 until present which include access to MEDLINE, and citations for selected articles in environmental health journals not included in MEDLINE. The search strings used were Medical Subject Headings (MeSH) and key text terms to produce the results. Table 1 lists the search terms and parameters applied. We also used a limit function in PubMed to exclude letters, editorials and commentaries.

We conducted a title and abstract review of these studies applying inclusion and exclusion criteria developed by the authors based on study type and treatment type. These inclusion and exclusion criteria are presented in Table 2.

The review of title and abstracts yielded a total of 11 potentially relevant studies. Full text articles for these studies were ordered and carefully reviewed and a precise classification of each of the articles was performed. After the full text review, a total of 8 unique, relevant studies were identified for inclusion in this study. However, there was an additional of unpublished study from US EPA (2010) to make a total of 9 studies in this review, as presented in Fig. 2.

Table 1. PubMed literature search strategy

Concept	Search string	Hits
Cyanide environment	("cyanides"[MeSH Terms] OR "cyanides"[All Fields] OR "cyanide"[All Fields]) AND ("environment"[MeSH Terms] OR "environment"[All Fields])	3428
Cyanide water	("cyanides"[MeSH Terms] OR "cyanides"[All Fields] OR "cyanide"[All Fields]) AND ("water"[MeSH Terms] OR "water"[All Fields] OR "drinking water"[MeSH Terms] OR ("drinking"[All Fields] AND "water"[All Fields]) OR "drinking water"[All Fields])	1967
Cyanide food	("cyanides"[MeSH Terms] OR "cyanides"[All Fields] OR "cyanide"[All Fields]) AND ("food"[MeSH Terms] OR "food"[All Fields])	1438
Cyanide occupational	("cyanides"[MeSH Terms] OR "cyanides"[All Fields] OR "cyanide"[All Fields]) AND occupational[All Fields]	306
Cyanide soil	("cyanides"[MeSH Terms] OR "cyanides"[All Fields] OR "cyanide"[All Fields]) AND ("soil"[MeSH Terms] OR "soil"[All Fields])	248
Cyanide ambient air	("cyanides"[MeSH Terms] OR "cyanides"[All Fields] OR "cyanide"[All Fields]) AND (ambient[All Fields] AND ("air"[MeSH Terms] OR "air"[All Fields]))	15

Table 2. Inclusion/exclusion criteria for abstract / title review

Included study types
~ Systematic review
~ Clinical trial
o Randomized controlled trial
o Controlled clinical trial
o Uncontrolled clinical trial
~ Epidemiology study
o Cohort study
o Case control study
o Cross sectional study
o Follow up study
o Evaluation study
o Case report study
Excluded study types
~ Non-systematic reviews
~ Guidelines
Included type of exposures
~ Ambient exposure
~ Air pollution
~ Fire
~ Smoke
Excluded type of exposures
~ Other type of exposures

Table 3. Summary of 9 studies for HCN level

No.	Concentration of Cyanide	Method	Symptom	Remark
1.	17 mg/m^3	24-h measurement 1 day after the factory had been closed	Eye irritation, fatigue, dizziness, headache, disturbed sleep, ringing in ears, paraesthesia of extremities, nausea, vomiting, dyspnoea, chest pain, palpitation and weight loss	36 former male workers of silver reclaiming facility in USA in 1983. Blanc P, Hogan M, Mallin K, Hryhorczuk D, Hessl S, Bernard B (1985) Cyanide intoxication among silver-reclaiming workers. Journal of the American Medical Association, 253:367–371.
2.	Between 1.11 and 4.66 "cyanide-hours" (mg/ m^3 × h).		An increase in the overall number of symptoms (headaches/heaviness in head, giddiness, lacrimation, itching of eyes, congestion of eyes, coated tongue) -found in 12.5% of the exposed workers. "Moderate" impairment in health-related scores showed an increase (no statistical analysis) at exposure levels in excess of 2.5 mg/ m^3 × h in one factory and 4.35 mg/ m^3 × h in the other, while findings classified as "diseased" were observed at levels in excess of 2.9 mg/ m^3 × h.	Occupational exposure (5–19 years) of 111 workers and 30 non-exposed referents to hydrogen cyanide were studied in two large case-hardening and electroplating facilities in India. Chandra H, Gupta BN, Mathur N (1988) Threshold limit value of cyanide: a reappraisal in Indian context. Indian Journal of Environmental Protection, 8:170–174
3.	The atmospheric cyanide concentrations ranged from 0.2- 0.9 mg/m^3 and breathing zone from 0.1-0.2 mg/ m^3 with a mean of 0.15 mg/m m^3.	Venous blood samples were taken at the end of the work shift, and urine samples were collected at the start of the work shift and every 2 hours throughout the shift. Smoking and non-smoking workers were considered separately for both the exposed workers and the 20 non-exposed control workers that were matched for age, sex, and socioeconomic status.	Experienced subjective signs of cyanide toxicity. Blood and urine cyanide and thiocyanate concentrations were elevated in the exposed workers as compared with the controls. The authors reported that the exposed workers complained of "typical symptoms" of cyanide toxicity, but these data were not presented. No effect levels were designated in this study.	23 workers chronically exposed to cyanide fumes in an electroplating and case-hardening factory. Chandra H, Gupta BN, Bhargava SK, Clerk SH, Mahendre PN (1980) Chronic cyanide exposure: a biochemical and industrial hygiene study. Journal of Analytical Toxicology, 4:161–165

No	Concentration of Cyanide	Method	Symptom	Remark
4.	The breathing-zone cyanide concentrations ranged between 0.01 and 3.6 mg/m^3	Cyanide workers were examined before and after a block of six shifts in the spring and autumn, while diphenyl oxide workers were seen during their shifts.	Haemoglobin and lymphocyte levels tended to be higher in the cyanide workers, although neither was pathologically raised, and no relationship between exposure and haematological findings was found. The absence of a dose–response relationship would suggest that cyanide work was not causal. Thyroid function was normal in both groups, and no goitres were found. Vitamin B12 and T4 levels revealed no differences between cyanide and diphenyl oxide exposure groups.	Potassium cyanide salt production workers from plants in a facility in the United Kingdom. Sixty-three employees from these cyanide salt plants were compared in a controlled study with 100 employees from a diphenyl oxide plant in the same facility. Leeser JE, Tomenson JA, Bryson DD (1990) A cross-sectional study of the health of cyanide salt production workers. Macclesfield, ICI Central Toxicology Laboratory. (*In press*)
5.	Mean serum thiocyanate concentration was 316 ± 15 umol/L	Thirty-five non-exposed workers who had worked outside the manufacturing building were matched with the exposed workers for age and dietary habits.	Mean serum thiocyanate concentration of the 35 non-smoking exposed employees was 316 ± 15 umol/L, which was significantly higher ($P < 0.01$) than that of the control subjects (90 ± 9.02 umol/L). Cyanide exposure resulted in a decrease of serum T4 and T3 concentrations ($P < 0.05$) and an increase in TSH concentration ($P < 0.05$) compared with the control subjects.	A study of 35 male cyanide workers (of 201 male workers) who had worked in an Indian electroplating process of a cable industry for more than 5 consecutive years. Banerjee KK, Bishayee B, Marimuthu P (1997) Evaluation of cyanide exposure and its effect on thyroid function of workers in a cable industry. Journal of Occupational Medicine, 39:255–260
6.	A simulation study revealed HCN and sulphur dioxide in the ambient air at 10 ppm and 7.5 ppm, respectively	A total of eight patients entered into a 27 m^3 well containing pickled bamboo shoots and immediately lost consciousness.	After rescue, two patients developed cardiac arrest, metabolic acidosis and died. Four other patients suffered metabolic acidosis, but recovered after supportive care. The remaining two regained consciousness and recovered soon after the event. Ambient air study and cyanide content of bamboo shoots helped confirm the diagnosis.	Sang-A-Gad P, Guharat S, Wananukul W. Clin Toxicol (Phila). 2011 Nov;49(9):834-9. doi: 10.3109/15563650.2011.618456. Epub 2011 Oct 5. A mass cyanide poisoning from pickling bamboo shoots.

No	Concentration of Cyanide	Method	Symptom	Remark
7.	The breathing zone cyanide concentrations ranged from 4.2-12.4 ppm (4.63-13.69 mg/m^3), with a mean of 6.4-10.4 ppm (7.07- 11.45 mg/m^3), in the three factories.	Participants were prohibited cyanide-containing foods during the course of the investigation. Complete medical histories were taken, and medical exams were performed. Thyroid function (uptake of radiolabeled iodine) was assayed and urinary levels of thiocyanate were recorded. The men were exposed for a duration of 5-10 years, although one man was exposed for 15 years	Symptoms reported more frequently in the exposed workers included (in decreasing order of frequency) headache, weakness, and changes in the senses of taste and smell. Lacrimation, abdominal colic, and precordial (lower stomach) pain, salivation, and nervous instability occurred less frequently. Twenty of the exposed workers had thyroid enlargement to a mild or moderate degree, although there was no correlation between the duration of exposure and either incidence or degree of enlargement.	A study involved 36 male workers employed in the electroplating sections of three factories in Egypt. Cyanide exposure was from a plating bath that contained 3% copper cyanide, 3% sodium cyanide, and 1% sodium carbonate. Twenty normal male volunteers of the same age group and socioeconomic status who had no exposure to cyanide were chosen as controls. None of the exposed or control workers currently smoked cigarettes. El Ghawabi SH, Gaafar MA, El-Sharati AA, Ahmed SH, Malash KK, Fares R (1975) Chronic cyanide exposure: a clinical, radioisotope, and laboratory study. British Journal of Industrial Medicine, 32:215–219.
8.	Ranging from 0.26 – 1.86 ppb (parts per billion)	Air samples were collected at monitoring stations.		To assess emission of HCN during operation of extracting gold from low grade ores near a gold heap leach field. K.G. Orloff et al. (2006). Hydrogen cyanide in ambient air near a gold heap leach field: Measured vs. modeled concentrations. Atmospheric Environment; Volume 40, Issue 17, June 2006, Pages 3022–3029.
No	**Concentration of Cyanide**	**Method**	**Symptom**	**Remark**
9.			Decreased in pulmonary function in 24 workers exposed for a mean duration of 24 years.	Workers at a metal tempering. Chatgtopadhyay, BP; Gangopadhyay, PK; Alam, JSK. (2000) Long term effect of cyanide fumes exposure on ventilatory pulmonary function among the workers of a metal tempering plant. Biomedicine 20(3):207–218.

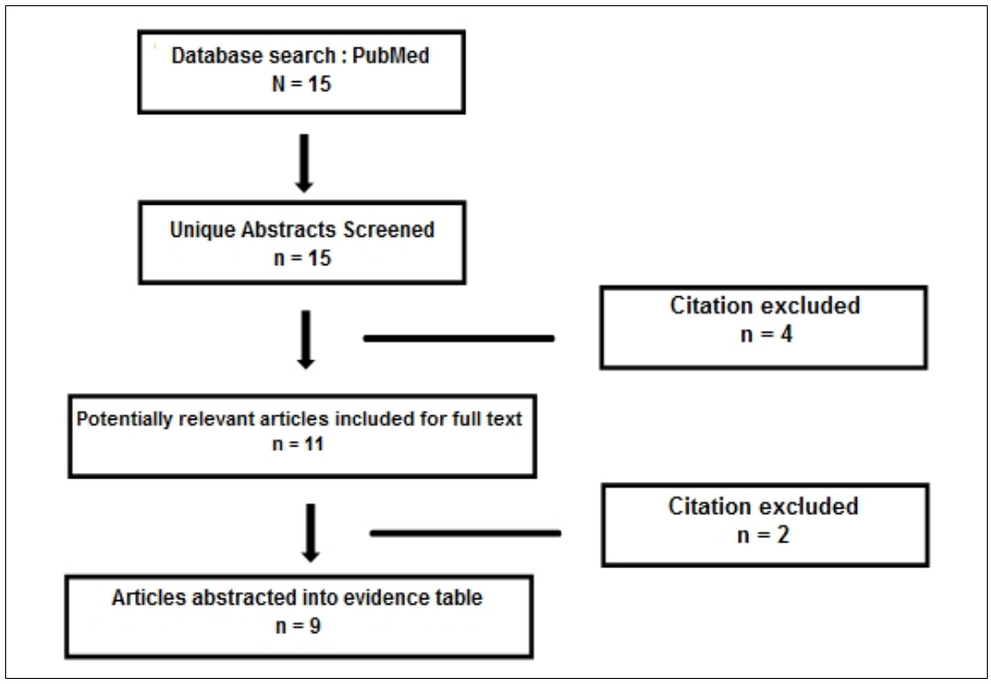

Fig. 2. Flow chart of search strategy

Although case reports and small case series studies are not typically included in an evidence review, we reviewed this study types for this report based on the assumption that there is little information on adverse events associated with cyanide exposure in the ambient air.

After classifying the study designs and extracting relevant data from the 9 included studies, they were summarized and presented in above Table 3.

3. RESULTS AND DISCUSSION

The aim of this paper was to review the safe level of cyanide in ambient air with 8 related published studies and 1 unpublished study between 1970 until present satisfying the criteria for inclusion in this review with 8 different concentration of cyanide under different circumstances. Limited data are available on the effects of long-term inhalation exposure to cyanide.

Majority of the population is exposed to very low levels of cyanide in the general environment. However, specific subgroups such as those involved in large-scale processing of cassava and those consuming significant quantities of improperly prepared foods containing cyanogenic glycosides, such as cassava, specialty foods such as apricot pits, and bitter almonds. Other subgroups include those in the vicinity of accidental or intended releases from point sources, active and passive smokers, and fire-related smoke inhalation victims. Workers may be exposed to cyanides during fumigation operations and during production and use of cyanides in many industrial processes such as electroplating, case-hardening of steel, and extraction of gold and silver from ores.

Cyanides are well absorbed through gastrointestinal tract or skin and rapidly absorbed via the respiratory tract. Once absorbed, it is rapidly and ubiquitously distributed throughout the body, although the highest levels are normally found in the liver, lungs, blood, and brain. No accumulation of cyanide in the blood or tissues following chronic or repeated exposure.

Exposure levels of 20–40 mg/m^3 showed slight effect in human and as the exposure increased to 50–60 mg/m^3, our body still can be tolerated without immediate or late effects for 20 min to 1 hour. However, 120–150 mg/m^3 may lead to death after 0.5–1 hour. 150 mg/m^3 is likely to be fatal within 30 min, 200 mg/m^3 is likely fatal after 10 min, and 300 mg/m^3 is immediately fatal. The lowest reported oral lethal dose for humans is 0.54 mg/kg body weight, and the average absorbed dose at the time of death has been estimated at 1.4 mg/kg body weight. Symptoms after severe acute intoxications may include neuropsychiatric manifestations and Parkinson-type disease. Cyanide from tobacco smoke has been found as a contributing factor in tobacco–alcohol amblyopia. Long-term exposure to lower concentrations of cyanide in occupational settings can result in a variety of symptoms related to central nervous system effects [12]. According to US Agency for Toxic Substances and Disease Registry (ATSDR) [7], smokers in general population could be exposed to 10 – 400

µg HCN per cigarettes compared to nonsmokers exposed to sidestream smoke could be exposed to 0.06 to 108 µg HCN per cigarettes [6].

The results of this review are presented in a framework and clearly show the concentration of HCN subjects and symptoms involved in the related studies. Out of 9, 3 of these studies provide evidence of effects on the thyroid. Occupationally exposed workers in these studies show that chronic exposure to low concentrations of cyanide can cause alterations of thyroid function and neurological symptoms [16,17,18]. Exposure to cyanide in occupational setting normally occurs primarily via inhalation, dermal and oral. Systemic toxicity by HCN is expected to occur at concentrations below those at which any direct respiratory tract effects is anticipated.

Banerjee et al. [16] conducted a study in electroplating factory that compare levels of the thyroid hormones T3, T4 and TSH in 35 male workers who had been exposed to cyanide via inhalation for >5 consecutive years to a randomly selected control group of 35 unexposed male workers matched for age and dietary habits. None of the subjects used tobacco products or had a prior history of thyroid disease. The results showed serum SCN- has elevated in workers compared to controls. A significant negative correlation between serum T4 and SCN– concentrations and a significant positive correlation between TSH and SCN– concentrations were observed. However, information was not provided on exposure levels; therefore, no NOAEL or LOAEL reported from this study.

Another selected study in this review was a silver-reclaiming facility in Illinois carried out by Blanc et al. [17]. The median time elapsed since last employment at the facility was 10.5 months; the median duration of employment was only 8.5 months. Environmental monitoring conducted the day after the plant was shut down found that the 24-hour time-weighted average (TWA) exposure was 15 ppm (16.6 mg/m3) HCN. According to US EPA (2010), there were multiple possible routes of cyanide exposure, including dermal exposure and contamination of food but the data do not support for the selection of a LOAEL for inhalation [12]. In addition, due to limitations of this study design and because El Ghawabi et al. [18] have reported lower levels for significant effects, this study was excluded for the derivation of the inhalation reference concentration.

Study done by El Ghawabi et al. [18] reported statistically significant in altered rates of iodide uptake by the thyroid, thyroid enlargement, and CNS symptoms in 36 workers exposed to HCN for 5–15 years in three electroplating factories. Mean cyanide air concentrations in the breathing zones of workers at each of the three plants were 10.4, 6.4, and 8.1 ppm (11.5, 7.1, and 8.9 mg/m^3, respectively, with a range of 4.2–12.4 ppm (4.6–13.7 mg/m^3) HCN. Based on the observed thyroid effects, the lowest mean concentration recorded in the three factories of 6.4 ppm (7.07 mg/m^3). HCN was designated as a LOAEL for thyroid enlargement and altered iodide uptake. A part from that, the study authors also found some co exposure of the workers to gasoline, alkali, and acid during the electroplating process.

An unpublished study done by Leeser et al. in 1990 involved of 63 male cyanide salt (NaCN, KCN, and $Cu(CN)_2$) production workers and 100 British workers as control from a diphenyl oxide (DPO) plant reported a LOAEL of 1 mg/m^3 cyanide for increased lymphocyte count and increased hemoglobin concentration. However, based on US EPA [12] a NOAEL for thyroid effects was not identified for this study based on the lack of measurement of sensitive thyroid parameters thus this study was not selected as the principal study.

Chandra et al. [19] reported on a group of 23 electroplating workers chronically exposed to average breathing zone concentrations of 0.15 mg/m^3 HCN. The authors noted that the workers complained of symptoms typical of cyanide poisoning, but provided no additional information on specific symptoms or further analysis. In the absence of information on measured effects, no NOAEL or LOAEL could be identified from this study, precluding its use in a quantitative risk assessment.

Effects of occupational exposure for 5 to19 years of 111 workers and 30 non-exposed referents to hydrogen cyanide were studied by Chandra et al. [19] in two large case-hardening and electroplating factories in India. The findings showed that workers were exposed between 1.11 and 4.66 “cyanide-hours” (mg/m^3 × h) and abnormal psychological test in delayed memory, visual ability, visual learning, and psychomotor ability was observed in 31.5% of the exposed workers. Increase in the overall number of symptoms such as headaches/heaviness in head, giddiness, lacrimation, itching of eyes, congestion of eyes and coated tongue were also observed in 12.5% of the exposed subjects. However, the authors did not provide the actual measurements of cyanide concentrations in the air [20].

Another study carried out by Chatgtopadhyay et al. [21]. Also suggests that chronic exposure to HCN in a metal-tempering plant may reduce pulmonary function in chronically exposed workers. Specifically, the authors observed decreased pulmonary function in 24

workers exposed for a mean duration of 24 years. This study however provided no information regarding the environmental exposure levels of the workers, and thus, no NOAEL or LOAEL could be identified, limiting this study's utility for risk assessment.

Mass cyanide poisoning from exposure to HCN in ambient air in a confined area was reported by Sang-A-Gad et al. [22]. HCN was produced from pickled bamboo shoot in a concrete well ($27m^3$) in a poorly ventilated plant. The well was partially filled with sliced bamboo shoot where they are pickled for a month and exhaust fan was not switched on. All 8 patients jumped into the well and immediately lost consciousness. Metabolic acidosis was the major clinical features in most of the patients. Two died at 13 and 30 hours after admission respectively of cardiac arrest. Meanwhile the rest were discharged on the 3rd day mostly with normal ventilation. Determination of cyanide level in whole blood was carried out 18 hours after the incident and the second deceased cyanide level was with 3.30 mcg/ml. This overlapped with the rest with 2.66 to 3.54 mcg/ml cyanide levels. Simulation study showed cyanide content of 39 to 196 mg/kg from sliced pickled bamboo shoots left over for 1 to 2 nights. Meanwhile HCN in ambient air in the well was 7.5 to 10 ppm of salted sliced bamboo shoots.

Measured HCN concentrations in ambient air near an active gold mining and cyanide heap leach field was carried out by Orloff et al. [23]. Five locations were selected that were 1200ft northwest, 1100 ft southeast, 1490 ft southeast and 2 residential areas that were located 2600 ft southeast (1/2 mile) near the leach field. Air samples were collected for 6 consecutive 8-h periods over 2 days. HCN concentrations in ambient air were determined using analytical measured method (detection level 0.2 ppb, 1 pbb = 1.12 $\mu g/m^3$). In addition, predicted air dispersion models (ISCST3 and AERMOD) were also used. Concentrations of HCN in ambient air using measured method were not detected to 1.86 ppb, in which not detected in residential areas and mostly not detected in northwest. The predicted HCN concentrations using ISCST3 were 0 to 2.48 ppb and using AERMOD were 0 to 0.90 ppb. None of the concentrations exceeded the chronic exposure RfC and do not pose a public health hazard.

In another way, at medium concentration, it took several years before toxicity to be noticed in contrast to immediately at high concentration. Therefore these hazardous levels could be used as risk indicators in different occupational settings. Proper preparation could be made and these could reduce toxicity incidents in workplace significantly. The safe duration of exposure to cyanide could also be used as indicators of safe length of working in these settings. Suitable length could be determined to suit different occupational settings and should be imposed at each workplace at risk. The summary of HCN hazardous level based on 9 studies in this review is presented in Table 4.

General and specific codes of practice and management plans of cyanide have been developed to utilize the operational experience and technical expertise in formulating a single unified document for global application [6].

Table 4. Summary of HCN hazardous level based on 9 studies in this review

Hazardous level	Environment	Occupational activity	References
0.03 -1.03 mg/m^3 (or 30-1,030 $\mu g/m^3$)	5 -15 years (No relationship between exposure and findings)	Cyanide salt (NaCN, KCN, and $Cu(CN)_2$) production workers	Unpublished report done by Leeser et al., in 1990 (US EPA, [12])
0.15 mg/m^3 (or 150 $\mu g/m^3$)	Chronically exposed (Symptoms)	Electroplating and case hardening factory	Chandra et al., [19]
0.26 – 1.86 ppb (1 pbb = 1.12 $\mu g/m^3$) (or 0.29-2.08 $\mu g/m^3$)	Air samples were collected for 6 consecutive 8-h periods over 2 days (Below chronic exposure RfC)	An active gold mining and cyanide heap leach field	Orloff et al., [23]
1.11 – 4.66 mg/m^3 x h. (or 1,110-4,660 $\mu g/m^3$x h) moderate>2.5-4.35 mg/m^3 x h (or 2,5000-4,350 $\mu g/m^3$ x h), diseased>2,9 mg/m^3 x h (or 2,900 $\mu g/m^3$ x h).	5-19 years (Increased symptoms)	Case hardening and electroplating facilities	Chandra et al., [19]
7.5 – 10 ppm (or 8,437.5-11,250 $\mu g/m^3$)	Immediately in a 27 m^3 unventilated well. (Cardiac arrest to lost consciousness)	Industrial bamboo shoots pickling	Sang-A-Gad et al., [22]

Table 4. Continued…..

6.4– 10.4 ppm; 7.07 – 11.45 mg/m^3 (or 7,070-11,045 µg/m^3)	5-10 years (Thyroid enlargement)	Electroplating bath	El Ghawabi et al., [18]
15 ppm; 17 mg/m^3 (or 17,000 µg/m^3)	8.5 – 10.5 months (Death to symptoms)	Silver reclaiming factory	Blanc et al., [17]
Not available	More than 5 years (increased serum T4, T3 and TSH concentrations)	Electroplating process of cable industry	Banerjee et al., [16]
Not available	24 workers exposed for a mean duration of 24 years (Decreased pulmonary function)	Metal-tempering plant	Chatgtopadhyay et al.,[21]

4. CONCLUSION

Our findings showed that there is no adverse effects of exposure to the low concentrations of cyanide that are generally present in the general environment (<1 µg/m^3 in ambient air). Exposure to HCN in the ambient air for at least 5 years at a concentration of >1,000 µg/m^3 may show symptoms of toxicity and >7,000 µg/m^3 may show signs of thyroid enlargement. Meanwhile exposure to HCN in the ambient air for at least 8.5 months or 24-hour in a confined area of 27m^3 at a concentration of > 17,000 µg/m^3 or >8,000 µg/m^3 respectively may lead to death.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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