
Chronic cyanide exposure: a clinical, radioisotope, and laboratory study

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El Ghawabi, Samir H., Gaafar, Mohamed A., El-Saharti, Aida A., Ahmed, Soheir H., Malash, Kamelia K., and Fares, R. (1975). *British Journal of Industrial Medicine*, 32, 215-219. **Chronic cyanide exposure: a clinical, radioisotope, and laboratory study.** The effect of chronic cyanide exposure in the electroplating sections of three factories employing 36 workers was studied and compared with a control group. The concentration of cyanides to which the workers were exposed was measured. The regression line showing the relationship between thiocyanates in urine and the concentration of cyanides in the air was plotted. Increased percentages of haemoglobin and lymphocyte count were present in all exposed workers, in addition to punctate basophilia in 28 workers. Cyanmethaemoglobin was found to be characteristic. Apart from other complaints, two men with psychosis similar to one case reported in therapeutic thiocyanate intoxication were found.

Twenty of the workers had thyroid enlargements to a variable degree and consistency, in two of whom it resembled lymphadenoid goitre. Thyroid¹³¹I uptakes at 4 and 24 hours were significantly higher than in the controls, while ¹³¹PBI was unchanged. The reason for this iodine deficiency-like action is discussed.

The industrial risks of cyanides are widely spread. Cyanides are used for extraction of gold and silver from their ores, in electroplating, for case-hardening of steel, and in photographic processes.

The cyanide ion is readily absorbed from the lungs, the gastro-intestinal tract, and even through the intact skin. It inhibits the cytochrome oxidase system in the mitochondria and competes with iodine in the thyroid gland. Cyanides are mostly metabolized in the body to thiocyanates and excreted in the urine. Thiocyanates were used extensively for the treatment of hypertension, but were abandoned because of their toxic side-effects, which included the occurrence of goitre. In contrast to thiocyanate poisoning, chronic cyanide intoxication has received little attention. It was first described by Souwers (1877/78). Other sporadic cases have been reported by Martin, 1888; Merzbach, 1899; Nolan, 1908; and Ullmann, 1926. Parmenter

(1926) in a review of the literature doubted whether chronic cyanide poisoning ever existed, but Saia, De Rosa, and Galzigna (1970) claimed that the chronic syndrome resulted from repeated subacute episodes.

Because of the paucity of information in the literature and controversy concerning chronic cyanide poisoning, we decided to investigate the subject and re-evaluate it.

Industrial process

The survey was carried out in the electroplating section of three factories. One of them is concerned with the production of cheap jewellery, the two others are engaged in the manufacture of spare-parts for cars and radio sets. Before plating, the articles are thoroughly cleaned with petrol to remove grease and dirt, and then scrubbed with solutions of strong soap and alkalis. They are next pickled in a

dilute solution of hydrochloric acid to remove scales, and rinsed in water. The articles are then wired together and lowered into a plating bath containing about 3% copper cyanide, 3% sodium cyanide, and 1% sodium carbonate. Finally, the articles are taken away from the plating baths and polished after unwiring.

Methods

Environmental study

Breathing-zone air samples were collected by means of a Midget impinger containing 0.1 N NaOH at the rate of 3 l/min for 15 minutes. The collected samples were analysed using the colorimetric method described by Elkins (1959).

Medical study

Altogether 36 male workers were interviewed. Details of present and past medical histories as well as their occupational history were obtained, and a thorough medical examination was performed. Special care was taken to detect any manifestation of thyroid disorder. A test dose of 15-20 μCi of ^{131}I was given to each worker on an empty stomach on the first day of the working week. Neck uptakes were counted at 4 and at 24 hourly intervals. Blood samples were taken after 72 hours, and the trichloroacetic acid precipitable fraction was assayed for ^{131}I (Silver, Fieber, and Yohalem, 1952). Blood samples were also analysed for haemoglobin concentration (Sahli), erythrocyte count, total and differential leucocyte counts, and for the spectroscopic detection of cyanmethaemoglobin (Miale, 1967). The laboratory investigations included determination of thiocyanates in a 24-hour specimen of urine by the pyrazolone method (Jacobs, 1967).

Twenty normal male control subjects of the same age group and of the same social and economic status as the exposed group were studied in the same manner. They had never been exposed to chemical hazards and were non-smokers, as all the exposed workers hated cigarettes. Certain types of food such as cabbage, almonds, and mustard were prohibited for both exposed and control groups during the period of investigation, as these may contribute to urinary thiocyanate concentration (Elkins, 1959).

Results and discussion

The ranges and mean concentrations (ppm) of cyanides in the breathing zones of the workers in the

TABLE 1
CYANIDE CONCENTRATION IN BREATHING
ZONES OF WORKERS IN THREE FACTORIES

Factory	No. of air samples	Concentration of cyanide ppm		
		Range	Mean	\pm SD
A	12	8.2-12.4	10.375	10.87
B	12	4.2- 8.8	6.416	6.85
C	12	5.9- 9.6	8.083	8.25

three factories surveyed are given in Table 1. From these results, it is apparent that environmental values in Factory A are higher than in the findings of the other two factories. This can be explained by the fact that Factory A is an old one and there is no local exhaust ventilation system. The threshold limit value for hydrogen cyanide, as issued in the Egyptian ministerial order No. 48 in 1967, is 10 ppm.

During the period of the study, there were 36 male workers in the three factories. Table 2 shows the number of workers exposed to cyanides in each factory and their distribution according to age and duration of exposure. All the workers, even those who were heavy smokers before working in these factories, hated the smell of cigarettes after employment. Such a finding made our laboratory investigations easier as smoking contributes to the amount of thiocyanate in urine.

Clinical aspects

Table 3 shows the incidence of different symptoms in the exposed workers compared with the control group. It is apparent that the most frequent symptoms were, in order of frequency, headache, weakness, changes in taste and smell, irritation of the throat, vomiting, and effort dyspnoea. Lachrymation, abdominal colic, and precordial pain were relatively less frequent. Disturbances of accommodation, salivation, and nervous instability were found in 8.33% of the exposed workers. These findings confirm those reported previously especially by Sfogliano (1955).

TABLE 2
DISTRIBUTION OF WORKERS ACCORDING TO AGE AND DURATION OF EXPOSURE

Factory	No. of workers	Age in years				Duration of exposure in years			
		30	30-	40-	50-	5	5-	10-	15-
A	9	5	1	1	2	5	2	1	1
B	12	2	5	5	—	2	8	2	—
C	15	4	8	2	1	7	4	4	—

TABLE 3
RELATIVE INCIDENCE OF SYMPTOMS AMONG EXPOSED WORKERS COMPARED WITH CONTROL GROUP

Symptoms	Exposed group		Control group	
	No. of cases (36)	%	No. of cases (20)	%
Headache	29	81	6	30
Weakness	28	78	4	20
Changes in taste and smell	28	78	—	00
Giddiness	20	56	3	15
Irritation of throat	16	44	1	5
Vomiting	16	44	1	5
Effort dyspnoea	16	44	2	10
Lachrymation	9	25	0	00
Precordial pain	7	19	1	5
Salivation	3	8	—	00
Disturbances of accommodation	3	8	—	00
Psychosis	2	6	—	00

Two workers suffering from psychotic episodes were encountered in Factory A. During the period of exacerbation they became confused, hallucinated, complained of vague abdominal pains, and had slurred speech. The symptoms were recognized early by supervisors and colleagues. The workers were isolated and they recovered within 36 to 48 hours. A similar condition has been reported by Barnett, Jackson, and Spaulding (1951) during the therapeutic use of thiocyanates in the treatment of hypertension but none, to the best of our knowledge, has been reported in relation to industrial exposure to cyanides. A syndrome that resembled acute poliomyelitis was described by Collins and Martland (1908), but it has never been confirmed (Polson and Tattersall, 1971).

During the survey no dermatitis was found in the exposed group. This is in agreement with the work of Schwartz, Tulipan, and Peck (1947) who found that hydrocyanic acid in the fumes of electroplating baths rarely causes dermatitis, but cyanide dusts frequently cause skin infection.

Thyroid and cyanates

None of the 36 workers examined showed any clinical manifestation of hypo- or hyperthyroidism. Twenty exposed workers (56%) had thyroid enlargement to a mild or moderate degree. The enlarged glands in 16 of them were soft and smooth. The remaining four workers had enlarged glands which were firm and slightly nodular, similar to those seen in lymphadenoid goitre. There was no correlation between the period of exposure and the incidence of enlargement, or size of the thyroid. Hunt (1904/05) found that cyanides in vegetables, especially cabbage, may be goitrogenic for animals. Some goitre cases after thiocyanate therapy for hypertension have been reported by Rawson, Hertz, and Means, 1943; Fahlund, 1942; Foulger and Rose, 1943; Potter, 1944. Such thiocyanate goitres have been described after four months or more of therapy at blood thiocyanate levels as low as 4.7 mg/100 ml resulting from daily ingestion of 0.3 g potassium thiocyanate. Elkins (1959), quoting from Hardy *et al.* (1950), calculated that the maintenance dose of

TABLE 4
¹³¹I THYROID UPTAKE AFTER 4 AND 24 HOURS AND 72 HOURS ¹³¹PBI

Workers	¹³¹ I Thyroid uptake (%)						72 hours ¹³¹ PBI		
	After 4 hours			After 24 hours			Range	Mean	SD
	Range	Mean	SD	Range	Mean	SD			
Exposed (36)	24-54	38.722 ± 6.63		30-57	49.33 ± 10.61		0.08-0.27	0.12 ± 0.039	
Controls (20)	10-40	22.42 ± 7.21		15-55	39.95 ± 4.80		0.05-0.27	0.11 ± 0.041	
Significance (P)	< 0.001			< 0.001			non-significant		

thiocyanate used therapeutically in hypertensive patients corresponded approximately to the daily exposure encountered in industry at the threshold limit value for hydrogen cyanide. However, apart from the two cases cited by Hardy *et al.* (1950), cyanide industrial goitre has not been reported.

At four hours ^{131}I thyroid uptake studies showed a much higher concentration of iodine in the glands of the exposed workers than in those of the control group ($P < 0.001$), Table 4. This rapid accumulation persisted throughout the 24 hours. The values for the 24-hourly uptake were higher than normal for our laboratory and in six cases were particularly high. All the controls fell within the normal range. The mean value for the 24 hours ^{131}I thyroid uptake in the exposed workers was also significantly higher ($P < 0.001$) than for the control group. On the other hand, the 72 hours ^{131}I PBI was within normal limits both in the control group and the exposed workers, and showed no significant difference between the two groups.

Rapid and persistent accumulation of iodine by the thyroid gland together with normal ^{131}I PBI values, as observed in the exposed workers, is a response similar to that reported in iodine deficiency goitre by Silver, Fieber, and Yohalem (1952). Cyanates are known to block iodine uptake and organification (the attachment of the organic iodine to tyrosine to form iodotyrosine) by the gland (Wollman, 1956), and it was expected that low uptake values might be obtained. As these workers were away from work on the two days preceding the test, the results obtained may be explained on the basis of acute cyanate withdrawal, as with other anti-thyroid agents where sudden cessation of the drug leads to rapid accumulation of iodine in the iodine-depleted gland.

Another possibility is that early in the exposure the induced iodine deficiency and consequent diminished thyroid hormone release led to increased secretion of thyrotropic hormone (TSH) with resultant increase in the gland size. On long exposure the metabolic enzymatic block was partially over-

come by the hypertrophied gland, and a steady state of functionally compensated but iodine-deficient goitre (wt/vol) was produced. It is interesting to note that Sanchez-Martin and Mitchell (1960) reported that animal thyroids rendered hyperplastic by TSH, metabolized thiocyanates more rapidly than those in controls and concomitantly the effectiveness of the cyanates on the glands was reduced.

Haematological findings

The results of blood examination of the exposed workers compared with those of the controls are shown in Table 5. The blood in exposed workers was nearly the same as in the control group except for significantly higher haemoglobin ($P < 0.001$) and lymphocyte count ($P < 0.001$), and the presence of punctate basophilia in 28 workers (78%). Punctate basophilia is not characteristic of cyanide exposure, and is encountered in other conditions such as lead poisoning and aniline intoxication. These findings confirm those reported by Gadzikiewicz and Luczak (1965). Cyanmethaemoglobin was not detected in the blood of the control group, thus its presence in the blood of the exposed workers was pathognomonic, especially as all of them were non-smokers and were prohibited certain types of food containing cyanates.

Urinary excretion of thiocyanates

The concentration of thiocyanate in urine increased towards the middle of the working week and became almost stationary during its last three days. This may be the reason why Maehly and Swensson (1970) were unable to correlate the blood levels of thiocyanate with the cyanide concentration in the air. The mean values of this metabolite in the second half of the working week during two successive months, were plotted against the mean values of the concentrations of cyanides in air during the same period. The regression line (Figure) showing the relationship between thiocyanates in urine and the concentration of cyanides in air is represented by the equation $M = 0.65 C$, (where M = thiocyanates

TABLE 5
HAEMATOLOGICAL STUDIES IN 36 EXPOSED WORKERS AND 20 CONTROLS

Blood	Workers		Controls	
	Range	Mean	Range	Mean
Haemoglobin g/dl	12.8-18.8	14.8	12.0-16.8	13.4
Red cell count ($10^{12}/l$)	3.7-5.9	4.4	3.2-5.1	4.1
Total leucocytes ($10^9/l$)	4.1-9.6	5.8	4.0-10.5	5.7
Eosinophils%	0-10	2.3	0-9	2.7
Basophils%	0-2	0.8	0-2	0.8
Neutrophils%	46-75	56.0	52-73	59.5
Lymphocytes%	32-50	42.0	26-40	30.15
Monocytes%	0-7	3.0	0-7	3.17

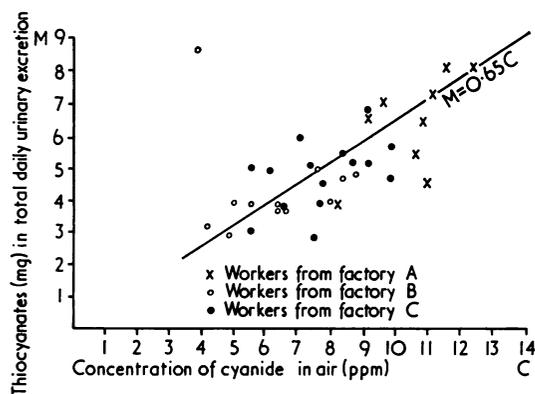


FIGURE Mean values of thiocyanate in urine of exposed workers during two successive months plotted against concentration of cyanide in air.

in total amount of urine excreted in 24 hours in mg and C = concentration of cyanides in air (ppm).

The concentration of urinary thiocyanates among the control group varied from 0 to 0.4 mg in the total daily urinary secretion, with a mean value of 0.11 mg.

From the above results it is evident that there is a potential and even real hazard to the health of workers who are exposed to cyanides. Environmental controls should therefore be adopted. These include both improvement of the general working site, and local exhaust ventilation for the removal of noxious air contaminants. If such measures are not available, personal protective equipment should be provided.

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