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Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure

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Objectives The goal of this study was to assess long-term neurobehavioral effects associated with low airborne concentrations of manganese in a ferroalloy plant.

Methods During a period of forced cessation of work (1 to 42 d) neurobehavioral performance on tests of simple reaction time, finger tapping, digit span, additions, symbol digit, and shapes comparison was evaluated for 58 workers exposed from 1 to 28 (mean 13, SD 7) years to manganese. Airborne manganese concentrations in total dust had been reduced in the last 10 years from 70—1590 $\mu g \cdot m^{-3}$ (geometric means in different areas) to 27—270 $\mu g \cdot m^{-3}$. For each worker, manganese concentrations in blood and urine were measured, and a cumulative exposure index was also calculated.

Results Blood manganese and urinary manganese ranged from 4 to 18 $\mu g \cdot l^{-1}$ (0.07 to 0.03 $\mu mol \cdot l^{-1}$) and from 0.7 to 7 $\mu g \cdot l^{-1}$ (0.01 to 0.13 $\mu mol \cdot l^{-1}$), respectively. Significant relationships were found between the blood manganese and urinary manganese levels and between these biological measures and the cumulative exposure index. Correlations were also found between the blood manganese level, the urinary manganese level, and the cumulative exposure index and the following tests: finger tapping, symbol digit, digit span, and additions. The correlation coefficients increased as the latency time after the cessation of exposure and work seniority increased.

Conclusions The results support the hypothesis that the neurobehavioral effects observed at exposure levels well below current occupational standards are related to manganese body burden, which is better reflected by the blood manganese level after the cessation of exposure.

Key terms central nervous system, neurotoxicity, occupational exposure.

Toxic effects of manganese (Mn) on the central nervous system have been well described by many authors in cases of exposure to high levels in mines (1, 2) and in intoxications occurring in a ferromanganese alloy factory, where an unrepaired ventilation control system caused exposure levels of more than 20 000 $\cdot \mu g \cdot m^{-3}$ (3).

However, clinical signs of manganese intoxication have been reported also at exposure levels below 5000 $\cdot \mu g \cdot m^{-3}$ (4, 5). In 1981 a group of experts of the World Health Organization (WHO) concluded that "signs of adverse effects on the CNS may occur at manganese concentrations in air ranging from 2000 to 5000 $\mu g/m^3$ [p 99]" (6). However, on the basis of a wide variation in individual susceptibility, WHO suggests that the minimum effect level is probably below 1000 $\cdot \mu g \cdot m^{-3}$ (6). In 1979 the American Conference of Governmental Industrial Hygienists (ACGIH) proposed a threshold limit value for a time-weighted average (TLV-TWA) of 1000 $\cdot \mu g \cdot m^{-3}$ for manganese fumes and in 1988 a TLV-TWA of 5000 $\mu g \cdot m^{-3}$ for manganese in inhalable dust. Recently, a TLV-TWA of 200 $\cdot \mu g \cdot m^{-3}$ was proposed for manganese in inhalable dust (7).

Therefore, in order to determine the lowest exposure level at which early effects on the central nervous system occur, neurobehavioral field studies have been carried out (8—12). In these studies, alterations of response speed, motor functions, and memory have been found at airborne manganese concentrations well below the ACGIH TLV-TWA of 5000 $\cdot \mu g \cdot m^{-3}$ for total dust. Exposure levels vary from 1000—4000 $\cdot \mu g \cdot m^{-3}$ in the

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German study by Siegl & Bergert (8) to 150 · μg · m^{-3} in the Swedish study by Iregren (10). In a more recent Belgian study (11), where the exposure level was approximately 950 · μg · m^{-3}, Roels and his colleagues also calculated a "permissible dose" below which no increase in effects on hand steadiness would result. Such a dose was estimated as a lifetime integrated exposure index to manganese of 3575 · μg · m^{-3} · $year^{-1}$ (for total dust) or 730 · μg · m^{-3} · $year^{-1}$ (for respirable dust). For a professional life of 40 years this permissible dose corresponds to approximately 90 · μg · m^{-3} for inhalable dust and to 18 · μg · m^{-3} for respirable dust.

Dose-effect and dose-response relationships between current and cumulative manganese indicators of exposure and neurofunctional effects have rarely been observed. This situation might partly be due to the lack of reliable biological indicators of manganese exposure. Still urinary manganese (U-Mn) levels seem to reflect mainly current exposure (9, 13), while blood manganese (B-Mn) concentrations could be related to manganese body burden (9, 14).

Interest in manganese hazards at low levels of exposure has increased in the last few years also because of possible environmental risks concerning the replacement of lead in gasoline with methylcyclopentadienyl-manganese-tricarbonyl (MMT) (15).

The objective of this study was to assess neurobehavioral functions in a group of manganese workers during a period of temporary cessation of exposure, therefore eliminating the influence of night shifts on behavioral functions and making the evaluation of eventual effects unrelated to recent exposure possible. In addition to response speed, motor function, and memory tests, more complex cognitive tests were examined. This study on early effects in the central nervous system was part of an environmental and biological monitoring program (16).

Subjects and methods

Study population

A group of 58 male workers from an Italian ferroalloy plant volunteered to participate in the study (only 2 of the total number of 60 workers contacted having refused to participate). On the basis of job duties and area of work in the plant, they were divided into the following three subgroups according to the degree of exposure: group A: high-exposure group, including 19 furnace workers; group B: medium-exposure group, including 19 workers occupied mainly with maintenance operations; group C: low-exposure group, including 20 clerks, foremen, or laboratory technicians. Group A alternated night and day shifts in the same workweek and were continuously occupied by furnace and casting duties.

The exposure to manganese in the plant had been reduced during the last 10 years through technical improvements of charging and exhausting systems. In the furnace area, airborne manganese concentrations in the total dust content decreased from 900—2600 · μg · m^{-3} (geometric mean 1590 · μg · m^{-3}) to 120—650 · μg · m^{-3} (geometric mean 270 · μg · m^{-3}); in the maintenance area, manganese decreased from 180—760 · μg · m^{-3} (geometric mean 319 · μg · m^{-3}) to 72—620 · μg · m^{-3} (geometric mean 124 · μg · m^{-3}); in the service areas from 30—150 · μg · m^{-3} (geometric mean 70 · μg · m^{-3}) to 9—40 μg · m^{-3} (geometric mean 27 · μg · m^{-3}).

Almost all of the manganese (around 95%) is in the form of manganese oxides (MnO_x) in the entire plant area, the respirable fraction of manganese particles being around 50—60%).

Number of school years, smoking habits, alcohol consumption, and general health status were assessed by a questionnaire and an interview. The information ascertained that the subjects were neither currently nor previously exposed to lead, mercury, or organic solvents. The subjects were screened for any neurological and neuropsychiatric illness and should not have taken medications that might have influenced their performance on psychometric tests.

Data collection

The subjects were examined during a period of temporary lay-off from work. The latency time after the cessation of exposure ranged from 1 to 42 d. Half of the workers (N = 29) were tested in the first 13 d, and the others later. The survey was conducted in the plant medical facility as follows: blood and urine sampling, administration of questionnaire, performance of neurobehavioral tests.

Air sampling

Air sampling for the measurement of airborne manganese concentrations was performed approximately one month before the beginning of the lay-off period. The exposure levels to airborne manganese concentrations in total dust were determined by personal and stationary sampling. The analyses were performed by electrothermal atomic absorption spectrometry (VARIAN SPECTRAA 400 Zeeman).

A cumulative exposure index (CEI) was calculated for each subject, multiplying the average annual airborne manganese concentration in respirable dust characteristic of each job by the number of years in which this activity was performed. The index was expressed in micrograms of manganese per cubic meter of air times duration of exposure in years.

Biological analyses

After a previous check of all the sampling materials for lack of metal contamination, a venous blood sample of 5 ml and a spot urine sample were collected immediately before the testing procedure, kept at 4°C and analyzed immediately. B-Mn and U-Mn were determined by electrothermal atomic absorption spectrometry coupled with a Zeeman effect background correction system (VARIAN SPECTRAA 400).

Neurobehavioral examinations

The psychometric test battery comprised seven tasks from the computer-administered test battery SPES (Swedish Performance Evaluation System) (17). The following tests were administered during a session of approximately 45 min with the use of a portable PC Toshiba T3200. The overall examination, which was carried out by three well-trained investigators, took approximately 1 h per subject.

Simple reaction time is a 6-min sustained attention task measuring response speed to an easily discriminated but temporally uncertain visual signal. The task is to press a key on the keyboard as quickly as possible when a bright square is presented on the display. Performance level is evaluated as the mean latency of 80 stimuli, and the variability is calculated as the standard deviation of these latencies.

Finger tapping measures the maximum speed of repetitive finger movement. Performance is evaluated as the mean number of taps during three 10-s trails for each hand (dominant/nondominant).

Digit span is a traditional test of short-term memory capacity. A series of digits are presented on the screen, and the task is to reproduce the series on a keyboard. Memory capacity is estimated from the performance on a minimum of 12 series of digits.

Additions measures the speed of simple mental arithmetic operations. Three horizontally placed digits are presented on the screen, and the task is to add them as quickly as possible and to enter the sum on the key board. The mean response latency is calculated from 40 trials.

Symbol digit is a revised version of a traditional test of perceptual speed. In this coding task digits should be paired to symbols according to a key. Performance is evaluated as the mean latency for 54 pairings.

Shapes comparison is a complex reaction time test. Each stimulus is a geometric figure circumscribed by another. The task is to respond as quickly as possible only when the figures are the same shape. Performance is evaluated as the mean latency to 48 critical stimuli.

Vocabulary is a test of verbal understanding comprising 45 stimuli. In this test the task is to indicate, among five alternatives, the correct synonym for a key word. The performance measure is the number of correct choices.

Statistical methods

An analysis of variance was performed to compare the mean values between the three different subgroups. In the testing for dose-effect relationships, the entire population of 58 subjects was considered, and the Pearson's correlation coefficient was calculated. Variables with a skewed distribution were logarythmically transformed to approximate the normal distribution. Analyses of multiple regression were also performed to control the influence of age, alcohol consumption, and educational level on certain variables. The level of statistical significance applied was $P = 0.05$.

Results

Population characteristics

In table 1 the principal characteristics of the workers in the three groups are reported according to the degree of exposure. The populations were similar regarding age, number of school years, smoking habits, and alcohol consumption, while a difference was noted in the vocabulary test score, for which the workers with low exposure showed generally better verbal abilities. This difference in the verbal test was not attributable to manganese expo-

Table 1. Characteristics of the three subgroups with different degrees of exposure.

Group	Age (years)			Exposure (years)			Education (years)			Vocabulary score			Smoking habit index			Alcohol consumption (g/day)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Low exposure (N = 19)	39.4	8.1	20—53	12.9	6.0	2—28	7.0	1.8	5—13	47.0	12.0	21—68	2.4	1.0	1—4	26.2	27.4	0—120
Medium exposure (N = 19)	38.1	10.1	25—52	11.8	6.3	4—25	6.0	1.6	3—8	31.7	11.1	9—52	2.1	1.4	1—4	33.3	37.0	0—100
High exposure (N = 20)	41.3	6.97	22—52	13.8	6.2	2—27	6.1	1.8	5—13	35.7	13.9	15—70	2.3	1.2	1—4	33.3	26.3	0—100

Table 2. Parameters of internal and external exposure in the three subgroups with different degrees of exposure. (B-Mn = manganese in blood, U-Mn = manganese in urine, CEI = cumulative exposure index)

Group	B-Mn			U-Mn			CEI		
	Geometric mean ($\mu g \cdot l^{-1}$)[a]	Geometric SD ($\mu g \cdot l^{-1}$)[a]	Range ($\mu g \cdot l^{-1}$)[a]	Geometric mean ($\mu g \cdot l^{-1}$)[a]	Geometric SD ($\mu g \cdot l^{-1}$)[a]	Range ($\mu g \cdot l^{-1}$)[a]	Geometric mean ($\mu g \cdot m^{-3} \cdot year^{-1}$)	Geometric SD ($\mu g \cdot m^{-3} \cdot year^{-1}$)	Range ($\mu g \cdot m^{-3} \cdot year^{-1}$)
Low exposure (N = 19)	6.0	0.7	4—7.4	1.7	1.2	0.7—7	176.7	213	1—943
Medium exposure (N = 19)	8.6	0.6	7.9—9.5	2.3	1.3	0.7—6	199.2	260	9—1023
High exposure (N = 20)	11.9	1.8	9.6—18	2.8	0.8	0.9—5	668	590	15—2130
Level of significance	P	< 0.0001			< 0.05			< 0.0001	

[a] 1 $\mu g \cdot l^{-1}$ = 0.018 $\mu mol \cdot l^{-1}$.

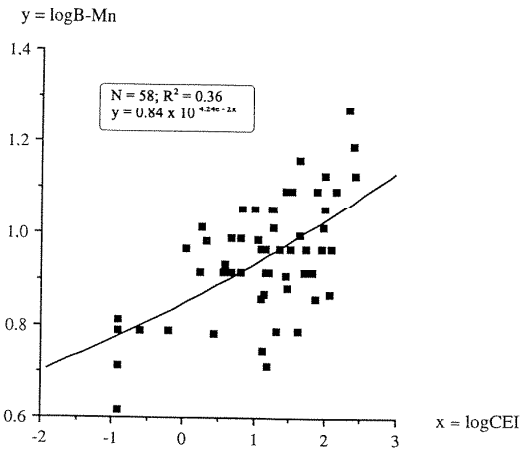


Figure 1. Correlation between logB-Mn and logCEI.

Table 3. Variations in the relationships between the indicators of internal and external exposure for the function of latency time after the cessation of exposure. (CEI = cumulative exposure index, B-Mn = manganese in blood, U-Mn = manganese in urine).

Correlation	N	R^2	P
CEI – B-Mn			
Entire group of workers	58	0.36	0.0001
Workers tested < 13 d after exposure cessation	29	0.31	0.002
Workers tested > 13 d after exposure cessation	29	0.41	0.0002
B-Mn – U-Mn			
Entire group of workers	58	0.23	0.0002
Workers tested < 13 d after exposure cessation	29	0.15	0.04
Workers tested > 13 d after exposure cessation	29	0.28	0.003
CEI – U-Mn			
Entire group of workers	58	0.16	0.002
Workers tested < 13 d after exposure cessation	29	0.00	0.8
Workers tested > 13 d after exposure cessation	29	0.15	0.03

sure, but to higher technical skill. Since the groups were not exactly comparable in cognitive abilities, the difference in the vocabulary tests was controlled for in the statistical calculations by means of an analysis of covariance, with the vocabulary test results as the covariate.

Exposure parameters

Table 2 shows the average values for the B-Mn and U-Mn levels and the CEI in the three exposure groups with the results of the analysis of variance. All of the internal and external exposure parameters were statistically different in the three exposure groups.

After the transformation of the B-Mn and U-Mn level and the CEI in the logarithmic form, a good correlation was observed, on an individual basis, between logB-Mn and logCEI ($r^2 = 0.36$, $P = 0.0001$) (figure 1), between logB-Mn and logU-Mn ($r^2 = 0.23$, $P = 0.0002$), and between logU-Mn and logCEI ($r^2 = 0.16$, $P = 0.0017$). In general the correlation coefficients (r^2) increased when only the subjects that had been tested more than 13 d after the cessation of exposure were considered (table 3).

The B-Mn and U-Mn concentrations were examined with regard to the latency time after the cessation of exposure, and they were found not to vary significantly.

Neurobehavioral effects

Performance data for the three groups of workers, as well as the significance levels for the differences between these groups, are shown in table 4. The workers of the high-exposure group exhibited poorer performance, as compared with the workers of the medium- and low-exposure groups, on several tasks. The differences were significant for the tests of additions, symbol digit, finger tapping, and digit span. The difference in vocabulary abilities between the groups was controlled by means of an analysis of covariance, which revealed that most of the performance differences observed between the three groups were not related to verbal abilities.

Table 4. Results of the neurobehavioral tests for the three subgroups with different degrees of exposure.

Group	Simple reaction time			Shapes comparison			Additions			Symbol digit			Finger tapping			Digit span		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Low exposure (N = 19)	237.2	16.1	207—277	623.3	53.1	500—729	3.6	0.8	2.2—5.9	3.2	0.672	2.3—4.8	69.1	8.1	55—99	7.9	1.1	5.5—9.5
Medium exposure (N = 19)	246.5	29.1	199—303	619.2	61.0	495—720	4.4	1.0	2.7—6.3	3.6	0.9	2.4—6.6	60.8	7.1	43—70	6.5	1.6	3.5—8.5
High exposure (N = 20)	241.5	23.9	194—316	638.5	56.3	496—758	5.0	0.9	3.0—7.3	4.0	0.7	2.9—6.0	64.7	5.5	48—75	6.7	1.2	4.5—9.5
Level of significance	P	NS		NS			< 0.001[a]			< 0.05[a]			< 0.001[a]			< 0.0001[a]		

[a] 95% significance of high exposure group versus low exposure group.

Regarding the analyses of dose-effect relationships, the effect measures were not related to the number of years employed in manganese-exposed work. Instead, a correlation was observed between the vocabulary test score and some of the tests (table 5). After the transformation in the logarithmic form of the data with a skewed distribution, significant correlations were found between logB-Mn and the tests of additions, log symbol digit, digit span, and log finger tapping; between logU-Mn and additions; and between logCEI and log symbol digit. Almost all of these relationships (except logCEI-log symbol digit) were still significant after control for vocabulary score (table 6).

As shown in tables 7 and 8, further analyses of dose-effect relationships also revealed different correlation degrees with regard to latency after the cessation of exposure and also to work seniority. However, no significant relationship was observed between the vocabulary score and the two parameters of latency after exposure and work seniority. Furthermore, no significant variation occurred in the correlations between the vocabulary test and the neurobehavioral tests with regard to latency after exposure and work seniority.

Table 5. Intercorrelations between the results of the neurobehavioral tests and the vocabulary test score.

Correlation	N	R^2	P
Vocabulary – simple reaction time	57	0.0	NS
Vocabulary – shapes comparison	56	0.1	NS
Vocabulary – additions	51	0.3	0.0001
Vocabulary – symbol digit	53	0.3	0.0001
Vocabulary – finger tapping	57	0.2	NS
Vocabulary – digit span	55	0.5	0.0001

Table 6. Dose-effect relationship between B-Mn, U-Mn, and CEI and the neurobehavioral tests before and after controlling for the vocabulary test score. (B-Mn = manganese in blood, U-Mn = manganese in urine, CEI = cumulative exposure index, NS = not significant)

Correlation	N	Before		After	
		R^2	P	R^2	P
B-Mn – symbol digit	54	0.22	0.0004	0.20	0.004
B-Mn – additions	52	0.26	0.0001	0.22	0.001
B-Mn – digit span	56	0.12	0.01	0.12	0.05
B-Mn – finger tapping	54	0.15	0.004	0.12	0.05
U-Mn – additions	52	0.12	0.01	0.13	0.02
CEI – symbol digit	54	0.15	0.004	0.02	NS

Discussion

The present investigation analyzed the results of a cross-sectional study among a group of male workers with different degrees of exposure to manganese dust. The duration of exposure was less than 30 years for all of the workers (range 1—28 years, average 13 years). In the last 10 years the average exposure levels in different work areas diminished from a range of 70—1590 $\mu g \cdot m^{-3}$ to a range of 27—270 $\mu g \cdot m^{-3}$. Since no major changes in the production volume, the production process, or ventilation system had occurred before this time, it can be assumed that previous levels were approximately in the same range as those of 10 years ago.

The finding of a significant correlation on an individual basis between external exposure, represented by CEI, and B-Mn and U-Mn is in contrast with the results from previous studies. In both of their studies, Roels and his colleagues (9, 11) found some correlation between U-Mn and current external exposure on a group basis only, and no correlation with B-Mn. Our hypothesis is that this difference between our results and those of previous studies may be due to the fact that the biological indicators of exposure were assessed after a period without exposure. This hypothesis is supported by the fact that the correlation coefficients between the biological and environmental indices of exposure increased with the time since the latest exposure.

Table 7. Variations between the dose-effect relationships in the function of latency time after the cessation of exposure. (B-Mn = manganese in blood, U-Mn = manganese in urine, CEI = cumulative exposure index, NS = not significant)

Correlation	N	R^2	P
B-Mn – symbol digit			
Entire group of workers	54	0.22	0.0004
Workers tested < 13 d after exposure cessation	27	0.20	0.02
Workers tested > 13 d after exposure cessation	27	0.27	0.006
B-Mn – additions			
Entire group of workers	52	0.26	0.0001
Workers tested < 13 d after exposure cessation	27	0.17	0.03
Workers tested > 13 d after exposure cessation	25	0.35	0.02
B-Mn – digit span			
Entire group of workers	56	0.12	0.01
Workers tested < 13 d after exposure cessation	29	0.06	NS
Workers tested > 13 d after exposure cessation	27	0.17	0.03
CEI – symbol digit			
Entire group of workers	54	0.15	0.004
Workers tested < 13 d after exposure cessation	27	0.04	NS
Workers tested > 13 d after exposure cessation	27	0.26	0.07

Table 8. Variations between the dose-effect relationships in the function of work seniority. (B-Mn = mangasese in blood, U-Mn = manganese in urine, CEI = cumulative exposure index, NS = not significant).

Correlation	N	R^2	P
B-Mn – digit span			
Entire group of workers	56	0.12	0.01
Workers with < 13 years of exposure	31	0.07	NS
Workers with > 13 years of exposure	25	0.20	0.024
CEI – symbol digit			
Entire group of workers	54	0.15	0.004
Workers with < 13 years of exposure	31	0.08	NS
Workers with > 13 years of exposure	23	0.22	0.02
CEI – additions			
Entire group of workers	52	0.04	NS
Workers with < 13 years of exposure	30	0.03	NS
Workers with > 13 years of exposure	22	0.29	0.009
U-Mn – additions			
Entire group of workers	52	0.12	0.01
Workers with < 13 years of exposure	30	0.02	NS
Workers with > 13 years of exposure	22	0.32	0.006

In addition, a different "bioavailability" of manganese could partly explain the associations between the indicators of exposure found in this study. The half-time of manganese dioxide particulate (which is the chemical form of manganese in this plant) deposited in the lung alveoli is about two to three months (18), while it is shorter for more soluble manganese compounds, like manganese sulfate and manganese chloride, which were present in the first Belgian study on workers of a manganese salt producing plant (9).

B-Mn was better related to life-estimated manganese exposure and thus confirmed the observation that this indicator can better reflect manganese body burden (9, 14).

Impairment of performance was observed in motor function tests (finger tapping and symbol digit) and memory tests (digit span) and thus confirmed the findings of the studies by Roels et al (9, 11), Iregren (10), and Mergler et al (12). In addition effects on more complex cognitive functions were noted, such as those revealed by the arithmetic task of the additions test and the coding task of the symbol digit test. The lack of effects on the response speed tests of simple reaction time and shapes comparison, a result in contrast with those of the studies by Siegl & Bergert (8), Roels et al (9, 11) and Iregren (10), may be related to the fact that these tests are generally more sensitive to "acute" or current exposure, therefore not being affected after its cessation. This discrepancy also appeared recently in the Montreal study of Mergler and her colleagues (12).

Dose-effect relationships were observed between the exposure parameters (B-Mn in particular) and additions, symbol digit, digit span and finger tapping. Also with these measures, the relationships improved with the latency time after the cessation of exposure and, to some degree, with work seniority.

The vocabulary score was lower for the most-exposed workers, a phenomenon frequently observed in neurobehavioral field studies. Nevertheless, the influence of intelligence, as measured by the vocabulary test, on performance, was fully eliminated by the covariance analysis. This analysis is likely to remove also some true effects of exposure, since part of these effects may be associated with the vocabulary score. In addition the improvement of the dose-effect relationships as a function of increased latency after exposure and of work seniority was clearly independent of any influence of the vocabulary test scores.

In conclusion, this study confirms the observation that exposure to manganese airborne concentrations well below the TLV of 5000 $\mu g \cdot m^{-3}$ for less than 30 years is associated with slight impairments of central neural functions in clinically asymptomatic workers.

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