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# Influence of environmental exposure to manganese in drinking water on cognitive, motor and behavioral functions in children

**Urszula Fałkowska[1], Julita Poleszak[1,*], Alicja Sobek[1], Karol Lorenc[1], Karol Wiśniewski[1], Joanna Milanowska[2]**

[1]Student Research Group of Applied Psychology, Medical University of Lublin, Poland
[2]Department of Applied Psychology, Medical University of Lublin, Poland

*E-mail address: julita.poleszak@wp.pl

## ABSTRACT

Manganese (Mn) is an essential chemical element for the human body, but it can be neurotoxic if the homeostatic range is exceeded. In this article, we review and summarize research on environmental exposure to manganese contained in drinking water and and the relationship of excess manganese to disorders of the nervous system in children. We identified and analyzed 17 original articles published in 1983-2017. The most common bioindicator of exposure to Mn was manganese content in the hair, but some studies measured manganese in blood and urine. One study concerned the content of this element in dentin, one in umbilical cord blood. The WISC, IQ, CALVT scales were the most commonly used to assess cognitive functions. Most studies indicate that higher Mn exposure is associated with worse cognitive functions, motor and hyperactive behavior. Despite some potential limitations in peer-reviewed studies, the negative impact of exposure to manganese on the developing brain is well demonstrated and preventive strategies should be promoted.

***Keywords*:** manganese, cognitive functions, neurobehavioral functions, motor functions

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## 1. INTRODUCTION

Manganese (Mn) is an element that unlike other heavy metals is essential for the proper functioning of the body. It is located in the centers of reactivity of many enzymes [1], it is involved in the metabolism of proteins and energy, and also has an effect on bone growth [2] [3].

The recommended daily dose of this element for an adult human is 1.6 mg. Over the years, it was thought that exceeding the demand for manganese does not bring any negative consequences. Tricarbonyl-cyclopentadienyl manganese replaced lead tetraethylate, which was added as an antiknock agent to gasolines and oils. The use of manganese became more and more common, so that the production of manganese ore increased even 30 times, and in the 90's of the twentieth century was 32 million tons per year. This was the reason for the increase in the concentration of manganese ions (II) in the atmosphere, drinking water and food [4]. Increasingly frequent health problems with a similar symptomatology in the employees of manganese mining plants led to the assumption that too large a dose of this element in the air adversely affects the human body [5,6]. Studies carried out during this period confirmed this hypothesis, proving that neurotoxic effects occur when inhaling manganese particles [7]. However, it is only in recent years that scientists have begun to analyze the health risk posed by exposure to Mn in water.

Several regions in Canada and other parts of the world have a naturally high concentration of manganese in groundwater. This differences between the regions can reach even several orders of magnitude, due to the weathering and washing out of minerals and manganese rocks. Children may be particularly at risk of poisoning due to poorly developed homeostatic mechanisms, a higher dose of body weight exposure and unique processes occurring in the developing nervous system [8].

The aim of this article is to summarize the research showing the relationship between exposure to manganese in drinking water and cognitive, motor and behavioral effects on children.

Standard criteria were used to review the literature data. The article was searched in English in the PubMed database and Google Scholar using the following keywords: manganese, neurodevelopmental disorders, cognitive deficit, motor deficit, behavioral deficit. We reduced the search to works presenting information on exposure to manganese occurring only in drinking water. Only full-length scientific articles were analyzed. We found 16 articles exploring children's populations in 10 different countries.

## 2. BIOMARKERS

The biological marker of exposure to manganese is blood, urine, saliva, nails and hair. However, it has not been established which of them has the highest diagnostic value[9]. Smith et al. [10] proved that the content of manganese in the blood and urine is poorly correlated with the exposure to this metal. Coetzee et al. [9] showed that the most commonly used biomarker in population studies is human hair. Saliva and nails are rarely used as markers of exposure to manganese [11].

## 3. SYMPTOMS OF MANGANISM COMPARED TO PARKINSON'S DISEASE

Manganese becomes neurotoxic if the homeostatic range is exceeded. It accumulates mainly in the basal ganglia [12], leads to disturbance of the GABA-ergic and serotoninergic balance [13] and abnormalities of the striataldopaminergic system. It induces motor and cognitive disorders [14] as well as neuropsychiatric symptoms [13]. Symptoms of chronic intoxication resemble Parkinson's disease. Irregularities appear gradually, often after several years of exposure to manganese, they can also occur many years after the exposure has been discontinued.

The neurotoxicity of manganese has been known since 1837, when Couper [15] described a set of symptoms similar to Parkinson's. He watched Scottish workers who, while grinding "black manganese oxide", were exposed to an extremely high level of dust in the inhaled air. Couper observation shows that workers showed weakness in muscle strength, gait disturbances, falling tendency, hypophilia and dysphonia, and salivation.

From the initial observations of Couper, subsequent reports also showed the toxic effects of manganese, although the number of studies from the early twentieth century is limited. Case reports confirmed the scientist's observations, but also added additional symptoms.

As of today, among the initial symptoms of manganism, there are non-specific symptoms of pseudo-dermatitis, weight loss, increasing fatigue with periods of hyperactivity, sleep disorders and short-term memory [16]. The patient usually complains of headaches, acroparestesis, or numbness of the fingers and painful cramps in the calf muscles. Small tremors in the head, tongue and hand are ahead of other neurological symptoms. The initial increase in dopamine leads to aggressive episodes with temporary psychotic states. As the level of dopamine diminishes, facial mimicry, eyelid blinking, bradykinesia are impoverished. Speech becomes monotonous and quiet, the character of the patient's writing turns into a micrograph. Stiffness of upper limb muscles and muscular tension of the type of toothed wheel are noticeable. Mellanum encephalopathy is irreversible and may increase despite treatment [17].

As you can see, the motor symptoms due to manganism are extremely similar to those that occur as a result of Parkinson's disease. However, the feature that distinguishes parkinsonism caused by manganese from Parkinson's disease is the lack of resting tremor, as well as the lack of response to levodopa.

## 4. CAUSES OF MANGANISM

The most common cause of manganese poisoning is occupational exposure to particles suspended in the air. However, there are also other situations that can contribute to a significant increase in the level of this element in the body.

Manganese toxicity can be seen in addicted people using petty-based psychoactive substances [18-20]. This applies mainly to the abuse of ephedrine. This psychostimulant is obtained from popular cold medicines containing ephedrine or pseudoephedrine, which is oxidized with potassium permanganate and acetic acid [21,22]. It is particularly popular in Eastern bloc countries. Dependents usually receive the resulting mixture intravenously, without prior purification. This causes the injected preparation to contain a high concentration of manganese. Normal concentration of Mn in whole blood is ≤ 10-12 μg / L, but Mn concentration in blood in addicts was measured at levels as high as 2000-3000 μg / L. [23]. Symptoms of misuse of this mixture are consistent with the symptoms of workers professionally exposed to manganese.

An important observation regarding the etiological role of manganese in parkinsonism in addicts is based on the fact that motor abnormalities are observed in users of ephedrone in Eastern Europe and Russia, where potassium permanganate is used as an oxidizing agent. In North America, however, Parkinson's syndrome has not been observed, in which chromate rather than potassium permanganate is used as an oxidizing agent [24]. The most likely explanation is that manganese is the causative agent in this atypical form of parkinsonism.

There is evidence of parkinsonism associated with chronic liver disease. Patients with advanced cirrhosis were documented with parkinsonism with clinical symptoms similar to Parkinsonism caused by Mn. This discovery is probably due to the fact that Mn is excreted in the bile, and in people with chronic liver disease, the excretion of Mn is significantly impaired and then accumulated in the brain.

## 5. IMPROVED MANGANESE CHANGE IN CHILDREN - A LITERATURE REVIEW

There are studies that indicate that exposure to high levels of manganese is associated with cognitive, motor and behavioral deficits in children. Table 1 provides a schematic summary of the studies with their general characteristics, such as the study publication year, country, size and age range of the population studied, biomarkers and study questionnaires.

**Table 1.** Characteristics of the reviewed research showing the relationship between exposure to manganese in drinking water and cognitive, motor and behavioral effects on children.

| Study | Year | Country | Study group | Age (years) | Biomarker | Test |
|---|---|---|---|---|---|---|
| Bouchard et al. | 2006 | Canada | 46 | 6-15 | MnH | CTRS-R |
| Bouchard et al. | 2011 | Canada | 362 | 6-13 | MnH | IQ |
| Menezes-Filho et al. | 2011 | Brazil | 83 | 6-12 | MnH, MnB | WISC-III |
| Torres-Augustin et al. | 2013 | Mexico | 174 | 7-11 | MnH, MnB | CALVT |
| Zhang et al. | 1995 | China | 92 | 9-12 | MnH, MnB | Results in school |
| Wright et al. | 2006 | USA | 32 | 11-13 | MnH, AsH | WASI, CVLT-C, WRAML |
| Wasserman et al. | 2011 | Bangladesh | 299 | 8-11 | MnB, AsB | WISC-IV |

| | | | | | | |
|---|---|---|---|---|---|---|
| Khan et al. | 2012 | Bangladesh | 840 | 8-11 | MnU, AsU | Results in school |
| Yeni et al. | 2009 | Korea | 261 | 8-11 | MnB, PbB | IQ |
| Lucchini et al. | 2012 | Italy | 299 | 11-14 | MnH, MnB, PbB | WISC |
| Baarlov et al. | 1983 | Great Britan | 86 | 8-11 | MnH | Hiperactivity |
| He et al. | 1994 | China | 92 | 11-13 | MnH, MnB | Santa Ana test, Benton test, *pursuitaiming test*, *digit symbol tes* |
| Ericson et al. | 2007 | USA | 27 | since birth till 3rd class | Mn in tooth enamel | play with a forbidden toy, impulsive errors on a continuous performance, children's Stroop test, the Child Behavior Checklist, Disruptive Behavior Disorders Scale |
| Hernández-Bonilla et al. | 2011 | Mexico | 195 | 7-11 | MnH, MnB | fingertapping, grooved pegboard, Santa Ana test |
| Henn et al. | 2012 | Mexico | 455 | 12, 18, 24, 30 and 36 month | MnB, PbB | BSID-IIS |
| Henn et al. | 2017 | Mexico | 224 | 2 | MnB | BSID-IIS |

The first published article investigating the possible negative neurobehavioral impact of manganese exposure was a case-control study conducted in Canada on the learning of children with intellectual disabilities [25]. The concentrations of 14 metals in hair in 31 children with intellectual disabilities and 22 healthy were determined. Both groups were compared in terms of the frequency of school attendance, grades and gender. The authors conclude that exposure to high levels of toxic substances, especially manganese, lead and cadmium, is associated with learning disabilities in children.

**5. 1. The cognitive effects of manganese on children**

The risk of exposure to Mn in drinking water brought the attention of researchers to one of the Canadian municipalities, where high levels of manganese occurred in the public water system. The researchers carried out two studies, published in 2006 and 2011 [26,27]. The first involved 46 children aged 6-15 years, divided into two groups depending on the concentration of manganese in the water supplying their homes (1 group 610 μg / L, 2 group 160μg / L). It was postulated that greater exposure to Mn via drinking water would be reflected in the higher content of Mn in hair (MnH), which in turn would lead to an increased level of hyperactive behavior. The level of Mn in the farm's feeding water was analyzed, the hair samples were collected from children, and the CTRS-R shortened scale was used to assess the behavior. The researchers showed that children whose homes were supplied with water with a higher content of manganese, had a higher concentration of manganese in the hair (on average 6.2 μg / g) than children in the second group (3.3 μg / g). In turn, MnH was significantly associated with the results of the CTRS-R test: in all children with hyperactivity MnH> 3.0 μg / g was found.

Five years later, the same research group evaluated the IQ of children according to the environmental exposure to manganese in drinking water. 362 children aged 6-13 were considered. The amount of manganese was measured in the tap water and in the hair of the children. The study showed that higher MnH was significantly associated with lower verbal and full IQ scores, with a difference of 6.2 points between children with the lowest and highest MnH was taken from the attention of the so-called corrected model, i.e. excluding disruptive factors such as family income and maternal intelligence. The authors also stated that the intake of Mn from water, but not from the diet, was significantly associated with MnH, suggesting that the exposure of Mn from water is metabolized differently than that consumed from the diet.

A similar study was carried out by Menezes-Filho et al. in 2011 [28]. Researchers analyzed the relationship between manganese levels in the hair and blood (MnB) and the intelligence quotient of children. 83 children from 6-12 years old, living near the manganese exploitation plant in Brazil, performed the WISC-III test. The results showed that the MnH and MnB levels showed a negative correlation with the WISC-III scores.

Torres-Augustin and others have assessed the impact of the manganese on the verbal memory and learning of children [29]. The study group consisted of 174 children aged 7-11 years, living in Mexico, 79 of which lived near a manganese mine plant, and 95 others lived in a community not exposed to manganese. Measured MnH and MnBoraz performed Children's Auditory Verbal Learning Test (CALVT). When comparing both groups, the authors observed significant differences in results. The group of children exposed to manganese in the environment presented higher concentrations of this element in the hair and blood than the uninfected group, as well as lower results in the CALVT test. The results of this study suggest that exposure to manganese has a negative effect on verbal memory and learning abilities of children.

The research was also carried out in China. A group of children living in areas where there was a significantly elevated concentration of manganese in drinking water due to industrial contamination, showed a significantly increased content of manganese in the hair and blood serum compared to the control group, which also correlated with worse academic performance [30]. Blood serum tests have also demonstrated a relationship between the concentration of neurotransmitters and academic performance. The serum concentrations of four neurotransmitters (noradrenaline, dopamine, serotonin and acetylcholine) were significantly lower compared to the control group, and the results in learning Chinese and mathematics were directly proportional to their concentration, while language skills were more correlated with the concentration of 5 HT, and math with NA.

Other studies, apart from exposure to manganese, also concerned exposure to other metals.

In Wright et al. the research group consisted of school-aged children (11-13 years old) living in the county of Ottawa, where zinc and lead ores are extracted, which results in the formation of waste abounding in manganese and cadmium compounds [31]. A hair sample was taken from each examined child to determine the concentration of heavy metals. Then, a battery test of neuropsychological tests was carried out. Among the participants, it was noticed that the concentration of manganese in the hair was inversely proportional to the total WASI score and the result in the verbal, but non-performance subscale. A similar correlation was demonstrated for arsenic concentration (As). A strong inverse relationship between the concentration of manganese and arsenic was also demonstrated, and the results in tests testing memory and learning ability. The high concentration of manganese reduced the amount of memorized elements in the CVLT-C and WRAML tests. In addition, it was shown that the effects of high concentrations of manganese and arsenic in these tests are cumulative, and children with the highest content of both metals in the hair obtained the lowest results in the studies.

Wasserman and others assessed the impact of arsenic and manganese exposure on the intellectual functions of children [32]. The studied population were 299 children (8-11 years old) living in Bangladesh, a country with common contamination of well water by As and Me. The results showed that MnB and arsenic in blood (AsB) were significantly and negatively related to the majority of WISC-IV subscales. After further adjustment of sociodemographic variables and ferritin, they observed an inverse relationship between MnB and perceptual reasoning and working memory from WISC-IV.

Khan et al. [33] also considered the possible impact of As and Me on the children's educational achievements. Researchers took into account the population of 840 children aged 8-11 years from Bangladesh, collecting well water from all children, urine samples and annual results in mathematics and humanities. They found a significant inverse relationship between the content of Mn in the urine (MnU) and the mathematical results, also in the corrected model. The relationship between MNU and language results was not significant. No relevant links were found between the content of As in urine and school ratings.

Yeni et al. in 2009 they published the results of the impact of exposure to manganese and lead (Pb) occurring in the environment on the intelligence of school-age children [34]. The study analyzed the results of IQ 261 Korean children aged 8-11 years, taking into account the levels of manganese and lead in the blood. The results showed that higher levels of both manganese and lead in the blood were significantly related to the lower results of verbal and full-blown IQ. The study also suggests the effect of addition of manganese and lead on the intelligence of children.

Also Lucchini et al. [35] investigated the effect of exposure to Mn and Pb on cognitive functions in early puberty. The study analyzed the results of the WISC scale in 299 adolescents (11-14 years), exposed to the environmental effects of Mn and Pb, considering as biomarkers, manganese in blood and hair and lead in the blood. Results showed a significant adverse effect of lead and manganese on cognitive functions. The presented studies evaluate the influence of manganese on cognitive functions. However, some studies focus on the effect of this element on behavior.

### 5. 2. The behavioral effects of manganese on children

Barlow [36] investigated the relationship between the possible impact of manganese on the hyperactivity of 68 children in the UK. Hair samples were taken from each to determine MnH. Slightly higher concentrations of MnH were detected in children with hyperactivity (0.84 μg / g) than in the control group (0.68 μg / g).

A research group in China has published an article [37] on the study of a rural community powered by high-Mn sewage water. The publication concerned the levels of Mn in drinking water and hair of children and related neurobehavioral effects. The vulnerable group consisted of 92 students from the village, in which the concentration of Mn in drinking water was from 0.24 to 0.35 mg per liter (L) for many years. They were compared with children from another rural village with a low Mn in water (<0.03 mg/L). Children in both groups were evaluated using neurobehavioral tests for emotional state, motor coordination, visual memory and reaction time. Children of the village with a high concentration of Mn in drinking water had average Mn hair concentration significantly higher than in control children (1.25 μg / g against 0.96 μg / g); the same difference was observed for Mn in blood (33.9 μg / L vs 22.6 μg / L). These children also had lower performance than the control group in neurobehavioral tests: Santa Ana test, Benton test, pursuit test, and digit symbol test. In addition, exposed children had significantly lower school performance than children from the control group. In another study, Ericson and colleagues [38] evaluated neurobehavioral effects using scales that measure the degree of inhibition. In contrast to previous studies, Mn levels were assessed based on its content in tooth enamel. Children were observed from birth to the completion of the 3rd grade of primary school. Three psychometric tests were used at 36 and 54 months: play with a forbidden toy, impulsive errors on a continuous performance, and children's Stroop test. Scales assessing behavior were also carried out in the first and third grade (the Child Behavior Checklist, Disruptive Behavior Disorders Scale). It was shown that the Mn level was significantly and positively correlated with measures of behavioral inhibition.

### 5. 3. The motor effects of manganese on children

Some researchers have turned their attention to the influence of manganese on motor disorders. Hernández-Bonilla et al. in 2011, they conducted a study assessing the relationship between environmental exposure to manganese and the motor functioning of children [39]. 195 children between the ages of 7 and 11 were assessed. Motor functions were tested on the basis of the following tests: Finger Tapping, Grooved Pegboard and Santa Ana test. Exposure to manganese was assessed by determining the level of manganese in the blood (MnB) and in the hair (MnH). Researchers showed that the average concentration of MnB and MnH was remarkably higher in children exposed to environmental manganese (12.6 μg / g) compared to non-infected children (0.6 μg / g). The authors also observed that the research group made mistakes more often during the Grooved Pegboard test, with no difference between the groups in the other two motor tests. The results of this study show that motor disorders occurring after being exposed to manganese in children are abnormal, but they are not as intense as in the case of occupational exposure to the element in adults.

Clauss Henn et al. in 2012 [40] investigated the relationship between exposure to manganese and lead with neurological underdevelopment. The population of 455 children from Mexico City was considered, assessing the neuronal development of a child aged 12, 18, 24, 30 and 36 months using the Bayley Scales of Infant Development-II (BSID-IIS) scale. Mn and Pb in whole blood (MnB) were measured. The results indicated that mixed exposure to Mn and Pb has more influence on mental and psychomotor development than exposure to one of only two metals, especially in potentially sensitive developmental stages, such as early childhood.

Researchers [41] investigated the relationship between prenatal manganese concentration and placental manganese transport, and neurological development in 224 2-year-old children living near Superfund Tar Creek. Maternal and umbilical blood was collected at birth, manganese concentration measurement was performed using inductively coupled plasma mass spectrometry and neurological development was assessed using the Bayley Scales of Infant Development-II. In the study population, the concentration of manganese in the mother's blood during labor was associated with lower neurodevelopmental results at the age of 2 years. In addition, preliminary evidence has been found to suggest that placental factors may also affect the relationship between prenatal manganese exposure and neurological development.

Meta-analyzes confirm the negative impact of manganese contamination on children's intellectual abilities [42]. In Rodriguez-Barranco et al. a total of 41 articles from around the world have been systematically reviewed, which met the inclusion criteria. 17 of them studied the influence of manganese. The analysis showed that increasing the concentration of manganese in the hair by 50% leads to a significant reduction in the intelligence quotient of children aged 6-13 by 0.70 points ($p < 0.001$). This effect is higher in the verbal intelligence subscale (-1.26 points, $p = 0.008$) In addition, out of five articles investigating the relationship between manganese exposure and the risk of developing behavioral disorders in children, three gave results confirming this hypothesis.

## 6. CONCLUSIONS

Manganese is a metal that, although it is part of many enzymes, is also characterized by significant toxicity at excessive exposure. It can occur through food, inhalation, as well as contaminated water in the event of contamination of water with manganese-containing compounds, for example in areas of iron or manganese mining.

Various markers can be used to assess exposure to manganese, including serum manganese, saliva, urine, hair and nails.

Many works describe its detrimental effect on cognitive abilities in children. The results of the study indicate a greater negative impact on scales assessing verbal intelligence. It is also believed that newborns are particularly vulnerable to its harmful effects, due to the yet undeveloped mechanisms of regulating the absorption of this element.

In people with hepatic failure, manganese poisoning can also be seen. In order to protect the public against the potential effects of poisoning, the WHO has set guidelines on the maximum concentration of metal compounds in drinking water.

Chronic poisoning is common among drug addicts taking intravenous psychostimulants containing large amounts of manganese, which is used to produce them.. The picture of chronic manganese poisoning is characterized by the presence of Parkinsonism symptoms without resting tremors, unresponsive to levodopa treatment. However, the initial symptoms of toxicity may be very unspecific.

Manganese is an essential element of life, which also has significant toxic effects. As a result of industrial development, the environment may become more and more contaminated with this metal, which may have drastic consequences, so it is important to conduct adequate supervision in exposed areas.

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