

# Nervous system disorders induced by occupational and environmental toxic exposure

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## ABSTRACT

**Encephalopathy, extrapyramidal features, neurodegenerative diseases, and peripheral neuropathy are commonly encountered in presentations of occupational neurotoxic syndromes. Epidemiological findings have suggested the role of pesticides, solvents and metals on the onset and progression of neurological diseases. The aim of this review is to present clinical manifestations of occupational and environmental neurologic disorders, to discuss toxic's implications of these conditions, and to give indications about occupational branches and main jobs concerned. Better to know and categorize the clinical manifestation of neurologic disorders and toxics implicated, will improve the clinical management of occupational neurologic diseases. We performed a research of studies, case reports and review, particularly among most recent, available into Pub Med databases about occupational and environmental neurologic disorders and main toxics incriminated.**

**Keywords:** Occupational Toxics; Neurological Diseases

## 1. INTRODUCTION

Neurotoxicity occurs when the exposure to toxic substances, called neurotoxins, induce adverse effects in the central nervous system, peripheral nerves or sensory organs. A chemical is considered to be neurotoxic if it is capable of damaging the nervous system or brain, usually by killing neurons or cells which transmit and process signals. These chemicals are omnipresent in the environment and particularly in occupational settings. Industrial process is major sources of some of the most well-known neurotoxicants. Neurotoxicity is generally manifested as multiple syndromes and effects, depending on the nature, level and duration of the exposure. We will

identify clinical manifestations of neurologic disorders and their relation with toxic exposures and provide precisions about occupational branches and main jobs involved.

## 2. MATERIAL AND METHODS

A search was conducted on occupational and also environmental exposure associated with defects of the nervous system. An online computer search on Pub Med data bases especially from the ten last years, with the keywords "nervous system diseases" or "disorders", in association with "toxics and environmental exposure" produced a large number of original articles and reviews. Additional papers were traced through the references listed in the reviews and by browsing through the major journals and books on occupational and environmental health. A selection was made from numbers of publications in accordance with the following inclusion criteria: The paper referred to agents used in occupational settings. Indications of nervous system disorders were described in relation to toxics exposure. The paper contained sufficient information to warrant conclusions. Twenty four references were selected. Some papers described a relation between certain occupations or occupational exposure and defects of the nervous system; other papers referred to studies on environmental exposure or to animal models; a great deal of caution is required when extrapolating from studies on laboratory animals to the human brain. Among the studies on humans, clinical series and case reports also have limited value for the estimation of effects and the effects of occupational and environmental exposure are best evaluated by epidemiological studies.

### 2.1. Main Diseases Induced by Toxics

#### 2.1.1. Central Nervous System Impairment

##### 2.1.1.1. Encephalopathy

Toxic encephalopathy is caused by a diffuse impairment of the brain and may result in a wide variety of

symptoms, which can include fatigue, impairment of learning, memory and concentration, anxiety, depression, elevated irritability and emotional instability. Because of the vagueness of the symptoms, it is difficult to have a swift and reliable diagnosis, especially in the early stages. Complaints (headaches, dizziness, changes in sleep pattern) are mild and vary from one individual to another. These features may be induced by a long-term, low-level exposure to several chemicals (solvents, heavy metals) but can also be seen in several disorders not related to work. Differentiation must be made from these other diseases, particularly in the areas of neuropsychiatry and internal medicine (Alcoholic encephalopathy, primary degenerative dementia, cerebrovascular diseases, hydrocephalus, compressive process, post traumatic disorders, drug addiction, affective and stress disorders, sleep apnea syndrome...). Specific chemicals such as manganese, toluene or mercury may also induce more specific neurological symptoms (Parkinsonism, or cerebellar symptoms).

Chemicals associated with central nervous impairment are Lead and its compounds, Mercury and its compounds, Manganese and its compounds, Carbon monoxide, Carbon disulphide, Organic phosphorous compounds, and Neurotoxic solvents: aliphatic hydrocarbons (n-hexane, n-heptane), Ketones (2-butanone, 2-hexanone), alcohols (methanol, ethanol, methyl glycol), Aromatic hydrocarbons (benzene, toluene, xylene, styrene), chlorinated aliphatic hydrocarbons (dichloromethane, 1,1,1-trichloroethane, trichloroethylene, tetrachlorethylene).

#### 2.1.1.2. Clinical Manifestations Associated with Neurotoxicity

##### *Headache*

It is listed as a complaint following exposure to metal fumes and also solvent vapors, which are used in industry to dissolve other compounds, and as fuels.

The source of intoxicant, its molecular form, route of entry and dose of exposure determine the acuteness and severity of the symptoms. Symptoms may not appear for years or can become gradually with more exposure. The mechanism for pain can be brain swelling (tin, lead), or may be transient hypoxia or vasodilatation (zinc, manganese, nickel).

For example, a case of recurrent headaches in a woman with a workplace exposure to airborne lubricating fluid containing Stoddard solvent has been reported. No etiology was discovered and after a lubricating fluid change to a non Stoddard solvent, the employee reported the complete resolution of her headaches within two days [1].

Warehouse worker's headache, is an infrequently reported form of carbon monoxide poisoning due to industrial exposure.

##### *Behavioral syndromes, disturbance of memory*

Subtle changes in mental functioning induced by intoxication often go unrecognized unless looked for, using sophisticated neuropsychological test batteries. Behavioral features such as psychosis, depression and chronic apathy have been described in some workers. It is important to differentiate memory impairment associated with other neurological diseases (Alzheimer's disease or presence of a brain tumor), from the cognitive deficits associated with exposure to organic solvents, metals or insecticides. Behavioral and subjective syndromes like vertigo, fatigue and personality change manifest as mild encephalopathy with inebriation, and may indicate the presence of exposure to carbon monoxide, carbon dioxide, lead, zinc, nitrates or mixed organic solvents for example.

Intoxication with manganese is manifested earliest by neuropsychological disturbances, including apathy, hallucinations, euphoria, flight of ideas, compulsivity, and agitation.

Inorganic mercury poisoning has been known to produce irritability, poor concentration, memory deficiencies, anxiety and depression. Jobs concerned may include for example battery manufacturing, fluorescent lighting and vapor lamp manufacturing, bronzing, photo engraving, fish canning. Dental practices and industry also constitute an occupational exposure.

Standardized neuropsychological testing is necessary to document elements of cognitive impairment in patients suspected of toxicant encephalopathy.

##### *Disorders of consciousness, seizures, coma*

Disturbances of consciousness occur when the brain is deprived of oxygen: for example, with presence of carbon monoxide, carbon dioxide, methane or agents such as hydrocyanic acid which block tissue respiration, or certain organic solvents which cause massive impregnation of the nerve. In industry, occupational carbon monoxide poisoning occurs in employees engaged in the manufacture of illuminating gas and water-gas, in blast furnace workers during metal-casting and in lime-kiln workers [2].

Seizures may be following by loss of consciousness in workers exposed to anticholinesterase substances such as organophosphate insecticides, farm workers for example. Seizure associated with brain swelling may also occur in lead encephalopathy. Organophosphates poisoning may result in autonomic nervous system manifestations precedent occurrence of dizziness, headache, blurred vision, myosis, chest pain, increased bronchial secretions, and seizures. These parasympathetic effects are explained by the inhibitory action of these toxicant substances on cholinesterase activity.

##### *Movement disorders and extrapyramidal features*

Workers exposed to manganese, carbon monoxide or carbon disulphide have reported disorders such as slow-

ness of movement, increased muscle tone, and postural abnormalities. Tremor is often related in mercury intoxication, and more obvious tremor, associated with ataxia (lack of coordination of muscular action), may be seen after toluene inhalation. Extrapyramidal features may be associated with long term exposure to pesticides, manganese, solvents or carbon monoxide in an occupational setting.

For example, Welders long term exposed to manganese by inhalation (welding fumes) were reported to have impaired neurobehavioral performance and increased tremor. Subtle effects appeared at 0.1 - 0.3 mg/m<sup>3</sup> in air (common in welding). Welders currently exposed to manganese may have slight alterations in motor speed and fine manual dexterity [3]. Persistent impairment in neuromotor function is described after long term exposure. Moreover, excessive manganese exposure may induce the development of a form of Parkinsonism known as manganism (cf manganese).

Extrapyramidal syndrome in case of organophosphates intoxication occurs after 4 - 40 days of severe intoxication and usually disappeared spontaneously in about 1 to 4 weeks with or without treatment [1]. It includes features such as dystonia, rest tremor, and cog-wheel rigidity. Occupational branches concerned are Agriculture, Forestry, Chemical, Gardening. Jobs implicated could be for example farms workers, but also forestry and nursery workers, employees of formulating pesticide. The mechanism underlying these manifestations may be the inhibition of Acetylcholinesterase by organophosphates, which have ready access to central neurons with their lipid solubility. Withal, exposure to pesticide may increase the risk of Parkinson's disease (cf pesticides).

### 2.1.2. Peripheral Nervous System Impairment

Polyneuropathy and peripheral neuropathy are diseases of the peripheral nervous system, which affects motor, sensory and autonomic fibers. The typical symptoms include paresis, usually most pronounced peripherally in the upper and lower extremities, paraesthesia (numbness, tingling in the fingers and toes). This may lead to difficulties in walking or in the fine coordination of hands and fingers. Heavy metals, solvents and pesticides, among other chemicals, may induce such disability.

Chemicals which may cause toxic polyneuropathy are Solvents such as n-hexane, chlorinated aliphatic or hydrocarbons (dichloromethane, 1,1,1-trichloroethane, trichloroethylene, tetrachlorethylene...), Metals (lead, arsenic, thallium, mercury), Pesticides, Organophosphates, acrylamides, and Carbon disulfide.

Painless and painful polyneuropathy may be distinguished:

Painless Polyneuropathy may be induced by chemicals such as Lead (very rarely seen today but seen in workers

in lead mining and lead smelting industry), or Tetrachloroethane, which may result in polyneuritis, especially of hands and feet (interosseous). There is no pain but paresthesia. Tetrachloroethane is used as a solvent for cleansing and degreasing metals, in paint removers, varnishes, lacquers, photographic film, resins and waxes, extraction of oils and fats.

Painful Polyneuropathy is related in case of chemicals poisoning such as Arsenic, N-hexane, or Carbon disulfide:

Arsenic exposure causes polyneuritis to the antero lateral leg, such as alcoholic polyneuritis, with spontaneous pain and on draft of the muscles. Diagnoses have to be considered with other signs of arsenic poisoning (keratoderma, melanoderma). Arsenic-induced polyneuropathy is usually a very serious and chronic disease. A complete recovery is observed in only 15% - 20% of patients. [2]. Arsenic induced encephalopathy is an irreversible process. Workers concerned are, for example, workers in pyrotechnics or microelectronics workers.

N-Hexane exposure remains in motor or sensitive motor polyneuritis. In industry, hexanes are used in the formulation of glues for shoes, leather products, roofing, and in textile manufacturing. Motor or sensitive polyneuritis may be especially seen on shoe workers (glues). Between 9 to 12 months after cessation of exposure to n-hexane, 83% of patients who had peripheral neuropathy and who changed to their visual evoked after exposition to n-hexane in a shoe factory, had a complete clinical recovery [3]. The electrophysiological studies also revealed improvement to the majority of motor and sensory nerve conduction velocities.

Carbon disulfide intoxication leads to a gradual onset of polyneuritis with paresthesia and difficulties in walking. These effects are observed especially on workers in viscose industry.

## 2.2. Main Toxics Associated with Neurotoxicity

### 2.2.1. Organic Solvents

Millions workers are exposed to organic solvents. These are people working for example as printer, spray painter, industrial cleaner, paint or glue manufacturer. Graphic industry, electronic industry, plastic industry, are also concerned. After dermal contact or inhalation, organic solvents may affect neuronal structures in the brain due to their lipophilic and hydrophilic properties. The resulting neurotoxic effects may include nausea, dizziness, headache, and problems in concentration.

Long term exposure leads in some workers (spray painters or microelectronics workers for example) to the development of "Chronic Solvent induced Encephalopathy". Various denominations exist for this syndrome, for example "psycho-organic syndrome" or "toxic solvent

syndrome". It is characterized by mild to severe cognitive impairment, generally seen as the key diagnostic feature; working memory and concentration dysfunction, defects of visual perception (deficits in visual contrast sensitivity contrast and in color perception). Psychiatric disorders are often diagnosed.

Many studies are in the agreement about Chronic Solvent Encephalopathy being a non-progressive disease in which no severe deterioration of functioning occurs after diagnosis. In a number of studies no significant changes, and in other studies improvement of functioning could be measured. Presumably cessation of exposure might be one of the causal factors for the non-progressive character of the disease. Future studies are needed to clarify the role of various prognostic factors on the course of Chronic Solvent Encephalopathy [4].

#### Toluene

Toluene is one of volatile organic solvents that cause different sensitivity in individuals. It is widely used in industry for the production of other chemicals and as a solvent for paints, coatings, glues... Painters and workers in the printing, rubber and leather industries, workers in many other industries, are exposed to this substance. Animal researches suggest that exposure to toluene may be neurotoxic, but less is known about the consequences of long-term exposure to humans. It would appear that toluene preferentially affects white matter structures and periventricular/subcortical regions. The commonly observed neuropsychological deficits such as impairments in processing speed, sustained attention, memory retrieval, executive function and language, are also consistent with white matter pathology [5].

Toluene TLV (threshold limit value) is of 50 ppm based on reports of headache and irritations as low as 50 ppm.

### 2.2.2. Pesticides

It includes insecticides, fungicides, rodenticides, fumigants and herbicides and exhibits a vast array of chemically diverse structures. Occupational exposure to neurotoxic pesticides is mainly associated with agricultural work, but pesticide manufacturing and formulating employees, highway and railway workers, as well as greenhouse, forestry and nursery workers, may have a substantial risk of being exposed to neurotoxic pesticides.

#### Parkinson's disease and pesticides:

Exposure to pesticides increases the risk of Parkinson's disease by almost 70%. 5% of individuals exposed to pesticides might develop the disease as against 3% for the general population [6]. This relationship appears strongest for exposure to herbicides and insecticides, and after long duration of exposure. Toxicologic data suggest that paraquat and rotenone may have neurotoxic actions that potentially play a role in the development of Parkinson's disease. A recent study show that Parkinson dis-

ease was positively associated with group of pesticides that inhibit mitochondrial complex (including rotenone), and a group of pesticides that increase oxidative stress (including paraquat) [7].

### 2.2.3. Metals

#### Lead

The lead normally found in the earth's crust is basically immobile and non-toxic. Once lead is mined and integrated into manufactured products and spread throughout the environment, it is highly toxic. Lead is widely used in the production of batteries, metal products (solder and pipes), ammunition and devices to shield X-rays. The effects of lead poisoning on the brain include delayed or reversed development, permanent learning disabilities, seizures, coma and death with severe toxicity. Death from lead encephalopathy was often seen during the 1960s but is rare today.

#### Mercury

It has been used commercially and medically for centuries. Mercury is primarily used for the manufacture of industrial chemicals or for electrical and electronic applications. It is used in thermometers, especially ones which are used to measure high temperatures, and their use is declining since the early 21st century. It is still used in some diuretics. Sources applications are also amalgams filling, and, as gaseous mercury, in fluorescent lamps.

Organic forms, specifically methyl mercury, are the most toxic among metals. Being lipophilic, methylmercury rapidly crosses the blood-brain barrier. It severely affects the central nervous system by causing psychiatric disturbances, ataxia, visual loss, hearing loss and neuropathy. Recently, the effects of mercury exposure at levels around 0.05 mg/m<sup>3</sup> or lower have been of concern and may include increased complaints of tiredness, memory disturbances, subclinical finger tremor, abnormal EEG by computerized analysis and impaired performance in neurobehavioral or neuropsychological tests. Inorganic mercury may play a role as a co-factor in the development of Alzheimer's disease [8].

#### Manganese

It is an essential trace metal that is widely used in industry, particularly in the manufacture of steel. Manganese mining, steel and aluminum production, battery production, chemical industries are at risk. For example, welders and alloy workers are especially exposed.

Exposure to high levels or chronic low-level of manganese can cause neurotoxicity, the clinical features included psychiatric symptoms, extrapyramidal features and dystonia:

- Psychiatric manifestations have been reported in cases of manganism, and mood disorders are often observed in manganese exposed workers. Hallucina-

tions and psychoses have been reported, referred to as “manganese madness”. It is suggested that past exposure to Manganese may have lasting consequences on neuropsychiatric symptoms [9].

- Excessive manganese exposure may induce the development of a form of Parkinsonism known as manganism. Similarities between the clinical manifestations of Parkinson disease and manganism may be seen: presence of generalized bradykinesia, widespread rigidity, masked facies, micrographia, speech disturbances, postural instability. Dissimilarities include less-frequent resting tremors (tended to be postural or actional), more frequent dystonia (consisted of facial grimacing, hand dystonia and/or plantar flexion of the foot), symmetrie of effects, a propensity to fall backward, and a characteristic “cock walk”, in which patients walk on their toes with elbows flexed and spin erect [10].

The similarities between the two disorders can be partially explained by the fact that the basal ganglia accumulate most of the Manganese excess, compared with other brain regions in manganism, and dysfunction in the basal ganglia is involved in Parkinson disease. Parkinson’s disease is primarily associated with the loss of dopaminergic neurons within the substantia nigra, allowing the caudate and putamen to become overly active and possibly cause continuous output of excitatory signals to the corticospinal motor control system [11]. The substantia nigra is spared in manganism, which is linked to the degeneration of GABAminergic neurons within the globus pallidus in pathways postsynaptic to the nigrostriatal system [12]. There are a few imaging procedures that may be used to distinguish manganism from Parkinson’s disease, including positron emission tomography (PET), computerized tomography (CT), and magnetic resonance imaging (MRI).

Observation of patients with manganism reveals a clinical disease entity different from Parkinson disease, not only in the clinical manifestations, but also in therapeutic responses. Even if there is an initial response to levodopa, the primary treatment option for Parkinson disease, a failure to achieve a sustained therapeutic response is observed in patients with manganism. In long-term follow-up studies, patients with Parkinson disease usually present a continuous deterioration, while patients with manganism present a rapid progression during the initial 5 - 10 years, followed by a plateau during the following 10 years [13].

#### Aluminum

It is the most widely used non-ferrous metal and the global production of aluminum in 2005 was 31.9 millions tones. It is used in transportation, packaging, construction... The following operations may involve aluminum and lead to workers exposure to this substance:

the processing and transportation of aluminum, the use in electrical transmission lines, the use in construction, manufacturing, explosives, petrochemical and paper industries, the use in desalinization, cryogenic technology, permanent magnets; the use in sugar refining, alloying metals, as a chemical intermediate and in containers for fissionable reactor fuels; the use in testing for gold, arsenic and mercury.

It has for a long time been implicated in the pathogenesis of Alzheimer’s disease. Evidence suggests that trace metal homeostasis plays a crucial role in the normal functioning of the brain, and any disturbance in it can exacerbate events associated with Alzheimer’s disease. It is concluded based on extensive literature that the neurotoxic effects of aluminium, as a factor in Alzheimer disease, can not be discarded [14]. However, the definite mechanism of aluminium toxicity in Alzheimer Disease is not known.

Withal, some epidemiological studies have found poor performance in cognitive tests and a higher abundance of neurological symptoms for workers occupationally exposed to aluminium. There was concurring evidence from different studies that urinary aluminium concentrations below 135 µg/l have an impact on cognitive performance.

Aluminium could cause impairments in mitochondrial bioenergetics which may play a major role in neurodegenerative disorders, according to current researches. It may lead to the generation of oxidative stress, which may consequently lead to a gradual accommodation of oxidatively modified cellular proteins [15].

#### Arsenic

Exposure to arsenic occurs occupationally in several industries such as mining, pesticide, pharmaceutical, pyrotechnics, glass and microelectronics. Inhalation is the principal route of arsenic occupational exposure, and ingestion of contaminated drinking water is the predominant environmental source of exposure.

The functions of the central and also peripheral nervous system may be impaired under conditions of exposure to arsenic. Arsenic poisoning is manifested by skin and mucous membrane lesions, disorders of psychic functions and polyneuropathies, disorders of peripheral circulation, risk for Raynaud’s syndrome. Clinical symptoms, such as sleeplessness or sleepiness, irritability, headache, painful spasms in the muscles’ extremities, extremity paresthesia and pain, and muscular fatigue, prevailed among functional disorders of the nervous system in workers chronically exposed to Arsenic. The findings of a recent study indicate that exposure to Arsenic concentrations, within the threshold limit values, can induce subclinical effects on the nervous system, especially subclinical neuropathy [16].

### 2.2.4. Gases

Some Gases require high doses over longer periods to give symptoms (carbon dioxide), and others are extremely toxic even in very small doses, (phosgene and cyanide, which have been used as war gases). There are widely used in industry, for general anesthesia (nitrous oxide), or for disinfection (formaldehyde).

They can be particularly dangerous when they are odorless: carbon monoxide intoxication, for example, may lead to cognitive, behavioral and emotional symptoms. Movement disorders or parkinsonian syndromes have been also reported. It occurs in employees engaged in the manufacture of illuminating gas and water-gas, in blast furnace workers during metal-casting and in lime-kiln workers [2].

Carbon disulfide poisoning frequently remain in vascular encephalopathy. The principal industrial uses of carbon disulfide are the manufacture of viscose rayon, cellophane film, carbon tetrachloride and electronic vacuum tube. It is also used in the manufacture of Bamboo Fiber. Features may include multiple brain infarctions, peripheral neuropathy, retinopathy, hypertension and glomerulosclerosis of the kidney. The basic mechanisms involved are atherosclerotic changes in blood vessels. In cases of chronic carbon disulfide intoxication, clinical manifestations of vascular encephalopathy (hemiparesis, speech disturbance) are similar to those observed in patients with atherosclerotic cerebrovascular disorders.

## 3. CONCLUSION

Typical but also less typical signs and symptoms of possible exposure to neurotoxins in workers shall be identified and recognized in order to a better handling occupational neurologic diseases. Prevention relies on strategies designed to control exposure. It includes especially a substitution of less toxic chemicals, which have naturally to be familiar, the use of ventilations systems and of personal protective equipment to reduce skin and respiratory absorption. Neurological occupational diseases have presumably multifactorial etiology, and the health risk after exposure depends on age, sex, genetic factors, socioeconomic and nutritional status, and environmental factors. Especially solvent, metals and pesticides are implicated. However, of the thousands of chemicals in current use, only a small fraction has been documented to cause developmental neurotoxicity in humans. Exposure information is still insufficient and effects of low-level environmental exposure are difficult to establish, but more and more studies indicate a link with the onset or progression of neurological diseases.

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