



## TOXIC CAUSES OF PARKINSON'S DISEASE

There are a number of known toxic causes of Parkinson's Disease. Toxicity has the potential to be the sole cause of Parkinson's Disease. To very varying extents, toxicity can also be a partial cause of Parkinson's Disease.

Symptoms normally develop when toxic exposure occurs or soon after, or gradually increase over time when exposure to toxicity persists. Symptoms do not develop years or decades later as is often claimed. In fact, there is a tendency for the effects of toxicity to decline over time, but with some toxic substances it can take years.

The prevalence of Parkinson's Disease that is due to toxicity is not known. However, reports suggest that the number of people whose Parkinson's Disease is due to toxicity is very low, being the exception rather than the norm.

The toxic causes of Parkinson's Disease each cause different symptoms because of the different biochemical means by which toxicity is caused, and because of the other biochemical functions that each particular toxin affects.

In order to cause Parkinson's Disease, the level of toxic exposure usually has to be either acute or chronic. Mild exposure to some known toxic causes, such as carbon monoxide would have no noticeable effect. Some other potentially toxic causes of Parkinson's Disease, such as copper and manganese are actually beneficial to health in normal quantities, and can only cause Parkinson's Disease in very large quantities.

### Carbon disulfide

Carbon disulfide, usually in solvents or pesticides, can cause Parkinson's Disease that is associated with other neurological symptoms. The effects can persist for years after exposure has ceased.

Potential sources : pesticides used as fumigants [1], disulfiram, which is a drug used in the treatment of chronic alcoholism [2], industrial solvents [3], solvents used in the production of viscose rayon and cellophane film [4, 5].

Means of toxicity : carbon disulphide interferes with pyridoxal 5-phosphate. Pyridoxal 5-phosphate is essential for the formation of dopamine from L-dopa. So carbon disulphide may cause Parkinson's Disease symptoms by reducing the formation of L-dopa.

Symptoms : atypical Parkinsonism (cerebellar signs, hearing loss, sensory changes, cogwheel

rigidity, decreased associated movements, distal sensory shading, intention tremulousness, resting tremulousness, and nerve conduction abnormalities) [1]; Parkinsonism and frontal lobe-like syndrome associated with bilateral lesions of the lentiform nuclei [2]; balance problems, impotence, and irritability, without tremor, cogwheel rigidity, bradykinesia, or changes in facial expression [6]; Parkinsonism, pyramidal signs, mild cognitive decline, and unresponsiveness to levodopa. Two patients had a predominantly axonal and sensory polyneuropathy of the lower legs with fasciculations in one of them. Parkinsonian features were progressive, even after the patients had stopped work [3]; encephalopathy with Parkinsonism, pyramidal signs, cerebellar ataxia, and cognitive impairments, as well as axonal polyneuropathy [7]; polyneuropathy, encephalopathy, tremor; Parkinsonian features, Parkinsonian features without polyneuropathy or cerebellar signs [8]; Carbon disulfide toxicity may persist for several years after exposure to carbon disulfide has ceased [9].

### Carbon monoxide

Carbon monoxide toxicity is frequent due to the formation of carbon monoxide by very common means such as gas cookers and exhaust fumes. However, it carbon monoxide rarely causes Parkinson's Disease. It normally requires the person having gone in to a coma as a result of the carbon monoxide poisoning before symptoms of Parkinson's Disease develop.

Common means : Motor vehicle exhaust fumes, cigarette smoke. It also forms when fuels like coal, paraffin, natural gas, oil or wood, and especially natural gas, do not burn completely in appliances such as heaters, furnaces, stoves, water heaters, and ovens.

Means of toxicity : Carbon monoxide causes hemoglobin, which transports oxygen, to turn in to carboxyhemoglobin, which does not transport oxygen. Oxygen is required for the formation of L-dopa. So carbon monoxide may cause Parkinson's Disease symptoms by interfering with the availability of oxygen to the brain. The precise means by which it causes Parkinson's Disease has still not been proven.

Symptoms : A Parkinsonian state with behavioural and cognitive impairment but could walk, or progressed further to an akinetic-mute state, and were bed-bound [10]; Parkinson's Disease symptoms such as tremor and rigidity were experienced in only a small number of people [11]; Delayed onset of Parkinsonism in some people from which they recovered [12]; In a small proportion of people, Parkinsonian symptoms occurred, such as gait disturbance, impaired mentality, urinary incontinence, and mutism. The most frequent signs were short-step gait, hypokinesia, masked face, increased muscle tone (rigidity), glabella sign, grasp reflex, and retropulsion. Intentional tremor was occasionally found, but resting tremor could not be seen [13].

### Copper

Parkinson's Disease is associated with Wilson's Disease, a genetic disorder in which copper accumulates. There do not appear to be published studies in which copper has otherwise caused Parkinson's Disease. This may be because copper is not normally formed in to a vapour or dust that can readily be inhaled or consumed. However, exposure to copper is

significantly associated with symptoms of Parkinson's Disease [14], and there is a known means via which toxicity would cause Parkinson's Disease symptoms [15].

Common means : due to Wilson's Disease in which there is a genetic accumulation of copper, copper mines, copper cooking pots, copper plumbing, extreme consumption of copper nutritional supplements.

Means of toxicity : Excessive copper can cause the formation of a copper-dopamine complex, which leads to the oxidation of dopamine to aminochrome [15].

Symptoms : Parkinsonism and depression when it is due to Wilson's Disease [16].

## Cyanide

Cyanide, usually from the consumption of potassium cyanide or sodium cyanide can result in Parkinsonism.

Common sources : Cyanide is contained in drugs such as potassium cyanide and sodium cyanide. Cyanides can be produced by certain bacteria, fungi, and algae, and are found in a number of foods and plants. Cyanide occurs naturally in cassava roots (also known as manioc), which are potato-like tubers of cassava plants grown in tropical countries. These must be processed, usually by extended boiling, prior to consumption. Fruits that have a pit, such as cherries or apricots, often contain either cyanides or cyanogenic glycosides in the pit. Bitter almonds, from which almond oil and flavoring is made, also contain cyanide. Hydrogen cyanide is contained in vehicle exhaust and in tobacco smoke. The smoke of burning plastics contains hydrogen cyanide, and house fires often result in cyanide poisonings. A deep blue pigment called Prussian blue, used in the making of blueprints, is iron (III) ferrocyanide. Cyanides are one of the very few soluble compounds of gold, and thus are used in electroplating, gold mining, metallurgy and jewellery for chemical gilding, buffing, and extraction of gold. Cyanides and hydrogen cyanide are used in the production of chemicals, photographic development, making plastics, fumigating ships, and some mining processes. Potassium Ferrocyanide is used to achieve a blue colour on cast bronze sculptures during the final finishing stage of the sculpture.

Means of toxicity : Cyanide interrupts the electron transport chain in the inner membrane of the mitochondrion because it binds more strongly than oxygen to the Fe<sup>3+</sup> in cytochrome a<sub>3</sub>, preventing this cytochrome from combining electrons with oxygen. Cyanide also occupies the place of oxygen in hemoglobin, which transports oxygen. Oxygen is required for the formation of L-dopa. So carbon monoxide may cause Parkinson's Disease symptoms by interfering with the availability of oxygen to the brain. However, the precise means by which it causes Parkinson's Disease has still not been proven.

Symptoms : Severe parkinsonian syndrome, characterized primarily by akinesia and rigidity [17]; Parkinsonism, which regressed slowly after the poisoning apart from dysarthria, bradykinesia of the upper limbs, and very brisk monosynaptic reflexes [18]; progressive Parkinsonism, dystonia and apraxia of eye opening [19]; severe Parkinsonian syndrome [20]; a combination of severe Parkinsonism and progressive dystonia [21]; severe parkinsonian

symptoms, including profound micrographia and hypersalivation [22]; Parkinsonism that regressed slowly after the poisoning apart from dysarthria, bradykinesia of the upper limbs and very brisk monosynaptic reflexes [23];

## Lead

Prolonged exposure to lead can double the likelihood of developing Parkinson's Disease [24]. Bone lead concentrations tend to be higher in people with Parkinson's Disease [83].

Common means : Lead contaminated soil, ingestion of lead dust or chips from deteriorating lead-based paints. Air pollution from the processing of lead, food grown in contaminated soil, drinking water from plumbing and fixtures that are either made of lead or have trace amounts of lead in them. Lead can be found in cosmetics in some countries, some herbal remedies, and in toys such as many from China.

Means of toxicity : Due to the similarity of their structures, lead can inadvertently replace iron in enzymatic reactions, but it does not properly function as a cofactor. This might cause a reduction in L-dopa because iron is an essential cofactor for L-dopa formation. Most lead poisoning symptoms are thought to occur by interfering with the enzyme Delta-aminolevulinic acid dehydratase (ALAD), which is required for hemoglobin biosynthesis, as is ferrochelatase, which is also inhibited by lead. Hemoglobin transports oxygen, which is required for the formation of L-dopa. So carbon monoxide may also cause Parkinson's Disease symptoms by interfering with the availability of oxygen to the brain. However, the precise means by which it causes Parkinson's Disease has still not been proven.

Symptoms : Serious and chronic exposure to lead can more than double the likelihood of developing Parkinson's Disease. Milder exposure to lead did not increase the likelihood of Parkinson's Disease [24].

## Maneb

Maneb is a fungicide. The major active element of Maneb is manganese ethylene-bis-dithiocarbamate. Pesticides are associated with an increased rate of Parkinson's Disease [25].

Common means : Maneb is used as a fungicide. There is a greatly increased likelihood of developing symptoms by people involved in horticulture and agriculture [26].

Means of toxicity : As Maneb contains manganese it is possible that it causes Parkinson's Disease symptoms via the same means as manganese, which is by inhibiting tyrosine hydroxylation, which is essential for the formation of dopamine. It would thereby lower dopamine levels. The effects of Maneb are potentiated when there is simultaneous exposure to the pesticide Paraquat [27, 28, 29, 30, 31].

Symptoms : Plastic rigidity with cogwheel phenomenon, headache, fatigue, nervousness, memory complaints, and sleepiness, other neurologic signs, such as postural tremor, cerebellar signs, and bradykinesia [32]; damaging effects on the dopaminergic system [27,

28, 29, 30, 31], that it can even effect prior to birth [27, 28, 29, 30, 31]. This suggests that somebody could be affected by the fungicide because of their Mothers exposure to it during their pregnancy.

## Manganese

Manganese can cause Manganism, an irreversible neurological disorder similar to Parkinson's disease.

Common means : Occupational exposures occur mainly in - welding, when highly exposed [33, 34, 75, 76], mining as miners are surrounded by manganese dust and airborne manganese particles, alloy production, processing, ferro-manganese operations especially in which manganese ore or manganese compounds are turned into steel, and work with agrochemicals [34, 35]. Manganese exposures in welders are less than those associated with the reports of manganism in miners and smelter workers [34]. The towns and communities surrounding the areas of manganese heavy industry could also become affected by exposure to manganese. It could occur with very excessive use of manganese supplements. It is also hypothesized that long-term exposure to the naturally-occurring manganese in shower water also puts people at risk.

Means of toxicity : Manganese inhibits tyrosine hydroxylation, which is essential for the formation of dopamine [82, 80]. So manganese causes Parkinson's Disease by lowering dopamine levels. It does not involve degeneration of dopaminergic neurons [80]. L-dopa is not an effective therapy [80].

Symptoms : A syndrome called Manganism, which is an irreversible neurological disorder virtually no different in its symptoms from Parkinson's disease [33, 35, 75, 76].

## Mercury

Mercury toxicity from a wide variety of sources is a known cause of symptoms that include those of Parkinson's Disease, especially tremor. It does this by lowering dopamine levels.

Sources of mercury : dietary fish intake, ethnic over-the-counter medications, occupational exposures to mercury vapour, possession of dental amalgam fillings, gold production, skin ointment, some soaps.

Means of toxicity : One of the chief targets of the toxin is the enzyme pyruvate dehydrogenase (PDH). The enzyme is irreversibly inhibited by several mercury compounds. The lipoic acid component of the multienzyme complex binds mercury compounds tightly and thus inhibits PDH. However, the cause of the symptoms of Parkinson's Disease is likely to be due to the fact that mercury potently causes the release of dopamine, thereby lowering dopamine levels.

Symptoms : Parkinson's Disease [36]; tremor [37, 38]; hand tremor, balance and gait disturbance with bradykinesia, paresthesias of the upper extremities, neurobehavioral

abnormalities, slight memory loss, and spatial disorientation. Psychoneurological examination revealed dementia, Parkinson's syndrome and ataxia of the lower limbs [39]; tremor, paralysis, and excessive salivation as well as tooth loss, skin problems, and pulmonary complaints [40]; fine hand tremor, depression, hypochondria symptoms, introvert behaviour, concentration difficulty, psychomotor, perceptual and motor co-ordination disturbances [41]; tremor, loss of memory, sleeplessness, metallic taste [42]; emotional changes (symptoms of depression and anxiety) and neurological changes (amnesia, insomnia and tremor of the tongue) [43]; impaired short term verbal and spatial memory, impaired sustained and divided attention, and impaired motor speed. They also suffered from elevated clinical levels of psychiatric symptomatology, including anxiety, depression and phobic avoidance, and neurological symptoms of tremor, weakness in the limbs, and excessive sweating [44]; intention tremor, dysdiadochokinesis and mild rigidity [45]; tremor, reduced coordination ability [46].

#### MPTP

MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) is a chemical that may be produced accidentally during illicit manufacture of the recreational drug MPPP, which is a synthetic heroin substitute. The neurotoxicity of MPTP was discovered in 1976 after a chemistry graduate student synthesized MPPP incorrectly and injected the result. It was contaminated with MPTP, and within three days he began exhibiting symptoms of Parkinson's disease.

Common means : The recreational drug MPPP. It was also developed but unused as a herbicide. Industrial toxin.

Means of toxicity : MPTP inhibits tyrosine hydroxylation, which is essential for the formation of dopamine. So MPTP causes Parkinson's Disease by lowering dopamine levels.

Symptoms : Parkinson's Disease [47, 48]

#### N-Hexane

N-Hexane, a constituent of solvents has been shown to cause Parkinsonism.

Common means : Most of the n-hexane used in industry is mixed with similar chemicals called solvents. The major use for solvents containing n-hexane is to extract vegetable oils from crops such as soybeans. These solvents are also used as cleaning agents in the printing, textile, furniture, and shoemaking industries. Use by chemists. Certain kinds of special glues used in the roofing and shoe and leather industries also contain n-hexane. Several consumer products contain n-hexane, such as gasoline, spot removers, quick-drying glues used in various hobbies, and rubber cement.

Means of toxicity : The precise means is not known

Symptoms : Parkinsonism [49, 50, 51]

## Paraquat

Paraquat is the trade name for N,N'-Dimethyl-4,4'-bipyridinium dichloride, a quaternary ammonium herbicide. Other members of this class include diquat, cyperquat, diethamquat, difenzoquat and morfamquat. There is a positive association between Parkinson's Disease and professional pesticide use that is related to dose and the duration of use [78]. Insecticide exposure increased the likelihood of Parkinson's Disease in men, particularly when the onset of Parkinson's Disease is at an older age, and when the doses are higher [78]. Pesticides are known to be associated with an increased rate of Parkinson's Disease [52], but the levels of most pesticides are not increased in people with Parkinson's Disease [74, 79].

Common means : Paraquat is used as a herbicide. There is a greatly increased likelihood of developing symptoms by people involved in horticulture and agriculture [53]. People with Parkinson's Disease are more than twice as likely to report heavy exposure to pesticides over their lifetime as family members without Parkinson's Disease. Those affected were usually those who used a lot of pesticides in their homes and in their hobbies, rather than those who routinely used pesticides for their occupation [54]. Pesticides are known to affect well water [55].

Means of toxicity : Paraquat structurally resembles MPTP and its metabolite MPP+. MPTP and MPP+ are neurotoxic chemicals, that can induce Parkinson's Disease in people exposed to it. Paraquat therefore might, as MPTP and MPP+ do, inhibit tyrosine hydroxylation, which is essential for the formation of dopamine. Some evidence suggests that it may cause toxicity through oxidative stress [56].

Symptoms : Paraquat can kill dopaminergic neurons in mice [57, 58], and is associated with the symptoms of Parkinson's Disease in humans [59]. However, it is claimed that Paraquat only potentiates the effect of Maneb [60, 61], and that it has no effect on humans on its own [62]. Paraquat caused hypokinesia in rats and mice on its own, but did not have the physical effects that would be expected if it caused Parkinson's Disease [73].

## Rotenone

Pesticides are known to be associated with an increased rate of Parkinson's Disease [63], as are some pesticides that are found in well water (methomyl, chlorpyrifos, propargite) [77]. There is a positive association between Parkinson's Disease and professional pesticide use that is related to the dose and duration of use [78]. Insecticide exposure increased the likelihood of Parkinson's Disease in men, particularly when the onset of Parkinson's Disease is at an older age, and when the doses are higher [78]. However, the levels of most pesticides are not increased in people with Parkinson's Disease [74, 79]. Rotenone can cause Parkinson's Disease by lowering dopamine levels.

Common means : Rotenone is used as an insecticide. There is a greatly increased likelihood of developing symptoms by people involved in horticulture and agriculture [64]. People with Parkinson's Disease are more than twice as likely to report heavy exposure to pesticides over their lifetime as family members without Parkinson's Disease. Those affected were usually those who used a lot of pesticides in their homes and in their hobbies, rather than those who

routinely used pesticides for their occupation [65]. Insecticides are also known to affect well water [66]. Rotenone is commonly used in powdered form to treat parasitic mites on chickens and other fowl, and so can be found in poultry. Rotenone is also used to eradicate exotic fish from their non-native habitats. Rotenone is produced by extraction from the roots, seeds, and leaves of certain tropical legumes. People have been known to catch fish by extracting rotenone from plants and releasing it into water.

Means of toxicity : Rotenone inhibits tyrosine hydroxylation, which is essential for the formation of dopamine. So Rotenone causes Parkinson's Disease by lowering dopamine levels. [67]

Symptoms : The neurochemical, neuropathological and behavioural features of Parkinson's disease [68]; hypokinesia and rigidity [69]. However, rotenone treated mice and rats remained without any symptoms [73].

### Toluene

Toluene is a solvent that has been shown to cause or that has been associated with people with Parkinson's Disease [70, 71].

Common means : Toluene is used as an octane booster in fuel, as a solvent in paints, paint thinners, chemical reactions, rubber, printing, adhesives, lacquers, leather tanning, disinfectants, and to produce phenol and TNT (a component of explosives). Toluene is also used as a raw material for toluene diisocyanate, which is used in the manufacture of polyurethane foams. Toluene is also used in the manufacture of dyes. Dyes are highly associated with the symptoms of Parkinson's Disease [81].

Means of toxicity : The means of toxicity is unknown.

Symptoms : Parkinsonism, pyramidal signs, mild cognitive decline, and no response to levodopa, a predominantly axonal and sensory polyneuropathy of the lower legs with fasciculations in one of them. Parkinsonian features were progressive, even after the patients had stopped work [70].

### Trichloroethylene

People that have been subjected to chronic industrial exposure to the solvent Trichloroethylene have been found to have Parkinson's Disease [72].

Common sources : Trichloroethylene is a solvent, that is used extensively in industry and the military and is a common environmental contaminant. It has been used to extract vegetable oils, in coffee decaffeination, and in the preparation of flavouring extracts from hops and spices.

Means of toxicity : The means of toxicity is unknown.

Symptoms : Workers with workstations adjacent to the source of trichloroethylene and who



were subjected to chronic inhalation and dermal exposure from handling trichloroethylene-soaked metal parts all had Parkinson's disease. Lesser chronic respiratory exposure to trichloroethylene led to many features of Parkinsonism, including significant motor slowing [72].

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