Organophosphorus compounds have three distinct neurotoxic actions. The primary action is the irreversible inhibition of acetylcholinesterase, resulting in the accumulation of acetylcholine and subsequent over-stimulation of the nicotinic and muscarinic acetylcholine receptors leading to cholinergic effects. Second, a delayed onset of ataxia, accompanied by a Wallerian-type degeneration of the axon and myelin in the most distal portion of the longest tracts in both the central and peripheral nervous systems that is known as organophosphorus ester-induced delayed neurotoxicity. A third is organophosphorus ester-induced chronic neurotoxicity, characterised by long-term, chronic neurotoxicity symptoms in individuals resulting from acute exposure to high doses that cause acute cholinergic toxicity, or from long-term, low-level, subclinical doses of these chemicals. Available data suggest that large toxic doses of organophosphorus compounds cause acute necrotic neuronal cell death in the brain, whereas sublethal or subclinical doses produce apoptotic neuronal cell death and involve oxidative stress.

KEYWORDS

- ORGANOPHOSPHORUS COMPOUNDS
- RESEARCH
- NEUROTOXICITY
- HEALTH SYMPTOMS
Introduction

Phosphorus-containing organic compounds may be divided into two major subgroups: one has a trivalent phosphorus atom with a pyramidal configuration, and the other has a pentavalent phosphorus atom with a tetrahedral configuration. Because the trivalent phosphorus atom is electron-deficient in tri-substituted phosphorus acid (triaryl or trialkyl phosphites), such as triphenyl phosphate and tri-iso-propyl phosphate, it is highly reactive and used as an antioxidant, while S,S,S-tri-n-butyl phosphorotrithioate (merphos) is used as a cotton defoliant. On the other hand, most synthetic organophosphorus compounds belong to the pentavalent group. These compounds are used in agricultural pesticides, nerve agents, pharmaceuticals, flame retardants, and so on. While most organophosphorus esters are organophosphates or organophosphorothioates, nerve agents are phosphonate esters (see Figure 1).

Organophosphorus compounds have three distinctive neurotoxic actions:

1. cholinergic neurotoxicity;
2. organophosphorus ester-induced delayed neurotoxicity (OPIDN); and
3. organophosphorus ester-induced chronic neurotoxicity (OPICN).

Cholinergic neurotoxicity

Acetylcholine (ACh) is a neurotransmitter involved in the functioning of the cholinergic nervous system. Acetylcholine is released in response to nerve stimulation and binds to postsynaptic ACh receptors, resulting in a muscle contraction or a gland secretion. The action of ACh is rapidly terminated by hydrolysis with the enzyme acetylcholinesterase (AChE). In the central nervous system, AChE is present in many areas, particularly in the cerebral cortex and striatum. In the peripheral nervous system, AChE is localised in the ganglia of the autonomic nervous system, in the parasympathetic nerve endings, and at the neuromuscular junction.

Organophosphorus esters inhibit AChE by phosphorylating the serine hydroxyl group at the catalytic triad site. The phosphoric or phosphonic acid ester formed with the enzyme is extremely stable and is hydrolysed very slowly. Phosphorylated AChE also undergoes ageing, a process that involves the loss of an alkyl group, resulting in a negatively charged monoalkyl enzyme. Organophosphorus compounds undergo detoxification by binding to other enzymes containing the amino acid serine. These enzymes include plasma butyrylcholinesterase and paraoxonase. They are also dealkylated or dearylated by the cytochrome P450 mixed function oxidase system.

Inhibition of AChE results in the accumulation of ACh at both muscarinic and nicotinic receptors in the central and peripheral nervous systems (see Figure 2). Initially, excess ACh causes excitation, then paralysis of the cholinergic transmission, resulting in some or all cholinergic symptoms, depending on the dose size, frequency of exposure, duration of exposure, route of exposure, as well as other factors such as combined exposure to other chemicals, and individual sensitivity and susceptibility.
Symptoms of cholinergic toxicity resulting from organophosphate poisoning

1. Central nervous system (brain and spinal cord): headache, dizziness, anxiety, apathy, confusion, restlessness, anorexia, insomnia, drowsiness, lethargy, fatigue, inability to concentrate, cognitive dysfunction, generalised weakness, tremors, depression of respiratory centres, depression of circulatory centres, convulsions, and coma.

2. Peripheral nervous system:
   (a) Parasympathetic autonomic postganglionic nerves (muscarinic symptoms):
       (i) sweat glands: increased sweating;
       (ii) salivation glands: excessive salivation;
       (iii) lacrimation glands: lacrimation (tearing);
       (iv) pupils: constriction (pinpoint and miosis), and spasm of accommodation;
       (v) ciliary body: blurred vision;
   (vi) respiratory tract: bronchial constriction, increased bronchial secretion, pulmonary oedema, wheezing, tightness in chest, cough, difficult or laboured breathing (dyspnoea), and slow breathing (bradypnoea);
   (vii) cardiovascular system: bradycardia, and decreased blood pressure;
   (viii) gastrointestinal system: nausea, swelling and cramps, abdominal pain, vomiting, diarrhoea, and faecal incontinence;
   (ix) urinary bladder: urinary frequency, and urinary incontinence; and
   (x) uterus: contraction.
   (b) Parasympathetic and sympathetic autonomic ganglia (nicotinic receptors):
       (i) cardiovascular system: tachycardia, and increased blood pressure; and
       (ii) skin: pale skin (pallor).
(c) Somatic motor neurones, and neuromuscular junction (nicotinic receptors): skeletal muscles: muscle fasciculations (eyelids, fine facial muscles), twitching, muscle weakness, cramps, tightness in chest, respiratory difficulty, tremors, paralysis, cyanosis, and arrest.

**Severity of symptoms**

In organophosphorus ester poisoning not all symptoms are seen in any one patient. The frequency and severity of the symptoms depend on the compound used and the level, frequency, duration and route of exposure.

**Mild poisoning:** initial symptoms are usually fatigue, dizziness and sweating. These symptoms may also be accompanied by headache, inability to concentrate, cognitive dysfunction, weakness, anxiety, tremors of the tongue and eyelids, miosis (pupil constriction), and tightness of the chest.

**Moderate poisoning:** in addition to the initial symptoms, the following symptoms may result: salivation, lacrimation, abdominal cramps, nausea, vomiting, slow pulse, bradycardia, fall in blood pressure, and muscular tremors.

**Severe poisoning:** pinpoint and non-reactive pupils, muscular twitching, wheezing, increase in bronchial secretion, respiratory difficulty, cough, pulmonary oedema, cyanosis, diarrhoea, loss of sphincter and urinary bladder control, tachycardia, elevated blood pressure, convulsions, coma, heart block, and possibly death.

**Acute and chronic exposure:** generally, the interval between a single acute toxic exposure to organophosphorus ester and the onset of symptoms is very short, usually ranging from five to 60 minutes. Some individuals, however, may not develop the symptoms of poisoning until 24 hours after exposure.

Repeated small exposures have cumulative effects. Early symptoms of chronic organophosphorus insecticide exposure are influenza-like symptoms. As exposure continues, clinical manifestations appear until a full picture develops.¹

**Effect of route of exposure**

Organophosphorus compounds are efficiently absorbed by inhalation, ingestion and skin exposure. The route of entry influences the development of symptoms. In mild cases, only some of the symptoms become evident depending on the route of absorption. In severe poisoning, however, most of the signs appear, irrespective of the route of entry.¹

**Inhalation:** inhalation of organophosphorus esters first affects the respiratory system and eyes. These effects may include: tightness of the chest, wheezing, a bluish discolouration of the skin, salivation, constriction of the pupils, aching in and behind the eyes, blurred vision, tearing of the eyes, runny nose, headache, inability to concentrate, and cognitive dysfunction.

**Ingestion:** ingesting organophosphorus esters causes loss of appetite, nausea, vomiting, abdominal cramps, and diarrhoea, possibly within two hours of exposure.

**Skin:** skin absorption results in sweating and twitching of the area affected, usually within 15 minutes to one hour of exposure.

Severe intoxication by organophosphorus esters via all routes may produce, in addition to the above symptoms, body weaknesses, generalised muscle twitching, and paralysis, leading to asphyxia and death. Furthermore, the following symptoms may also occur: dizziness, confusion, staggering, slurred speech, generalised sweating, irregular or slow heartbeat, convulsions, and coma.

**Human exposure**

Recent human exposure, mostly via inhalation, to the organophosphorus nerve agent, Sarin, has been documented in two terrorist incidents in Japan. Sarin was released at midnight in Matsumoto city on 27 June 1994.⁷ Of the 600 people who were exposed, 58 were admitted to hospital and seven died. While miosis was the most common symptom, severely poisoned patients developed central nervous system symptoms and cardiomyopathy. A few victims complained of arrhythmia and showed
cardiac contraction. Following a terrorist attack with Sarin in the Tokyo subway trains, at 8:05 am on 20 March 1995, a total of 5,000 people were hospitalised and 11 died. Patients with high exposure to Sarin in the Tokyo subway terrorist incident exhibited the following symptoms: marked muscle fasciculation, tachycardia, high blood pressure (nicotinic responses), sneezing, rhinorrhea, miosis, reduced consciousness, respiratory compromise, seizures, and flaccid paralysis. Patients with mild exposure complained of headache, dizziness, nausea, chest discomfort, abdominal cramps, and miosis. Interestingly, patients had pupillary constriction even when their cholinesterase activity was normal. Furthermore, inhibition of red blood cell AChE activity was more sensitive than serum butyrylcholinesterase activity. The absence of bradycardia and excessive secretions, which are common in dermal or ingestion exposure, suggests that the major route of exposure to the Sarin gas was via inhalation. These patients were treated with atropine eye drops for marked miosis, and pralidoxime iodide (2-PAM).

Organophosphorus ester-induced delayed neurotoxicity

Although many organophosphorus esters cause cholinergic neurotoxicity, only some of these compounds are capable of producing organophosphorus ester-induced delayed neurotoxicity (OPIDN). The results of studies that tested 237 organophosphorus compounds for the potential to produce OPIDN showed that only 109 compounds were positive. Figure 3 shows these chemicals according to their chemical structure.

Characteristics of OPIDN

Organophosphorus ester-induced delayed neurotoxicity is a neurodegenerative disorder characterised by a delayed onset of prolonged ataxia and upper motor neurone spasticity from a single or repeated exposure to organophosphorus esters. The neuropathological lesion is a central–peripheral distal axonopathy, caused by a chemical transection of the axon known as a Wallerian-type degeneration of the axon, followed by myelin degeneration of distal parts of long and large diameter tracts of the central and peripheral nervous systems.

Incidents of OPIDN have been documented for over a century (Table 1). The earliest recorded cases were attributed to the use of tri-ortho-cresyl phosphate (TOCP)-containing creosote oil for the treatment of pulmonary tuberculosis in France in 1899. In 1930, TOCP was identified as the chemical responsible for an estimated 50,000 cases of OPIDN in the southern and midwestern regions of the United States. More recently, Himuro et al reported that a 51-year-old man who was exposed to Sarin during the Tokyo subway incident and survived its acute toxicity, died 15 months later. Neuropathological alterations and neurological deficits were consistent with dying-back degeneration of the nervous system that is characteristic of OPIDN. This incident indicates that humans are more sensitive than experimental animals to Sarin-induced OPIDN, since it required 26–28 x LD₅₀ (25 µg/kg, im) lethal daily doses of Sarin to produce OPIDN in the hen.

Organophosphorus ester-induced delayed neurotoxicity has been classified into three types: Type I, caused by phosphates and phosphonates as well as their sulfur analogues; Type II, produced by phosphites; and recently, previously unknown neurotoxicity produced by phosphines has been classified as Type III.

Factors involved in the development of OPIDN

To evaluate the potential for an organophosphorus compound to produce OPIDN, several factors should be considered (see Table 2).

Species

Although humans are very susceptible to OPIDN, not all animal species are sensitive. The susceptible species include cows, sheep, water buffalos, dogs, cats and chickens, while rodents are
much less sensitive. Also, since the young of susceptible species are not sensitive, the adult hen has become the animal model in which to study this disorder. Thus, a positive result that an organophosphorus insecticide can produce OPIDN in the hen is indicative that this compound is capable of causing this effect in humans. On the other hand, a negative result in the hen screening does not indicate that the test compound will not induce OPIDN in humans. This conclusion is supported by several clinical reports indicating that some organophosphorus pesticides are capable of causing OPIDN in humans, despite the result that they did not produce it in the hen. These pesticides include: omethoate, trichloronate, trichlorfon, parathion, methamidophos, fenthion, and malathion. Subsequent studies have shown that malathion can produce OPIDN in hens and cats.

Dose size
Chronic or subchronic exposures to small daily doses of organophosphorus compounds are more toxic and efficient in producing OPIDN than large single doses (see Table 2 and Figure 4). While the threshold for a single oral dose of the organophosphorus ester TOCP that produced OPIDN in hens was 250 mg/kg, a total of 36 daily 0.5 mg/kg doses induced OPIDN, indicating that daily small doses were seven times as effective as a single oral dose in producing OPIDN.

Also, while 200 mg/kg was the minimum single oral dose of leptophos required to produce OPIDN, it took 64 daily 1.0 mg/kg doses of leptophos (totalling 64 mg/kg) to produce OPIDN (see Table 2 and Figure 5), demonstrating that daily small oral doses of leptophos were three times as effective as a single oral dose in producing OPIDN.

Similarly, small daily dermal doses of the delayed neurotoxic organophosphorus compound DEF (see Table 2 and Figure 6) were three times as effective as a single dermal dose.

While the threshold for a single oral dose of organophosphorus insecticide EPN to produce OPIDN in hens was 25 mg/kg, it took 20 daily oral doses of 0.1 mg/kg to reach the same condition (see Table 2 and Figure 7). Thus, the minimum daily oral dose and the cumulative total dose of EPN required to cause OPIDN are 250 and 13 times less than that of the single oral dose, respectively.

Route of exposure
Organophosphorus compounds have greater access to the neurotoxicity target through inhalation and skin penetration than the gastrointestinal tract, with inhalation being the most effective route of entry, preceded only by intravenous injection. The results of studies show that dermal exposure is a more effective route for the development of OPIDN.
Table 2 and Figure 8). Thus, while daily oral administration of 1.0 mg/kg of leptophos for 64 days produced OPIDN in hens, only 25 daily dermal applications of 0.5 mg/kg caused OPIDN[^19]. The results indicate that dermal application is eight times as effective as oral administration in causing OPIDN.

Also, the threshold daily oral administration of EPN that produced OPIDN was a topical dose of 0.1 mg/kg/day for 20 days[^23]. These studies indicate that the minimum total daily dermal dose was 10 times as effective as daily oral administration in producing OPIDN.

### Exposure to other chemicals

Concurrent exposure to organophosphorus compounds and other chemicals may increase their potency to induce OPIDN. The non-neurotoxicant solvent methyl iso-butyl ketone, given either via inhalation or dermal application, increased the severity of OPIDN that was induced by EPN[^26,27]. Also, propetamphos, an organophosphate that is capable of producing OPIDN (see Figure 9), decreased the threshold oral dose of chlorpyrifos to induce the disorder[^28].

Other chemicals, such as the insect repellent DEET, may enhance the transdermal delivery of other pesticides that compete with organophosphates for blood and liver esterases, for example, arylesterases and aliesterases decrease the body’s ability to detoxify these organophosphates, allowing larger concentrations of them to reach the neurotoxicity target[^29]. Recent studies have demonstrated that the combined exposure to pyridostigmine bromide, DEET, and permethrin and DEET and permethrin increased the neurotoxic action of individual compounds[^30,31].

### Neurological dysfunction of OPIDN in humans

Organophosphorus ester-induced delayed neurotoxicity is characterised by a motor-sensory deficit resulting from Wallerian-type degeneration of the axon, followed by demyelination of the central and peripheral nervous systems. Early changes in OPIDN result from degeneration of the peripheral...
nerves, leading to flaccid paralysis. Long-lasting effects are followed by degeneration of the central nervous system, producing spasticity. The course of the neurological deficits of OPIDN in humans may be divided into the following distinct phases (usually, not all of the signs and symptoms are exhibited in a patient all of the time):13,14

Latent period
Following exposure to organophosphorus compounds, there is a delay before the onset of neurological deficits. The length of this latent period varies from a few days to weeks, depending on the following factors:

1. the nature of the chemical;
2. the route of exposure;
3. the dose size and the duration and frequency of exposure;
4. exposure to other chemicals; and
5. individual differences.

Progressive phase
The early stage of OPIDN is a peripheral neuropathy which is characterised by:

1. symmetric cramping, burning and/or stinging pain in the calves of the legs and less often in the ankles and feet;
2. numbness and tingling in the feet and legs;
3. bilateral dragging of the toes on the floor (foot-drop);
4. next, the weakness spreads symmetrically to the hand;
5. “glove-and-stocking”-type decreased insensitivity;
6. steppage gait;
7. positive Rhomberg;
8. absence of Achilles heel and ankle joint reflexes;
9. neurological dysfunction may progress to flaccid paralysis; and
10. some patients exhibit urinary and bowel irregularities.

Stationary phase
After the early progression of symptoms, neurological deficits become stationary. During this phase, bilateral paraplegia or quadriplegia persists.

Improvement phase
During this phase, sensory symptoms disappear first, followed by an improvement in motor function, with hands and arms recovering before feet and legs. As improvement resulting from regeneration of the peripheral nervous system occurs, central nervous system damage becomes unmasked and is characterised by spasticity and exaggerated knee jerk.

Prognosis
The prognosis of patients with OPIDN depends on the severity of the neurological deficits resulting from nervous system damage. Some patients with

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TABLE 2
Threshold single and daily doses of organophosphorus compounds for the production of OPIDN in hens

<table>
<thead>
<tr>
<th>Compound</th>
<th>Single dose</th>
<th>Repeated doses (mg/kg)</th>
<th>Single/daily repeated</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOCP</td>
<td>250</td>
<td>Oral17 0.5</td>
<td>36 Oral17 500</td>
</tr>
<tr>
<td>Leptophos</td>
<td>200</td>
<td>Oral18 1.0</td>
<td>64 Oral19 200</td>
</tr>
<tr>
<td>Leptophos</td>
<td>0.5</td>
<td>Oral19 25</td>
<td>19 Dermal20 400</td>
</tr>
<tr>
<td>EPN</td>
<td>25</td>
<td>Oral21 0.1</td>
<td>1.9 Oral22 250</td>
</tr>
<tr>
<td>EPN</td>
<td>0.01</td>
<td>Dermal23 0.2</td>
<td>2 Dermal23 2,500</td>
</tr>
<tr>
<td>DEF</td>
<td>100</td>
<td>Dermal24 0.5</td>
<td>36 Dermal25 200</td>
</tr>
</tbody>
</table>

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mild cases of OPIDN will show clinical improvement and recovery, as peripheral nerves regenerate. In contrast, severe cases of OPIDN that involve damage to the central nervous system would persist, as the central nervous system does not regenerate. On the other hand, reversible changes in the central nervous system, such as oedema, may subside with time. Also, other neurones may take over the function of damaged neurones, resulting in functional improvement. Patients with severe neurological dysfunction may suffer permanent neurological deficits despite the regeneration of their peripheral nerves.

Mechanisms of OPIDN

Previous studies have eliminated the involvement of AChE and butyrylcholinesterase in the mechanisms of OPIDN. The hypothesis that the inhibition and ageing of the neurotoxicity target esterase (NTE), an enzymatic activity preferentially inhibited by organophosphorus compounds, results in OPIDN has not been proven. The most convincing evidence against this hypothesis is the recent finding that NTE-knockout mice are sensitive to the development of OPIDN, indicating that this enzyme is not involved in the mechanisms of OPIDN.

It has been hypothesised that the increased aberrant protein kinase mediated phosphorylation of cytoskeletal proteins could result in the destabilisation of microtubules and neurofilaments, leading to their aggregation and deregulation in the axon. Protein kinases are able to amplify and distribute signals, since a single protein kinase is able to phosphorylate many different target proteins. Several protein kinases are turned on by second messengers. For example, calcium/calmodulin-dependent protein kinase II is inactive until it is bound by the calcium-calmodulin complex that induces conformational changes and causes the enzyme to unfold an inhibitory domain from its active site.
It has been demonstrated that aberrant hyper-phosphorylation of cytoskeletal proteins is central to the pathogenesis of OPIDN. Results have shown that aggregated cytoskeletal proteins are not only a feature of OPIDN, but also a mediator of axonal dysfunction.\(^{39-51}\) Sustained hyperphosphorylation of cytoskeletal proteins perturbs the dynamics of the cytoskeleton and disrupts axonal functions and stability.

**Organophosphorus ester-induced chronic neurotoxicity**

Numerous epidemiological studies have demonstrated that individuals who were exposed to a single large toxic dose or small subclinical doses of organophosphorus compounds have developed long-term neurological deficits that last for years after exposure and that are distinct from both cholinergic and OPIDN effects. These studies have described a nervous system disorder induced by organophosphorus compounds that involves neuronal degeneration and subsequent neurological, neurobehavioural and neuropsychological consequences; it has been referred to as organophosphorus ester-induced chronic neurotoxicity, or OPICN.\(^{52}\)

**Characteristics of OPICN**

The concept of OPICN encompasses structural, functional, physiological, neurological and neurobehavioural abnormalities, including neuropsychiatric alterations. Organophosphorus ester-induced chronic neurotoxicity has the following characteristics:

1. it is produced by exposure to large acutely toxic or small subclinical doses of organophosphorus compounds;
2. clinical signs consist of neurological and neurobehavioural abnormalities;
3. persistent, long-term clinical signs continue for a prolonged time, ranging from weeks to years after exposure;
4. nervous system damage is present in the peripheral and central nervous systems, with more involvement of the latter;

**FIGURE 5**

Threshold single and daily oral doses of leptophos for producing OPIDN\(^{19,24}\)

![Graph showing threshold single and daily oral doses of leptophos for producing OPIDN](image)
5. in the brain, neuropathological lesions are seen in various regions, including the cortex, hippocampal formation and cerebellum;

6. the lesion is characterised by neuronal cell death resulting from early necrosis or delayed apoptosis;

7. neurological and neurobehavioural alterations are exacerbated by combining exposure with stress or other chemicals that cause neuronal cell death or oxidative stress; and

8. because central nervous system injury predominates, improvement is slow and complete recovery is unlikely.

**Neurological and neurobehavioural alterations**

Although the symptoms of OPICN are caused by damage to the peripheral and central nervous systems, they are primarily related to injury of the central nervous system, leading to neurological and neurobehavioural abnormalities. Studies on the effects of exposure to organophosphorus compounds over the past 50 years have shown that chronic neurological and neurobehavioural symptoms include headache, drowsiness, dizziness, anxiety, apathy, mental confusion, restlessness, labile emotion, anorexia, insomnia, lethargy, fatigue, inability to concentrate, memory deficits, depression, irritability, confusion, generalised weakness, and tremors. Respiratory, circulatory and/or skin problems may also be present in cases of chronic toxicity. It should be noted that not every patient exhibits all of these symptoms. In 1997, Jamal carried out an extensive review of the health effects of organophosphorus compounds and concluded that either acute or long-term, low-level exposure to these chemicals produce a number of chronic neurological and psychiatric abnormalities that he called organophosphate-induced neuropsychiatric disorder, or COPIND.
OPICN following large toxic exposures to organophosphorus compounds

Numerous studies have reported that some individuals, who were exposed to large toxic doses of organophosphorus compounds and experienced severe acute poisoning with subsequent recovery, have eventually developed the long-term and persistent symptoms of OPICN that were not related to AChE inhibition. Individuals with a history of acute organophosphate exposure reported an increased incidence of depression, irritability, confusion and social isolation. Such exposure resulted in a decrease in verbal attention, visual memory, motoricity and affectivity.

Exposure to organophosphorus pesticides

In 1991, Rosenstock et al reported that even a single exposure to organophosphates requiring medical treatment was associated with a persistent deficit in neuropsychological functions. A study of the long-term effects in individuals who had acute toxicity from organophosphorus insecticides indicated a decrease in sustained visual attention and vibrotactile sensitivity that were dose-dependent. In another study, one-fourth of the patients who were hospitalised following exposure to methamidophos exhibited an abnormal vibrotactile threshold for between 10 and 34 months after hospitalisation. Callender et al have described a woman with chronic neurological sequelae after acute exposure to a combination of an organophosphorothioate insecticide, pyrethrin, piperonyl butoxide and petroleum distillates, and an initial development of symptoms of acute cholinergic toxicity. Twenty-eight months after exposure, she developed “delayed sequelae of gross neurological symptoms” consisting of coarse tremors, intermittent hemiballistic movements of the right arm and leg, flaccid fasciculations of muscle groups, muscle cramps, and sensory disturbances. Colosio et al have reviewed the literature on the neurobehavioural toxicity of pesticides, and reported that some individuals, who were acutely poisoned with organophosphorus compounds, developed long-term impairment of their neurobehavioural performance that was...
“an aspecific expression of damage and not of direct neurotoxicity”.[66] These results are consistent with neuronal necrosis induced by the organophosphorus insecticide fenthion.[67]

**Exposure to organophosphorus nerve agents**

Organophosphorus nerve agents such as Sarin and Soman cause damage to the blood brain barrier, leading to neuronal cell death with subsequent neurological deficits.[68,69] In the 1995 Tokyo subway incident involving Sarin, some victims who developed acute cholinergic neurotoxicity, also developed long-term chronic neurotoxicity which was characterised by central nervous system neurological deficits and neurobehavioural impairments.[70,71] Six to eight months after the Tokyo poisoning, some victims showed delayed effects on psychomotor performance, the visual nervous system, and the vestibular-cerebellar system.[71] Furthermore, females were more sensitive than males in exhibiting delayed effects on the vestibular-cerebellar system. Three years after the Matsumoto attack in Japan, some patients complained of fatigue, shoulder stiffness, weakness and blurred vision.[72] Others complained of insomnia, bad dreams, husky voice, slight fever, and palpitations.

Petras has investigated the neuropathological alterations in rat brains 15–28 days after intramuscular injections of large, acutely toxic doses (79.4–114.8 µg/kg) of the nerve agent Soman.[73] He reported that the brain damage in all four animals that developed seizures was comparable to the brain damage in three of the four animals that only exhibited limb tremor. Neuropathological lesions were characterised by axonal degeneration, seen in the cerebral cortex, basal ganglia, thalamus, subthalamic region, hypothalamus, hippocampus, fornix, septum, preoptic area, superior colliculus, pretectal area, basilar pontine nuclei, medullary tegmentum, and corticospinal tracts. Although the mechanism of Soman-induced brain injury was not known, he noted that the lesions did not resemble those present in foetal hypoxia or OPIDN.[74,75] These results are consistent with later findings obtained after acute exposure to Soman or Sarin.[76-78] Although Petras indicated that Soman-treated animals did not need to have a seizure to develop brain lesions, other investigators have recently reported that only mice exhibiting long-lasting convulsions developed neuropathological alterations in the brain.[73]

Abdel-Rahman et al have demonstrated neuropathological alterations in rat brains 24 hours
after the administration of an intramuscular LD$_{50}$ (100 µg/kg) dose of Sarin. Neuronal degeneration was present in the cerebral cortex, dentate gyrus, CA1 and CA3 subfields of the hippocampal formation, and the Purkinje cells of the cerebellum. In these animals, both superficial (I–III) and deeper (IV–V) layers of the motor cortex and somatosensory cortex showed degenerating neurones. In the deeper layers of the cortex, degenerating neurones were seen in layer V. The layers III and V neurones in the cortex are the source of axons of the corticospinal tract which is the largest descending fibre tract (or motor pathway) from the brain, controlling movement of the contralateral muscle group. Thus, Sarin-induced death of layer V neurones of the motor cortex could lead to considerable motor and sensory abnormalities, ataxia, weakness, and loss of strength. Furthermore, disruption of hippocampal circuitry because of the degeneration of neurones in different subfields can lead to learning and memory deficits. Lesions in the cerebellum could result in gait and coordination abnormalities. Because the severely affected areas, such as the limbic system, corticofugal system and central motor system, are associated with mood, judgment, emotion, posture, locomotion and skilled movements, humans exhibiting acute toxicity symptoms following exposure to large doses of organophosphates may develop psychiatric and motor deficits. Since the damaged areas of the brain do not regenerate, these symptoms are expected to be long-term effects. The 0.50 x LD$_{50}$ Sarin dose did not cause motor convulsions and only caused some Purkinje neurone loss. The 0.1 and 0.01 x LD$_{50}$ Sarin doses did not cause any alterations 24 hours after dosing. These results indicate that Sarin-induced acute brain injury is dose-dependent.

Shih et al have demonstrated that lethal doses (2 x LD$_{50}$) of all tested nerve agents (that is, Tabun, Sarin, Soman, Cyclosarin, VR and VX) induced seizures accompanied by neuropathological lesions in the brains of guinea pigs that were similar to those reported for Soman in other species. Recent reports have indicated that anticonvulsants protected guinea pigs against Sarin and Soman-induced seizures and the development of neuropathological lesions. Time-course studies have also reported that Sarin-induced brain lesions exacerbated over time and extended into brain areas that were not initially affected. Similar results have been reported in a variety of species. A subcutaneous dose of 104 µg/kg of Soman-induced status epileptus in rats, followed by a degeneration of neuronal cells in the piriform cortex and CA3 of the hippocampus. Only mice treated with a subcutaneous dose of 90 µg/kg of Soman developed

![Chemical Structures](image-url)
long-lasting convulsive seizures and exhibited neuropathological alterations.\textsuperscript{96} Twenty-four hours after dosing, there were numerous cosinophilic cells and DNA fragmentation (TUNEL-positive) cells in the lateral septum, the endopiriform and entorhinal cortices, the dorsal thalamus, the hippocampus, and the amygdala. Animals that had only slight tremors and no convulsions did not show any lesions. Guinea pigs which were given a subcutaneous dose of 200 $\mu$g/kg of Soman ($2 \times LD_{50}$) developed seizures and exhibited neuropathological lesions between 24 and 48 hours after dosing in surviving animals in the amygdala, the substantia nigra, the thalamus, the piriform, the entorhinal and perirhinal cortices, and the hippocampus.\textsuperscript{92} Male guinea pigs developed epileptiform seizures after receiving $2 \times LD_{50}$ subcutaneous doses ($\mu$g/kg) of the nerve agents Tabun 240, Sarin 84, Soman 56, Cyclosarin 114, VX 16, or VR 22, accompanied by necrotic death of neuronal cells, with the amygdala having the most severe injury, followed by the cortex and caudate nucleus.\textsuperscript{85}

\textbf{Exposure to other organophosphates}

Kim et al reported that an intraperitoneal injection of 9 mg/kg ($1.8 \times LD_{50}$) of diisopropyl phosphorofluoridate (DFP) in rats protected with pyridostigmine bromide and atropine nitrate caused tonic-clonic limbic seizures, followed by prolonged mild clonic epilepsy, accompanied by early necrotic and delayed apoptotic neuronal degeneration.\textsuperscript{97} Early necrotic brain injury was seen between one and 12 hours after dosing in the hippocampus and piriform/entorhinal cortices. On the other hand, typical apoptotic (TUNEL-positive) cell death began to appear in the thalamus 12 hours after dosing. An intraperitoneal injection of 9 mg/kg ($1.8 \times LD_{50}$) of DFP caused severe, early (15–90 minutes) tonic-clonic limbic seizures, followed by prolonged mild clonic epilepsy.\textsuperscript{97} Necrotic cell death was seen one hour after DFP administration, mostly in the CA1 and CA3 subfields of the hippocampus and piriform/entorhinal cortices, which was exhibited as degeneration of neuronal cells and spongiform of neuropils. While the severity of hippocampal injury remained the same up to 12 hours after dosing, damage to the piriform/entorhinal cortices, the thalamus, and the amygdala continued to increase for up to 12 hours. Furthermore, apoptotic death (TUNEL-positive) of neuronal cells was seen in the thalamus at 12 hours and peaked at 24 hours.

\textbf{OPICN following subclinical exposures to organophosphorus compounds}

Reports on OPICN in individuals following long-term, subclinical exposures, without previous acute poisoning, have been documented in humans and animals.

\textbf{Exposure to low-level organophosphorus pesticides}

Professional pesticide applicators and farmers who had been exposed to organophosphorus pesticides showed elevated levels of anxiety, impaired vigilance and reduced concentration.\textsuperscript{98} A significant increase in hand vibration threshold was reported in a group of pesticide applicators.\textsuperscript{99} Male fruit farmers who had been chronically exposed to organophosphorus insecticides showed significant slowing of their reaction time.\textsuperscript{100} Female pesticide applicators exhibited longer reaction times, reduced motor steadiness, and increased tension, depression, and fatigue compared with the controls.\textsuperscript{101} Workers who had been exposed to the organophosphorus insecticide quinalphos during its manufacture exhibited alterations in the function of the central nervous system that were manifested as memory, learning, vigilance and motor deficits, despite having normal AChE activity.\textsuperscript{102}

Kaplan et al have reported persistent long-term cognitive dysfunction and defects in concentration, word finding and short-term memory in individuals who have been exposed to low subclinical levels of the organophosphorus insecticide chlorpyrifos.\textsuperscript{103} These neurological deficits are in agreement with a recent study that evaluated the effects (that is, neurobehavioural impairments) of chronic low-level exposure to chlorpyrifos in 22 patients.\textsuperscript{104}
The study demonstrated, for the first time, an association between chlorpyrifos sprayed inside homes and offices and neurophysiological impairments in body balance, visual fields, colour discrimination, hearing, reaction time, and grip strength. Furthermore, these patients also had psychological impairments in verbal recall and cognitive function, and two-thirds of them had been prescribed antidepressant drugs. The patients also exhibited excessive respiratory symptoms that were accompanied by airway obstruction. Other chlorpyrifos-induced neurotoxicity incidents in humans have been reported.105

The published results of chlorpyrifos-induced OPICN in humans are consistent with a recent report that a daily dermal application of 1.0 mg/kg of chlorpyrifos to adult rats resulted in sensorimotor deficits.106 Also, maternal exposure to 0.1 mg/kg of chlorpyrifos during gestational days 4–20 caused an increased expression of glial fibrillary acidic protein (GFAP) in the cerebellum and hippocampus of offspring on postnatal day 30.107 A major component of astrocytic intermediate neurofilament, GFAP is upregulated in response to reactive gliosis resulting from insults such as trauma, neurodegenerative diseases, and exposure to neurotoxicants.108 Also, a daily dermal administration of 0.01 x LD50 of malathion for 28 days caused neuronal degeneration in the rat brain that was exacerbated by a combined exposure to the insect repellent DEET and/or the insecticide permethrin.109

Exposure to “sheep dip” pesticides

Significant cognitive and neuropsychological deficits have been found in sheep dippers who had been exposed to organophorous insecticides.110 Pilkington et al reported a strong association between chronic low-level exposure to organophosphate concentrates in sheep dips and neurological symptoms in sheep dippers, suggesting that long-term health effects may occur in at least some sheep dippers who are exposed to these insecticides over their working lives.111

Exposure to low-level Sarin

Three years and nine months after the Tokyo attack, rescue workers and some victims who did not develop any acute neurotoxicity symptoms nevertheless complained of a chronic decline in memory.112 On their return from the Gulf War, thousands of American and British veterans complained of a range of unexplained illnesses, including chronic fatigue, muscle and joint pain, headache, loss of concentration, forgetfulness, and irritability.113 Many of the military personnel were exposed to low levels of the nerve agent Sarin that was released into the atmosphere in the Khamisiya region, following the destruction of the enemy’s arsenal during the war.114 Follow-up studies in rats have established that large toxic doses of Sarin cause acute necrotic death of brain neurones,69 whereas small doses result in delayed apoptotic neuronal cell death.1 Thus, OPICN can explain the report that Gulf War veterans are at an almost two-fold greater risk of developing amyotrophic lateral sclerosis than other veterans.115 This is also in agreement with the suggestion that the increase in amyotrophic lateral sclerosis is “a war-related environmental trigger”.116

Exposure to hydraulic fluids and jet engine lubricating oils

Hydraulic fluids and jet engine lubricating oils have been identified as possible contaminants in the recent incidents of smoke and/or fumes in aircraft cabins.117 For example, since 1989, a total of 760 incidents involving 900 flight attendants have been reported.118 The components of some of these jet engine oils and hydraulic fluids (that include several organophosphates) have been identified and are listed in Table 3.

The main components of tri-cresyl phosphate (TCP) are approximately 15–25% tri-meta-cresyl phosphate, 5–10% tri-para-cresyl phosphate, 60–75% mixed meta- and para-cresyl phosphates, and small amounts of ortho-cresyl isomers (mainly in the mono-ortho-cresyl form), with low amounts of di-ortho-cresyl isomers and minute amounts of the tri-ortho-cresyl isomer, resulting in more than 10 cresyl isomers. Because jet oils contain up to 3%
TCP as an anti-wear agent, inhalation exposure to the chemical constituents in this product is likely. Although the cholinergic neurotoxicity of TCP isomers is low, six members of this group of chemicals contain one or more ortho-cresyl moiety and are capable of causing OPIDN (see Table 4). Consistent with this is the finding that inhalation exposure to TCP, in a manufacturing plant, produced toxic polyneuritis.\textsuperscript{119} Furthermore, jet engine lubricating oils contain up to 3\% TCP — including 0.1\% TOCP, the potent OPIDN-producing isomer.\textsuperscript{120} Also, long-term inhalation exposure of chickens to concentrations of between 23 and 110 mg/m\textsuperscript{3} produced neurotoxic effects.\textsuperscript{121} It has been suggested that humans are 10 to 100 times as susceptible to developing OPIDN as chickens.\textsuperscript{122}

The available information suggests that the inhalation of contaminated aircraft cabin air may be related to OPICN. Aircrew members (including pilots and flight attendants) have consistently complained of neurological illnesses, such as headache, dizziness, cognitive dysfunction, difficulty concentrating, tremors, generalised weakness and lack of motor control, which are typical of OPICN. Although the neurotoxic effects of TCPs have been associated with the ortho-isomer, the results of experimental studies cannot be explained by the presence of the ortho-isomer alone. A recent study reported an unexpected high neurotoxic potency of aviation engine lubricants containing 3\% TCP levels and less than 0.02\% of the ortho-isomer.\textsuperscript{123} In addition to the ortho-isomer, the presence of TPCP has been confirmed in two jet engine lubricating oils, Castrol 5000 and Exxon 2380.\textsuperscript{124} Furthermore, preliminary results have shown that dermal exposure to each of the three isomers (that is, TOCP, TMCP, and TPCP) caused sensorimotor deficits in rats and neuropathological lesions in the brain.\textsuperscript{1} Although most of the investigations of the health effects caused by contaminated cabin air have focused on OPIDN, TCP and its constituent isomers, other components of the hydraulic fluids and engine lubricating oils should also be studied for their action in producing OPICN. These chemicals include: tributyl phosphate; tri-isobutyl phosphate; butyl diphenyl phosphate; dibutyl phenyl phosphate; and triphenyl phosphate. These chemicals may cause OPICN or contribute to its occurrence.

**TABLE 3**

Components of some jet engine oils and hydraulic fluids

<table>
<thead>
<tr>
<th>Product</th>
<th>Components (wt%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Engine lubricating oils</strong></td>
<td></td>
</tr>
<tr>
<td>Mobil Jet Oil 254</td>
<td>Tricresyl phosphate (TCP, 3%)</td>
</tr>
<tr>
<td>Mobil Jet Oil II</td>
<td>Tricresyl phosphate (TCP, 3%), N-phenyl-1-naphthtylamine (PAN, 1%)</td>
</tr>
<tr>
<td><strong>Hydraulic fluids</strong></td>
<td></td>
</tr>
<tr>
<td>Skydrol 5 (Solutia Inc)</td>
<td>Triisobutyl phosphate, triphenyl phosphate, epoxy-modified alkyl ester</td>
</tr>
<tr>
<td>Skydrol 500B (Solutia Inc)</td>
<td>Tributyl phosphate, dibutyl phenyl phosphate, butyl diphenyl phosphate, epoxy-modified alkyl ester, 2,6-Di-tert-butyl-p-cresol</td>
</tr>
<tr>
<td>Skydrol LD-4 (Solutia Inc)</td>
<td>Tributyl phosphate, dibutyl phenyl phosphate, epoxy-modified alkyl ester</td>
</tr>
<tr>
<td>Hyjet IV-A (Chevron)</td>
<td>Tributyl phosphate (79%), cyclic aliphatic epoxide (&lt; 2.9%), additives (&lt; 21%)</td>
</tr>
</tbody>
</table>

**TABLE 4**

Isomers of TCP

(there are 10 possible TCP isomers)

<table>
<thead>
<tr>
<th>Ortho content</th>
<th>Isomers</th>
<th>OPIDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-ortho-TCP</td>
<td>o,o,o</td>
<td>✓</td>
</tr>
<tr>
<td>Di-ortho-TCP</td>
<td>o,o,m,  o,o,p</td>
<td>✓</td>
</tr>
<tr>
<td>Mono-ortho-TCP</td>
<td>o,m,m,  o,m,p,  o,p,p</td>
<td>✓</td>
</tr>
<tr>
<td>Non-ortho-TCP</td>
<td>m,m,m,  m,m,p,  m,p,p,  p,p,p</td>
<td>X</td>
</tr>
</tbody>
</table>
Neuronal and glial autoantibodies as biomarkers for neuronal injury induced by OPICN

Alterations to the cytoskeletal structure are prominent features in some neurological diseases and chemically induced neurological disorders. Neurofilament proteins (NFP) and Tau proteins are major constituents of the axon, and microtubule associated protein-2 (MAP-2) is mostly present in the dendrites. Increased autoantibodies of these proteins are indicative of axonal degeneration. Also, increased autoantibodies against myelin basic protein (MBP) are consistent with axonal demyelination. The increase of GFAP autoantibodies is suggestive of neuronal injury.

Sera obtained from eight flight crew members and from healthy adults (controls) were assayed for the presence of autoantibodies against proteins associated with:

- neurogenesis, that is, high molecular weight neurofilament protein (NFP-200), MAP-2, and Tau proteins;
- myelogenesis, that is, MBP; and
- gliogenesis, that is, GFAP,

that have been used as markers for injury to the central nervous system. Autoantibodies against tubulin (a protein that is present in all tissues, including the nervous system) have been determined as markers for global tissue damage. Finally, autoantibodies against the glial calcium-binding protein S-100 were determined as markers for acute traumatic brain injury. Autoantibodies against neuronal proteins, NFP-200, MAP-2, Tau proteins, and MBP, and those against the proteins associated with gliogenesis, GFAP, that were increased in some sera correlated with the neurological condition of the patients. Autoantibodies against the global protein, tubulin, were not significantly higher than the controls. Autoantibodies against the S-100 protein are used as an internal standard to determine the precision of the assay. The results showed that the level of these autoantibodies was low in the flight crew members and in the controls — indicating the high precision of the results. They also suggest the absence of acute traumatic brain injury in the flight crew members and in the controls.

Many neurotoxicants, such as organophosphorus esters, as well as other insecticides, solvents and heavy chemicals, cause neuronal cell death and axonal degeneration and over-expression of GFAP, with a subsequent release of neuronal, myelin and glial proteins into circulation, followed by the formation of autoantibodies against these proteins. While not diagnostic for specific disease, the presence of circulating autoantibodies against neuronal and glial proteins at higher levels in the crew members who had been exposed to neurotoxic chemicals and developed neurological deficits than in the controls can be used as further confirmation for chemical-induced nervous system injury. The low level of autoantibodies of the S-100 protein in the serum indicates that the neurological condition is not related to an acute injury, but is rather a chronic condition.

The serum profile of increased autoantibodies against nervous system proteins in flight crew members is consistent with neurological deficits and, in the absence of other neurological diseases, it is concluded that it is consistent with chemical (such as TCP)-induced nervous system injury.

Mechanisms of OPICN

Recent studies have shown that large toxic doses of organophosphorus compounds cause early convulsive seizures and subsequent encephalopathy, leading to the necrotic death of brain neuronal cells, whereas small doses produce delayed apoptotic death. Pazdernik et al have proposed the following five phases that result in organophosphorus compound-induced cholinergic seizures: initiation, limbic status epilepticus, motor convulsions, early excitotoxic damage, and delayed oxidative stress. Necrosis: in addition to breaking down the blood brain barrier and producing early seizures, large toxic doses of organophosphorus compounds result in the activation of the glutamergic system and the
involvement of the Ca^{2+}-related excitotoxic process, possibly mediated by the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Accumulated ACh, resulting from acute inhibition of AChE by organophosphorus compounds, leads to the activation of glutamatergic neurones and the release of the excitatory L-glutamate amino acid neurotransmitter that is a major agonist of NMDA receptors and a major excitatory neurotransmitter in the central nervous system, as well as being a potent excitotoxin. This leads to increased depolarisation and subsequent activation of the NMDA subtype of glutamate receptors, and the opening of NMDA ion channels, resulting in massive Ca^{2+} fluxes into the postsynaptic cell and the disruption of postsynaptic calcium homeostasis. This results in the production of free radicals and the degradation of intracellular components and mitochondrial damage, causing neuronal degeneration (see Figure 10).

The activation of nitric oxide synthase, following stimulation of NMDA receptors, increases the level of nitric oxide which functions as a signalling or cytotoxic molecule responsible for neuronal cell death. As a retrograde messenger, nitric oxide induces the release of several neurotransmitters, including excitatory amino acid L-glutamate which alters neurotransmitter balance and affects neuronal excitability. The production of nitric oxide is enhanced in AChE inhibitor-induced seizure. Kim et al have demonstrated the involvement of nitric oxide in organophosphate-induced seizures and the effectiveness of nitric oxide synthesis inhibitors in preventing such seizures.

Apoptosis: small doses of organophosphorus compounds cause delayed neuronal cell death that involves free radical generation, that is, reactive oxygen species (ROS). Organophosphates that cause mitochondrial damage/dysfunction, cause depletion of adenosine triphosphate (ATP) and increased generation of ROS, which results in oxidative stress. Reactive oxygen species cause fatal depletion of mitochondrial energy (ATP), induction of proteolytic enzymes and DNA fragmentation, leading to apoptotic death.

These results are consistent with the DNA damage detected in the lymphocytes in peripheral blood in eight individuals following residential exposure to the organophosphorus insecticides chlorpyrifos and diazinon. The brain is highly susceptible to oxidative stress-induced injury for several reasons: its oxygen requirements are high; it has a high rate of glucose consumption; it contains large amounts of peroxidisable fatty acids; and it has relatively low antioxidant capacity. A single 0.5 x LD_{50} sublethal dose of Sarin which did not induce seizures, nevertheless caused delayed apoptotic death of rat brain neurones in the cerebral cortex, the hippocampus, and the Purkinje cells of the cerebellum 24 hours after dosing. Furthermore, rats treated with a single 0.1 x LD_{50} dose of Sarin which did not exhibit brain histopathological alterations one, seven or 30 days after dosing, nevertheless showed apoptotic death of brain neurones in the same areas mentioned above, one year after dosing. These results are consistent with the sensorimotor deficits exhibited by Sarin-treated animals three months after exposure; the animals continued to deteriorate when tested six months after dosing.

Increased AChE gene expression: recent studies have suggested that AChE may play a role in the pathogenesis of OPICN, similar to that reported for Alzheimer’s disease. It has been demonstrated that Sarin induced AChE gene in the same regions of the brain that underwent neuronal degeneration. It has also been shown that AChE is neurotoxic in vivo and in vitro, and accelerates the assembly of amyloid peptide in Alzheimer’s fibrils, leading to death through apoptosis. Further studies have demonstrated an increased AChE expression in apoptotic neuroblastoma SK-N-SH cells after long-term culture. These results support the association between AChE and neuronal apoptosis in Alzheimer’s disease. Brain AChE was shown to be toxic to neuronal (Neuro 2a) and glial-like (B12) cells. Also, transgenic mice over-expressing human AChE in brain neurones underwent progressive cognition deterioration. The results suggest that Sarin provokes an
endogenous cell suicide pathway in susceptible neurones such as caspase-3 pathway, resulting in the release of AChE into adjacent brain tissues. Acetylcholinesterase aggregates and initiates more apoptotic neuronal death. Thus, this cascade amplification results in the progressive neuronal loss that is the hallmark of Sarin-induced chronic neurotoxicity. It is noteworthy that a common symptom of both OPICN and Alzheimer’s disease is memory deficit, suggesting that OPICN accelerates the ageing process following exposure to organophosphorus compounds.

**Conclusion**

Previous reports have indicated that, after exposure to organophosphorus compounds, an individual could develop acute cholinergic neurotoxicity, followed by OPICN. In a few cases, OPIDN may occur with or without the development of cholinergic neurotoxicity, and then later OPICN ensues. Furthermore, OPICN may take place after long-term, low-level exposure to organophosphorus compounds and without the development of acute neurotoxicity. Because the long-term, persistent effects of OPICN result from neuronal degeneration of the peripheral and central nervous systems induced by organophosphates, it is unlikely that improvement is the consequence of the regeneration of brain neurones, since such a repair phenomenon is not typical of the central nervous system. Clinical improvement may take place, however, through the repair of the peripheral nervous system. Also, reversible changes in the central nervous system that might initially be present (for example, oedema) could later subside and result in the appearance of repair. Furthermore, if the damage is not too extensive, other neurones having the same function could meet the added demands and maintain normal activity. When the central nervous system is severely damaged, neither of these repair mechanisms is possible and some loss of function could occur.
Organophosphorus ester-induced chronic neurotoxicity

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† Unpublished data.


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Organophosphorus ester-induced chronic neurotoxicity


