

Low level exposures to organophosphorus esters may cause neurotoxicity

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Abstract

A large number of published studies support the notion that long term, low level (LTLL) exposure to organophosphorus (OP) esters may cause neurological and neurobehavioral effects. In order to differentiate these from other effects of OP such as the acute cholinergic episodes, intermediate syndrome and organophosphate induced delayed neuropathy (OPIDN), the term Chronic Organophosphate Induced Neuropsychiatric Disorder (COPIND) will be used purely for the ease of reference. The question addressed in this particular review is whether LTLL exposure to OP may produce neurotoxicity. The profile and the degree of overlap of the various components of COPIND have been addressed elsewhere and description of the possible mechanisms for COPIND is outside the scope of this article. COPIND can be classified under two headings; those produced following one or more acute clinical cholinergic episodes, and those produced without such preceding attacks. With regards to the first group, there are a total of 11 studies, all of which support the existence of a positive link between exposure to OP and neurotoxicity; six of these studies comprise descriptions of large numbers of cases without controls while five additional studies employ controls. Appearance of neurotoxicity does not seem to be related to the number or the intensity of acute cholinergic attacks. With regards to the second group, three types of studies can be identified. Firstly, there are five studies using experimental animals, all of which showed a positive link between OP and neurotoxicity. Secondly, a total of seven case studies without controls, some involving large numbers of patients, concluded that there is a positive link between OP and neurotoxicity. Thirdly, 19 studies investigated such a link using cases and control groups. Of these, 15 studies (about 80%) showed a positive link and only four failed to identify any link between OP and neurotoxicity. Annotation of *all* the 19 studies according to ideal set of criteria showed that only a few of these comply with the rules of excellence and all of these few showed a positive link. Furthermore, the only study carried out blind without the identification of subjects or controls, showed a positive link between OP and neurotoxicity. This blind study estimated the overall incidence of a form of neurotoxicity in people exposed to OP to be about 40 times higher than in the general population. The type of neurological involvement was unique and different from OP induced syndromes previously described. The profile of the neurological involvement was similar to that in COPIND whether or not preceded by acute cholinergic episodes, thus providing further evidence that these two neuropathies probably share a similar mechanism. There is a characteristic pattern of involvement of 15 functional indices of the autonomic nervous system examined in our laboratory. There are, in addition, preferential anatomical sites of target organs affected, selective preservation of

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cholinergic function within the same neuropathy-positive site, and evidence of mal-function of cardiac chemoreceptors in patients exposed to OP. The peripheral nerve involvement in OP exposure is predominantly sensory in nature affecting both small and large fibre populations. Neurobehavioral involvement of mainly cognitive dysfunction and other features are also described in other studies. The weight of current evidence is therefore very much in favor of the motion that chronic low-level exposure to OP produces neurotoxicity. Criticisms levelled against this motion are unfounded and probably misconceived.

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1. Introduction

Exposure to organophosphorus (OP) esters can cause several syndromes including acute cholinergic clinical episodes, the so-called Intermediate syndrome, organophosphate induced delayed neuropathy (OPIDN) and chronic neurological effects. Acute toxicity is produced by irreversible inactivation of the enzyme cholinesterases, the exact mechanism of the intermediate syndrome is not understood while the OPIDN is claimed to be 'marked' by the inhibition and subsequent ageing (dealkylation) of a protein enzyme in nerve cells called neuropathy target esterase (NTE). The ability to produce OPIDN is not even related to the degree of inhibition of AchE and there is no indication that the intermediate syndrome is related to the cholinergic effect of OP compounds. It took the medical and scientific body more than 50 years to recognise OPIDN despite its dramatic nature of clinical presentation.

Chronic neurological effects have been reported to occur either following one or more attacks of acute cholinergic episodes or following long-term, low-level (LTLL) exposure to OP compounds. In order to differentiate the chronic neurological effects from the rest of the OP syndromes, the term Chronic Organophosphate Induced Neuropsychiatric Disorder (COPIND) is used for ease of reference. The remit of this review is confined to providing affirmative evidence to the title statement that low-level exposure to OP esters *may* cause neurotoxicity. It is not the remit of this article to describe the *profile* of the chronic toxicity or to discuss the possible underlying *mechanisms* of such chronic toxicity. These have been described

elsewhere (Jamal, 1997) but will be mentioned briefly, given the limited space.

2. Review of studies in the literature

Studies concerning the chronic effects of OP esters are discussed in this review under two different headings; studies of COPIND following one or more acute cholinergic episodes *and* COPIND without preceding cholinergic attacks.

2.1. COPIND following acute cholinergic episodes

All the studies identified in the literature in this respect reach similar conclusion that there is a positive link between exposure and neurotoxicity. These studies can be divided into two groups. There are six studies which describe a large number of cases with a history of acute cholinergic episodes which developed long-term chronic neurotoxicity (Table 1) and these studies did not utilise control subjects. Table 2 shows a further five studies, which used controls for comparison and all the five studies concluded that there are positive links between OP exposures and chronic neurotoxicity. Analysis of all the above 11 studies show that neither the incidence nor the severity of development of chronic neurotoxicity had any relation with either the number nor the severity of the acute cholinergic episodes. In some of the cases described, the acute episodes were so mild that they escaped clinical detection (Kaplan et al., 1993; Jamal et al., 2001).

Table 1
Studies of chronic OP neurotoxicity following acute episode(s) that used no matched control groups

Reference	Exposed group	Parameters studied	Link	Controls
Holms, 1955	Workers	EEG	+	–
Tabershaw and Cooper, 1966	Workers	Psychiatry	+	–
Korsak and Sato, 1977	Workers	EEG Psychometric	+ +	–
Hirschberg and Lerman, 1984	Workers	EEG Psychiatry	+ +	–
Kaplan et al., 1993	Mixed	Neurology Neurophysiology Psychometric	+ + +	–
Callender et al., 1994	Workers	Neurology SPECT scan	+ +	–

2.2. COPIND without previous acute cholinergic episodes

Three types of studies investigated the link between LTLL subclinical exposure and chronic neurotoxicity:

- 1) Five studies in experimental animals all showed a positive link between OP exposure and neurotoxicity (Table 3). These studies looked at OP effects on the central as well as the peripheral nervous systems and all were of very high quality with proper experimental controls.
- 2) Seven studies conducted in apparently *healthy* groups of individuals, who were still working

at the time of the study, all concluded that there was a positive link between LTLL OP exposure and neurotoxicity (Table 4). Large numbers of cases were studied but *without* matched controls or any other kind of controls. The procedures included assessment of the central and peripheral nervous systems and the findings were judged against predetermined criteria of abnormality for the particular tests or neuropathy assessments employed.

- 3) Nineteen studies conducted on human subjects of different occupations and in which matched controls were used (Table 5). Of these, 15 (about 80%) demonstrated and concluded that there was a positive link

Table 2
Studies of chronic OP neurotoxicity following acute episode(s) that used matched control groups

Reference	Exposed group	Parameters studied	Link	Controls
Savage et al., 1988	Workers	Psychometric Neuronal necrosis	+ +	Matched
Rosenstock et al., 1991	Workers	Psychometric	+	Matched
Steenland et al., 1994	Mixed	Neurology Neurophysiology Psychometric	+ + +	Matched
McConnell et al., 1994	Workers	Neurophysiology	+	Matched
Jamal et al., 2001	Farmers	Neurology Neurophysiology	+ +	Matched

Table 3
Studies of chronic OP neurotoxicity following LTLL exposure using experimental animals

Reference	Exposed animals	Parameters studied	Link	Controls
Burchfiel et al., 1976	Primates	EEG	+	control and pre-exp EEG
Duffy and Burchfiel, 1980	Rhesus monkeys	EEG	+	Non-exposed
Kelly et al., 1994	Mice	EPP jitter	+	Self control
Kelly et al., 1997	Mice	EPP jitter	+	Self control
Prendergast et al., 1997	Rats	Spatial learning	+	Self control

between LTLL exposure to OP esters and the development of chronic neurotoxicity. Only four studies failed to demonstrate such a link but these are relatively old and most of them can be criticised for their design and strict relevance to the question. For example, in the study by [Maizlish et al. \(1987\)](#), subjects were only exposed for the duration of 39 days in total, which is hardly relevant to long-term exposure. Three of the four studies with negative results looked at small numbers in addition to other methodological shortcomings. All these four negative studies except one, looked almost exclusively at psychometric aspects, indicating the restricted number of neuropathy parameters examined in the studies.

We have attempted to annotate these 19 studies of group three using the following criteria: (1) Subjects selected represented the population studied i.e. no selection bias; (2) the controls used were appropriate and matched; (3) the sample size was adequate and the statistics used were appropriate; (4) the study design was cross-sectional; (5) examiner groups worked blind of each other's findings; and (6) all examiners were blind to the identity and category of subjects, that is whether subjects were controls or otherwise. Out of the total of 19, only four studies fulfilled the first four of the rules above and these are: [Stephens et al. \(1995\)](#), [Cole et al. \(1997\)](#), [Fiedler et al. \(1997\)](#), [Horowitz et al. \(1999\)](#). One study fulfilled the first five rules; [Jamal et al. \(2001\)](#) and only one study fulfilled all the six rules above, the study by

Table 4
Studies in humans of chronic OP neurotoxicity following LTLL exposure in which no matched control groups were included

Reference	Exposed group	Parameters studied	Link	Controls
Gershon and Shaw, 1961	Workers/scientists	Psychiatry	+	–
Dille and Smith, 1964	Workers	Psychiatry	+	–
Metcalf and Holmes, 1969	Workers	Psychometric EEG	+ +	High/low dose
Korsak and Sato, 1977	Workers	Psychometric EEG	+ +	–
Burger et al., 1991	Workers	Neurology Neurophysiology	+ +	–
Ahmed and Davies, 1997	Farmers	Psychiatry Neurophysiology	+ +	–
Amr, 1999	Applicators (300)/Formulators (300)	Neurology (40%) Neurophysiology (40%) EEG (25%) Psychiatry (40%)	+ + + +	–

Table 5
Studies of human chronic OP neurotoxicity following LTLL exposure in which matched control groups were included

Reference	Exposed group	Parameters studied	Link	Controls
Stoller et al., 1965	Workers	Psychometric	–	Non-exposed
Rodnitzky et al., 1975	Sprayers	Psychometric	–	Non-exposed
Levin et al., 1976	Sprayers	Psychiatry	+	Non-exposed
Duffy et al., 1979	Workers	EEG+(MultivarAnal)	+	Non-exposed
Maizlish et al., 1987	Workers	Psychometric	–	Non-exposed
Misra et al., 1994	Applicators	Neurology + Psychometric + P300 (CEP) +	+ + +	Non-exposed and matched
Ames et al., 1995	Applicators	Psychometric – Neurophysiology –	– –	Non-exposed
Stokes et al., 1995	Applicators	Neurology + Neurophysiology +	+ +	Non-exposed
Stephens et al., 1995	Farmers	Neurobehavioral + Psychometric +	+ +	Non-exposed quarry workers
Beach et al., 1996	Farmers	Neurology +	+	Quarry workers
Parron et al., 1996	Farmers	Psychiatry +	+	Non-exposed
Cole et al., 1997	Applicators	Neurobehavioral + Psychometric +	+ +	Non-exposed
Fiedler et al., 1997	Farmers	Neurobehavioral – Psychometric +	– +	Non-exposed
Al-Shehab et al., 1998	Workers	Neurology +(68%) Neurophysiology +	+ +	Non-exposed
Horowitz et al., 1999	Applicators	Neurology +(44%) Neurophysiology +	+ +	Non-exposed
Kilburn, 1999	Exposed (indoor)	Neurology + Psychometric + Neurobehavioral +	+ + +	Non-exposed
Davies et al., 1999	Farmers	Psychiatry + Neurobehavioral +	+ +	Non-exposed
IOM/INS 2001	Farmers	Neurology + Neurophysiology + Neurobehavioral + Psychometric +	+ + + +	Non-exposed farmers, quarry workers and blind
Jamal et al., 2001	Farmers	Neurology + Neurophysiology + Neurobehavioral +	+ + +	Non-exposed farmers and blind

Pilkington et al. (1999). All of these high quality studies showed evidence of a positive link between LTLL exposure to OP esters and chronic neurotoxicity. The most accurate study available to date estimated the overall incidence of one form of neurotoxicity, distal axonal peripheral neuropathy,

to be about 40 times in people exposed to OP compared to the incidence in the general population (Pilkington et al., 1999). This involved 612 subjects exposed to OP and they were compared with a large group of unexposed subjects of the same occupational group as well as with another

large group of control subjects belonging to a different occupational group but with a similar physical effort, socio-economic background and geographical location. The study included a complex OP exposure assessment model, a detailed field study followed by a comprehensive and exhaustive hospital-based examination and investigation. All investigators were kept completely blind of the identity and category of subjects, their exposure history or the outcome of the field study. The investigators were also blind to each other's findings. The study concluded that there was a positive link between LTLL exposure to OP esters and chronic neurotoxicity. The study also provided important insight into the profile of neurotoxicity, which confirmed earlier findings and showed that there was a positive correlation between abnormal neurological tests and evidence of anxiety and depression in patients exposed to OP. In another study (Jamal et al., 2001), the neuropathy profile confirmed earlier observations (Kaplan et al., 1993; Steenland et al., 1994; McConnell et al., 1994; Horowitz et al., 1999; Pilkington et al., 1999) that this neuropathy linked to LTLL exposure to OP, unlike OPIDN, was predominately involving the sensory nerve fibres and affected both small and large fibre populations. This neuropathy profile linked with LTLL exposure to OP was also compared with another one seen in chronic neurotoxicity following one or more acute cholinergic episodes (Jamal et al., 2001). The two neuropathy-profiles were found to be similar, though generally more pronounced in the group where cholinergic attacks preceded neuropathy thus providing further evidence that the neuropathies linked with OP exposure probably have similar pathophysiology.

2.3. *The objective neurological evidence of OP neurotoxicity*

A variety of objective neurological and neuropsychometric tests and procedures have been used to investigate the link between LTLL exposure to OP esters and chronic neurotoxicity. These include psychometric tests, EEG, neurological examination, nerve conduction studies, needle EMG studies, quantitative sensory testing, neuromuscular

jitter testing, cognitive evoked potentials, SPECT scanning. Other abnormalities found included speech abnormality, extrapyramidal features, frontal lobe syndrome and organic psychiatric manifestations. Of all these parameters and the groups of tests listed above, a slight inconsistency was found in the literature in only the first four, nevertheless, the absolute majority of studies have demonstrated clear and consistent abnormal findings in patients exposed to OP. A battery of Psychometric tests is sophisticated, the sensitivity is not high and different methods are used which may explain the apparent inconsistency of the results of such studies. Inconsistencies are also encountered in conditions where there is no argument of the presence of psychological changes, for example, in post-traumatic head injury patients. Studies using the remaining neurological parameters listed above all demonstrated clear abnormalities in patients exposed to OP. As for the EEG, it is generally agreed that computer-based EEG analysis always detects abnormality. As for nerve conduction studies, care must be taken in the choice of the nerves and methods used. Bedside neurological examination alone is not always sensitive enough to be used to obtain sufficient evidence of neurological dysfunction.

2.4. *The autonomic evidence of OP neurotoxicity*

Recent advances in clinical examination of the autonomic nervous system (Julu et al., 1997b, 2000, 2001; Moran et al., 2001) can now allow profiling of target organ functions in various diseases. We have carried out target-organ orientated examination of the autonomic nervous system initially in 15 patients with LTLL exposure to OP (Julu et al., 1997a), but have now expanded it to 40 patients with exposure periods ranging between 5 and 25 years (Julu et al., 1997 unpublished data). These patients were referred to us for examination of autonomic function because their symptoms gave the clinical impression of COPIND. A total of 15 indices of autonomic functions were examined according to predetermined criteria of normality (Julu et al., 1997b, 2000) and autonomic target organs situated in the skin, large blood vessels including the heart, the brainstem,

splanchnic bed and skeletal muscles were covered in this clinical assessment. A unique combination of the type of target organs affected immersed among the 40 patients, quite different from what we have observed in other diseases during our regular clinical autonomic assessments. What was also unique among OP exposed patients was that certain cholinergic functions were selectively preserved; for example, the sudomotor function in the skin and respiratory modulation of cardiac vagal tone in the bulbar reticular formation in the brainstem were often not affected and yet other functions that do not require cholinergic nerves in the same anatomical sites were abnormal. It is well known that chronic low level of anticholinesterase activity protects cholinergic synapses from episodic large anticholinesterase poisoning, but could it at the same time damage non-cholinergic synapses in the same area? This is a strong possibility given the evidence from our patients chronically exposed to LTLL of OP.

The anatomical sites where autonomic target-organs were most often affected were the skin, the large blood vessels including the heart and the brainstem. Each of these commonly affected anatomical sites has a unique feature, for example, there is selective preservation of sudomotor function in the skin mentioned above. In the heart, there is non-vagal bradycardia in most patients, the type evoked by stimulation of sub-endocardial chemoreceptors using noxious chemicals (Eckberg et al., 1974). It is suggestive of malfunction of these cardiac chemoreceptors in patients with LTLL exposure to OP. In the brainstem, there is a selective central parasympathetic abnormality resulting in a low resting cardiac vagal tone in a system where monoaminergic function is required (Jordan, 1995), while the vasodepressor function of the baroreflex and respiratory modulation of cardiac vagal tone where there is a known participation of cholinergic neurones (Jordan, 1995) are often both normal. This observation in the brainstem is consistent with the central nervous system involvement in chronic exposure to OP, featuring characteristic neurobehavioral manifestations mainly involving the cognitive function and other features (Ahmed and Davies, 1997;

Davies et al., 1999) known to be influenced by monoaminergic neurones.

The above studies provide a body of evidence that LTLL exposure to OP selectively damages certain autonomic synapses or nerves.

2.5. Answers to counter arguments

The following arguments put forth against the association of LTLL to OP with neurotoxicity are invalid and weak for these reasons.

2.5.1. Studies suffer from selection bias

As annotated above, there are some extremely powerful and well-designed studies concluding that there is a link.

2.5.2. There is lack of follow up as to what happens in the long term after cessation of exposure

This is not an argument as such against the existence of chronic neurotoxicity. We do agree on the necessity of such studies. We have done some work in this regard and our early results indicate that some patients show clear improvement after cessation of exposure and peripheral neurophysiological parameters may even normalise, while other patients do not. This is typically seen in other chronic toxic neuropathies such as those caused by lead and thallium.

2.5.3. The mechanism of chronic toxicity is not known

There are many well established neurological diseases for which the mechanism is not known such as Motor Neurone Disease (MND), Parkinson disease, migraine, etc. Furthermore, the mechanism of intermediate syndrome of OP is also unknown but nobody doubts its existence. There are several possible postulated mechanisms to explain chronic toxicity, but their discussion is beyond the scope of this article (Table 6).

2.5.4. Studies fail to establish dose–response relationship

It is much more difficult to measure exposure in cases of LTLL exposure to any chemical and OP is not different in this regard. A number of complicating factors, which make exposure assessment

Table 6
Possible mechanisms of chronic OP neurotoxicity

Proposed mechanism	Suggesting authors and papers
Prolonged AChE inhibition	Duffy and Burchfiel, 1980
Abnormal cerebral circulation	Duffy and Burchfiel, 1980
Long term pre-synaptic disorder and variable synaptic safety factor	Duffy and Burchfiel, 1980 Baker and Sedgwick, 1996 Jamal, 1997 Albuquerque, 1998
Disturbed cellular protein turnover and trans-membrane signaling	Berman, 1992
Damaged proteins other than Ach and NTE	Jamal, 1997 Glynn, 2000
Alteration of cytoskeletal proteins: microtubules, neurofilament triplet proteins and MAP	Abou-Donia et al., 1996 Abou-Donia and Garretson, 2000
CNS receptor deregulation	Corrigan et al., 1994 Albuquerque, 1998 Davies et al., 1999

Table 7
Factors influencing estimation of chronic low level exposure dose

1. Quantity	Size of individual episode exposure Number of cumulated episodes of exposure
2. Time factor	Duration of individual episode exposure Overall years of exposure Frequency of exposure (per year) Intervals between exposures
3. Use and quality of protective equipment	
4. Combination exposure or 'cocktail effect' exposure to other chemicals	
5. Exposure to impurities	
6. Other factors (e.g. physical and mental stress, state of blood–brain barrier)	

extremely difficult (Table 7, may be responsible for absence of dose–response relationship in some studies. Furthermore, the high quality studies did show a dose–response relationship (Stephens et al., 1995; Pilkington et al., 1999).

2.5.5. Studies describe electrophysiological effects of uncertain significance

Abnormal neurophysiology is a marker for abnormal function. The correlation of its various parameters with symptoms or measurement of the severity of neurological involvement are different matters altogether and should not be confused.

2.5.6. Neurotoxicity even if detected is subtle and in some cases not associated with signs

The parameters used are markers of dysfunction and they do not necessarily measure severity. It is extremely difficult to measure the severity of some crippling symptoms such as fatigue, changes in concentration, disturbances of memory, nausea, dizziness, sweating and many other symptoms. Furthermore, all the studies done compare a 'healthy and working' occupational group with controls and the studies are therefore not designed to look at severity anyway.

2.5.7. Neuropathy does not improve, even several months after cessation of exposure

This is typical of and evidence for chronic neurotoxicity. Even demyelinating neuropathies may take up to 30 months to improve, and improvement of most axonal neuropathies is less consistent, with some improving, but others not.

2.5.8. Reports of psychogenic tests show inconsistent results and changes may be in the opposite direction

The psychometric tests are a battery of various tests that are carried out according to different protocols. The overall picture is important and this is consistent in the vast majority of the studies. Occasional inconsistencies are found in some of the studies, but this may be due to different methodologies or variation in subject selection. Such variations are also encountered in psychometric tests in relation to other entities, such as

head injury, in which there are well-recognised psychometric changes.

3. Conclusion

- Each and every study available in the literature concludes that chronic neurotoxicity can follow one or more acute cholinergic episodes. The development of chronic neurotoxicity seems to be unrelated to the number or the severity of the acute cholinergic attacks.
- With regards to the relationship between long term low level exposure to OP (with no history of preceding acute cholinergic episodes) and development of chronic neurotoxicity, the following conclusions can be made: All studies done so far on experimental animals (five in total) show positive link; All human studies conducted without controls (seven in total) concluded a positive link; About 80% of studies on humans which used controls (19 in total) showed a positive link. Furthermore, in the last group, studies that ranked high in quality using set criteria, all showed a positive link.
- There seems to be a characteristic profile of involvement of the various neurological parameters in chronic neurotoxicity and this profile is similar in both types of chronic toxicity (i.e. whether or not preceded by acute cholinergic episodes).
- The weight of evidence in the literature is heavily in favor of the motion.
- Criticisms levelled against the motion are not valid.

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