Chapter 7
Pesticides and Chronic Neurological Effects (draft)

The brain and peripheral nervous system are directly affected by pesticides both as targets of action and deposition sites. All classes of pesticides can affect brain and neural tissue even if they do not cause observable acute effects. The pesticides that most directly affect the nervous system are the organophosphate and N-methyl carbamate insecticides, which are responsible for most acute poisonings (see Chapter 3).

In addition to acute poisoning, organophosphates can produce subacute, delayed and chronic neurological, neurobehavioural and psychiatric syndromes. Evidence for chronic neurological and psychiatric effects of OP compounds have come from case reports, clusters of neurological diseases and from studies of exposed workers and other populations.

Both high and low level chronic exposures can affect the peripheral nervous system by slowing of conduction velocity, and denervation and other electromyographic findings (Table 1). Vibrotactile sensitivity impairment , and posture abnormalities have also been reported (Table 2).

Chronic Neurological Effects Associated with Pesticide Exposure

Nerve Conduction Velocity	Slowing
Reaction Time	Slowing
Motor/visual speed tests	Slowing
Learning / memory tasks	Poorer performance
Vibrotactile Sensitivity	Impaired
Postural Sway	Abnormal
Electroencephalogram	Increased beta activity
Visual Evoked Potentials	Decreased amplitude
Muscle strength	Decreased

Central nervous system effects are assessed by batteries of neurobehavioral and neuropyschological tests, which include learning, memory, and mood among others (Tables 3-A and 3-B).

Electroencephalograms are not often done in pesticide exposure. An increase in beta activity slowing has been reported; most findings are of small changes or no associations (Table 4).

Psychological and neurological effects of pesticides may be subtle and difficult to demonstrate unless a comprehensive set of test are done. This is usually not the case because of time constrains, and an effort to develop a test battery that can be used through out the world, in both literate and non-literate populations, so diverse population can be comapred.

Chronic neurological sequelae have been reported after apparent full recovery from acute organophosphate poisoning.

Parkinson's Disease: The chronic disease most consistently associated with pesticides is Parkinson's disease. Parkinson's disease is one of the most common neurodegenerative disorders associated with aging. It is characterized by a loss of the neurotransmitterdopamine in the substancia nigra, in the part of the brain that controls movement. First described in 1871, the cause of the disease. is still unknown.

Parkinson's Disease Incidence / 100,000 Ferrara, Italy 1967-1987

Urban areas	3.11
Rural Areas	6.32
Agric. workers	20.6

Source: Reference 91

Laboratory studies show exposure to a wide variety of neurotoxic compounds, including pesticides, can deplete dopamine in the brain in a variety of animals.

The first studies to link pesticides with agricultural production were done in Canada, suggesting an association with living in rural areas and drinking well water. More recent studies confirm an association with pesticide exposure, both occupational and in the home (Table 6).

Organophosphate Induced Delayed Neuropathy (OPIDN)
In severe cases of poisoning by some organophosphate, after a delay period of apparent recovery, muscle weakness, ataxia, and paralysis develop. This condition called organophosphate induced delayed neuropathy (OPIDN) is characterized by axon degeneration and degeneration of myelin in the peripheral and central nervous systems. Mild cases may recover, but more severe cases show symptoms of an upper motor neuron lesion in the lower limbs. The condition is rare, and most cases are due to suicidal ingestion of concentrated formulations (Table 7).

Pesticides* Linked to OPIDN

Chlorpyrifos
Dichlorvos (DDVP)
Fenthion
Femnitrothion
Leptophos
Malathion
Methamidophos
Mipafox
Trichlorfon
Trichloronate
TOCP*

* Not a pesticide (see text)

The delayed neurotoxic action is not related cholinesterase inhibition, but to the binding (phosphorylation) of a specific enzyme in the nervous tissue called neurotoxic-esterase. The cause is still not known.

Ginger Jake: Tthe capacity to produce delayed neurotoxicity is widespread among OP esters. The first cases of OPIDN in the U.S. were seen during the prohibition era before organophosphate insecticides came on the market. Triorthocresylphosphate (TOCP), an industrial degreaser which causes demyelination and paralysis when ingested was used an adulterant in an alcoholic extract of Jamaican ginger. Thousands of people who drank 'Ginger Jake' during prohibition developed paresthesia of the feet and aching of the calves in about 12 days, followed two to three days later by ataxia, and paralysis. [1,2,3].

Other Neurological Diseases Possibly Associated with Pesticide Exposure

Amyotrophic Lateral Sclerosis
Eye Disorders
Guillain Barre Syndrome
Movement Disorders
Multiple System Atrophy
Psychiatric Disorders
Reflex Sympathetic Dystrophy

Other Disease: There are few epidemiological studies of pesticide exposure and other neurological diseases. A study in Canada found no association with Alzheimer's disease. There are case reports of pesticide exposure associated with amyotrophic lateral sclerosis, eye disorders, Guillain Barre syndrome, movement disorders, multiple system atrophy, reflex sympathetic dystrophy, and several reports of psychiatric disorders (see Table 5).

Table 1
Nerve Conduction Velocity - Occupational Exposure
(See Appendix F for explanation of table)

Bulgaria OP[a].sprayers - median[4]	Incr. ampl. sig
Peroneal velocity	Decreased
England sensory deficits, mainly small fibers[5]	
Egypt Zn phos EMG part. denerv. ant tibial[6]	35%
Part. denerv. flexor digiti minimi	6.7%
Egypt formulators, applicators- depression[7]	Increased
Finland dipehnyl paper mill EMG abnornalities[8]	Increased
France methyl bromide peripheral neuropathy[b] [9]	Case report
Germany PCP median, radial nerves [©] [10]	Normal range
Peroneal, sural nerves	Normal range
Germany agric pest 3 ys or more WHAT? [11]	Decreased
India agric. fenthion ERPs[d] - P3 amplitude[12]	No sig diff
India agric.fenthion[e] cond. velocity slowing[13]	p < 0.05
Median latency increased	p < 0.1
Peroneal latency increased	p < 0.05
F min.H reflex. latency increased	p < 0.01
India OP[a] factory perip. neuropathy[14]	Increase sig.
Japan ETO[d] neuropathy lower limbs [15]	Case report
Japan ethylene oxide polyneuropathy[f] [16]	Case report
Netherlands agric OP[a] sensory off season[17,18]	Decr. p=.04
Motor velocity off season	Decr. P=.04
Sensory during spray season	Decr. p <.01
Netherlands flower growers 20 y median motor[19]	-1.1 m/sec
Median sensory decrease	-1.4 m/sec
Sural sensorydecrease	-0.9 m/sec
Peroneal motor -1.2 -1.3 m/sec	Decrease
Sural, peroneal refractory period	Increased
Netherlands flower growers >10 y NCV[20]	Small dec.sig
Sri Lanka OP[a] sprayers sensory velocity	Decr. p =0.01
US exterminators NCV vs total population[21]	No sig diff.
US Hispanic farm workers low OP[a] exposure[22]	
Sural nerve latency/amplitude	No sig diff
Ulnar nerve conduction velocity	No sig diff
Ulnar neuromuscular junct. function	No sig. diff
US ethylene oxide subacute polyneuropathy[f] [23]	Case report
Bilat. foot-drop, EMG denerv. potentials	
US ethylene oxide hospital workesr NCV[24]	No sig. diff
US Arkansas 2,4-D, 2,4,5-T factory workers [25]	
NCV slowing 46% exposed vs 5% control	Sig. diff
Sural nerve mean slowing	~5.2 m/sec
Median motor nerve slowing	~1.9 m/sec
Yugoslavia ethylene oxide polyneuropathy legs[26]	Case report

a) Organophosphates. **(b**) In one patient, symptoms improved in five months. In the other, paresthesia still present 2 yrs later, and visual after-effects. **[c]** Pentachlorophenol. Exposure from carpets, moth killers, pesticide sprays, wood preservatives. **(d)** Event related potentials. **(e)** No clinical evidence neuropathy or muscle weakness. **(f)** Ethylene oxide sterilizing facility -reverse flow of an exhaust fan, a blocked air conditioner filter, lack of protective mask. **(e)** Confirmed by sural nerve biopsies. **(f)** Gradual and complete return of strength in the lower extremities occurred 4 to 7 months after removal from exposure
(g) Standard deviation.

Table 2
Vibrotactile Sensitivity (VTS) and Postural Sway

Chile methyl bromide applicators[27]			
Threshold prior to exposure	2..4 seconds		
Threshold post exposure	2..85 seconds		
England OP(a) sheep dippers VTS[b] [28]	Increased		
England OP[a] sheep dippers[29]	**Symp.**	**No symp.**	
Contls			
2 point discrimination hand mm	22	13	8
2 pt discriminationr foot mm	34	10	11
Mean calf circumference cm	35.0	36.3	38.6
Nicaragua methamidophos pois. VTS incr.[c] [30]	> 25 %		
South Africa OP[a] sprayers exposure[31]	Pos. assoc.		
US chlorpyrifos applicators VTS and tremor[56]	No assoc.		
Postural stability and TCP[e] levels	Assoc.		
US exterminators postural sway[21]	Worse sig.		
VTS threshold	No sig. diff		
US chlordane nonocc. abnormal balance[32]	7 of 9 cases		
US California OP poisoned not hosp. VTS[33]	Poor perform.		
Hospitalization OP pois	Worse		
US Cali. fumigators[f] methyl bromide VTS [34]	Worse sig.		
US New York OP[a] applicators VTS[35]	Increased		
Methyl bromide, sulfuryl fluor. appl. VTS	Increased		
US NY farmer pest appl VTS dominant hand[36]	Incr. p <.001		
Non-dominant hand	Incr. p <.04		

Table 3-A
Neurobehavioral and Psychometric Testing - Farmers and Farm Workers
(See Appendix F for explanation of table)

Farmers	
Belgium mild cognitive dysfunction[37]	
Cross sectional study	OR 1.47
Prospective study	OR 2.02
England OP exposed sheep farmers[38]	
Sustained attention poorer perf	Poorer sig.
Speed information processing poorer perf	Poorer sig.
Short-term memory and learning	No difference
Ecuador farmer members of cooperative[39]	
WHO NCTB[(a)] Visual-spatial	Most sensitive
Netherlands Flower growers pest use >10yrs[20]	
Attention, perceptual coding	Small diff. sig
South Africa farm/sprayers chronic OP expos.[31]	
WHO NCTB[(a)] Pursuit-Aiming	Small assoc
Santa Ana pegboard	Small assoc.
US male farmers heavy expos. OPs [40]	
Reaction time, dominant hand	Slower sig.
Agricultural Workers	
Chile men chronic methyl bromide exposure.[27]	
Dynamometry prior to exposure	51.4 kg
Post exposure 2-5 weeks	47.2 kg
Nothingham - neg.auto-percep prior	11.2
Post exposrue	13.6
Costa Rica poisoned banana workers[(b)] [41]	
Psychomotor, visuomotor skills perf.	Poorer
Language skills, affect performance	Poorer
Digit-Symbol test performance	Poorer sig.
Neuropsychiatric symptoms	Marked incr.
Expos. che inhibitors[c] prior 3 months	Poorest perf.
France vineyard workers pest. exp[(d)] [42]	
Neuropsychiatric test. Poorer perf.	OR $\geq$ 2
India agric. sprayers exposed fenthion (Misra 1994)	
Benton poorer performance	Sig.
Memory poorer performance	Sig
Lexand poorer performance	Sig
Passalong poorer performance	Sig
Poland ♀ greenhouse wrkrs OP exposure[43]	
WHO NCTB[(a)] Reaction times	Increased
Motor steadiness	Reduced
US Hispanic children agric vs nonagric[44]	No diff.
US Dieldrin occupational exposure[45]	
Psycholog. tests performance 5/58	Poorer
Psychomotor tests[(h)] 47 /58	Poorer p < 05
Cognitive tests performance	Poorer
US New York male pest applicators OPs [35]	
Electrophysiological abnormalities one	
US CaliforniaCholinesterase-inhibited subjects[(f)] [46]	
Serial digits better performance	Sig.
US Washington apple orchard OP applicators[47]	
Neuropsychiatric tests pre- vs post-season	No diff
Acute Pesticide Poisoning in the Past	
Germany post acute pyrethroid poisoning[48]	
Cerebro-organic dis.; sensomoto neuropathy	
Nicaragua farm workers 2 yr post hospitalization[49]	
WHO NCTB[(a)] performance 5/6 subtests[(e)]	Poorer
Motor steadiness/dexterity vs controls poorer	Poorer sig.
US chlorpyrifos poisoned pest control operators[21]	
Pegboard turning poorer peformance	Poorer sig..
2 of 6 neurobehavioral tests performance	Poorer sig.
5 of 5 mood scale tests performance	Poorer siig.
Postural sway performance	Poorer
US California severe OP poisoning group[33]	
Sustained visual attention performance	Poorer sig.
Mood scales performance	Poorer sig.
US former OP poisoned (Savage 1988)	
Memory, abstraction, mood	No sig diff
Halstead-Reitan cerebral damage/dysfxn	Abnormal
MMPI[(g)] distress items	Increased
PRAPFI[(h)] complaints of disability	Increased
Audiometry, vision tests	No sig diff

a) World Health Organization Neurobehavioral CoreTest Battery. **(b)** 81 workers treated for mild OP and CB poisoning not requiring hospitalization compared to 130 with symptoms who did not seek treatment . **[c]** Cholinesterase inhibitors, OPs and CBs **(d)** 528 directly mixing/spraying (mean 22 years), 173 indirectly treated plants, 216 never exposed. **(e)** Verbal/visual attention and memory, visuo-motor speed, sequencing, problem solving. **(f)** RBC Che activity $\leq$ 70% of baseline, or plasma che$\leq$ 60% . Reductions present without symptoms of poisoning. **(g)** Minnesota Multiphasic Personality Inventory. **(h)** Patient's and Relative's Assessment of Patient Functioning Inventories .

Table 3-B
Neurobehavioral and Psychometric Testing
Pest Control Operators and Factory Workers, and Non-occupational Exposure
(See Appendix F for explanation of table)

Pest Control Operators / Factory Workers	
Costa Rica DDT exposed malaria workers[50]	
Overall perform (mean)	20% decr.
Verbal attn, visuomotor. speed, seq	> difference
5 motor, senory, cognitive. tests, yrs expos.	Sig. diff
Increase neuropsyc/psychiatric symptoms	OR 3.98
India factory Memory, learning , vigilance [©] [51]	Poorer
US Chlorpyrifos applicators [52]	
Lanthony color vision and TCP[(a)] levels	Assoc.
Contrast sensitivity 1 test and TCP levels	Assoc.
Olfactory dysfunction, visual acuity	No assoc.
Manual dexterity, eye–hand coordination	No assoc.
US exterminators Pegboard turning poorer perf.[21]	Sig.
Smell, vision	No sig. diff.
Visual/motor skill	No sig. diff.
US FL sulfuryl fluoride fumigators Pattern Memory[53]	Worse sig.
Olfactory testing vs all fumigant exposed	Worse sig
Santa Ana dom. hand vsl fumigant exposed	Worse sig
US CA methyl bromide fumigators[(b)] 23 of 27 tests[54]	Worse sig.
Ccognitive test poorer performance	Sig.
US ETO[(d)]. hosp. workers neuropsych. tests[24]	No sig. diff
Non-occupational Exposure	
Germany females residential exposure WPC[(e)] [55]	
Paired-assoc. learning poorer performance	Sig.
Benton poorer performance	Sig.
Reading/naming speed. poorer performance	Sig.
PCP blood levels poorer performance	Sig.
India Bhopal MIC[(f)] victims[(g)] sev/mod exposure[56]	
Learning, motor precision poorer performance	p< 0.01
Disability score significant correlation	r = 0.68.
US chlordane exposure - residential[32]	
Reaction time poorer perf	Sig.
Digit symbol, poorer perf	Sig.
Trail-making poorer perf	Sig.
Verbal recall poorer perf	Sig.
Mood-state	No diff.
Long-term memory	No diff
US Case report methyl bromide poisoning[57]	
Concentration, learning , memory	Impaired

(a) 3,5,6-trichloropyridinol a metabolite of chlorpyrifos. **(b)**Soil and structural applicators of methyl bromide and sulfuryl fluoride (Vikane). **(c)**Quinalphos manufacturing workers. **(d)**Ethylene oxide, gas used to sterilize hospital/dental equipment. **(e)**Wood preservatives, pentachlorophenol (PCP), lindane, others. **(f)**Methylisocyanate, toxic chemical released in explosion at factory manufacturing carbaryl (Sevin) in December 1984. **(g)**15 severely, 14 moderately, 23 mildly affected; mean age 38.2 (15-65); 30 males. Neurological examination was normal.

Table 4
EEG and Visual Evoked Potentials (VEP)

Bulgaria VEP amplitude OP[(a)] sprayers[4]	Sig. Incr.
Egypt EEG abnormal zinc phos. appts[6]	17.4%
Finland diphenyl paper mill workers [8]	37.5%
Netherlands VEP bulb flower growers	No sig. diff
EEG fast (beta) activity	Increase
Netherlands EEG farmers spectral freq.	Changes
Netherlands EEG-β farmer >10 yrs[20]	Sig diff
US EEG ethylene oxide hosp. wrkrs[24]	No sig diff.
US EEG prior OP poisoning	No sig. diff.
US sleep EEG REM sabin[(b)] workers	Increase
β-activity temp/occip/ central li	increase
Background voltage	Decrease
Alpha activity	Decrease

(a) Organophosphate insecticides.
(b) Sarin is not a pesticide but a nerve gas. It's mode of action is the same as organophosphate insecticides but it is much more potent.

Table 5
Other Nervous System Effects
(See Appendix F for explanation of table)

Alzheimer disease	
Canada Quebec Pesticide exposure[(a)58]	No assoc.
Amyotrophic Lateral Sclerosis	
Italy Conjugal 30 months apart [59]	Case report
Pesticides levels artesian wells	Not signif.
US Michigan Dow 2,4-D worker deaths(b)[60]	OR 3.45
US Washington agricutural chemical expo[61]	OR 2.0
Men any amount of exposure	OR 2.4
Men high vs no exposure, trend p= 0.03	OR 2.8
Men low vs no exposure	OR 1.5 ns
Women low vs no exposure	OR 0.9 ns
Eye Disorders	
France retrobulbar ocular neuritis methamidophos[62]	Case report
France persistent visual problems methyl bromide[63]	Case report
US IA,NC farmers retinal dege. fungicide applicators[64]	OR 1.8
Cumulative days of fungicide use trend	p= 0.011
US TE cortical blindness carbofuran ingestion[65]	Case report
US California optic atrophy methyl bromide[66]	Case report
US CA. OP reentry pois. visual probs. 4 mons[67]	
Guillain Barre Syndrome	
Switzerland farm worker OP exposure[68]	Case report
India OP poisoning[69]	Case report
Paraguay children[70] possible OP exposure	30% cases
US Arizona 28 y farm worker merphos spill[71]	Case report
Movement Disorders	
France myoclonus methyl bromide poisoning[(c)72]	Case report
Israel isofenphos ingestion pyramidal findings[73]	Case report
Multiple System Atrophy	
US pesticides/environ. toxins [(d)74]	11% cases
US pesticide exposure.[75]	Sig incr.
Psychiatirc Disorders	
England OP exposed sheep farmers incr. vulner[42]	Increased
Spain suicide rate farmers agricultural area s[76]	Increased
US CO farmers pesticide illness - depression[77]	OR 5.87
US CA dicofol pois. cogn/emot probs. 18 mos[78]	12 yr male
US methyl bromide pois[(e)] psych. symp. weeks[79]	Case report
US 2 crop duster pilots OP psychiatric sequelae[80]	Case report
Reflex Symphathetic Dystrophy	
Turkey secondary neuropathy dimethoate poisoning[81]	Case report

(a) Based on residential histories, agriculture census (1971-1991) herbicide, insecticide spraying in the area. **(b)** All 3 worked in manufacture /formulation of 2,4-D (1947-49, 1950-51, 1968-86), for varying durations of time (1.3, 1.8, and 12.5 years). **[c]** Lived 5 years in a stuporous state. Brain at autopsy: necrosis inferior colliculi, gliosis upper brain stem reticular formation, changes in dentate and pontine nuclei. **(d)** 1 case heavy occupational exposure to malathion, diazinon and formaldehyde. **(e)** 4 farm workers removing plastic sheets from treated soil.

Table 6
Parkinson's Disease and Pesticide Exposure - Increased and Decreased Risk
(See Appendix F for explanation of table)

Increased Risk - Farming/Agriculture	
Canada BC orchard workers[82]	OR 3.69
Any pesticide exposure	OR 2.3
Paraquat - postural tremors	p = 0.01
China Taiwan paraquat, trend signifcant[83]	Increase
Exposed but not to paraquat	Decrease
China Hong Kong herbicide use[84]	Increase sig.
Denmark men and women[85]	SHR[(a)] 1.3
Germany pesticides[86]	Increase
India, OPs[(b)] akinetic-rigidity[87]	Case report
International studies farming[88]	OR 1.42
Pesticide exposure	OR 1.85
Israel field work pre-parkinsonism[89]	p< .0001
Italy farming occupation[90]	OR 7.7
Italy pesticide/herbicide exposure[91]	OR 1.14[#]
Italy maneb extrapyramidal disorder[[c] 92]	Case report
Italy, 10% diquat spill[(d)93]	Case report
Italy, Ferrara agricultural workers[94]	IR 20.6[(e)]
Spain Caceres[95]	Increase[*]
Sweden handling agric. pesticides[96]	OR 1.9[#]
Handling agric. insecticides	OR 2.2[#]
US pilot organophosphate poisoning[97]	Case report
US California mortality by residence[(f)98]	OR 1.65
US Hawaii plantation worker > 20 yrs[99]	RR 1.9[*]
Pesticide exposed vs nonexposed	Increase[#]
US Iowa, North Carolina farm wives[100]	SMR 2.7[#]
US Michigan agricultural work[101]	OR 1.74[#]
Herbicide exposure[102]	OR 4.1
Insecticide exposure	OR 3.6
Farming occupation	OR 2.8
US National pesticide exposure[78]	OR 2.16
Farming occupation	OR 1.72
US Washington orchard workers[103]	PR 2.0[*]
Farming	No assoc.
US Washington farm job[104]	OR 3.2[#]
Increased Risk - Other Pesticide Exposure	
Brazil glyphosate accident[(g)105]	Case report
Germany wood preservatives[76]	Increase
Israel urban population exposed to pest.[106]	Increase
Sweden handling pest. any occupation	OR 2.8[#]
US Kansas occupational herbicides[107]	Increase
US Washington onset age les than 50[108]	
Insecticide exposure	OR 5.75
Herbicide exposure	OR 3.22
Residence fumigated house	OR 5.25
Increased Risk - Rural Living	
Australia[109]	OR 1.8
Canada raised in a rural area[110]	Increase
China, Hong Kong[74]	Increase
Finland[111]	No assoc.
International meta-analysis[78]	OR 1.56
US blacks [112]	Increase
US Kansas[113]	Increase
US National meta-analysis[78]	OR 2.17
US Washington State onset < age 50[98]	OR 2.72
Increased Risk - Well Water Use	
China, Taiwan onset age < 40[114]	OR 10.92
Spring water	OR 10.57
India for more than 10 years[115]	Increase
International studies meta-analysis[78]	OR 1.26[*]
Italy (on a farm)[9]	OR 2.0
Italy[10]	OR 2.8
Spain Madrid for 30 yrs or more[116]	Increase
US Kansas[32]	Increase
US meta-analysis[7]	OR 1.44[*]
U.S. drinking unfiltered water[102]	Increase
Decreased Risk - Farming/Agriculture	
Canada Quebec farm work[117]	No assoc
Finland pesticide/herbicides[30]	No assoc.
International studies meta-analysis[118]	No assoc.
Italy Sicily[119]	OR 0.6
Spain Caceres[85]	No assoc.
US Kansas[97]	No assoc.
US Washington[22]FIXX	No assoc.
US Hispanics[31] FIXX	Decrease
Decreased Risk - Other Pesticide Exposure	
Australia pesticides/herbicides[99]	No assoc.
Canada Que. pesticides/herbicides[107]	No assoc.
Spain, Madrid past exposure[106]	No assoc.
US sibling pairs[120]	No assoc.
US New England[121]	No assoc.
US Kansas[97]	No assoc.
US onset < age 40 and > age 60[122]	No assoc.
US Washington home use[98]	No trends
Decreased Risk - Rural Living	
Canada, Calgary[123]	No assoc.
Canada Quebec[107]	OR 0.31
Germany rural factors[76]	No assoc.
US < age 40 and > age 60[112]	No assoc.
Decreased Risk - Well Water Use	
Australia[99]	Decrease
Canada, Calgary[113]	No assoc.
Canada Quebec[36]	No assoc.
Finland[101]	No assoc.
US New England[111]	Decrease
US Washington State[93]CHECK	No assoc.
US < age 40 and > age 60[112]	No assoc.

* Borderline significance # Not significant

(**a** Standardized Hospitalization Ratio **(b**) Organophosphates. 4 recovered, 1 repeat on re-exposure. **[c**] 37 yr old man, 2 years between exposure and onset. **(d**) 72 yr farmer. CT, MRI abnormal. Persisted 4 mon. later.**(e**)Incidence/100,000. IR in urban areas 3.1, in rural areas 6.32.**(f)** 1982 data, when all use was not reported.**(g**) Parkinsonian syndrome 1 month after, MRI changes 2 yrs later

Table 7
Organophosphate Induced Delayed Neuropathy

Australia chlorpyrifos termite applicators[124]	
Mean NTE [(a)] activity	Slightly higher
Mean serum Che compared to controls	52% reduction
Belgium fenthion ingestion 65 yr female[125]	Case report
7 days post-exposure distal axonopathy	
Brazil trichlorfon poisoning farm worker[126]	Case report
3 mon later distal predom motor neuropathy	
EMG denervation changes	
NCV reduced sensory and motor	
Sural nerve biopsy axonal degeneration	
China methamidophos poisoning OPIDN[127]	13.5% cases
All recovered 1½ yrs wo perm. disability	
China, Taiwan complication mevinphos pancreatitis[128]	Case report
China, Taiwan carbofuran 23 m suicide[129]	Case report
EMG sensorimotor neuropathy	
4 months to recovery .	
England research chemist - Mipafox[130]	Case report
England 2-8 wks post trichlorfon poisoning[131]	Case report
France farm workers mod. pois. methamidophos[65]	Case report
Sensory and motor peripheral neuropathy	
Full recovery after 18th months	
Germany physotol 39-year-old woman farmer[132]	Case report
Severe polyneuropathy	
NTE inhibition	
Greece attempted suicide mecarbam[133]	Case report
Polyneuropathy	
Greece, Crete 1/6 poisoning[134]	Case report
Hungary trichlorfon 2 suicide attempts[135]	Case report
Polyneuropathy 2 wks after apparent recovery	
Hypesthesia, paresthesia, paresis peroneal	
EMG severe axon degen. primarily motor	
Biopsy revealed demyelination	
Recovered 18 months, residual peroneal paresis	
India bilateral recurrent laryngeal nerve palsy[136]	Case report
Italy suicide attempt chlorpyrifos ingestion[137]	Case report
30 d later lymphocytic NTE 60% inhibited	
43rd d paresthesia and leg weakness	
EMG, biopsy axonal polyneuropathy	
Italy 2 cases 1 chlorpyrifos poisoning[138]	Case report
Japan 1st report of malathion OPIDN (in alcoholic)[139]	Case report
7th hosp d glove/stocking flaccid quadriplegia	
2 months neurogenic bladder, spinal automatism	
7 months, spasticity lower limbs.	
Sural biopsy axonal degen., Schwann cell clusters	
Nicaragua methamidophos, chlorpyrifos pois[140]	
Hand grip 7 wks post poisoning	Imaired
Pinch strength 7 wks post poisoning	impaired
In intentional poisonings impairment	More severe
2 year follow-up hand strength impairment[141]	Persistent
Suicidals worse second examination	
Deficits not related to pesticide type	
Poland suicide attempt trichloronate[142]	Case report
Romania 4 accidental ingestion trichlorfon[143]	Case reports
3-5 wks distal predom. motor neuropathy	
Distal weakness, foot drop, hypotonia.	
Ankle jerk lost, other DTRs normal	
2 mon. later knee jerks brisk, patellar clonus	
Loss abdom. cutaneous reflexes, Babinski sign	
EMG- dying-back neuropathy	
Spain farm worker expos. age 14-24[144]	Case report
EMC predom. motor axonal polyneuropathy	
Nerve biopsy 'dying back' axonopathy	
Sri Lanka 3 suicide attempts[145]	Case report
25-35 d after bilateral vocal cord paralysis	
Sri Lanka methamidophos agric sprayers[146]	33%
Turkey suicide attempts trichlorfon, fenthion[147]	Case reports
Turkey of 32 cases 21.8% intermed. syndrome[148]	
US child chlorpyrifos ingestion vocal cord paralysis[149]	
US carbaryl ingestion[150]	Case report
Acute weakness of arms and legs	
EMG axonal peripheral neuropathy	
Recovery continued for 9 months	
US workers DEF, merphos[151]	
Lymphocyte NTE aerial/grnd applicatorss	No effects
US 16-y boy methamidophos[152]	Case report
Day 3 lymphocyte NTE 77% decr. activity	
2 wks neuropathy profound LE weakness	
Decr. ulnar, absent tibial action potentials	
NCVs normal	
Serum IgG neural antibodies increased	
US Velsicol leptohpos workers[153]	
12 workers serious neurological disorders, 2 milder	
63/155 abnormalities one or more objective tests	
11/63 abnormal nerve function, psychological tests	
US Texas 12 leptophos workers[154]	

(a) Neuropathy target esterase.

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