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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 19 1995

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Review of chlorpyrifos-associated cases of delayed neuropathy

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I. Introduction

Case summaries supplied by DowElanco and recent reports in the literature suggest that chlorpyrifos may be a cause of delayed peripheral neuropathy. The purpose of this review is to summarize the available human evidence and recommend steps to determine whether chlorpyrifos is a significant cause of this disease.

Peripheral neuropathies include a diverse group of disorders (Berger and Schaumberg 1994). Most cases seen in human populations are related to hereditary diseases or diabetes. Peripheral neuropathy due to toxic exposures are comparatively rare and less well studied. In a peripheral neuropathy, sensory and motor nerves to the arms and legs are impaired. As a result, victims may experience paresthesias (abnormality of sensation), muscle weakness, and inability to coordinate movement.

II. Conclusion

Available evidence from case reports suggests that chlorpyrifos may be a cause of delayed peripheral neuropathy. The best evidence of this effect comes from the published literature, especially 8 cases reviewed by Kaplan et al. (1993) and one suicide case reviewed by Lotti et al. (1986). An epidemiologic study of organophosphate poisoning cases provides evidence of peripheral neuropathy based on tests of nerve conduction and sensation among 17 workers poisoned by chlorpyrifos (Steenland et al. 1994). Twenty-one additional summaries of legal cases submitted by DowElanco provide some, albeit limited, evidence of this effect. A full review of the medical records associated with the DowElanco cases is recommended (See appendix 2). Specific records to be requested should include any evaluations by a neurologist or neurological test results including tests of sensation, reflexes, nerve conduction studies, electromyography, and nerve biopsy.

Available evidence does not address important questions about the circumstances and prevalence of peripheral neuropathy associated with chlorpyrifos. In most cases, appropriate tests have not been performed. Therefore it will not be possible to determine how often and under what circumstances chlorpyrifos exposure leads to peripheral neuropathy. A prospective epidemiologic study or survey is recommended for that purpose, supplemented by a case-finding effort which fully documents exposure and effects. The study and case finding effort should be imposed on DowElanco under a Data-Call-In and conducted by the American Association of Poison Control Centers with assistence from the National Center for Environmental Health.

The three questions the prospective study of chlorpyrifos poisoning cases should answer are:

1. How often does chlorpyrifos poisoning lead to peripheral neuropathy or, alternatively phrased, how common or rare is peripheral neuropathy as an outcome?
2. What exposure situations lead to peripheral neuropathy (e.g., life-threatening poisoning, mild poisoning, or low-level repeated exposures or single acute exposure)?
3. In cases of peripheral neuropathy, how severe are the symptoms and how much recovery is there over time?

The case finding effort would take cases identified from various sources and document peripheral neuropathy through proper neurological evaluation. Sources for cases would include incidents submitted to OPP's Incident Data System, calls to the National Pesticide Telecommunications Network, and contacts with organizations representing neurologists. The National Center for Environmental Health may be able to assist in arranging for appropriate neurological evaluation of cases that are not well documented. The evaluation should include careful consideration of other known causes of peripheral neuropathy.

Evidence already exists that organophosphates cause chronic neuro-behavioral effects in a portion of acutely poisoned cases. This evidence is reviewed in appendix 3. The most common symptoms reported include memory impairment, inability to concentrate, confusion, depression, and irritability. Also prevalent were visual disturbances, persistent headaches, fatigue, nervousness, and muscle aches and pains. Among the 217 incidents submitted by DowElanco, 14 individual cases complained of having three or more of these symptoms. Seven of these were among the 21 cases with evidence of peripheral neuropathy. Further review of their medical records is not recommended because cause and effect are unlikely to be documented in individual cases. However, these effects should be documented to the extent possible in those cases with evidence of peripheral neuropathy.

III. Detailed Considerations

Organophosphate-induced delayed neuropathy (OPIDN) typically occurs from several days up to four weeks after an acute exposure. According to the World Health Organization (1986), "there is reasonable evidence" that 7 pesticides have caused delayed neuropathy in humans. These seven pesticides are leptophos, mipafox, EPN, triclorfon, trichlornat, methamidophos, and chlorpyrifos. Of these only trichlorfon, methamidophos, and chlorpyrifos have active registrations. The evidence for chlorpyrifos is based on a suicidal ingestion (Lotti et al. 1986) and is summarized below.

Early symptoms of OPIDN include paresthesias in the extremities, especially the legs, and motor weakness. Paresthesia is defined as any abnormality of sensation, but typically involves a feeling of numbness, tingling, burning, or pain. These symptoms may occur along with weakness in the extremities, difficulty with coordinated movement (ataxia), and, in severe cases, a flaccid paralysis on account of extreme muscle weakness. The disease is usually progressive, though mild cases may slowly recover.

A review of the literature determined that the following information is useful for establishing a diagnosis of OPIDN.

1. A history of exposure which may include acute poisoning symptoms and evidence of cholinesterase depression,
2. A delay of about 1-4 weeks between exposure and onset of symptoms,
3. Symptoms of parethesia, muscle weakness, ataxia, and in advanced cases, muscular atrophy, changes in gait, or flaccid paralysis,
4. A diagnosis of peripheral neuropathy, preferably by a neurologist, and
5. Physician findings consistent with peripheral neuropathy based on tests of reflexes, sensory testing, nerve conduction studies, electromyography (EMG), and a nerve biopsy.

Table 1 below summarizes the available evidence from 4 published articles and from summaries of legal cases submitted by DowElanco. To be included in this listing a case had to have evidence of bilateral sensory or motor effects primarily in the extremities. Cases limited to the arms or hands were excluded as recommended in the review by Berger and Schaumburg (1994). Also excluded from this listing were cases with pre-existing peripheral neuropathy or clear evidence of other exposures or diseases known to cause peripheral neuropathy.

Information on the specific exposure situation, symptoms and laboratory results for each incident are summarized in Appendix 1. Note that the published cases have, by far, the most evidence that chlorpyrifos can cause peripheral neuropathy. These cases include evidence of acute exposure (either direct exposure, classic symptoms of poisoning, or cholinesterase depression), symptoms specific for peripheral neuropathy occurring after the expected latency period, a physician diagnosis, and consistent findings from appropriate tests such as reflexes, nerve conduction studies, or EMG. The summary information provided by DowElanco, by contrast, do not contain sufficient evidence on which to base a diagnosis of peripheral neuropathy. It should be noted that such a diagnosis was made in 12 of the 21 cases submitted by DowElanco, but the basis for this diagnosis is seldom fully explained. Therefore, it is appropriate to request additional information on these cases. A listing of information to be requested on these cases is provided in Appendix 2.

Steenland et al. (1994) studied chronic neurological sequelae in 128 workers poisoned by organophosphates between 1982 and 1990 and 90 controls. The poisoned group performed significantly worse on measures of sustained visual attention and mood. If the poisoned group was restricted to those with documented cholinesterase inhibition or those who had been hospitalized, the poisoned subjects also showed poorer performance on vibrotactile sensitivity tests. Additional review of this study may be found in Appendix 3.

The Steenland et al. (1994) study included 10 cases with primary exposure to chlorpyrifos and 7 additional cases with exposure to chlorpyrifos and at least one other OP at the time of poisoning. Analysis of the 10 cases primarily poisoned by chlorpyrifos found worse peroneal motor nerve conduction velocity ($p = .04$) and ulnar sensory amplitude ($p = .03$). Among those with any exposure to chlorpyrifos at the time of poisoning (N=17) there was more tension on mood scales and worse finger vibrotactile sensitivity for those classified as definitely poisoned (supporting cholinesterase tests). These findings are consistent with chlorpyrifos poisoning being a cause of peripheral neuropathy.

Table 1. Summary of incidents of peripheral neuropathy or symptoms associated with peripheral neuropathy (i.e., paresthesias, muscle weakness, changes in gait, or muscle atrophy) associated with exposure to chlorpyrifos.

Reference	Age	Sex	Initial Symptoms	Peripheral symptoms*	Physician diagnosis	Physician findings**	Comments
Osterloh	26	M	Yes		Yes	NTE↓	
Lotti	46	M	Yes ChE↓	P W G	Yes	NTE↓ N B R	
Aiuto	3	M	Yes ChE↓	W d	Yes	N E R	
Kaplan 1	33	M	Yes	P d	Yes	N E	
Kaplan 2	33	F		P d	Yes	N	
Kaplan 3	40	M	Yes ChE↓	P W	Yes	N R	
Kaplan 4-7	Family-4		Yes	P d	Yes	N	
Kaplan 8	42	F	none	P d	Yes	R S	
Dow 23154	Child	M		W G A F	Yes	N E B R	
Dow 23158	Adult	F		P W d	Yes	E	
Dow 23159	Adult	M		W G A	Yes	B R	
Dow 23162	Adult	F		P W			
Dow 23166	Adult	F		P W?			
Dow 23168	Couple			P	Yes	tenderness	Diabetic?
Dow 23192	Adult	F		lame			No records

* P = paresthesia, W = muscle weakness, G = gait abnormal, A = muscular atrophy, F = flaccid paralysis, d = delay of about 1-4 weeks between exposure and onset of peripheral symptoms
** NTE↓ = neuropathy target esterase depressed, N = nerve conduction studies abnormal, E = EMG abnormal, R = reflexes abnormal, S = sensory testing abnormal, B = nerve biopsy

Table 1. Summary of incidents of peripheral neuropathy or symptoms associated with peripheral neuropathy (i.e., paresthesias, muscle weakness, changes in gait, or muscle atrophy) associated with exposure to chlorpyrifos (continued).

Reference	Age Sex	Initial Symptoms	Peripheral symptoms*	Physician diagnosis	Physician findings**	Comments
Dow 23206	Adult F		W	Yes	E	
Dow 23207	Adult F		W	Yes		
Dow 23216	Family-3	Yes	P W			
Dow 23289	Couple		P			
Dow 23322	Adult M		P	Yes	E	
Dow 23347	Adult M	Yes	P W G	Yes		
Dow 23369	Adult M		P W	Yes		
Dow 23406	Adult M		P W	Yes	E N	
Dow 23415	Adult M?	Yes	P W d			
Dow 23478	Couple		P	Yes		
Dow 23523	Teacher?		P	Yes		
Dow 23578	Adult F		F			
Dow 23585	Couple		P			
Dow 23623	School		P W G			

* P = paresthesia, W = muscle weakness, G = gait abnormal, A = muscular atrophy, F = flaccid paralysis, d = delay of about 1-4 weeks between exposure and onset of peripheral symptoms
** NTE↓ = neuropathy target esterase depressed, N = nerve conduction studies abnormal, E = EMG abnormal, R = reflexes abnormal, S = sensory testing abnormal, B = nerve biopsy

Other potential sources of case reports

One physician has notified EPA of 17 litigation-related chlorpyrifos cases which she reports have peripheral nervous system dysfunction that may qualify as peripheral neuropathy. The summary information submitted so far is too limited to make a determination. Questions similar to those submitted to DowElanco, will be submitted to this physician to document as fully as possible any additional cases of peripheral neuropathy. It appears likely that only two of her 17 cases overlap the 21 cases submitted by DowElanco.

A review of all chlorpyrifos incident calls submitted to the National Pesticide Telecommunications Network (NPTN) since 1980 revealed 23 cases which make some mention of peripheral neuropathy or symptoms of peripheral neuropathy related to chlorpyrifos exposure. NPTN only collects limited information on each case, too limited to document a case of peripheral neuropathy. Again, some of these cases may overlap those submitted by DowElanco. An attempt will be made to contact these cases to seek documentation.

Recommended studies

Prospective studies require a large number of cases to obtain meaningful results. The single largest source of chlorpyrifos poisonings is the Toxic Exposure Surveillance System maintained by the American Association of Poison Control Centers. Based on the chlorpyrifos report submitted by DowElanco, this system receives a total of 1,000 poisonings (symptomatic cases deemed related to the exposure) each year. This number of cases seems the minimum appropriate number for follow-up. Absence of any documented cases of peripheral neuropathy after follow-up on 1,000 poisonings would be a basis for finding that this effect, if it occurs at all, is very rare. Consideration should be given to having a control group made up of symptomatic cases exposed to other poisons known not to be associated with peripheral neuropathy. Symptoms of peripheral neuropathy are not uncommon in the general population and a control group would help exclude any background occurrence of symptoms unrelated to chlorpyrifos exposure. A questionnaire would be administered to each documented case by Poison Control Centers approximately 45 days after the acute exposure. The questionnaire would cover both symptoms and signs of peripheral neuropathy and effects to the central nervous system as outlined in appendix 3.

Too few documented cases of peripheral neuropathy exist to fully understand the extent of risk posed by exposure or poisoning from chlorpyrifos. A case-finding effort is recommended. Once potential cases are located medical records should be requested to document peripheral neuropathy. If appropriate medical tests have not been performed then a mechanism would need to be developed to arrange for a proper examination. Sources of cases could include cases identified by the Poison Control Centers in the prospective study, telephone calls to the NPTN (including those resulting from the CBS

story), and cases submitted by DowElanco and others to the Incident Data System. Funding to provide for such testing might be provided through a Data-Call-In with DowElanco or the National Center for Environmental Health. Otherwise it would be necessary to request that each case seek proper evaluation by a neurologist.

References

Aiuto LA, Pavlakis SG, Boxer RA. Life-threatening organophosphate-induced delayed polyneuropathy in a child after accidental chlorpyrifos ingestion. Journal of Pediatrics 122:658-660, 1993.

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Kaplan JG, Kessler J, Rosenberg N, Pack D, Schaumburg HH. Sensory neuropathy associated with Dursban (chlorpyrifos) exposure. Neurology 43:2193-2196, 1993.

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Osteroh J, Lotti M, Pond SM. Toxicologic studies in a fatal overdose of 2,4-D, MCPP, and chlorpyrifos. Journal of Analytical Toxicology 7:125-129, 1983.

Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. American Journal of Public Health 84:731-736, 1994.

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APPENDIX 1.

SUMMARY OF POTENTIAL OPIDN INCIDENTS RELATED TO CHLORPYRIFOS

Incident 1: 26 year old male, suicidal ingestion

Reference: Osteloh J, Lotti M, Pond SM. Toxicologic studies in a fatal overdose of 2,4-D, MCPP, and chlorpyrifos. Journal of Analytical Toxicology 7:125-129, 1983.

Exposure: ingested 360 ml of 6.7% chlorpyrifos and similar amount of 11% 2,4-D and 12% MCPP mixture.

Initial symptoms:
agitated
hostile
unresponsive
myoclonus
miosis
tachycardia
hypertension
diarrhea
pulmonary edema
death 1 day later

laboratory findings and later symptoms:
chlorpyrifos detected in body tissues
peripheral nerve NTE was about 30% of normal and control values
cerebral cortex NTE was normal
Plasma BuChE was zero
Lymphocyte NTE normal initially, 50% inhibited at 14 hours, and normal thereafter.

Incident 2: 46 year old male, suicidal ingestion

Reference: Lotti M, Moretto A, Zoppellari, Dainese R, Rizzuto N, Barusco G. Inhibition of lymphocytic Neuropathy Target Esterase predicts the development of organophosphate-induced delayed polyneuropathy. Archives of Toxicology 59:176-179, 1986.

Exposure: drank "a large amount" of 41% chlorpyrifos and went to sleep. Dose estimated at 300 mg/kg based on amount left in bottle.

Initial symptoms (next morning):
unconscious
wheezing
incontinent
at 18 hours taken to hospital where he had:
tearing
salivation

sweating
bronchorrhea
miosis
fasciculations

at 36 hours plasma ChE was nearly zero
coma and symptoms lasted 17 days

laboratory findings and later symptoms:
at 36 hours plasma Che was nearly zero
Day 30 lymphocyte NTE and Che were depressed with slow recovery over next 60 days
Day 43 patient complained of weakness and paresthesias in legs, symmetrical reduction in tendon reflexes, and sensory nerve conduction velocity reduced and signs of denervation in muscles.
Day 62 leg weakness more severe, tendon reflexes absent, gait impaired, and nerve biopsy shows evidence of axon and myelin degeneration.
Day 94 no changes from day 62, patient discharged.
Concluded: OPIDN started 6 weeks after poisoning not the usual 3-4 weeks. However, chlorpyrifos found in blood 1 week later, symptoms lasted 3 weeks, and ChE depression lasted 4 weeks or more. Considering increase in NTE levels, it would have been 60% inhibited initially.

Incident 3: 3 year old boy, playing near bottle of chlorpyrifos

Reference: Aiuto LA, Pavlakis SG, Boxer RA. Life-threatening organophosphate-induced delayed polyneuropathy in a child after accidental chlorpyrifos ingestion. Journal of Pediatrics 122:658-660, 1993.

Exposure: 3 year old boy found playing near open bottle of chlorpyrifos.

Initial symptoms:
crying
salivating
respiratory distress
jerky eye movements
at hospital comatose
pinpoint pupils
unresponsive to deep pain
twitching in extremities and eyelids

laboratory findings and later symptoms:
heart rate 160 beats per minute
ChE depressed 90%
Treated with atropine, 2-PAM, phenytoin, and sent to hospital.
After treatment, neurologic exam showed decreased tone and inability to follow commands.

Deep tendon reflexes were normal.
Atropine and 2-PAM continued and muscle tone improved.
Complications on third day: severe respiratory distress, harsh breathing sound, upper airway edema, though ChE was normal.
Then recovered.
Day 11 severe breathing (harsh sound) returned. Reintubation required, vocal cord paralysis occurred, and areflexia noted.
Day 18 areflexia noted, EMG shows absence of voluntary motor units.
NCS tests mostly normal except F latencies. Vocal cord paralysis persisted.
Day 27 deep tendon reflexes normal.
Day 31 EMG and NCS are normal.

Incident 4: 33 year old physician, exposed at work

Reference: Kaplan JG, Kessler J, Rosenberg N, Pack D, Schaumburg HH. Sensory neuropathy associated with Dursban (chlorpyrifos) exposure. Neurology 43:2193-2196, 1993.

Exposure: 4 weeks earlier, an exterminator inadvertently sprayed chlorpyrifos into the ventilating system at his place of employment.

Initial symptoms:
nausea
vomiting
light headedness

Symptoms at 4 weeks:
paresthesias in feet
urinary frequency
pain in groin and thigh area

laboratory findings and later symptoms:
neurologic exam at 2 weeks was normal
lumbar puncture found elevated protein in CSF
EMG and nerve conduction studies (NCS) consistent with distal axonopathy.
Then experienced mild paresthesias in hands and feet and labile pulse and blood pressure.
Symptoms slowly resolved over next 8-10 weeks
Several months later chlorpyrifos sprayed again at work and paresthesias in feet recurred (though milder) and resolved in 5-8 weeks. Asymptomatic for 10 years since then.

Incident 5: 33 year old housewife, after PCO treatment in home

Reference same as for Incident 4.

Exposure: exterminator sprayed chlorpyrifos around her radiators.

Initial symptoms: none reported

Symptoms at 4 weeks:
burning, numbing, cramps, and a sensation of vibration in her hands and feet.
Slowly improved.
At 6 months had normal sensation, normal strength and reflexes, but abnormal findings on NCS.
At 9 months NCS results were normal except sural nerve action potential.
At 12 months all was normal.

Incident 6: 40 year old exterminator, repeated indoor exposure

Reference same as for Incident 4.

Exposure: repeated exposure from application over 6 month period.

Symptoms at end of 6 months:
diarrhea
muscle twitching
tearing
paresthesias

Laboratory findings and later symptoms:
RBC ChE was initially low and returned to normal in 2 months.
6 weeks later had sensory loss in stocking-glove distribution.
Also mild distal weakness and areflexia in legs.
NCS results consistent with peripheral neuropathy.
1 year follow-up found NCS and sensory threshold studies normal.

Incidents 7: Family of 4, home treated by exterminator

Reference same as for Incident 4.

Exposure: house sprayed by exterminator

Initial symptoms:
headache
nausea
muscle cramps

symptoms at 1 month:
All had numbness and paresthesias, mainly in legs.
Memory impairment
2 teenagers had decline in school performance lasting 6 months.

laboratory findings and later symptoms:
1 month later (?) elevated levels of chlorpyrifos found in home, especially the kitchen.

At 6 months mild short term memory loss, "neuro-psychological testing was declined", but rest of neurologic exam was normal.
NCS showed low amplitude sural nerve action potential in all 4.
6 months later NCS test of sural nerve normal in 3 out of 4.
At 6 months no longer complaints or evidence of cognitive dysfunction.

Incident 8: 42 year old physician, basement treated

Reference same as for Incident 4.

Exposure: chlorpyrifos applied in her basement eight times over 3 week period before onset of symptoms.

Initial symptoms:
none reported at time of application

Symptoms 3 weeks after application:
impaired memory
slowed thinking
electrical sensations in hands and feet
pins-and-needles sensations in both legs

Laboratory findings and later symptoms:
sensory loss in feet (especially to vibration), ankle reflexes depressed. Symptoms abated over next 3 months.
At 6 months neurologic exam was normal.
At 18 months patient complained of memory loss and cognitive slowing, though neurologic exam and NCS were normal.
Neuropsychological exam showed impaired memory and poor intellectual functioning

Authors' conclusion based on cases 4-8:
Because chlorpyrifos is a potent inhibitor of acetylcholine esterase, its AChE/NTE index suggests it does not have strong neurotoxic potency. However this index may not be relevant in instances of repeated low-level exposures as reported in this case series. Mild sensory neuropathy in these cases may be due to self-promotion with low-level, long-period exposure, interaction of NTE inhibition with other unrecognized cause of neuropathy, or due to other idiosyncratic reactions to chlorpyrifos unrelated to NTE inhibition.

Incident 9: male child, repeated applications at home

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23154, October 12, 1994. Incident package number I001290.

Exposure: May 3, 1988, several crack and crevice applications of Dursban 2E and LO, diazinon, safrotin, and pyrethroid were made at home by PCO prior to and after child's birth. There is no indication of misapplication.

Symptoms within a few weeks of birth:
born May 17, 1988, treated July 28, 1988.
loss of weight
respiratory failure
diarrhea
peripheral neuropathy diagnosed Dec. 19, 1988.

child did not develop normally
respirator dependent
quadriplegic

Incident 10: Adult female, repeated applications at work

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23158, October 12, 1994. Incident package number I001287.

Exposure: Adult female reported her place of employment was treated monthly with Dursban LO and a pyrethroid by a PCO using crack and crevice treatment. Date of exposure Sept. 20, 1988.

Initial symptoms alleged:
none reported

Symptoms alleged one month (6 weeks) after application:
numbness in legs and arms
hot flashes
sweating
dizziness
numbness on right side of face
sores in mouth
swollen gums
hand tremors
blurred vision
eye twitching
neck ache
tightness in chest
tightness in lungs
upper arm tremors

Symptoms few months later:
All symptoms subsided except numbness and tingling in arms and legs
No indication of misapplication
ChE tests were normal (timing of tests not reported)

Sensory/Motor peripheral neuropathy diagnosed Nov. 17, 1988.

Incident 11: Adult male, repeated applications at work

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23159, October 11, 1994. Incident package number I001288.

Exposure: Adult male reported his place of employment was treated with Dursban 2E and 6, diazinon and a carbamate crack and crevice treatment for 16 years, 1966-1982. Sought treatment for leg weakness in 1981 which he claimed started about 4 years ago.

Symptoms alleged:
progressive muscle atrophy and weakness in limbs
progressive denervation
weakening of bladder spinctor control
poor erective ability
periodic diarrhea
periodic protracted colds and nosebleeds
flatulence
hyperacidity
difficulty with climbing stairs, sitting, or squatting
thinning of muscles
elevated creatine-phosphokinase
muscular fibrillations
diminished deep tendon reflexes
difficulty grasping
inability to walk on heels, waddling gait
nausea and malaise
psychological overlay, depression, irritability, nervousness, anxiety, and insomnia.
injury to surrounding nerves, blood vessels, fascia, and subcutaneous tissue.
Dr. Fleck diagnosed as polyneuropathy due to insecticides Dec. 7, 1981. Other physicians have diagnosed a myopathy, spinal muscular atrophy, or limb-girdle dystrophy.

Incident 12: adult female, termite application at her home

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23162, November 2, 1994. Incident package number not assigned.

Exposure: professional application of Dursban TC at her home on June 10, 1987. Dursban odor noted when heating system was turned on in Sept./Oct. 1987 and again in fall of 1988.

Symptoms alledged in January 1988:

extreme weakness and shakiness
fatigue
sweating
dizziness
tingling
hot and cold sensations
symptoms persisted through 1989
preexisting case of asthma
physicians seen include family physician, urologist, allergist, and clinical ecologist (Dr. Theron Randolph).

Incident 13: family of five, termite application at their home

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23166, October 13, 1994. Incident package number not assigned.

Exposure: professional application of Dursban TC at their home on May 9, 1991.

Symptoms alledged by one family member after application:
memory loss
fatigue
difficulty breathing, tight chest
upper respiratory infections
nausea, diarrhea
frequent urination
aggravation
headaches
lack of concentration
tingling in toes and hands
increased salivation

Adult female (may or may not be same as family member above?) alledges she continues to have memory loss, fatigue, difficulty breathing, tight chest, and stress. Does fatigue refer to muscle weakness in legs?

Incident 14: Adult male and female, application at their home

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23168, October 13, 1994. Incident package number not assigned.

Exposure: professional application of Dursban and other insecticides for carpenter ants at their home on June 12, 1987. Application alledged to have resulted in puddles on floor, dripping off walls, and having to wring out carpeting.

Symptoms October 1991 (4 years later):

"tenderness over digital nerves, peripherally, deep and superficial peroneal nerveas at the ankle and the sural nerve"
blurred vision
decreased appetite
increased sleep
decrease balance
abdominal discomfort
slurred speech
increased sweating
current medication includes mexetil, prozac, and methadone.
Dr. David Klein diagnosed peripheral sensory neuropathy on Oct. 31, 1991, as apparently did Dr. Overby on March 15, 1990. October 1990 reported as diabetic. Other psychiatric symptoms reported, not clear which symptoms apply to which adult on account of names deleted. Is quote above based on diabetic case? Ask Dow to help sort these out?

Incident 15: Adult female, application at her apartment

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23192, November 2, 1994. Incident package number not assigned.

Exposure: June 1979 - April 1988, no details available.

Symptoms:
violently ill
unable to breathe
nervous shock
lame and diabled
no medical records provided?

Incident 16: Adult female, home contaminated by nearby application

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23206, October 13, 1994. Incident package number I001335.

Exposure: June 22, 1989 nursery next door to alledged victim used Dursban 6 periodically.

Symptoms:
seizures
collagen vacular disorder
connective tissue disorder

low back pain
hair loss
rash
weakness, fatigue
astigmatism
tinnitus
headaches
loss of memory
anxiety
July 1990 Dr. Dennis Bonner reports EMG show evidence of mild peripheral neuropathy and a positive ANA(?). Subsequent neurological exams in March 1991 and May 1991 reported normal.

Incident 17: Adult female, employed with pest control company

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23207, November 2, 1994. Incident package number not assigned.

Exposure: July 1984 to June 1985 employed with PCO company.

Symptoms reported:
April 1985 Admission statement degenerative neuromuscular disease, seizure disorder, and paraparesis.
Jan. 1987 in wheelchair due to neuromuscular disease
Jan. and April 1992 diagnosed with myasthenia syndrome by Dr. Love.

Incident 18: 3 family members, application at their home

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23216, October 13, 1994. Incident package number not assigned.

Exposure: April 16-17, 1992 their home was treated with Dursban TC by PCO and they allege their well water was contaminated.

Initial symptoms:
nausea
headaches

laboratory findings and later symptoms:
ChE tests at 48 hours, one week, and 2 months were normal for adult male and young male.
Jyly/Aug. 1993 continue to experience headaches (all 3 family members), diarrhea (1 0f 3), paresthesia (3 of 3), weakness (2 of 3), chest pains (1 of 3), dizziness (1 of 3), inability to concentrate (1 of 3), rapid heart rate (1 of 3), breathing and sinus problems (1 of 3). Seen by clinical ecologist.

Incident 19: adult male, applications at work

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23218, October 13, 1994. Incident package number not assigned.

Exposure: crack and crevice treatment of Dursban 2E applied periodically over a period of 5 years at his place of employment, starting in 1981.

Symptoms occurring after last application:
aplastic anemia diagnosed Jan. 1986
shortness of breath, wheezing, chest pains
legs hurting
light headedness, headaches
weakness, loss of strength
numbness on fingers of left hand
miosis and vision impairment
excessive salivation
muscle cramps, twitching
partial paralysis
vomiting
diarrhea
urinary problems
insomnia

Incident 20: family of 3, crack and crevice treatment in log cabin

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23289, November 3, 1994. Incident package number not assigned.

Exposure: April 1, 1990. Log cabin treated by professional applicator.

Symptoms:
extensive list of symptoms for all 3 family members: A, B, and C.
9/19/90 A. feeling of heat in rear of foot and muscle weakness.
10/11/90 B. dysesthesias in extremeties
Other symptoms for A. include hot flashes, malaise, facial paresthesias, disorientation, tongue swelling, confusion, heartburn, diarrhea, sinus irritation, joint pain, spacy feeling, off balance, intermittent red ears, flushed face, acne form rash, sugar intolerance, inability to think, hair loss, difficulty swallowing, itching eyes.
Other symptoms of B. include pain in tongue, dysgeusia, abdominal pain, insomnia, chest pain, pain around bladder area, diarrhea, respiratory burning, breathing difficulties, intermittent cramping, rapid pulse, incontinence, endometriosis, mood swings, inability to

concentrate, bad breath, excessive thirst, visual changes, dizzy, poor coordination, heavy/irregular menses, low back pain, kidney pain.

Incident 21: adult male, employed as pest control operator

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23322, November 2, 1994. Incident package number not assigned.

Exposure: from about 1974-79 to 1989 used dursban as a PCO.

Symptoms:
10/13/88 Dr. Ilydio Polachini "axonal polyneuropathy in lower extremities."
11/14/88 Dr. Jeffrey Kornblum "EMG suggesting bilateral polyneuropathy."
patient history includes arthritis and 1972 back injury which apparently resulted in numbness of left foot that never improved.

Incident 22: adult male, exposure not specified

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23347, November 3, 1994. Incident package number not assigned.

Exposure: April 30, 1987 apparently at place of work. Crack and crevice treatment with Dursban 4-E and a pyrethrum fogger.

Initial symptoms:
stomach cramps
runny nose
nausea and vomiting
watering eyes
tightness in chest
headache
blurred vision
dry mouth and throat
general weakness

Subsequent symptoms:
not as strong or resilient
unable to run and jump like before
numbness in legs
agitation and nervousness
Dr. Dombroski diagnosed mild axionopathy

Incident 23: adult male, apartment treated with 3 pesticides

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23369, November 2, 1994. Incident package number not assigned.

Exposure: Jan. 23, 1987 apartment sprayed with Dursban ME, Safrotin, and bendiocarb.

Symptoms reported in February 1987:
thirst
fatigue and muscle weakness
respiratory irritation and cough
nausea
night sweats
increased sweating
difficulty concentrating
muscle cramps and twitching
paresthesias
mentally dull
neck stiffness
8/31/87 diagnosed with chronic fatigue syndrome
2/25/88 Dr. Christopher Degeorgia "the symptoms the patient gives initially of cramping, fasciculations, and progressive muscle weakness" may be consistent with organophosphate exposure.
Records show complaint of fatigue (malaise, rundown feeling) in 1984 prior to exposure.

Incident 24: adult male, employed as applicator, hose broke

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23406, November 2, 1994. Incident package number not assigned.

Exposure: Employed as applicator from April 1986 through June 1988. While treating residence in fall 1987 hose broke drenching him with the chemical.

Symptoms reported:
memory loss
fatigue
muscle twitches and cramps
tight feeling
numbness in arms, legs, and face
difficulty concentrating
intermittent confusion
cloudy vision
dull taster
sensitive skin and smell

history of Raynaud's disease
Dr. Demetrius Statsiuk 8/88 complaints of grip loss, numbness, and tingling in both hands, tetroscapular pain, and muscle spasms which continue through 1989 resulting in diagnoses of upper cervical arthritis with reflex myospasm and secondary thoraic outlet syndrome, strained spine.
Sematosensory evoked response test performed at UC Irvine medical center in Feb. 1990. EMG shows marked abnormalities.
Dr. Nachman Brautbar 8/30/91 diagnosed "peripheral neuropathy secondary to industrial exposure."
Dr. Doug Chang 11/92 diagnosed peripheral neuropathy. Nerve conduction studies performed 12/92, concludes borderline prolonged distal sensory latencies may be seen with a polyneuropathy. Then in 1/93 diagnosed myotonic disorder only.

Incident 25: adult male and female, home treated by PCO

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23415, November 2, 1994. Incident package number not assigned.

Exposure: Home treated May 18th and June 14th 1989 with Dursban LO and Dursban 2E for ants and fleas.

Symptoms reported for adult male (?) which started 6/27/89:
nausea, vomiting, diarrhea
loss of appetite
hot sweats and cold chills
numbness in extremeties
nightmares and insomnia
difficulty breathing
nosebleeds
ringing in ears
coughing and sore throat
hair loss
panic attacks
forgetfulness
depression
confusion
severe weakness, tremors
abdominal pain, joint pain
dizziness, headaches

Incident 26: 2 adult males and adult female, home treated by PCO

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23478, November 1, 1994. Incident package number not assigned.

Exposure: Home treated July 29 1988 with Dursban LO and Dursban 50WSP for fleas.

Symptoms reported:
Adult female reportedly had tingling and paresthesias in hands, feet, and legs (timing?), headaches, nausea, fatigue, tearing, pressure behind eye
One of the adult males reported headaches, fatigue, muscle spasms, pain in leg and ankles, inability to concentrate, rash, and flu-like symptoms.

Incident 27: teachers and students, school treated by PCO

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23523, November 1, 1994. Incident package number not assigned.

Exposure: Two schools treated with Dursban TC. Number affected was not specified.

Symptoms reported:
Teacher reported flu-like symptoms, abdominal cramps, nausea, headaches, and disorietation. News article reported children with headaches, nausea, skin rashes, and fatigue.
Dr. Wagner may have diagnosed teacher (after 4-6 weeks) peripheral neuropathy, paresthesia, headaches, and swelling around eyes.
Ask for records only for those people with paresthesias or peripheral neuropathy.

Incident 28: adult female, home treated with Dursban TC 4 times

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23578, November 2, 1994. Incident package number not assigned.

Exposure: Home treated with Dursban TC four times during 3 month interval (Feb. to April 1992). Treatment apparently directed by Dept. of Agriculture to bring house to minimum standards.

Symptoms reported 2-3 weeks after last application:
Dr. Rapheal Levine states "She has a neuropathy-paralysis in certain areas from head to toe, that her nerve endings are exposed and she has cramps."
no medical records provided

Incident 29: adult male and female, home treated by PCO

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23585, November 3, 1994. Incident package number not assigned.

Exposure: Closets treated with Dursban 4E, date unknown.

Symptoms reported:
sore throat, tightness in throat, tongue feels thick
nausea
weakness, fatigue
ringing and itching in ears
memory problems
sensitivity to foods and drugs
constipation
insomnia
rash
sweating, excessive saliva, watery eyes
poor balance
slurs words
loss of sensation in both feet
Which adult had symptoms and timing of symptoms not reported.

Incident 30: 70 teachers/students, junior high school

Reference: McCormick RA. Letter to Document Processing Desk - 6(a)(2), Office of Pesticide Programs, U.S. Environmental Protection Agency. RE: FIFRA 6(a)(2) Report, DERBI no. 23623, November 3, 1994. Incident package number not assigned.

Exposure: School treated by custodians and PCOs from 1983 through 1991?. Some applications allegedly left rug soaked or squishy.

Symptoms reported:
Long list of symptoms reported includes numbness, falling down - legs give out, numbness in hands, toes and fingers, feet and legs, and numbness and tingling of extemities. Five plaintiffs claim neuropathy as a symptom, however brief review of doctors diagnoses and symptoms for these five cases does not support a finding of organophosphate-induced delayed neuropathy.

APPENDIX 2.

INFORMATION TO BE REQUESTED FROM DOWELANCO

The DowElanco Submission on Claims-Related Notifications to the Agency form October 13, 1994 to November 4, 1994 contains the following case summaries of interest to the U.S. Environmental Protection Agency:
DERBI (DowElanco Research Business Index) numbers 23154, 23158, 23159, 23162, 23166, 23168, 23192, 23206, 23207, 23216, 23218, 23289, 23322, 23347, 23369, 23406, 23415, 23478, 23523, 23578, 23585, and 23623.

For each of these cases, we would like to obtain the following information:

1. Information which documents the acute exposure, including any measurements of chlorpyrifos or its metabolites from environmental or biological sampling. Any additional information on results of cholinesterase testing not already provided.

2. Medical records or patient/victim/plaintiff reports that document symptoms and signs of exposure at the time (within 48 hours) of the acute exposure.

3. Full reporting of any medical records provided by a physician identified as a neurologist and any neurological test results to include tests of reflexes, tests of sensation or the motor system, nerve conduction studies, evoked response, Electromyography, and nerve biopsies.

4. Full reporting of any testing performed on psychological or neuro-behavioral status to include tests of memory, attention, concentration, mood, visual disturbances, intelligence, and cognitive functioning.

5. Identification by name, address, title, affiliation, and telephone number (to the extent available) of any individual who is associated with a case and has provided a diagnosis of peripheral neuropathy, has performed a neurological evaluation (to include any of the tests listed in number 3 above), or is identified as a neurologist.

6. Sufficient information about patient/victim/plaintiffs that alledge peripheral neuropathy or its symptoms to permit interviewing their physician or other individual identified in item 4 above. This information may include age, sex, occupation, date of birth, date of evaluation, or name. Name need not be provided if other information is sufficient to permit the health care provided identify their patient.

7. Notify EPA of additional records that DowElanco receives.

Specific information requested on individual cases

DERBI Number 23168: Please identify in the summary which symptoms and diagnoses relate to the adult male and which to the adult female. Any additional information about the diagnosis of diabetic dated 10/90.

DERBI Number 23206: What does the abbreviation ANA stand for on page 203.

DERBI Number 23216: Please provide identifiers on pages 233-4 of individuals as adult male, adult female, or young male.

DERBI Number 23289: Please provide identifiers on pages 292-7 of individuals as adult male, adult female, or young male.

DERBI Number 23415: Please provide identifiers on pages 538-9 of individuals as adult male or adult female.

DERBI Number 23478: Please provide identifiers on pages 624-7 of individuals as adult males A and B, and adult female.

DERBI Number 23623: Please provide additional information (as specified in the list of items above) on cases diagnosed as neuropathy and any cases reporting numbness, tingling, or that "legs give out."

APPENDIX 3.

REVIEW OF EPIDEMIOLOGIC STUDIES OF CHRONIC NEUROBEHAVIORAL EFFECTS OF ORGANOPHOSPHATE INSECTICIDES

Neurobehavioral epidemiology is a comparatively new field and is dependent on practical, reliable, and sensitive tests of adverse effects. In a review sponsored by the National Research Council, Hanninen points out that more sensitive tests are needed to assess memory deficits, more valid and practical tests are needed to assess attention, and more comprehensive tests are needed to measure affect or mood states and personality (4). Despite the lack of optimal tests, deficits in memory, attention, and mood have been identified repeatedly in epidemiologic studies of organophosphate poisoned workers as will be shown below.

In epidemiology the ideal is to have a well-controlled study. Anger emphasizes this in his review, also sponsored by the National Research Council: "An appropriate control group should consist of people who are not only unexposed to toxic chemicals, but are also similar to the exposed subjects in terms of age, education, job activities or movements, and socioeconomic variables. This is extremely difficult to achieve, and field researchers are virtually always concerned with the accuracy of the controls as a basis for judging the performance of the exposed group" (1).

Case Reports

Several independent reports have noted long-lasting effects of OP poisoning. Case reports are not epidemiologic studies in the strictest sense but "it is recognized that such studies can be very useful as indicators of environmentally-induced disease" (8).

Rosenstock et al. presented a case report of a 60 year old farm worker who experienced headaches, memory loss, confusion, and fatigue after applying parathion in an apple orchard (14). Two years later he was still reported to have an inability to concentrate, severe impairment of memory, confusion, and depression.

Grace reported on a 33-year old farmhand in California who was severely poisoned by parathion after working in the orchard for 10 days and repairing farm machinery in the field (3). The family of the worker reported that he usually drank a pint of whiskey a day and his serum alcohol level on admission to the hospital was 0.19%, legally drunk. This patient developed memory impairment, personality changes, thought disorders, confusion, and depression that persisted months after his poisoning. Alcohol may have contributed to these symptoms.

Two three-year olds who had been poisoned by parathion were examined 1-2 years later in a follow-up study of 8 acute poisoning cases (5). Family history revealed that one child had become more nervous and emotionally less stable since his poisoning. This child who could not complete the physical examination because he was completely uncooperative and "his mother believed this type of behavior to be a direct result of the poisoning". The other victim of parathion poisoning was also reported to be irritable and less stable than his siblings. The investigators, who had not used any sophisticated neurobehavioral tests, judged their results inconclusive.

Case Series

Gershon and Shaw (1961) reported on 16 workers with 1-10 years duration of exposure to organophosphates (2). These 16 workers are not a representative sample of workers, but a selected group. Assessment of psychiatric symptoms revealed that 8 had impaired memory, 7 depression, 6 impaired concentration, 5 had schizophrenic reactions, 4 had irritability, and 4 had persistent headaches. Lack of controls and sampling methodology prevent concluding that the symptoms seen in this case series were necessarily due to the chronic exposure or poisoning from organophosphates.

Metcalf and Holmes (1969) examined two datasets based on workers involved in the manufacture of organophosphates (12). The first dataset examined 56 exposed workers and 22 controls. The OP exposed workers exhibited more forgetfulness (53% of exposed versus 20% of controls), visual difficulty (30% versus 0%), general fatigue (35% versus 5%), muscle aches and pains (12% versus 0%) and difficulty thinking (12% versus 5%).

Their subsequent study of the same workforce included psychological testing, electroencephalograms (EEG), and a neurological examination. The authors reported that the exposed group demonstrated "disturbed memory and difficulty maintaining alertness and appropriate focusing of attention" from the psychological testing. Direct interviews of these workers with multiple or severe exposures elicited complaints of being slowed down, less energetic, and having more memory difficulty and irritability than the minimally exposed workers. Neurological tests did not show differences between highly and minimally exposed workers on tests of sensory or motor deficits. The EEG examination was conducted on all workers in the study and did show changes. These changes were characterized as "a minimal type of EEG disturbance, but it mirrors, to a lesser degree, the more severe EEG disturbances seen after acute exposure".

Both this study and the earlier one by Metcalf and Holmes are marred by a lack of description of the sources of cases and controls, lack of case definition, absence of statistical testing

for significance, and lack of any discussion of possible biases or confounders. Due to these deficiencies, the study must be treated more as a case series than as a controlled epidemiologic study. This means that the findings can be characterized only as suggestive or supportive of the results from other studies.

Holmes and Gaon (1957) examined 600 patients who were factory workers with exposure to organophosphates, principally parathion and TEPP (7). In this survey 25 or 4 percent reported symptoms of irritability, nervousness, fatigue, lethargy, memory impairment, confusion, decreased mental concentration, and various problems with muscle aches and pains including sensations of numbness and weakness in the limbs. These persistent symptoms occurred "in the more severe exposures and in those with multiple exposures" (7).

In one case of severe exposure to an organophosphate, Holmes and Gaon recorded the patients subsequent mental confusion in the patient's own words: "Get tired--hard to breathe--short of breath, just like I'd run up a hill. This usually happens when I do anything that requires some energy--(fast walking--short runs, etc.). Had a couple of restless nights--nervous. I still get quite nervous--lot more irritable than before. Very absent-minded since last exposure. My mind seems to like to wander--quite marked. I cleaned out garage just after the exposure and now I don't know where I put half the stuff. I distinctly remember trying to store it in places where I could remember, but now I have to go through all the stuff to find it. It was 2 weeks sometimes before I found what I wanted. My thinking seems rather flighty--I've been fairly good in arithmetic, but can't do it too well in my head now. Can't concentrate on more than one thing at one time".

Two physicians in California examined 114 OP poisoning cases 3 years afterward to look for chronic effects (17). They originally sought 235 subjects that had OP poisoning in 1960, but only 114 were located, examined and included in the final analysis. Of the 114 cases, 6 were classified as severe (coma or convulsions present, hospitalized an average of 8 days), 54 were considered moderate based on clinical notes, and 54 were considered mild (patient remained ambulatory or recovered rapidly from limited therapy). Nearly half, 53 cases required hospitalization. In 6 individuals visual disturbances were reported which the patients insisted had not been present before the poisoning episode and which they attributed to the poisoning. Another 7 patients complained of persistent headaches. Five poisoning victims complained of nervousness or irritability. Notably 22 of the 114 workers (19%) reported they could no longer tolerate smelling or contacting pesticides. Of the 22, 16 had given up work involving contact with pesticides because of their intolerance and six continued to work on the farm but avoided contact as much as possible. One wonders how many of the 61 poisoned workers that could not be located for this study may have left because of persistent symptoms or intolerance. Other studies attempting to

measure such effects may miss recruiting affected individuals because they have left pesticide-related work after being sensitized. A controlled epidemiologic study would be needed to confirm the results identified in this report of a case series.

Hirshberg and Lerman collected data on 236 case records of organophosphate and carbamate poisoning from 8 hospitals in Israel from 1958 to 1979 (6). OP poisoning was confirmed by laboratory evidence of cholinesterase depression. Carbamate poisoning was confirmed by unequivocal evidence of direct exposure. Only 5 cases of carbamate poisoning were included. Accidental exposure accounted for 89% of the cases and 26 or 11% were attempted suicides by oral ingestion. According to the authors: "Depression, confusion, and agitation were noted in nine patients after recovery from the acute phase of poisoning. Other complaints were insomnia and motor weakness without objective neurological deficits". Seven of these 9 cases were considered to have only mild poisoning based on their clinical symptoms. All of the 9 cases had been poisoned by organophosphates.

Controlled epidemiologic studies

Both the studies by Savage et al., Rosenstock et al., and Steenland et al., presented below, are examples of high quality epidemiologic studies. A study by Savage et al. in Colorado and Texas examined 100 cases poisoned by organophosphates and 100 matched controls for neurological and neuropsychological function (16). Controls were matched on age, sex, race, ethnic background, education, and occupational class. Significant differences were found on tests of memory, abstraction, depression, and mental impairment. On average the exposed subjects were poisoned 9 years before testing. Poisoned subjects scored significantly worse on 4 of 5 summary scores of psychoneurological function and on 18 of 34 subtests. Among the tests that poisoned subjects scored worse on were the Wechsler Adult Intelligence Scale, logical analysis, abstract reasoning, verbal fluency, problem solving, concentration, sensitivity to social stresses, and fine motor coordination and speed. Relatives of the 100 poisoned subjects and controls were questioned about psychological function in 22 areas. Statistically significant differences were found in four areas, depression, irritability, social withdrawal, and confusion. Again, the controls performed better in these areas than the case group.

It was not possible from this single study to state that organophosphate poisoning leads to adverse effects on psychoneurological function. A number of potential sources of bias, particularly selection factors may have affected the results of this one study. However, results from this study have been replicated on poisoned workers in Nicaragua and again in California.

Rosenstock et al. performed a retrospective cohort study of agricultural workers in Nicaragua who had been hospitalized with organophosphate poisoning (15). Of 52 eligible patients hospitalized over a two year period, 38 men were located, and 36 agreed to participate in the study. Controls were a close male friend or sibling from the same community who had never been treated for pesticide poisoning and was no more than 5 years different in age from the case participant. Both members of the pair (case and control) were examined during May-June 1989 before the onset of the 4-5 month spraying season. Six of the seven tests from the World Health Organization core neurobehavioral test battery were administered, along with a brief symptom inventory, 6 additional Spanish-translated tests, and a 16 item self-reported symptom inventory. These tests were administered an average of 2 years after the time of hospitalization for poisoning.

Poisoned workers scored significantly worse on five of the six WHO core neurobehavioral tests, 3 of the 6 Spanish-translated tests, and the 16 item self-reported inventory. Deficits were noted in auditory and visual attention, visual memory, visuomotor skills, steadiness and dexterity. These findings replicated, to a large degree, those of Savage et al., which is an important consideration when judging the weight of evidence for a conclusion that OP poisoning is a cause of chronic neurobehavioral effects.

Steenland et al. studied chronic neurological sequelae in 128 workers poisoned by organophosphates between 1982 and 1990 and 90 controls. The poisoned group performed significantly worse on measures of sustained visual attention and mood. If the poisoned group was restricted to those with documented cholinesterase inhibition or those who had been hospitalized, the poisoned subjects also showed poorer performance on vibrotactile sensitivity tests. This study concluded "The evidence of some long-term effects of poisoning is consistent with two prior studies." (20).

This study had certain limitations common to many epidemiologic studies. However, these limitations do not effect the conclusion. The 128 poisoned cases were only 31% of the 416 potential participants sought for the study. Of the remainder 37% could not be located, 19% could not be contacted (mailings sent to their listed address were not responded to), and 13% refused to participate. Some of the individual were excluded from some or all of the tests. The first 16 individuals examined did not receive the test for mood which was added after the first round of testing. Eighteen subjects could not take the neurobehavioral tests primarily because of inability to read. Thirty-eight of the poisoned cases (30%) failed to bring a friend to serve as a control for the study. One disadvantage of the use of friends as controls is that they might be selected by the cases on the basis of similarities in mood and other personality factors under study that would tend to prevent discovery of significant effects.

Unlike the two earlier case-control studies, this report attempted to determine whether effects were associated with exposure to particular organophosphate insecticides. The Steenland et al. study mentions in their introduction that a subset of organophosphates may cause delayed-onset peripheral neuropathy by effects on the neuropathic target esterase, a property not shared by other organophosphates. No similar mechanism is suggested as to why in the current study some organophosphates and not others would effect either the peripheral nervous system or the central nervous system. All of the organophosphates under study poison primarily by their ability to inhibit the cholinesterase enzyme. Both central and peripheral nervous systems may be affected. Therefore, if chronic effects are brought about by depression of neural and brain cholinesterases, then such effects can be expected from any organophosphate insecticide.

Levin et al., and in a separate report, Rodnitzky et al. examined 11 farmers and 13 commercial applicators (11,13). Farmers tested prior to the spraying season and farmers not involved in pesticide application were used as controls and matched on sex, age, and education. While no significant differences were seen on neurobehavioral tests, there was some increased anxiety in commercial applicators. In order to participate in the study, pesticide applicators had to have been exposed in the past two weeks to organophosphates. Therefore, this study tested for immediate neurobehavioral effects of exposure and has no bearing on long term neurobehavioral effects of poisoning or exposure. The study may have been confounded by selecting farmers as controls who did have neurobehavioral deficits as a result of previous exposure (more than two weeks ago) or even poisoning to organophosphates. Therefore, these studies are not relevant to a review of chronic neurobehavioral effects of organophosphate poisoning.

Weight-of-Evidence Conclusion

The studies presented above do provide surprisingly consistent results of neurobehavioral damage due to organophosphates. While the association is not especially strong, it is fairly specific and has been found in a variety of different populations. Evidence of the direct effects of organophosphates on the brain mean the effects observed may be considered biologically plausible. In my judgement, alternative explanations such as chance, bias, and confounding are less likely explanations for the associations seen in these studies than exposure to organophosphates.

Taking these case reports and studies together, it now appears reasonable to conclude that some subset of organophosphate poisoned subjects probably experience persistent neurobehavioral effects (9,18,19). A recent review by Karalliedde and Senanayake (1989) came to a similar conclusion: "Behavioural changes have been documented following acute or chronic OP poisoning. These symptoms

may take months to regress. In human subjects exposed to OP agents to an extent sufficient to depress plasma or erythrocyte [red blood cell] cholinesterase, some or all of the following observations have been made: (1) Impairment of vigilance, information processing, psychomotor speed and memory. (2) Poor performance and perception of speech. (3) Increased tendency to faster frequencies and higher voltages in EEG records" (9).

The World Health Organization suggests that 5 percent of occupational poisonings due to organophosphates result in these effects (19). The Office of Technology Assessment of the U.S. Congress has arrived at a similar conclusion (18): "The pesticides parathion, mevinphos (Phosdrin), and malathion are frequently reported as causing health problems. Case reports and studies of acute poisonings of agricultural and other workers indicate that 4 to 9 percent of the acutely poisoned individuals experienced delayed or persistent neurological and psychiatric effects." These effects include "irritability, depression, mood swings, anxiety, fatigue, lethargy, difficulty concentrating, and short-term memory loss. These symptoms may persist for weeks and months after the initial exposure (18)." Given the results from controlled studies by Savage et al. and Rosenstock et al. and others listed above this last sentence can be changed to read: "These symptoms may persist for months or years after the initial exposure."

Results from key studies supporting a relationship between organophosphate poisoning and chronic neurobehavioral effects.

Reference	study type	Latency	Symptoms
Case reports Rosenstock et al. 1990	case report	2 years later	severe memory impairment, deficits in attention, depression, psychomotor impairment.
Grace 1985	case report	months later	memory impairment, personality changes, thought disorders, confusion, depression.
Harmon et al. 1975	case report	1 year later	temper tantrums, irritability.
Harmon et al. 1975	case report	2 years later	Excitability, emotionally less stable than siblings.
Case series Gershon and Shaw 1961	16 OP cases	1-10 years later	8 had impaired memory, 7 had depression, 6 impaired concentration, 5 schizoid, 4 headache, 4 irritability.
Metcalf and Holmes 1969	56 OP cases	6 years average	disturbed memory, difficulty in maintaining alertness, irritability, visual difficulty, muscular aches and pains.
Holmes and Gaon 1957	600 OP cases	?	increased irritability, marked forgetfulness, confusion in thinking, inability to concentrate.
Tabershaw and Cooper 1966	114 OP cases	3 years later	7 persistent headaches, 6 visual disturbances, 5 nervousness and irritability, 22 chemically sensitive.

Hirshberg and Lerman 1984	236 OP cases	after acute poisoning	9 depression, confusion, and agitation.
<u>matched case-control studies</u> Savage et al. 1988	100 cases and controls	9 years later on average	case performed poorer on: academic skills, motor skills, abstraction, flexibility in thinking, memory, depression, irritability, withdrawal, confusion.
Rosenstock et al. 1991	36 cases and controls	2 years later on average	cases performed poorer on: auditory and visual attention, visual memory, visuomotor skills, steadiness, dexterity.
Steenland et al. 1994	128 cases and 90 controls	5 years later on average	cases performed poorer on: visual attention and mood (confusion and tension).

<u>Most often reported effects</u>

Irritability
Memory impairment
Inability to concentrate
Confusion
Depression

<u>Reported in two or more studies</u>

Visual disturbances
Persistent headaches
Muscle aches and pains
Fatigue
Psychomotor impairment
Nervousness

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