

EVALUATION OF SUSPECTED CHRONIC PESTICIDE POISONING AMONG RESIDENTS NEAR AGRICULTURE FIELDS

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The present study was performed to evaluate the incidence of organophosphorus toxicity among agrarian and non agrarian subjects residing near agriculture fields. The location of this study was Nawakot village, Multan. From the cotton producing area of Multan, 225 volunteers (farmers) including 103 females and 122 males were selected. Children <12 years of age constitute 15% of the population. A total of 100 volunteers (non agrarians) from Multan city were taken as control. Blood (4 ml) was drawn from the volunteers to test the level of acetylcholine esterase (Ach E) in plasma. The blood samples were then analysed at the laboratory of National Poison Control Center (NPCC). Organo-phosphate (OP) & carbamates (CM) both act to block Ach E hydrolysis, necessary for synaptic response in the CNS. Acute illnesses were seen in 6 (2.67%), children (group 1). They had fever and signs of pulmonary infections. Generalised weakness was found in 9 males and 13 females. Paraesthesia was found in 11 volunteers of group IV. Blood sampling test revealed that 6 volunteers (2.67%) had plasma Ach E below 5300 IU/ml (\leq 50% reduction), whereas 4 volunteers had Ach E level between 5300 - 5500 IU/ml (\leq 45% reduction), 81 volunteers fall in group "c", and 126 individuals had an Ach E reduction of at least 25% and 8 volunteers had the serum cholinesterase level above 10000 IU/ml. None of volunteers had the value above 11000 IU whereas plasma Ach E level of control population was between 11500 - 13500 IU/ml. Medical tests of the level of Ach E in plasma suggest that the overall incidence of poisoning from exposure to OP & CM is quite high, and appears to be consistent with the results from other studies in other developing countries.

Indiscriminate use and improper handling of synthetic pesticides in agriculture have resulted into serious problems for human health in many developing countries. However, the true extent of the problem is hard to determine for a variety of reasons. First, farmers with mild pesticide poisoning often do not report because treatment services are costly, inaccessible, or fear that drawing attention to themselves may result in the loss of employment opportunities. Second, health-care professionals in rural areas often fail to correctly diagnose poisoning, as many of the related symptoms are quite general in nature or mimic other common health problems e.g. headaches, dizziness, vomiting¹³ (FAO, 2001) etc. At least 20,000 workers die from exposure every year, the majority in developing countries. World Health Organization.^{18,26,30,40}

Although the health hazards of pesticides are serious, support from policy makers for remedial measures has been lukewarm in developing countries. There is a widespread concern about diverting resources to alternative pest control methods wh-

en poverty, illiteracy and infant mortality are still major problems. In part, the resistance of policy makers is due to uncertainty about the severity of the problem, its sources, and suitable interventions. Their uncertainty is understandable, since systematic studies of the health effects of pesticides are scarce. Most existing studies rely on farmers' self-reported symptoms, as appropriate pathological tests are costly and relatively difficult for many developing country institutions to administer.

To assess the potential health hazards of pesticides, the NPCC with the technical collaboration of WHO studied the pesticide poisoning among the families of agriculture workers.^{41,42} The study included clinical examination by doctors from the NPCC, along with blood tests for cholinesterase inhibition due to contamination by organophosphate and carbamate. Epidemiological studies have linked carbamates (CM) and organophosphates (OP) with foetal death, hormonal changes, DNA damage, birth defects, and abnormal sperm and ova.⁴³ In addition, OP, as a class of insecticides,

has been linked with Non-Hodgkin's lymphoma, leukaemia, and lung cancer. In children OP have been linked to aplastic anaemia, the failure of the bone marrow to produce blood cells, and leukemia. Children with asthma may have severe reactions to OP in particular.⁴⁴

Human beings have three types of cholinesterases: red blood cell (RBC) cholinesterase, called "true cholinesterase"; plasma cholinesterase, called "pseudocholinesterase"; and brain cholinesterase. RBC cholinesterase is the same enzyme that is found in the nervous system, while plasma cholinesterase is made in the liver. When a cholinesterase blood test is taken, two types of cholinesterases can be detected. Physicians find plasma cholinesterase readings helpful for detecting the early, acute effects of organophosphate poisoning, while RBC readings are useful in evaluating long-term, or chronic, exposure. In this study we only performed the plasma AchE level due to limited resources.

Human exposure to cholinesterase-inhibiting pesticides can result from inhalation, ingestion, or eye or skin contact during the manufacture, mixing, or applications of these chemicals. Signs and symptoms of cholinesterase inhibition from exposure to CM or OP include the following:

1. Mild cases: tiredness, weakness, dizziness, nausea and blurred vision.
2. Moderate cases: headache, sweating, tearing, drooling, vomiting, tunnel vision, and twitching.
3. Severe cases: abdominal cramps, diarrhea, muscular tremors, staggering gait, pinpoint pupils, hypotension, slow heartbeat, breathing difficulty, and possibly death, if not promptly treated by a physician.

SUBJECTS AND METHODS

To investigate the health impacts of pesticide use, structured questionnaires designed by NPCC team were used to collect information on farming systems, pesticide use and practices, applicator precautions, and protective measures. The study was carried out to determine the incidence of organophosphate toxicity in the families of agriculture workers who were not involved directly in agriculture. Outskirts of Multan city, Nawakot village, was selected, that is basically, a cotton producing area. The families of farmers, include children, young and elderly of both genders. A total of 225 volunteers were evaluated in three days among which 103 (46%) were females and 122 (54%) were males. Children, < than 12 years of age constitutes 15% of the population. All participants were examined by doctors from NPCC. 100 volunteers from Multan city and its outskirts were taken as control

population (non-agrarians). They all were healthy individuals, who underwent the same protocol of clinical examination and blood test (Fig. 1 and 2).

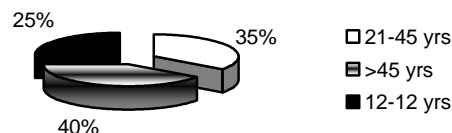


Fig. 1: Age Groups of volunteers from control population

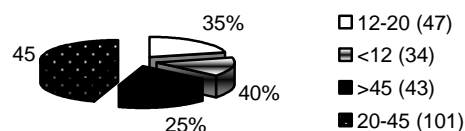


Fig. 2: Age groups of volunteers from farmer families

Using clinical examination results, the team collected the blood samples for cholinesterase inhibition test. In each case, a 4 ml blood sample drawn from the volunteer was used to test the level of AchE in plasma (Serum Butyryl Cholinesterase Kit, Randox Laboratories Ltd. UK). The normal value for serum AchE ranges between 5300 – 13300 IU/ml according to the kit used. The blood samples were then analysed at the laboratory of NPCC. OP and CM act so as to inhibit acetylcholine hydrolysis, a necessary task for synaptic response in the central nervous system. The presence of cholinesterase inhibiting chemicals prevent the breakdown of acetylcholine. Acetylcholine can then build up, causing a "jam" in the nervous system. The normal value for serum cholinesterase according to the kit used in this study ranges between 5300-13300 IU/ml. Groups have been constituted showing age and cholinesterase levels (Fig. 3).

RESULTS

Total 225 volunteers were included in the study out of which 122 were males and 103 were females. Various age groups has been constituted, the largest population size was between 20-45 years (45%), and the smallest was found in group I (≤ 12 years) that constitutes 15% of the total (Fig. 1 & 2)

(Table 1).

History taking and physical examination revealed that 64 volunteers were symptom free that includes 39 males and 25 females. A total of 133 volunteers (55 males and 78 females) had complaints of decrease appetite (59.1%), abdominal pain in 103 (45.78%), and diarrhoea in 94 volunteers (41.78%). Acute illnesses were seen in 6 (2.67%) children (group I), who had fever and signs of pulmonary infections. Generalised weakness and easy fatigability were found in 9 males and 13 females. Peripheral numbness and tingling were present in 11 volunteers of group IV (Fig. 3).

Building upon the initial clinical examination, the medical team carried out blood tests for 225 volunteers to check for cholinesterase enzyme inhibition from exposure to organophosphate and carbamate pesticides. The results displayed in graph IV indicate that (2.67%) 6 volunteers had plasma AchE below 5300 IU/ml ($\leq 50\%$ reduction), whereas 4 volunteers had AchE level between 5300 and 5500 IU/ml ($\leq 45\%$ reduction), 81 volunteers fall in group "C", 126 individuals had an AchE reduction of at least 25%, and 8 volunteers had the serum cholinesterase level just above 10000 IU/ml. No single individual had the value above 11000 IU whereas plasma AchE level of control population ranged between 11500 – 13500 IU/ml with an average of 12500 IU/ml.

We calculated the correlation of the blood test results against an index of equally weighed symptoms that are commonly associa-

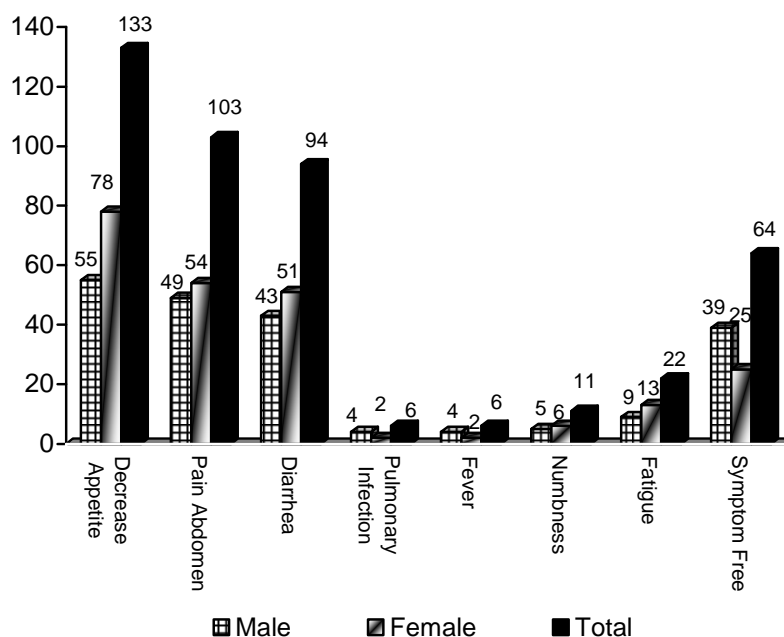


Fig. 3: Clinical evaluation data for organophosphate exposure

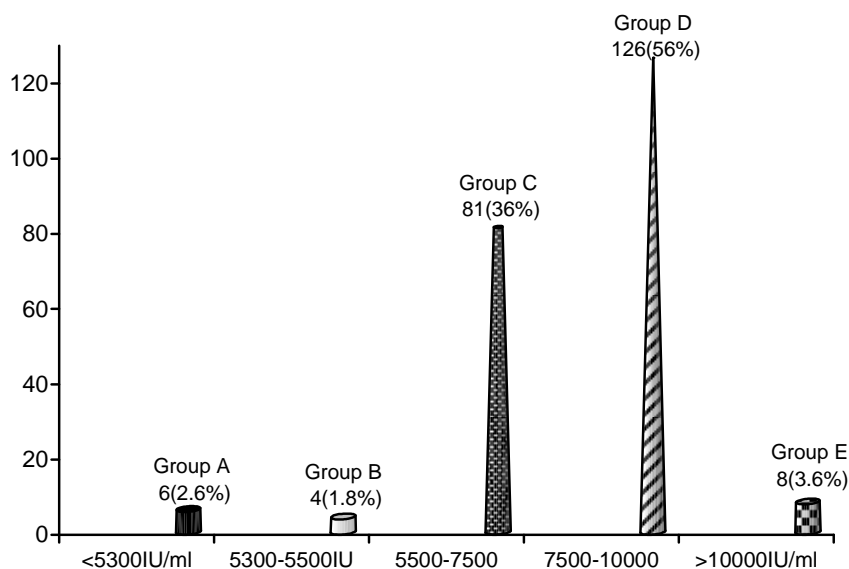


Fig. 4: Age groups showing serum cholinesterase

Table 1: Age groups of volunteers and control population

	Group I < 12 Years	Group II 12 – 20 Years	Group III 21 – 45 Years	Group IV > 45 Years
Volunteers	34	47	101	43
Control	0	25	35	40

ted with poisoning. Our evidence does not lend support to the use of self-reported symptoms as indicators of actual pesticide poisoning. Given the relatively high incidence of poisoning in the sample, however, our results strongly support regular medical testing for people who are exposed to highly or moderately toxic organophosphate and/or carbamate pesticides.

According to the medical literature, the types and severity of cholinesterase inhibition symptoms depend on the amount of pesticide involved in the exposure, the toxicity of the pesticide, the route of exposure, and the duration of exposure.¹²

DISCUSSION

Unintentional poisonings kill an estimated 355000 people each year.^{41,42} Two-thirds of these deaths occur in developing countries, where such poisoning is strongly associated with excessive exposure to, and inappropriate use of, toxic chemicals. In many such settings, the toxic chemicals may be emitted directly into soil, air and water.⁴³

There are many pesticides with thousands of trade names. Two-thirds of their total use is in agriculture.⁴² Chronic pesticide exposure is often a problem in occupational settings, particularly among poor rural populations, where men, women and children all work and live in close proximity to fields on which chemicals are applied and stored.

There is a paucity of data on the possible deleterious effects of chronic exposure to OPCs in occupational and/or environmental settings. In general, the literature brings out three types of 'non-acute' OPC poisoning: occupational exposure with reductions in AchE levels; occupational exposure with no reduction in AchE levels; and environmental exposure. However, the relationships between chronic exposure, AchE inhibition and symptoms do not, as yet, seem to be well established.

Available evidence suggests that there is a possibility of adverse effects occurring below OPC concentrations that are generally considered to be safe based on measurements of AchE inhibition; i.e. these effects are not clearly related to the inhibition of cholinesterases^{1,27,32,34} Studies on health hazards to agricultural workers who handle, store and use OPC pesticides have documented a range of non-specific self-reported symptoms that have been attributed to chronic exposure. These include: burning or prickling of the skin; tingling or numbness of hands and face; muscular twitching or cramps in the face, neck, arms and legs; respiratory symptoms, including chest pain, cough, running nose, wheezing, shortness of breath, irritation of the throat; excessive sweating; nausea, vomiting, diarrhoea; excessive salivation; abdominal

pain; lacrimation and irritation of the eyes; difficulty in seeing; restlessness; difficulty in falling asleep; trembling of hands; and irritability.^{1,24} In this study acute toxicity was observed in 13.5% cases below 12 years of age.^{22, 31} Volunteers showed 59.1% gastrointestinal symptoms referred as loss of appetite, off and on abdominal pain and diarrhoea.³⁸ 64 individuals had no symptoms and their serum cholinesterase levels ranged from 7500 – 1100 IU/ml. No individual in the study was directly involved in the farming or spray even then they are suffering from sub clinical and delayed effects of pesticide toxicity. The expected source of exposure observed was the use of empty cans of pesticide as drinking water reservoir, storage of pesticides in houses and bad hygiene. If we look into serum cholinesterase level it was observed that 6 individuals had the value below 5300 IU/ml that means acute exposure whereas rest of them had their cholinesterase level within range, although none of them reached the upper limit. This shows that the individuals even with cholinesterase levels within range were also suffering from sub clinical long-term exposure to organophosphates.

After literature search and evaluation of our findings we came to the conclusion that sub clinical damage does occur, however longer follow up studies are needed. It is suggested that the government in collaboration with pesticide industry should encourage awareness programs for the farmers that may help in the reduction of pesticide mortality and morbidity.

Detailed, long-term studies of occupational or environmental exposures to OPC are needed to distinguish the effects of the active OPC. Subtle abnormalities on neurological examination, such as impaired two-point discrimination and vibration sensation, have also been reported in workers chronically exposed to OPCs.^{4,38} Some report evidence of nerve abnormalities during occupational exposure^{9,36} while others do not.^{11,23} A recent study from Sri Lanka has shown inhibition of AchE enzyme activity and impairment of sensory and motor nerve conduction due to long-term, low-level exposure to OPC.²⁵ Evidence of toxicity was found not only among the farmers who directly handled (sprayed) OPCs, but also among those employed in inland fisheries living within a 25 km radius of the cultivated land, who were not directly exposed.

Chronic organophosphate-induced neuropsychiatric disorders (COPIND) occur without cholinergic symptoms, and although the underlying mechanisms are not established, they do not seem dependent on AchE inhibition.^{6,28,29,34} Clinical features reported include: anxiety disorder; depression; psychotic symptoms; dysthymic disorder

(DSM-III-R); problems with short-term memory, learning, attention, information processing, eye-hand coordination and reaction time; autonomic dysfunction; and extra pyramidal symptoms.^{3,32,34,37} Similar clinical features have also been reported by soldiers suffering from the much-publicised Gulf-war Syndrome, which led to the, so far unproven, hypothesis that the illness was caused by chronic exposure to chemical agents with similar effects to OPCs.¹⁴ Some organophosphates (such as methamidophos, leptophos, fenthion, merphos) inhibit a second enzyme, neuropathy target esterase (NTE). Severe inhibition of this enzyme may be accompanied by a peripheral neuropathy 10-14 days after exposure. This delayed neuropathy typically affects the motor and sensory nerves of the legs and is caused by a "dying back" of the distal axons. Symptoms include tingling sensations with weakness and ataxia that develop into paralysis in severe cases. Effects are often reversible but may persist.^{7,33} In our study 22 individuals have the complaints of weakness and easy fatigability among which 11 had the symptoms of peripheral neuropathy indicating low level long term exposure.^{10,17}

Chronic toxicity to OPCs may be related to the rate of regeneration of AchE and the speed at which pesticide metabolites are hydrolysed and eliminated from the body. This 'fast' or 'slow' enzymatic hydrolysis status seems to be determined by gene polymorphisms of hydrolases such as paraoxonase.²¹ However, in some situations where there is chronic exposure to OPC, there seems to be poor correlation between evidence of toxicity and the degree of AchE inhibition.^{29,34} It may well be that toxicity in these situations is mediated more by other mechanisms, such as oxidative stress through OPC-induced generation of free oxygen radicals leading to lipid peroxidation,^{5,15} rather than inhibition of AchE.

In this study, we have assessed the incidence and determinants of pesticide poisoning among the family members of farmers in Pakistan. We believe that our results are of particular interest because they rely on explicit medical parameters for poisoning, rather than conventional self-reporting of symptoms by farmers. Medical tests of the level of AchE in plasma suggest that the overall incidence of poisoning from exposure to OP and CM is quite high, and appears to be consistent with the results from other studies in other developing countries.^{8,16,19,20,35,39}

Using the laboratory test results as benchmarks, we find that self-reported symptoms have very weak associations with actual poisoning. Both the incidence of poisoning and their own apparent inability to distinguish its symptoms from other health problems suggest that regular checkups and

blood tests should be conducted for those who were directly or indirectly exposed to toxic organophosphate and carbamate pesticides although there is no definite relationship established yet between the signs and symptoms of poisoning and AChE activity.

REFERENCES

1. Ames et al., 1989 R.G. Ames, S.K. Brown, D.C. Mengle, E. Kahn, J.W. Stratton and R.J. Jackson, Cholinesterase activity depression among Californian agricultural pesticide applicators, *Am. J. Ind. Med.* 15 (1989), pp. 143-150.
2. Ames R, Steenland K, Jenkins B, Chrislop D, Russo J. Chronic neurologic sequel to cholinesterase inhibition among agricultural pesticide applicators. *Arch Environ Health* 1995; 50: 440-3.
3. Amr et al., 1997 M.M. Amr, Z.S. Halim and S.S. Moussa, Psychiatric disorders among Egyptian pesticide applicators and formulators, *Environ. Res.* 73 (1997), pp. 193-199.
4. Beach et al., 1996 J.R. Beach, A. Spurgeon, R. Stephens, T. Heafield, I.A. Calvert, L.S. Levy and J.M. Harrington, Abnormalities on neurological examination among sheep farmers exposed to organophosphate pesticides, *Occup. Environ. Med.* 53 (1996), pp. 520-525.
5. Bebe and Panemangalore, 2003 F.N. Bebe and M. Panemangalore, Exposure to low doses of endosulphan and chlorpyrifos modifies endogenous antioxidants in tissues of rats, *J. Environ. Sci. Health B* 38 (2003), pp. 349-363.
6. Brown and Brix, 1998 M.A. Brown and K.A. Brix, Review of health consequences from high-, intermediate-, and low-level exposure to organophosphorus nerve agents, *J. Appl. Toxicol.* 18 (1998), pp. 393-408.
7. Cherniak M. Toxicological screening for organophosphorus-induced delayed neurotoxicity: complications in toxicity testing. *Neurotoxicology* 1988; 9: 249-72.
8. Dien and Vong, 2003 Dien, B.V., Vong, V.D., 2003. Assessment of the Pesticide Poisoning among Workers in 719 Coffee Farms in Dak Lak. The Book of Abstracts. Medical Publishing House, Hanoi, pp. 123-124.
9. Drenth et al., 1972 H.J. Drenth, I.F. Ensberg, D.V. Roberts and A. Wilson, Neuromuscular function in agricultural workers using pesticides, *Arch. Environ. Health* 25 (1972), pp. 395-398.
10. Duffy F, Burchfiel J, Bartels P, Gaon M, Sim V. Long-term effects of an organophosphate on the human electroencephalogram. *Toxicol Appl Pharmacol* 1979; 47: 161-76.
11. Enegel et al., 1998 L.S. Enegel, M.C. Keifer, H. Checkoway, L.R. Robinson and T.L. Vaughan, Neurophysiological function in farm workers exposed to organophosphate pesticides, *Arch. Environ. Health* 53 (1998), pp. 7-14.
12. Extension Toxicology Network (ECOTOXNET), 2004 Extension Toxicology Network (ECOTOX-

- NET), 2004. Cholinesterase Inhibition. Toxicology Information Brief. Cornell University.
13. FAO, 2001. Farmer Self-Surveillance of Pesticide Poisoning Episodes: Report on One Month Pilot: August 15–September 15, 2000. FAO Programme for Community IPM in Asia, Field Document.
 14. Gronseth, 2005 G.S. Gronseth, Gulf war syndrome: a toxic exposure? A systematic review, *Neurol. Clin.* 23 (2005), pp. 523–540.
 15. Gultekin et al., 2000 F. Gultekin, M. Ozturk and M. Akdogan, The effect of organophosphate insecticide chlorpyrifos-ethyl on lipid peroxidation and antioxidant enzymes (in vitro), *Arch. Toxicol.* 74 (2000), pp. 533–538.
 16. Hruska and Corriols, 2002 A. Hruska and M. Corriols, The impact of training in integrated pest management among Nicaraguan maize farmers: increased net returns and reduced health risk, *Int. J. Occup. Environ. Health* 8 (2002), pp. 191–200.
 17. Jamal G. Long-term neurotoxic effects of organophosphate compounds. *Adverse Drug React Toxicol Rev* 1995; 14: 85–99.
 18. Kishi et al., 1995 M. Kishi, N. Hirschhorn, M. Qjajadisastra, L.N. Satterlee, S. Strowman and R. Dilts, Relationship of pesticide spraying to signs and symptoms in Indonesian farmers, *Scand. J. Work Environ. Health* 21 (1995), pp. 124–133.
 19. Kunststadter et al., 2001 P. Kunststadter, T. Prapantontol, B.O. Siroroj, A. Sontirat, A. Tansuhaj and C. Khamboonruang, Pesticide exposures among Hmong farmers in Thailand, *Int. J. Occup. Environ. Health* 7 (2001) (4), pp. 313–325.
 20. Ky and Ngoc, 1998 Ky, H.H., Ngoc, D.M., 1998. Investigation on Health Status of Workers Exposed to Pesticides. The Third National Scientific Conference on Occupation Health, The Book of Abstracts, Hanoi, p. 143.
 21. Lee et al., 2003 B.W. Lee, L. London, J. Paulauskis, J. Myers and D. Christiani, Association between human paraoxonase gene polymorphism and chronic symptoms in pesticide-exposed workers, *J. Occup. Environ. Med.* 45 (2003), pp. 118–122.
 22. Leon-S F. E, Pradilla G., and Vesga E. Neurological effects of organophosphate pesticides. *BMJ*, September 14, 1996; 313 (7058): 690c - 691.
 23. Misra et al., 1988 U.K. Misra, D. Nag, W.A. Khan and P.K. Ray, A study of nerve conduction velocity, late responses and neuromuscular synapse functions in organophosphate workers in India, *Arch. Toxicol.* 61 (1988), pp. 496–500.
 24. Ohayo-Mitoko et al., 2000 G.J.A. Ohayo-Mitoko, H. Kromhout, J.M. Simwa, J.S.M. Boleij and D. Heederik, Self reported symptoms and inhibition of acetylcholinesterase activity among Kenyan agricultural workers, *Occup. Environ. Med.* 57 (2000), pp. 195–200.
 25. Peiris-John et al., 2002 R. Peiris-John, D.K. Ruberu, A.R. Wickremasinghe, L.A.M. Smit and W. Van der Hoek, Effects of occupational exposure to organophosphate pesticides on nerve and neuromuscular function, *J. Occup. Environ. Med.* 44 (2002), pp. 352–357.
 26. Pimental et al., 1992 D. Pimental, H. Acquay and M. Biltonen, Environmental and economic costs of pesticide use, *Bioscience* 42 (1992), pp. 750–760.
 27. Popendorf, 1990 J.W. Popendorf, Effects of organophosphate insecticide residue variability on re-entry intervals, *Am. J. Ind. Med.* 18 (1990), pp. 313–319.
 28. Prendergast et al., 1998 M.A. Prendergast, A.V. Terry Jr. and J.J. Buccafusco, Effects of chronic, low-level organophosphate exposure on delayed recall, discrimination, and spatial learning in monkeys and rats, *Neurotoxicol. Teratol.* 20 (1998), pp. 115–122.
 29. Ray and Richards, 2001 D.E. Ray and P.G. Richards, The potential for toxic effects of chronic, low-dose exposure to organophosphates, *Toxicol. Lett.* 120 (2001), pp. 343–351.
 30. Rosenstock et al., 1991 L. Rosenstock, M. Keifer, W.E. Daniell, R. McConnell and K. Claypoole, Chronic central nervous system effects of acute organophosphate pesticide intoxication, *Lancet* 338 (1991), pp. 223–227.
 31. Rotenberg J. S. and Newmark. J Nerve Agent Attacks on Children: Diagnosis and Management. *Pediatrics.*, September 1, 2003; 112(3): 648 - 658.
 32. Salvi et al., 2003 R.M. Salvi, D.R. Lara, E.S. Ghisolfi, L.V. Portela, R.D. Dias and D.O. Souza, Neuropsychiatric evaluation in subjects chronically exposed to organophosphate pesticides, *Toxicol. Sci.* 72 (2003), pp. 267–271.
 33. Savage E, Keefe T, Mounce L, Heaton R, Lewis J, Burcar P. Chronic neurological sequelae of acute organophosphate pesticide poisoning. *Arch Environ Health* 1990; 43:38-45.
 34. Singh and Sharma, 2000 S. Singh and N. Sharma, Neurological syndromes following organophosphate poisoning, *Neurol. India* 48 (2000), pp. 308–313.
 35. Soogarun et al., 2003 S. Soogarun, V. Wiwanitkit, A. Suyaphan, J. Suwansakri and N. Pathompat-tama, Decreased serum cholinesterase levels among a sample of a rural Thai population, *Med-scape Gen. Med.* 5 (2003) (2).
 36. Stalberg et al., 1978 E. Stalberg, P. Hilton-Brown, B. Kolmodin-Hedman, B. Holmstedt and K.B. Augustinsson, Effect of occupational exposure to organophosphorus insecticides on neuromuscular function, *Scand. J. Work Environ. Health* 4 (1978), pp. 255–261.
 37. Stephens et al., 1995 R. Stephens, A. Spurgeon, I.A. Calvert, J. Beach, L.S. Levy, H. Berry and J.M. Harrington, Neuropsychological effects of long-term exposure to organophosphates in sheep dip, *Lancet* 345 (1995), pp. 1135–1139.
 38. Stokes et al., 1995 L. Stokes, A. Stark, E. Marshall and A. Narang, Neurotoxicity among pesticide applicators exposed to organophosphate pesticides, *Occup. Environ. Med.* 52 (1995), pp. 648–653.
 39. Thuy et al., 2003 Thuy, A.B., Wangsuphachart, V., Kaewkurgwal, J., 2003. Cholinesterase Screening Test among Organophosphate Exposure of Rice Farmers in Southern Vietnam. The Book of Abstracts, Medical Publishing House, Hanoi, pp. 186–187.

40. WHO, 1990 WHO, 1990. Report on Pesticides in Agriculture. World Health Organization, Geneva.
41. WHO, 2003 WHO, 2003. World Health Report: Shaping the Future. World Health Organization, Geneva.
42. World Health Organization (WHO), 1990. Public Health Impact of Pesticides Used in Agriculture.
43. Yáñez et al., 2002 L. Yáñez, D. Ortiz, J. Calderon, L. Batres, L. Carrizales, J. Meija, L. Martinez, E. Garcia-Nieto and F. Diaz-Barriga, Overview of human health and chemical mixtures: problems facing developing countries, *Environ. Health Perspect.* 110 (2002), pp. 901–909.
44. Zahm et al., 1997 S.H. Zahm, M.H. Ward and A. Blair, Pesticides and cancer. In: M. Keifer, Editor, *Occupational Medicine: State of the Art Reviews. Vol. 12: Pesticides*, Hanley and Belfus, Inc., Philadelphia (1997), pp. 269–289.