Neuropsychological Syndrome and long term effects of Exposure to Organophosphate Pesticides in Humans

Dr.Maida Zameer, Dr. Sunbal Siddique, Dr.Maria Baig

Abstract

Organophosphorous compounds, the anticholinesterases, produce significant morbidity and mortality in Pakistan. Neuropsychological assessment was traditionally carried out to assess the extent of impairment to a particular skill and to attempt to determine the area of the brain which may have been damaged following brain injury or neurological illness. With the advent of neuroimaging techniques, location of space-occupying lesions can now be more accurately determined through this method, so the focus has now moved on to the assessment of cognition and behaviour, including examining the effects of any brain injury or neuropathological process that a person may have experienced. Although exact estimates are not available, hospital based statistics suggest that nearly half of the admissions to emergency with acute poisoning are due to organophosphates. Following accidental or suicidal exposure, these anticholinesterases lead to three well defined neurological syndromes i.e. initial life threatening acute cholinergic crisis which often requires management in intensive care unit, intermediate syndrome in which cranial nerve palsies, proximal muscle weakness and respiratory muscle weakness are common and patients often require respiratory support and delayed organophosphate induced polyneuropathy. In addition to these three classical neurological syndromes following acute exposure and in some following low dose chronic exposure, several neurobehavioural changes have been observed and these have been termed together as 'chronic organophosphate induced neuropsychiatric disorders' (COPIND). Organophosphates (also known as phosphate esters, or OPEs) are a class of organophosphorus compounds with the general structure O=P(OR)3. They can be considered as esters of phosphoric acid. Like most functional groups organophosphates occur in a diverse range of forms, with important examples including key biomolecules such as DNA, RNA and ATP, as well as many insecticides, herbicides, nerve agents and flame retardants. The clinical features of 33 patients with significant histories of chronic exposure to organophosphate pesticides (OPs) are reported. Disorders of mood, cognition, perception and motor performance are consistently linked to the point that it is suggested that a distinct and specific syndrome of neuropsychiatric disorder resulting from chronic OP exposure exists and tentative operational criteria for its diagnosis are proposed. Attention is drawn to the fact that this syndrome differs significantly from chronic fatigue syndrome (myalgic encephalitis) both in terms of the nature of symptoms reported and in particular the difference in consistency of reporting. There is, thus, a need to determine exact extent of the problem and to develop appropriate strategies to manage these cases with available resources in these countries.

Keywords: *Organophosphates, Neuropsychiatric Disorder, Neurochemistry, Chronic Toxicity Disability,Syndrome.*

1. INTRODUCTION:

Neuropsychological assessment was traditionally carried out to assess the extent of impairment to a particular skill and to attempt to determine the area of the brain which may have been damaged following brain injury or neurological illness. With the advent of neuroimaging techniques, location of space-occupying lesions can now be more accurately determined through this method, so the focus has now moved on to the assessment of cognition and behaviour, including examining the effects of any brain injury or neuropathological process that a person may have experienced. A core part of neuropsychological assessment is the administration of neuropsychological tests for the formal assessment of cognitive function, though neuropsychological testing is more than the administration and scoring of tests and screening tools. It is essential that neuropsychological assessment also include an evaluation of the person's mental status. This is

especially true in assessment of Alzheimer's disease and other forms of dementia. [1] Aspects of cognitive functioning that are assessed typically include orientation, new-learning/memory, intelligence, language, visuoperception, and executive function. However, clinical neuropsychological assessment is more than this and also focuses on a person's psychological, personal, interpersonal and wider contextual circumstances.

1.1 Assessment may be carried out for a variety of reasons, such as:

- Clinical evaluation, to understand the pattern of cognitive strengths as well as any difficulties a person may have, and to aid decision making for use in a medical or rehabilitation environment.
- Scientific investigation, to examine a hypothesis about the structure and function of cognition to be tested, or to provide information that allows experimental testing to be seen in context of a wider cognitive profile.
- Medico-legal assessment, to be used in a court of law as evidence in a legal claim or criminal investigation.

Miller outlined three broad goals of neuropsychological assessment. Firstly, diagnosis, to determine the nature of the underlying problem. Secondly, to understand the nature of any brain injury or resulting cognitive problem (see neurocognitive deficit) and its impact on the individual, as a means of devising a rehabilitation programme or offering advice as to an individual's ability to carry out a certain tasks (for example, fitness to drive, or returning to work). And lastly, assessments may be undertaken to measure change in functioning over time, such as to determine the consequences of a surgical procedure or the impact of a rehabilitation programme over time. [2]

1.2 Diagnosis of a neuropsychological disorder

Certain types of damage to the brain will cause behavioral and cognitive difficulties. Psychologists can start screening for these problems by using either one of the following techniques or all of these combined

1.3 History taking

This includes gathering medical history of the patient and their family, presence or absence of developmental milestones, psychosocial history, and character, severity, and progress of any history of complaints. The psychologist can then gauge how to treat the patient and determine if there are any historical determinants for his or her behavior.

1.4 Interviewing

Psychologists use structured interviews in order to determine what kind of neurological problem the patient might be experiencing. There are a number of specific interviews, including the Short Portable Mental Status Questionnaire, Neuropsychological Impairment Scale, Patient's Assessment of Own Functioning, and Structured Interview for the Diagnosis of Dementia.[3]

1.5 Test-taking

The scores on standardized tests taken by children is a strong predictor of future or current neuropsychological problems. Standardized tests allow psychologists to compare a child's results with other children's because it has the same components and is given in the same way. It is representative of the child's behavior and cognition. The results of a standardized test are only a tool used to discover if there is a disorder. Further testing is needed to officially diagnose the patient.[4]

1.6 Intelligence testing

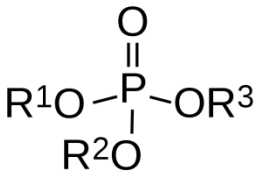
Testing one's intelligence can also give a clue to whether there is a problem in the brain-behavior connection. The Wechsler Scales are the tests most often used to determine level of intelligence. The variety of scales available, the nature of the tasks, as well as a wide gap in verbal and performance scores can give clues to whether there is a learning disability or damage to a certain area of the brain.[3]

1.7 Testing other areas

Other areas are also tested when a patient goes through neuropsychological assessment. These can include sensory perception, motor functions, attention, memory, auditory and visual processing, language, problem solving, planning, organization, speed of processing, and many others. Neuropsychological assessment can test many areas of cognitive and executive functioning to determine whether a patient's difficulty in function and behavior has a neuropsychological basis. [4] Pesticides have led to increased worldwide agricultural production. However, when not applied safely, they can cause environmental pollution and adverse health effects, which are sometimes irreversible.Exposure to OPs is usually assessed through analysis of blood and urine biomarkers to determine acetylcholinesterase levels. Depression of plasma acetylcholinesterase activity in the blood is indicative of OP exposure. Biomarkers that measure concentrations of erythrocyte cholinesterase are used to assess chronic exposure and acute poisoning. The measurement of plasma cholinesterase is used only for the diagnosis of acute poisoning because of the difficulty in determining chronic exposure at low doses.Currently, urinary biomarkers are the most sensitive measurement of OP exposure. The presence of dialkyl phospate metabolites or specific metabolites of OP pesticides such as chlorpyrifos, methamidophos, malathion, diazinon, and dimethoate are measured in urine. The metabolites analyzed include dimethyl phosphate (DMP), dimethyl tiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), diethyl tiophosphate (DETP), and diethyl dithiophosphate (DEDTP). Each of these metabolites corresponds to one or more types of OP pesticides. An increasing number of studies have focused on understanding the activity of the enzyme paraoxonase (PON1) and its relationship to genetic polymorphisms PON1 192 and PON155. [5] This enzyme is linked to the detoxification of OP pesticides; and its activity is modified by the oxidative stress caused by these pesticides.

2. ORGANOPHOSPHATES

Organophosphates (also known as phosphate esters, or OPEs) are a class of organophosphorus compounds with the general structure O=P(OR)3. They can be considered as esters of phosphoric acid. Like most functional groups organophosphates occur in a diverse range of forms, with important examples including key biomolecules such as DNA, RNA and ATP, as well as many insecticides, herbicides, nerve agents and flame retardants.



2.1 Properties

The phosphate esters bearing OH groups are acidic and partially deprotonated in aqueous solution. For example, DNA and RNA are polymers of the type [PO2(OR)(OR')−]n. Polyphosphates also form esters; an important example of an ester of a polyphosphate is ATP, which is the monoester of triphosphoric acid (H5P3O10).

2.2 Pesticides

The word "organophosphates", when appearing in communications (e.g., from the press or the government), in areas such as agriculture, the environment, and human and animal health, very often refers to a group of insecticides (pesticides) that act on the enzyme acetylcholinesterase[citation needed] (see also carbamates).[citation needed] Today, organophosphates make up about 50% of the killing agents in chemical pesticides.[6]

Organophosphate pesticides (OPPs), like some nerve agents, inhibit this neuromuscular enzyme, which is broadly essential for normal function in insects, but also in humans and many other animals.[7] OPPs affect this enzyme in varied ways, a principle one being through irreversible covalent inhibition, and so create potentials for poisoning that vary in degree. The brain sends out neurotransmitters to the nerve endings in the body; organophosphates disrupt this process from occurring.This chemical, organophosphate works by disrupting the enzyme acetylcholinesterase. Acetylcholinesterase break down the acetylcholine neurotransmitter, which sends out signals to other nerve endings in the body.

For instance, parathion, one of the first OPPs commercialized, is many times more potent[clarification needed] than malathion, an insecticide used in combating the Mediterranean fruit fly (Med-fly) and West Nile Virus-transmitting mosquitoes.[8] Human and animal exposure to them can be through ingestion of foods containing them, or via absorption through the skin or lungs.

3. HEALTH EFFECTS

3.1 Organophosphate poisoning

Many "organophosphates" are potent nerve agents, functioning by inhibiting the action of acetylcholinesterase (AChE) in nerve cells. They are one of the most common causes of poisoning worldwide, and are frequently intentionally used in suicides in agricultural areas. Organophosphosphate pesticides can be absorbed by all routes, including inhalation, ingestion, and dermal absorption. Their inhibitory effects on the acetylcholinesterase enzyme lead to a pathological excess of acetylcholine in the body. Their toxicity is not limited to the acute phase, however, and chronic effects have long been noted. Neurotransmitters such as acetylcholine (which is affected by organophosphate pesticides) are profoundly important in the brain's development, and many organophosphates have neurotoxic effects on developing organisms, even from low levels of exposure. Other organophosphates are not toxic, yet their main metabolites, such as their oxons, are. Treatment includes both a pralidoxime binder and an anticholinergic such as atropine.

3.2 Chronic toxicity

Repeated or prolonged exposure to organophosphates may result in the same effects as acute exposure including the delayed symptoms. Other effects reported in workers repeatedly exposed include impaired memory and concentration, disorientation, severe depressions, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking, drowsiness, or insomnia. An influenza-like condition with headache, nausea, weakness, loss of appetite, and malaise has also been reported.[8]

A recent study done by Madurai Kamaraj University in India have shown a direct correlation between usage of organophosphates and diabetes among Indian agricultural population.[9]

3.3 Low-level exposure

Even at relatively low levels, organophosphates may be hazardous to human health[citation needed]. The pesticides act on acetylcholinesterase.[10] an enzyme found in the brain chemicals closely related to those involved in ADHD, thus fetuses and young children, where brain development depends on a strict sequence of biological events, may be most at risk.[11] They can be absorbed through the lungs or skin or by eating them on food. According to a 2008 report from the U.S. Department of Agriculture,"detectable"traces of organophosphate were found in a representative sample of produce tested by the agency, 28% of frozen blueberries, 20% of celery, 27% of green beans, 17% of peaches, 8% of broccoli, and 25% of strawberries.[12] An organic diet is an effective way to reduce exposure to the organophosphorus pesticides commonly used in agricultural production. Organophosphate metabolite levels rapidly drop, and for some metabolites, become undetectable in children's urine when an organic diet is consumed.[13] This is speculative based on a short study of 23 children, in which only a few organophosphate compounds were potentially reduced, no effect was shown for the majority of them that were found in the samples.

3.4 Cancer

The International Agency for Research on Cancer (IARC), found that some organophosphates may increased cancer risk. Tetrachlorvinphos and parathion were classified as "possibly carcinogenic", whereas malathion and diazinon were classified as probably carcinogenic to humans.[14]

4. ORGANOPHOSPHATE POISONING

Organophosphate poisoning is poisoning due to organophosphates (OPs). Organophosphates are used as insecticides, medications, and nerve agents. Symptoms include increased saliva and tear production, diarrhea, vomiting, small pupils, sweating, muscle tremors, and confusion. While onset of symptoms is often within minutes to hours, some symptoms can take weeks to appear.[15] Symptoms can last for days to weeks. Organophosphate poisoning occurs most commonly as a suicide attempt in farming areas of the developing world and less commonly by accident. Exposure can be from drinking, breathing in the vapors, or skin exposure. The underlying mechanism involves the inhibition of acetylcholinesterase (AChE), leading to the buildup of acetylcholine (ACh) in the body.Diagnosis is typically based on the symptoms and can be confirmed by measuring butyrylcholinesterase activity in the blood.[12] Carbamate poisoning can present similarly.Prevention efforts include banning very toxic types of organophosphates. Among those who work with pesticides the use of protective clothing and showering before going home is also useful.[16] In those who have organophosphate poisoning the primary treatments are atropine, oximes such as pralidoxime, and diazepam.General measures such as oxygen and intravenous fluids are also recommended.Attempts to decontaminate the stomach, with activated charcoal or other means, has not been shown to be useful.While there is a theoretical risk of health care workers taking care of a poisoned person becoming poisoned themselves, the degree of risk appears to be very small. OPs are one of the most common causes of poisoning worldwide. There are nearly 3 million poisonings per year resulting in two hundred thousand deaths. Around 15% of people who are poisoned die as a result.[17] Organophosphate poisoning has been reported at least since 1962.

4.1 Signs and symptoms

The symptoms of organophosphate poisoning include muscle weakness, fatigue, muscle cramps, fasciculation, and paralysis. Other

symptoms include hypertension, and hypoglycemia.Overstimulation of nicotinic acetylcholine receptors in the central nervous system, due to accumulation of ACh, results in anxiety, headache, convulsions, ataxia, depression of respiration and circulation, tremor, general weakness, and potentially coma. When there is expression of muscarinic overstimulation due to excess acetylcholine at muscarinic acetylcholine receptors symptoms of visual disturbances, tightness in chest, wheezing due to bronchoconstriction, increased bronchial secretions, increased salivation, lacrimation, sweating, peristalsis, and urination can occur.[18] The effects of organophosphate poisoning on muscarinic receptors are recalled using the mnemonic SLUDGEM (salivation, lacrimation, urination, defecation, gastrointestinal motility, emesis, miosis) An additional mnemonic is MUDDLES: miosis, urination, diarrhea, diaphoresis, lacrimation, excitation, and salivation.[19] The onset and severity of symptoms, whether acute or chronic, depends upon the specific chemical, the route of exposure (skin, lungs, or GI tract), the dose, and the individuals ability to degrade the compound, which the PON1 enzyme level will affect.

4.2 Diagnosis

A number of measurements exist to assess exposure and early biological effects for organophosphate poisoning. Measurements of OP metabolites in both the blood and urine can be used to determine if a person has been exposed to organophosphates. Specifically in the blood, metabolites of cholinesterases, such as butyrylcholinesterase (BuChE) activity in plasma, neuropathy target esterase (NTE) in lymphocytes, and of acetylcholinesterase (AChE) activity in red blood cells. Due to both AChE and BuChE being the main targets of organophosphates, their measurement is widely used as an indication of an exposure to an OP. The main restriction on this type of diagnosis is that depending on the OP, the degree to which either AChE or BuChE are inhibited differs; therefore, measure of metabolites in blood and urine do not specify which OP agent is responsible for the poisoning. However, for fast initial screening, determining AChE and BuChE activity in the blood are the most widely used procedures for confirming a diagnosis of OP poisoning.[20] The most widely used portable testing device is the Test-mate ChE field test,13 which can be used to determine levels of Red Blood Cells (RBC), AChE and plasma (pseudo) cholinesterase (PChE) in the blood in about four minutes. This test has been shown to be just as effective as a regular laboratory test and because of this, the portable ChE field test is frequently used by people who work with pesticides on a daily basis.[21]

4.3 Treatment

Current antidotes for OP poisoning consist of a pretreatment with carbamates to protect AChE from inhibition by OP compounds and post-exposure treatments with anti-cholinergic drugs. Anti-cholinergic drugs work to counteract the effects of excess acetylcholine and reactivate AChE. Atropine can be used as an antidote in conjunction with pralidoxime or other pyridinium oximes (such as trimedoxime or obidoxime), though the use of "-oximes" has been found to be of no benefit, or to be possibly harmful, in at least two meta-analyses.[21] Atropine is a muscarinic antagonist, and thus blocks the action of acetylcholine peripherally.These antidotes are effective at preventing lethality from OP poisoning, but current treatment lack the ability to prevent post-exposure incapacitation, performance deficits, or permanent brain damage. While the efficacy of atropine has been well-established, clinical experience with pralidoxime has led to widespread doubt about its efficacy in treatment of OP poisoning.Enzyme bioscavengers are being developed as a pretreatment to sequester

highly toxic OPs before they can reach their physiological targets and prevent the toxic effects from occurring. Significant advances with cholinesterases (ChEs), specifically human serum BChE (HuBChE) have been made. HuBChe can offer a broad range of protection for nerve agents including soman, sarin, tabun, and VX. HuBChE also possess a very long retention time in the human circulation system and because it is from a human source it will not produce any antagonistic immunological responses.[22][23] HuBChE is currently being assessed for inclusion into the protective regimen against OP nerve agent poisoning.[23] Currently there is potential for PON1 to be used to treat sarin exposure, but recombinant PON1 variants would need to first be generated to increase its catalytic efficiency. Another potential treatment being researched is the Class III anti-arrhythmic agents.[24][25] Hyperkalemia of the tissue is one of the symptoms associated with OP poisoning. While the cellular processes leading to cardiac toxicity are not well understood, the potassium current channels are believed to be involved.[26] Class III anti-arrhythmic agents block the potassium membrane currents in cardiac cells, which makes them a candidate for become a therapeutic of OP poisoning.[27][28]

5. CONCULSION AND FUTURE WORK

Currently, more research is being done on animal fetuses to determine the effects of OP's during critical periods of development. Due to children's decreased size, faster rate of respiration, and continuing organ development, this area is important to research. Research to determine the variability on the PON1 enzyme in humans is also currently being researched. In another study, Singh et al observed the reversal of neuro-electrophysiological effect of organophosphorous poisoning with the use of intravenous magnesium sulphate. The actual role of magnesium in the management of organophosphorous poisoning remains to be studied in randomized controlled trials. Intermediate syndrome is treated by providing respiratory support in the form of mechanical ventilation. The use of atropine is of no clinical significance in intermediate syndrome and full functional recovery of the involved muscle group is the rule. The muscles of respiration are the last to recover and this fact should be borne in mind while weaning the patient from mechanical ventilator. The use of the organophosphates in aviation lubricating oils and hydraulic fluids and its impact on health and flight safety is currently being researched. Aerotoxic syndrome is a medical condition allegedly caused by exposure to contaminated bleed air.

6. RAFERENCES

[1] Baer, Lee; Blais, Mark A., eds. (3 October 2009). Handbook of Clinical Rating Scales and Assessment in Psychiatry and Mental Health. Springer. ISBN 978-1-58829-966-6. Retrieved 17 June 2014.

[2] Davis, Andrew, ed. (2011). Handbook of Pediatric Neuropsychology. New York: Springer Publishing. ISBN 978-0-8261-0629-2. Retrieved 28 May 2013. Lay summary – Archives of Clinical Neuropsychology (17 June 2014).

[3] Lezak, Muriel D.; Howieson, Diane B.; Bigler, Erin D.; Tranel, Daniel (2012). Neuropsychological Assessment (Fifth ed.). Oxford: Oxford University Press. ISBN 978-0-19-539552-5. Retrieved 17 June 2014. Lay summary – Journal of the International Neuropsychological Society (17 June 2014).

[4] Loring, David W., ed. (1999). INS Dictionary of Neuropsychology. New York: Oxford University Press. ISBN 978-0-19-506978-5. Lay summary (21 November 2010). This standard reference book includes entries by

Kimford J. Meador, Ida Sue Baron, Steven J. Loring, Kerry deS. Hamsher, Nils R. Varney, Gregory P. Lee, Esther Strauss, and Tessa Hart.

[5] Gonzalez V, Huen K, Venkat S, Pratt K, Xiang P, Harley KG, et al. Cholinesterase and paraoxonase (PON1) enzyme activities in Mexican–American mothers and children from an agricultural community. J Expo Sci Environ Epidemiol. 2012;22(6):641–648.10.1038/jes.2012.61

[6] Organophosphates: Background, Pathophysiology, Epidemiology". 2016-11-29. Archived from the original on 2017-04-24.

[7]Goodman, Brenda (21 Apr 2011). "Pesticide Exposure in Womb Linked to Lower IQ". Health & Pregnancy. WebMD. Archived from the original on 2011-04-24.

[8] Peter, J. V.; Sudarsan, T. I.; Moran, J. L. (2014). "Clinical features of organophosphate poisoning: A review of different classification systems and approaches". Indian Journal of Critical Care Medicine. 18 (11): 735–745. doi:10.4103/0972-5229.144017. PMC 4238091. PMID 25425841.

[8] "Organophosphates FAQs". Centers for Disease Control and Prevention. DHHS Department of Health and Human Services. Archived from the original on 20 January 2016. Retrieved 6 February 2016.

[9] Jurewicz, Joanna; Hanke, Wojciech (9 Jul 2008). "Prenatal and Childhood Exposure to Pesticides and Neurobehavioral Development: Review of Epidemiological Studies". International Journal of Occupational Medicine and Environmental Health. Versita, Warsaw. 21 (2): 121–132. doi:10.2478/v10001-008-0014-z. ISSN 1896-494X. PMID 18614459.

[10] Study: ADHD linked to pesticide exposure". CNN. 17 May 2010. Archived from the original on 18 May 2010.

[11] Parathion (CASRN 56-38-2)". IRIS Summaries. U.S. EPA. 9 Aug 2012. Archived from the original on 2006-10-10.

[12] Lu, Chensheng; Toepel, Kathryn; Irish, Rene; Fenske, Richard A.; Barr, Dana B.; Bravo, Roberto (2006). "Organic Diets Significantly Lower Children's Dietary Exposure to Organophosphorus Pesticides". Environmental Health Perspectives. 114 (2): 260–3. doi:10.1289/ehp.8418. PMC 1367841. PMID 16451864.

[13] "IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides" (PDF). World Health Organization. Archived (PDF) from the original on 2017-04-17.

[14] "Archived copy" (PDF). Archived (PDF) from the original on 2017-04-17. Retrieved 2016-05-20.

[15] Rauh V, Arunajadai S, Horton M, et al. (2011). "Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide". Environmental Health Perspectives. 119 (8): 1189–1195. doi:10.1289/ehp.1003160. PMC 3237355. PMID 21507777.

[16] Jump up to:a b c Jokanovic M, Kosanovic M (2010). "Neurotoxic effects in patients poisoned with organophosphate pesticides". Environmental Toxicology and Pharmacology. 29 (3): 195–201. doi:10.1016/j.etap.2010.01.006. PMID 21787602.

[17] Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell N, Barr D, Furlong C, Holland N (2004). "Association of in Utero

Organophosphate Pesticide Exposure and Fetal Growth and Length of Gestation in an Agricultural Population". Environ Health Perspect. 112(10): 116–1124. doi:10.1289/ehp.6789. PMC 1247387. PM ID 15238287.

[18] Jump up to:a b "IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides" (PDF). World Health Organization. Archived (PDF) from the original on 2017-04-17.

[19] "Cholinesterase Inhibition". Archived from the original on 2013-04-02.

[20]"Pesticide Application and Safety Training for Applicators of Public Health Pesticides". Archived from the original on 2010-08-29. Retrieved 2013-03-25.

[21] "Because some foods carry organophosphate residues".

[22] "Methyl Parathion Risk Management Decision". Archived from the original on 2013-04-01. Retrieved 2013-03-25.

[23]": Health Effects of 30 Commonly Used Lawn Pesticides" (PDF). Archived (PDF)from the original on 2011-11-12.

[24] Jump up to:a b c d Costa L, Cole T, Vitalone A, Furlong C (2005). "Measurement of paraoxonase (PON1) status as a potential biomarker of susceptibility to organophosphate toxicity". Clinica Chimica Acta. 352 (1–2): 37–47. doi:10.1016/j.cccn.2004.09.019. PMID 1565 3099.

[25] "Organophosphorous Cumulative Risk Assessment 2006 Update" (PDF). US EPA Office of Pesticide Programs. Archived (PDF) from the original on 2011-06-04. Retrieved 2011-12-10.

[25] Ames RG, Steenland K, Jenkins B, Chrislip D, Russo J. 1995. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. *Arch Environ Health* 50(6):440–444.

[26] Amr MM, Abbas EZ, El-Samra M, El Batanuoni M, Osman AM. 1997. Neuropsychiatric syndromes and occupational exposure to zinc phosphide in Egypt. *Environ Res* 73(1–2):200–206.

[27] Azaroff LS, Neas LM. 1999. Acute health effects associated with nonoccupational pesticide exposure in rural El Salvador. *Environ Res* 80(2 Pt 1):158–164.

[28] Burns CJ, Cartmill JB, Powers BS, Lee MK. 1998. Update of the morbidity experience of employees potentially exposed to chlorpyrifos. *Occup Environ Med* 55(1):65–70.