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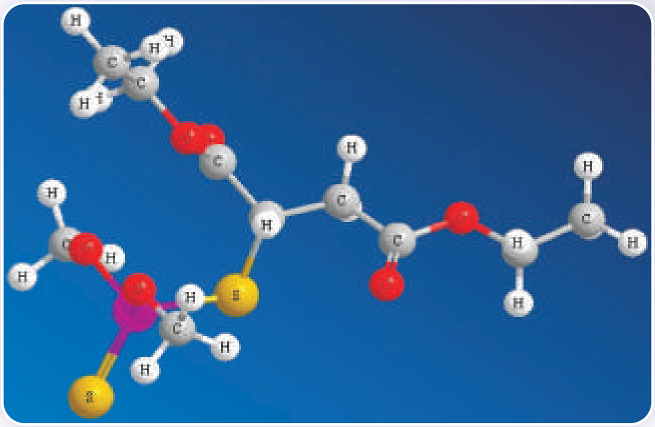
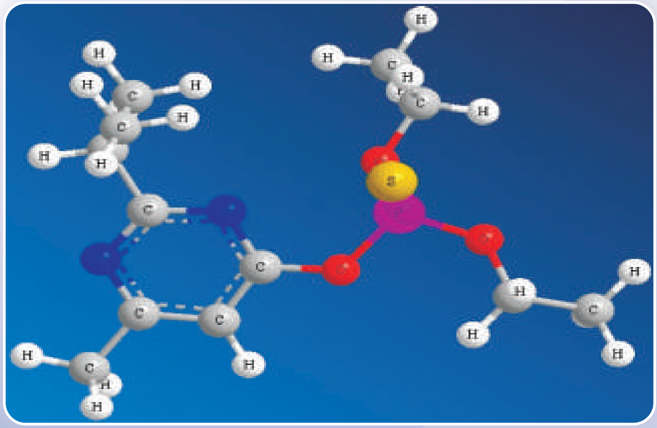


Malathion



Diazinon

CSIR-Indian Institute of Toxicology Research
Lucknow, India

August 2011 Vol. 18, No. 3

IN THIS ISSUE

EDITORIAL

Organophosphate compounds include some of the most toxic chemicals used in agriculture. They are disulfoton, phorate, dimethoate, ciodrin, dichlorvos, dioxathion, ruelene, carbophenothion, supona, TEPP, EPN, HETP, parathion, malathion, ronnel, coumaphos, diazinon, trichlorfon, paraoxon, potasan, dimefox, mipafox, schradan, sevin, chlorpyrifos and dimeton. Generally these insecticides are esters, amides, or simple derivatives of phosphoric and thiophosphoric acids. Some less toxic compounds of this group are used as systemic insecticides in animals against parasitc infection. These include chlorthion, thichlorphon, diazinon, fenchlorphos, and dichlorvos. The organophosphate insecticides can be grouped according to their toxic action on insects. Many of these compounds are excreted in milk and are able to cross placental membranes causing toxicity in offsprings. The chemicals in this class kill insects by disrupting their nervous system. Unfortunately, these chemicals can also cause toxicity to brain and nervous system of animals and humans. These chemicals inhibit the activity of a key enzyme in the nervous system called cholinesterase from working, and this can make people ill. It has been reported that children, with higher levels of organophosphate pesticide metabolites in their urine suffer from Attention-Deficit/Hyperactivity Disorder (ADHD) than children with lower levels. Amy Marks, School of Public Health, University of California (UC) said in a statement "Given that these compounds are designed to attack the nervous system of organisms, there is reason to be cautious, especially in situations where exposure may coincide with critical periods of fetal and child development,". Young children are vulnerable to organophosphate exposure at a greater extent than elders, as they have lower levels of acetylcholinesterase to detoxify these pesticides. Symptoms of acute exposure include nausea, headaches, twitching, trembling, excessive salivation and tearing, difficulty in breathing due to paralysis of the diaphragm, convulsions, and some times at higher doses lead to death. Organophosphates are also among the most common active ingredients in pesticide poisonings as well as suicidal attempts. As per the researchers a number of less-toxic alternatives to organophosphate pesticides are available these are: Pheromones: chemicals secreted by insects for communication--to disrupt insect mating; Cultural controls: crop rotations, manipulating planting dates, reducing of pest habitats and improving crop vigor; Less toxic, more pest-specific alternative insecticides

Editors

Dr. Poonam Kakkar

Dr. Anvita Shaw

Published by :

Distributed Information Centre on Toxic Chemicals

Environmental Information System (ENVIS)

at CSIR-Indian Institute of Toxicology Research

Lucknow, India

ODDS AND ENDS

Neurobehavioral function and organophosphate insecticide use among pesticide applicators in the Agricultural Health Study.

Although persistent decrements in cognitive function have been observed among persons who have recovered from clinically overt organophosphate (OP) pesticide poisoning, little is known about the cognitive effects of chronic OP exposures that do not result in acute poisoning. To examine associations between long-term pesticide use and neurobehavioral (NB) function, NB tests were administered to licensed pesticide applicators enrolled in the Agricultural Health Study (AHS) in Iowa and North Carolina. Between 2006 and 2008, 701 male participants completed nine NB tests to assess memory, motor speed and coordination, sustained attention, verbal learning and visual scanning and processing. Data on ever-use and lifetime days of use of 16 OP pesticides were obtained from AHS interviews conducted before testing between 1993 and 2007 and during the NB visit. The mean age of participants was 61years (SD=12). Associations between pesticide use and NB test performance were estimated with linear regression controlling for age and outcome-specific covariates. NB test performance was associated with lifetime days of use of some pesticides. Ethoprop was significantly associated with reduced performance on a test of motor speed and visual scanning. Malathion was significantly associated with poor performance on a test of visual scanning and processing. Conversely, authors observed significantly better test performance for five OP pesticides. Specifically, chlorpyrifos, coumaphos, parathion, phorate, and tetrachlorvinphos were associated with better verbal learning and memory; coumaphos was associated with better performance on a test of motor speed and visual scanning; and parathion was associated with better performance on a test of sustained attention. Several associations varied by state. Overall, authors found no consistent evidence of an association between OP pesticide use and adverse NB test performance among this older sample of pesticide applicators. Potential reasons for these mostly null results include a true absence of effect as well as possible selective participation by healthier applicators.

[Neurotoxicol Teratol. 2011 Aug 28. (doi:10.1016/j.ntt.2011.08.014 Epub ahead of print)]

Organophosphate Pesticide Exposure and Attention in Young Mexican-American Children: The CHAMACOS Study

Organophosphate (OP) pesticides are well-known neurotoxicants that have been associated with neurobehavioral deficits in children. Authors evaluated attention-related outcomes among Mexican-American children participanting in the CHAMACOS study (331 children 3.5 years and 323 children 5 years of age), and measured urinary dialkyl phosphate (DAP) metabolites in the children and in their mothers during pregnancy to determine OP exposure. The authors report that prenatal DAP levels were positively but not significantly associated with maternal reports of attention problems or attention deficit/hyperactivity disorder (ADHD) at 3.5 years, and were significantly associated with these outcomes at 5 years. Some associations appeared to be modified by sex, with associations found only among boys. There was also limited evidence of associations between the outcomes and DAP levels measured in the children. The authors conclude that in utero DAPs and, to a lesser extent, DAPs in children, were associated adversely with attention.

[Environ Health Perspect 118:1768-1774.]

Association of organophosphate pesticide exposure and paraoxonase with birth outcome in mexicanamerican women.

Epidemiologic studies suggest that maternal organophosphorus (OP) pesticide exposure is associated with poorer fetal growth, but findings are inconsistent. The authors explored whether paraoxonase (PON1), a key enzyme involved in detoxification of OPs, could be an effect modifier in this association. The study population included 470 pregnant women enrolled in the CHAMACOS Study, a longitudinal cohort study of mothers and children living in an agricultural region of California. The authors analyzed urine samples collected from mothers twice during pregnancy for dialkyl phosphate (DAP) metabolites of OP pesticides. They analyzed maternal and fetal (cord) blood samples for PON1 genotype (PON1(192) and PON1(-108)) and enzyme activity (paraoxonase and arylesterase). Infant birth weight, head circumference, and gestational age were obtained from medical records. Infants' PON1 genotype and activity were associated with birth outcome, but mothers' were not. Infants with the susceptible PON1(-108TT) genotype had shorter gestational age (β=-0.5 weeks, 95% Confidence Interval (CI): -0.9, 0.0) and smaller head circumference (β=-0.4 cm, 95% CI: -0.7, 0.0) than those with the PON1(-108CC) genotype. Infants' arylesterase and paraoxonase activity were positively associated with gestational age. There was some evidence of effect modification with DAPs: maternal DAP concentrations were associated with shorter gestational age only among infants of the susceptible PON1(-108TT) genotype (p-value(interaction)=0.09). However, maternal DAP concentrations were associated with larger birth weight (p-value(interaction)=0.06) and head circumference (p-value (interaction) <0.01) in infants with non-susceptible genotypes.The conclusion was that infants whose PON1 genotype and enzyme activity levels suggested that they might be more susceptible to the effects of OP pesticide exposure had decreased fetal growth and length of gestation. PON1 may be another factor contributing to preterm or low birth weight birth.

[PLoS One. 2011;6(8):e23923.]

Organophosphate acetylcholine esterase inhibitor poisoning from a home-made shampoo.

Organophosphate acetylcholine esterase inhibitor poisoning is a major health problem in children. Here authors report an unusual cause of organophosphate acetylcholine esterase inhibitor poisoning. Two children were admitted to the pediatric intensive care unit due to organophosphate acetylcholine esterase inhibitor poisoning after exposure from a home-made shampoo that was used for the treatment of head lice. Owing to no obvious source of poisoning, the diagnosis of organophosphate acetylcholine esterase inhibitor poisoning in one of these patients was delayed. Both patients had an uneventful recovery. Organophosphate acetylcholine esterase inhibitor poisoning from home-made shampoo is possible. In cases where the mode of poisoning is unclear, direct questioning about the use of home-made shampoo is warranted, in these cases the skin and particularly the scalp should be rinsed thoroughly as soon as possible.

[J Emerg Trauma Shock. 2011 Jul;4(3):433-4.]

Pollution of soils with organophosphorus flame retardants and plasticizers.

The detection of the three organophosphate esters TCEP, TCPP and TBEP in soil samples indicates that pollution of soils from diffuse atmospheric sources has to be considered in risk assessments.

[J Environ Monit. 2011 Aug 24.(doi:10.1039/c1em10538h Epub ahead of print)]

A case report of motor neuron disease in a patient showing significant level of DDTs, HCHs and organophosphate metabolites in hair as well as levels of hexane and toluene in blood.

Motor neuron disease is a devastating neurodegenerative condition, with the majority of sporadic, non-familial cases being of unknown etiology. Several epidemiological studies have suggested that occupational exposure to chemicals may be associated with disease pathogenesis. Authors report the case of a patient developing progressive motor neuron disease, who was chronically exposed to pesticides and organic solvents. The patient presented with leg spasticity and developed gradually clinical signs suggestive of amyotrophic lateral sclerosis, which was supported by the neurophysiologic and radiological findings. This report is an evidence based case of combined exposure to organochlorine (DDTs), organophosphate pesticides (OPs) and organic solvents as confirmed by laboratory analysis in samples of blood and hair confirming systematic exposure. The concentration of non-specific dialkylphosphates metabolites (DAPs) of OPs in hair (dimethyphophate (DMP) 1289.4pg/mg and diethylphosphate (DEP) 709.4pg/mg) and of DDTs (opDDE 484.0pg/mg, ppDDE 526.6pg/mg, opDDD 448.4pg/mg, ppDDD+opDDT 259.9pg/mg and ppDDT 573.7pg/mg) were considerably significant. Toluene and n-hexane were also detected in blood on admission at hospital and quantified (1.23 and 0.87µg/l, respectively), while 3months after hospitalization blood testing was found negative for toluene and n-hexane and hair analysis was provided decrease levels of HCHs, DDTs and DAPs.

[Toxicol Appl Pharmacol. 2011 Aug 6. (doi:10.1016/j.taap.2011.07.022 Epub ahead of print)]

Nerve agent intoxication: Recent neuropathophysiological findings and subsequent impact on medical management prospects.

This manuscript provides a survey of research findings catered to the development of effective countermeasures against nerve agent poisoning over the past decade. New neuropathophysiological distinctive features as regards organophosphate (OP) intoxication are presented. Such leading neuropathophysiological features include recent data on nerve agent-induced neuropathology, related peripheral or central nervous system inflammation and subsequent angiogenesis process. Hence, leading countermeasures against OP exposure are down-listed in terms of pre-treatment, protection or decontamination and emergency treatments. The final chapter focuses on the description of the self-repair attempt encountered in lesioned rodent brains, up to 3months after soman poisoning. Indeed, an increased proliferation of neuronal progenitors was recently observed in injured brains of mice subjected to soman exposure. Subsequently, the latter experienced a neuronal regeneration in damaged brain regions such as the hippocampus and amygdala. The positive effect of a cytokine treatment on the neuronal regeneration and subsequent cognitive behavioral recovery are also discussed in this review. For the first time, brain cell therapy and neuronal regeneration are considered as a valuable contribution towards delayed treatment against OP intoxication. To date, efficient delayed treatment was lacking in the therapeutic resources administered to patients contaminated by nerve agents.

[Toxicol Appl Pharmacol. 2011 Sep 15;255(3):229-41.]

Organophosphate poisoning in a 12-day-old infant: case report.

A 12-day-old infant girl was admitted with increasing lethargy and respiratory distress. Initial treatment was for pneumonia but deterioration despite appropriate treatment prompted review of her diagnosis and consideration of organophosphate poisoning. There was a brisk response to atropine. This is the youngest infant reported to have been exposed to poisoning by organophosphates.

[Ann Trop Paediatr. 2011;31(3):263-7.]

Organophosphate pesticide exposure and residential proximity to nearby fields: evidence for the drift pathway.

Residential proximity to pesticide-treated farmland is an important pesticide exposure pathway. In-person interviews and biological samples were collected from 100 farmworker and 100 non-farmworker adults and children living in Eastern Washington State. Authors examined the relationship of residential proximity to farmland to urinary metabolite concentrations of dimethylphosphate (DMTP) and levels of pesticide residues in house dust. DMTP concentrations were higher in farmworkers than non-farmworkers (71 µg/L vs 6 µg/L) and in farmworker children than non-farmworker children (17 µg/L vs 8 µg/L). Compared to non-farmworker households, farmworker households had higher levels of azinphos-methyl (643 ng/g vs 121 ng/g) and phosmet (153 ng/g vs 50 ng/g). Overall, a 20% reduction in DMTP concentration was observed per mile increase in distance from farmland. Lower OP metabolite concentrations correlated with increasing distance from farmland.

[J Occup Environ Med. 2011 Aug;53(8):884-91.]

Maternal prenatal and child organophosphate pesticide exposures and children's autonomic function.

Organophosphate pesticides (OP), because of their effects on cholinergic fibers, may interfere with the functions of the autonomic nervous system (ANS). Authors conducted a study to assess the relation of *in utero* and child OP pesticide exposures and children's autonomic nervous system (ANS) dysregulation under resting and challenge conditions. They hypothesized that children with high OP levels would show parasympathetic activation and no sympathetic activation during rest and concomitant parasympathetic and sympathetic activation during challenging conditions. OP exposures were assessed by measuring urinary dialkylphosphate metabolites (DAPs, total diethyls-DEs, and total dimethyls-DMs) in maternal and children's spot urine samples. ANS regulation was examined in relation to maternal and child DAPs in 149 children at 6 months and 1 year, 97 at 3 1/2 years and 274 at 5 years. Authors assessed resting and reactivity (i.e., challenge minus rest) measures using heart rate (HR), respiratory sinus arrhythmia (RSA), and preejection period (PEP) during the administration of a standardized protocol. Cross-sectional (at each age) and longitudinal regression models were conducted to assess OP and ANS associations. To estimate cumulative exposure at 5 years, authors used an area-under-the-concentration-time-curve (AUC) methodology. They also evaluated whether children with consistently high versus low DAP concentrations had significantly different mean ANS scores at 5 years. Child DMs and DAPs were significantly negatively associated with resting RSA at 6 months and maternal DMs and child DEs were significantly positively associated with resting PEP at 1 year. No associations with resting were observed in 3 1/2- or 5-year-old children nor with reactivity at any age. There was no significant relationship between the reactivity profiles and maternal or child DAPs. Cumulative maternal total DEs were associated with low HR (-3.19bpm decrease; 95% CI: -6.29 to -0.09, p=0.04) only at 5 years. In addition, there were no significant differences in ANS measures for 5-year-olds with consistently high versus low DAPs. Although authors observe some evidence of ANS dysregulation in infancy, authors report no consistent associations of maternal and child OP pesticide exposure, as measured by urinary DAPs, on children's ANS (HR, RSA, and PEP) regulation during resting and challenging conditions up to age 5 years.

[Neurotoxicology. 2011 Jun 29. [Epub ahead of print]]

Electroencephalogram, cognitive state, psychological disorders, clinical symptom, and oxidative stress in horticulture farmers exposed to organophosphate pesticides.

The aim of this paper was to study the toxicity of organophosphate (OP) pesticides in exposed farmers for electroencephalography, cognitive state, psychological disorders, clinical symptom, oxidative stress, acetylcholinesterase, and DNA damage. A comparative cross-sectional analysis was carried out in 40 horticulture farmers who were exposed to OPs in comparison to a control group containing 40 healthy subjects with the same age and sex and education level. Lipid peroxidation (LPO), superoxide dismutase (SOD), catalase, glutathione peroxidase, DNA damage, total antioxidant capacity (TAC), total thiol molecules, and acetylcholinesterase (AChE) activity were measured in the blood of subjects. Clinical examination and complete blood test were undertaken in order to record any abnormal sign or symptoms. Cognitive function, psychological symptoms, and psychological distress were examined and recorded. Comparing with controls, the farmers showed higher blood levels of SOD and LPO while their TAC decreased. Farmers showed clinical symptoms such as eczema, breathing muscle weakness, nausea, and saliva secretion. Regarding cognitive function, the orientation, registration, attention and calculation, recall, and language were not significantly different in farmers and controls. Among examinations for psychological distress, only labeled somatization was significantly higher in farmers. The present findings indicate that oxidative stress and inhibition of AChE can be seen in chronically OP-exposed people but incidence of neuropsychological

disorders seems a complex multivariate phenomenon that might be seen in long-term high-dose exposure situations. Use of supplementary antioxidants would be useful in the treatment of farmers.

[Toxicol Ind Health. 2011 Jun 1. [doi: 10.1177/0748233711407243 (Epub ahead of print)]

Organophosphate and phthalate esters in indoor air: a comparison between multi-storey buildings with high and low prevalence of sick building symptoms.

An extensive study has been conducted on the prevalence of organophosphorous flame retardants /plasticizers and phthalate ester plasticizers in indoor air. The targeted substances were measured in 45 multi-storey apartment buildings in Stockholm, Sweden. The apartment buildings were classified as high or low risk with regard to the reporting of sick building symptoms (SBS) within the project Healthy Sustainable Houses in Stockholm (3H). Air samples were taken from two to four apartments per building (in total 169 apartments) to facilitate comparison within and between buildings. Association with building characteristics has been examined as well as association with specific sources by combining chemical analysis and exploratory uni- and multivariate data analysis. The study contributes to the overall perspective of levels of organophosphate and phthalate ester in indoor air enabling comparison with other studies. The results indicated little or no difference in the concentrations of the target substances between the two risk classifications of the buildings. The differences between the apartments sampled within (intra) buildings were greater than the differences between (inter) buildings. The concentrations measured in air ranged up to 1200 ng m(-3) for organophosphate esters and up to 11000 ng m(-3) for phthalate esters. Results in terms of sources were discerned e.g. PVC flooring is a major source of benzylbutyl phthalate in indoor air.

[J Environ Monit. 2011 Jul;13(7): 2001-9.]

A highly sensitive and rapid organophosphate biosensor based on enhancement of CdS-decorated graphene nanocompo site.

This work reports a rapid and sensitive organophosphates (OPs) amperometric biosensor based on acetylcholinesterase (AChE) immobilized on CdS-decorated graphene (CdS-G) nanocomposite. The as-prepared biosensor shows high affinity to acetylthiocholine (ATCl) with a Michaelis-Menten constant (K(m)) value of 0.24 mM. A rapid inhibition time (2 min) is obtained due to the integration of the CdS-G nanocomposite. Based on the inhibition of OPs on the enzymatic activity of the immobilized AChE, and used carbaryl as the model compound, the resulting biosensor exhibits excellent performance for OPs detection including good reproducibility, acceptable stability, and a reliable linear relationship between the inhibition and log[carbaryl] from 2 μg mL?1 up to 2 μg mL?1 with a detection limit of 0.7 μg mL?1, which provides a new promising tool for analysis of enzyme inhibitors.

[Anal Chim Acta. 2011 Jun 10;695(1-2):84-8.]

Acute and late complications of organophosphate poisoning.

To describe the acute and late complications of organophosphate (OP) poisoning a total of 300 patients with organophosphate poisoning admitted to the Medical ICU were included. Baseline investigations included blood complete picture, urea, creatinine, arterial blood gas values, and serum cholinesterase levels. Data was retrieved from the files on a structured proforma. Studied variables included gender, mode of exposure, acute (occuring within 4 weeks) and delayed (occuring after 4 weeks onwards) complications There were 50 (16.66%) males and 250 (83.33%) females with ratio of 1:5. Two hundred and forty eight (82.6%) had ingested while 18 (6%) had inhaled the poison. Acute complications included fits in 50 (16.66%) bradycardia in 30 (10%) and hyperglycemia in 15 (5%) patients. Delayed complications (after 4 weeks and later) included monoplegia and mild sensory loss of lower limbs in 4 (2.66%) and paraplegia and weakness of upper limbs in 2 (0.66%) patients each. A total of 50 patients died due to different complications in acute period making a mortality rate of 16.66%. Frequency of acute organophosphate (OP) poisoning complications is much higher and related with high mortality and morbidity and where as late complications are less frequent and less life threatening.

[J Coll Physicians Surg Pak. 2011 May;21(5):288-90.]

Organophosphorus poisoning (acute).

Acetylcholinesterase inhibition by organophosphorus pesticides or organophosphate nerve agents can cause acute parasympathetic system dysfunction, muscle weakness, seizures, coma, and respiratory failure. Prognosis depends on the dose and relative toxicity of the specific compound, as well as pharmacokinetic factors. Authors conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for acute organophosphorus poisoning? They searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2010. Authors included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). Authors found 62 systematic reviews, RCTs, or observational studies that met our inclusion criteria. They performed a GRADE evaluation of the quality of evidence for interventions. In this systematic review authors present information relating to the effectiveness and safety of the following interventions: activated charcoal (single or multiple doses), alpha(2) adrenergic receptor agonists, atropine, benzodiazepines, butyrylcholinesterase replacement therapy, cathartics, extracorporeal clearance, gastric lavage, glycopyrronium bromide (glycopyrrolate), ipecacuanha (ipecac), magnesium sulphate, milk or other home remedy immediately after ingestion, N-methyl-D-aspartate receptor antagonists, organophosphorus hydrolases, oximes, removing contaminated clothes and washing the poisoned person, and sodium bicarbonate.

[Clin Evid (Online). 2011 May 17;2011. pii: 2102.]

Organophosphate poisoning in pregnancy.

Organophosphate poisoning during pregnancy is rarely reported in the literature. In this study, authors report the outcome of 21 cases of organophosphate poisoning during pregnancy. All patients received atropine injection until the tracheobronchial tree is cleared of the secretions and most secretions were dried. In addition, ventilatory care was needed in five women. Two patients (9.52%) died of the organophosphorus poisoning during the acute stage of poisoning and three patients were lost to follow-up. One woman had a spontaneous abortion. The remaining 15 women had no significant complication during pregnancy or labour and delivery. There was no congenital abnormality and no neurological deficit in any baby. However, long-term follow-up of neonates was lacking in the study population.

[J Obstet Gynaecol. 2011 May; 31(4):290-2.]

Comparative protective effects of HI-6 and MMB-4 against organophosphorous nerve agent poisoning.

The oximes pralidoxime (2-PAM), its dimethanesulphonate salt derivative P2S, and obidoxime (toxogonin) are currently licensed and fielded for the treatment of chemical warfare (CW) organophosphorous (OP) nerve agent poisoning. While they are effective against several of the identified threat CW OP agents, they have little efficacy against others such as soman (GD) and cyclosarin (CF). In addition, they are also significantly less effective than other investigational oximes against the nerve agent known as Russian VX (RVX). Among the oximes currently being investigated, two in particular, HI-6 (asoxime) and MMB-4 (ICD-039, methoxime) have been proposed as replacement therapies for the currently licensed oximes. HI-6 has been safely used in individuals to treat OP insecticide poisoning, as well as in human volunteers, although its efficacy against OP nerve agent poisoning in humans cannot be demonstrated due to ethical considerations. It is currently available for use in defined military settings in Canada, Sweden and the Czech Republic, and is also under development in a number of other countries. The oxime MMB-4 has not yet been studied clinically, but is fielded by the Czech Republic, and is being developed by the United States armed services as a replacement for the currently fielded 2-PAM. This review compares the effectiveness of HI-6 and MMB-4 against nerve agent threats where comparisons can be made. HI-6 has been demonstrated to be generally a superior reactivator of nerve agent inhibited enzyme, particularly with human and non-human primate derived enzyme, and has also shown better protective effects against the lethality of most OP agents in a variety of species. Both compounds appear to be clearly superior to the available oximes, obidoxime and 2-PAM.

[Toxicology. 2011 Jul 29;285(3):90-6.]

Gene-environmental interactions and organophosphate toxicity.

Organophosphates (OPs) are an important class of insecticides that in the UK have been widely used for treating sheep for ectoparasites as well as in other sectors of the farming industry. Health problems associated with acute OP toxicity are well defined but, ill-health induced by chronic exposures to OPs remains controversial. A substantial number of sheep farmers complain of chronic ill-health which they attribute to repeated exposure to OPs. If OPs were associated with chronic ill-health then individuals with specific defects in OP metabolism might be expected to be at greater risk of ill-health following exposure. To examine such a hypothesis, the characterisation of both OP exposure and those pathways which lead to the formation and removal of the active OP metabolites becomes important. A wide range of OPs have previously been used to treat sheep but currently the only OP licenced for treating sheep is diazinon. Immediately after treatment, farmers' urines contain detectable levels of OP metabolites but few farmers have a significant decrease in plasma cholinesterase activity. Diazinon, like chlorpyrifos, is an organothiophosphate which is metabolised, particularly by cytochrome p450s, to the corresponding active oxon form. CYP metabolism also leads to the inactivation of the parent compound and the relative balance of inactivation and activation can depend upon the specific OP and the CYP isoform. OP oxons are inactivated by serum paraoxonase (PON1) and mice lacking PON1 activity are susceptible to oxon and parent OP induced toxicity. PON1 polymorphisms at positions 192 (R form with arginine at 192 and Q with glutamine) and 55 (L form with a leucine and a M form with methionine) influence paroxonase activity. The effect of the Q192R polymorphism is substrate specific with reports indicating that diazoxon is metabolised less by the R isoform. In a study of sheep farmers within the UK, the R allele was associated with an increased risk of self-reported chronic ill-health, a result consistent with the hypothesis that this ill-health may have been caused by OPs. Studies in other populations exposed to pesticides also show associations between ill-health and PON1 Q192R polymorphisms but not consistently so. This is not surprisingly given that exposure is often poorly characterised. *In vivo* models also suggest that PON1 genotypes may have little influence on susceptibility at low doses of the parent OP. Hence further work is required not only to better characterise OP exposure in humans populations but also to identify those populations susceptible to OP toxicity.

[Toxicology. 2010 Dec 30;278(3):294-304.]

Enzymes and bioscavengers for prophylaxis and treatment of organophosphate poisoning.

Organophosphorus (OP) pesticide poisoning causes significant morbidity and mortality, particularly in the developing world, with upwards of 3 million people poisoned each year. Although OP poisoning is not common in developed countries, recently greater attention has been given to these chemicals because of their similarity to chemical warfare agents. Despite the agricultural use of OP pesticides for roughly 60 years, no new therapies have been developed since the 1960s. A promising field of novel antidotes for OP poisoning, OP hydrolases, has recently garnered increased support. These bacterial enzymes have demonstrated tremendous prophylactic and antidotal efficacy against a few different OP classes in animal models. These studies, as well as the limitations and challenges of therapeutic development of these enzymes, are discussed.

[Front Biosci (Schol Ed). 2010 Jan 1;2:209-20.]

DID YOU KNOW ?

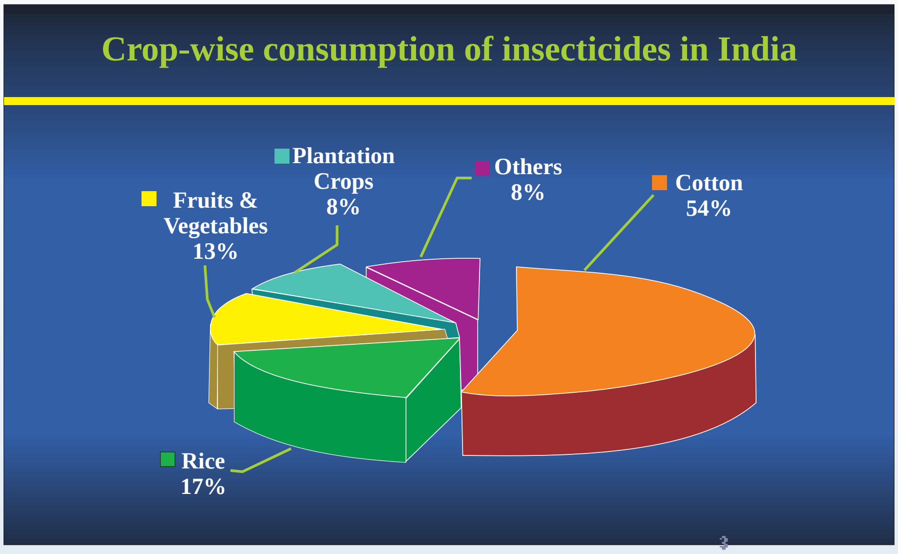
- The wide use of organophosphates is based on several factors:

  They are relatively inexpensive.

  They are broad spectrum (most organo phosphates can be used on several crops to control a variety of insect/ pests).

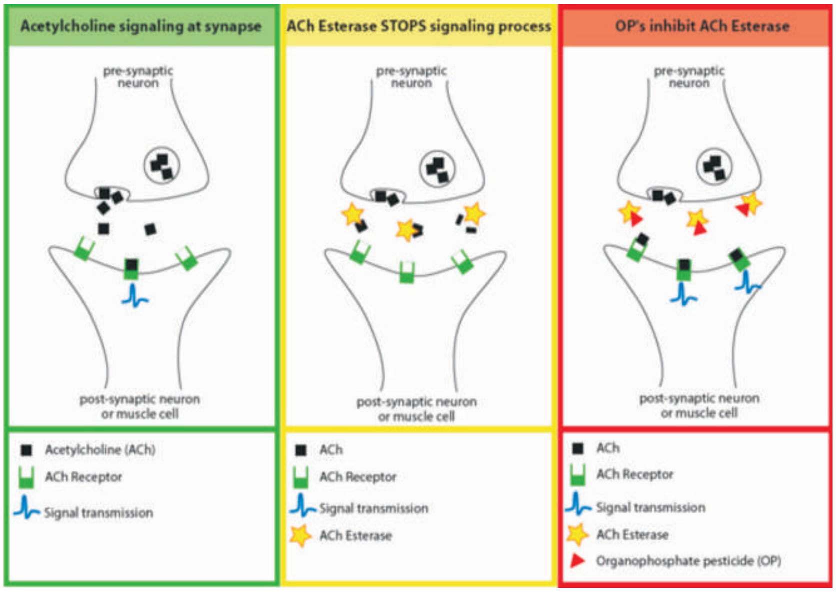
  Because of this broad spectrum of activity, one organophosphate might control the insects that would require three or four non-organophosphate insecticides.

  In general, insects have not developed resistance to organophosphates as they have to some other pesticides.



(Source: http://mv.picse.net/pesticides/cotton/toxicity-of-insecticides/)

- Organophosphate toxicity is due to the ability of these compounds to inhibit acetylcholinesterase at cholinergic junctions of the nervous system resulting in respiratory, myocardial and neuromuscular transmission impairment.
- Many of these compounds are excreted in milk and are able to cross placental membranes causing toxicity in offspring.
- Organophosphate compounds vary greatly in their toxic capabilities and have the advantage over other types of insecticides in that they produce little or no tissue residues



Mechanism of Organophosphate Toxicity

(Source: http://depts.washington.edu/opchild/acute.html)

CURRENT CONCERNS

Organophosphate pesticides have rapid degradability as compared to persistent organochloride pesticides. They hydrolyse easily on exposure to sunlight, air, and soil. Their ability to degrade make them a better and attractive alternative to the persistent organochlorine pesticides, such as DDT, aldrin and dieldrin. Although organophosphates degrade more easily than the organochlorides, they have greater acute toxicity, posing considerable risks to people exposed to this pesticide. Organophosphate pesticides are of great concern for scientists as well as regulators because they work by irreversibly blocking an enzyme that's critical to nerve function in both bugs and people. Even at relatively low levels, organophosphates may be most hazardous to the brain development of foetuses and young children. Organophosphates are one of the most common causes of poisoning worldwide, and used frequently for suicides in agricultural areas. Organophosphorus pesticides can be absorbed by all routes, including inhalation, ingestion, and dermal absorption

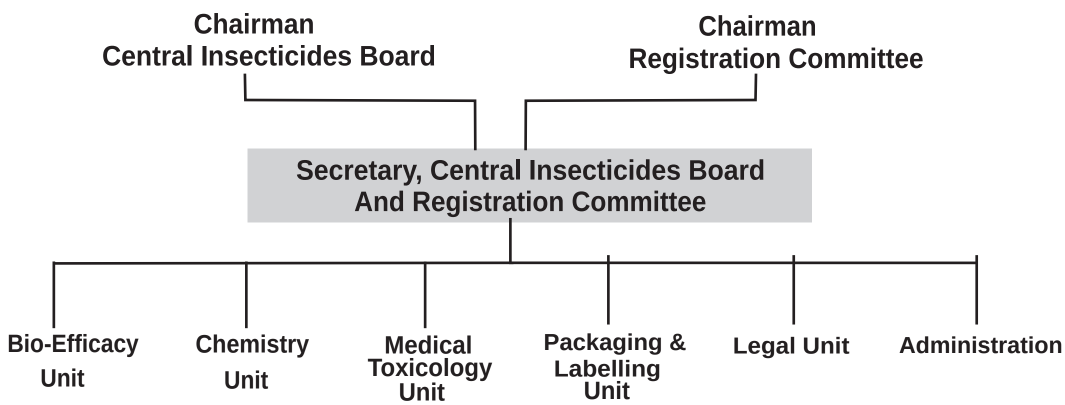
REGULATORY TRENDS

In 1958 Government of India appointed a Commission of enquiry to suggest *Inter-alia* remedial measures following a number of deaths in Kerela and Tamil Nadu by poisoning through the consumption of imported wheat contaminated with pesticide. The whole question of pesticide use and legislation was studied in 1964-67 by an Expert Committee of Indian Council of Agricultural Research headed by Prof. M.S. Thacker. Based on the recommendations of the Expert Committee a comprehensive Insecticides Act was passed in 1968 to regulate the import, manufacture, sale, transport, distribution and use of insecticides with a view to prevent risks to human beings and animals. The enforcement of Act was transferred to the Ministry of Agriculture in the year 1970 by the Ministry of Health and family Planning. Department of Agriculture framed the rules and constituted Central insecticides Board and

Registration committee. The states were simultaneously advised to appoint all functionaries mentioned in the Act. After the stage was fully set, all the provisions of the Insecticides Act were brought into force with effect from 1st August, 1971. In the Act and the Rules framed there under, there is compulsory registration of the pesticides at the Central level and licence for their manufacture, formulation and sale are dealt with at the State level. With the enforcement of the Insecticides Act in the country, pesticides of very high quality are made available to the farmers and general public for house-hold use. They help in protecting the agricultural crops from the ravages of pests, humans from diseases and nuisance caused by public health pests and the health hazards involved in their use have been minimised to a great extent. For the effective enforcement of the Insecticides Act, the following bodies have been constituted at the Central level -

- **Central Insecticides Board**
- **Registration Committee**

Organizational Chart of Central Insecticides Board And Registration Committee



(Source: http://cibrc.nic.in/about_us.htm)

ON THE LIGHTER SIDE

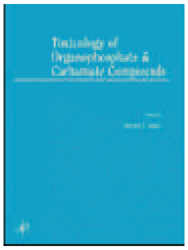
- Dr. Francis Gunther, known to his peers as the father of pesticide residue chemistry, once said regarding humankind's ever increasing ability to detect infinitesimal quantities of pesticides in food and the paranoia that attends it in the minds of some: "Yesterday we looked for little bits of a few things in some things; today we look for less of more things in anything; tomorrow we will look for nothing in everything."
- A deep-sea diver is twenty feet below sea level when he sees another guy with no scuba gear. He goes down another thirty feet, and the guy with no equipment stays with him. He takes out a waterproof chalkboard and writes, "How the hell can you stay down this deep without equipment?" The guy takes the chalkboard and writes, "You idiot, I'm drowning."

CONFERENCES

- **14th International Fresenius AGRO Conference: Behaviour of Pesticides in Air, Soil and Water**
  25- 26 June 2012 in Mainz/ Germany
  http://www.akademie-fresenius.de/english/konferenz/output.php?kurs=295
- **2nd International Conference on "Agrochemicals Protecting Crops, Health and Natural Environment - Role of Chemistry for Sustainable Agriculture"** 15-18 February 2012 in New Delhi (India)
  http://www.apchne.com
- **4th International Symposium on Pesticide and Environmental Safety & 8th International Workshop on Crop Protection Chemistry and Regulatory Harmonization**
- 15-20 September 2012 in Beijing - China
  http://www.2012iupac.com

BOOK STOP

Toxicology of Organophosphate & Carbamate Compounds

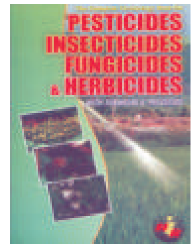


Edited : Ramesh Gupta

Published : DEC-2005
ISBN : 0-12-088523-9/978-0-12-088523-7
Publisher : ACADEMIC PRESS

The Complete Technology Book on Pesticides, Insecticides, Fungicides and Herbicides with Formulae & Processes

Author : H. Panda
ISBN : 8186623728



Published : 2003
Publisher : National Institute of Industrial Research

MINI PROFILE

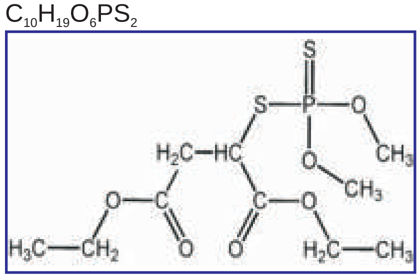
CHEMICALNAME MALATHION

SYNONYM American-cyanamid-4,049-; s-(1,2-bis(carbethoxy)ethyl) o,o-dimethyl dithiophosphate; s-(1,2-bis(ethoxycarbonyl)ethyl) o,o-dimethyl phosphorodithioate; s-1,2-bis(ethoxycarbonyl)ethyl-o,o-dimethyl thiophosphate; butanedioic acid,((dimethoxyphosphinothioyl)thio)-, diethyl ester; camathion-; carbetovur-; carbetox-; carbofos-; carbophos-; caswell-no-535-; chemathion-; cimexan-; cythion-; diethyl-mercaptosuccinate,-o,o-dimethyl-thiophosphate-; o,o-dimethyl s-(1,2-dicarbethoxyethyl) dithiophosphate; o,o-dimethyl s-(1,2-dicarbethoxyethyl)phosphorodithioate; o,o-dimethyl s-1,2 di(ethoxycarbamyl)ethyl phosphoro dithioate;o,o-dimethyldithiopho sphatediethylme rcaptosuccinate-; o,o-dimethyl-dithiophosphate-of-diethyl-mercaptosuccinate-; dorthion-; ethiolacar-; etiol-; extermathion-; flair-; fog-3-; forthion-; fosfothion-; fosfotion-; fyfanon-; hilthion-; karbofos-; kill-a-mite-; kop-thion-; kypfos-;malacide-; malafor-; malagran-; malakill-; malamar-50-; malasol-; malaspray-; malataf-; malathiazol-; ortho-malathion-; malathion-e50-; malathion-lv-concentrate-; malathon-; malathyl-; malatol-; malatox-; malmed-; malphos-; mercaptosuccinic-acid-diethyl-ester-; mercaptothion-; moscarda-; nci-c00215-; oleophosphothion-; paladin-; phosphothion-; prioderm-; sadofos-; sadophos-; sf-60-; siptox-i-; sumitox-; tak-; tm-4049-; vetiol-; xmc-; zithiol-

RTECS NO WM8400000

CAS NO 121-75-5

MOLECULAR FORMULA $C_{10}H_{19}O_6PS_2$



MOLECULAR WEIGHT 330.36000000000001

PROPERTY Colour- Clear amber liquid; Odour -mercaptan-like odour; Solubility- soluble in water: 45 ppm at 25 °C; miscible in most organic solvents; BP- 156-157 °C; MP- 2.85 °C; Density- 1.23 at 25 °C; Compatibilty- incompatible with alkaline pesticides and is corrosive to iron.

USES Malathion is an effective insecticide against most household pests and has been used to control houseflies, cockroaches, mosquitos, aphids, animal ectoparasites and human head and body lice.

TOXICITY DATA

Oral- Rat : LD_{50}: 290 mg/kg

Oral- Mus : LD_{50}:190 mg/kg

Dermal- Rabbit : LD_{50}: 4100 mg/kg

Oral-Guinea-pig: LD_{50}: 570 mg/kg

ANTIDOTE Atropine

Route of Exposure	Symptoms	First aid	Target organs
Inhalation/ Ingestion	Headache, nausea, vomiting, dizziness, muscle weakness, sluggishness, difficulty in breathing and nervousness.	Fresh air, rest, half-upright position, rinse mouth. Give slurry of activated charcoal in water to drink. Refer for medical attention.	Central Nervous System
Contact	Eye tearing, & sweating	Rinse eyes with water and skin with water and soap. Refer for medical attention.	Skin and Eyes

STORAGE and DISPOSAL Should be stored in clearly labelled rigid and leak proof containers. No food or drink should be stored in the same compartment. Decontaminated containers should not be used for food and drink. Containers that are not decontaminated should be burned or should be crushed and buried below topsoil. Care must be taken to avoid subsequent contamination of water sources.

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MAY WE
HELP YOU

To keep abreast with the effects of chemicals on environment and health, the ENVIS Centre of
Indian Institute of Toxicology Research, deals with:

Maintenance of toxicology information database on chemicals

Information collection, collation and dissemination

Toxic chemical related query response service

Preparation of monograph on specified chemicals of current concern

Publishing Abstract of Current Literature in Toxicology

for further details do write to

Scientist In-Charge

ENVIS CENTRE

CSIR-INDIAN INSTITUTE OF TOXICOLOGY RESEARCH

Post Box# 80, Mahatma Gandhi Marg, Lucknow-226 001 India.
Phone : (0522) 2284 591, Fax : (0522) 2628227
Email : itrc@envis.nic.in
Website : http://www.itrcenvis.nic.in