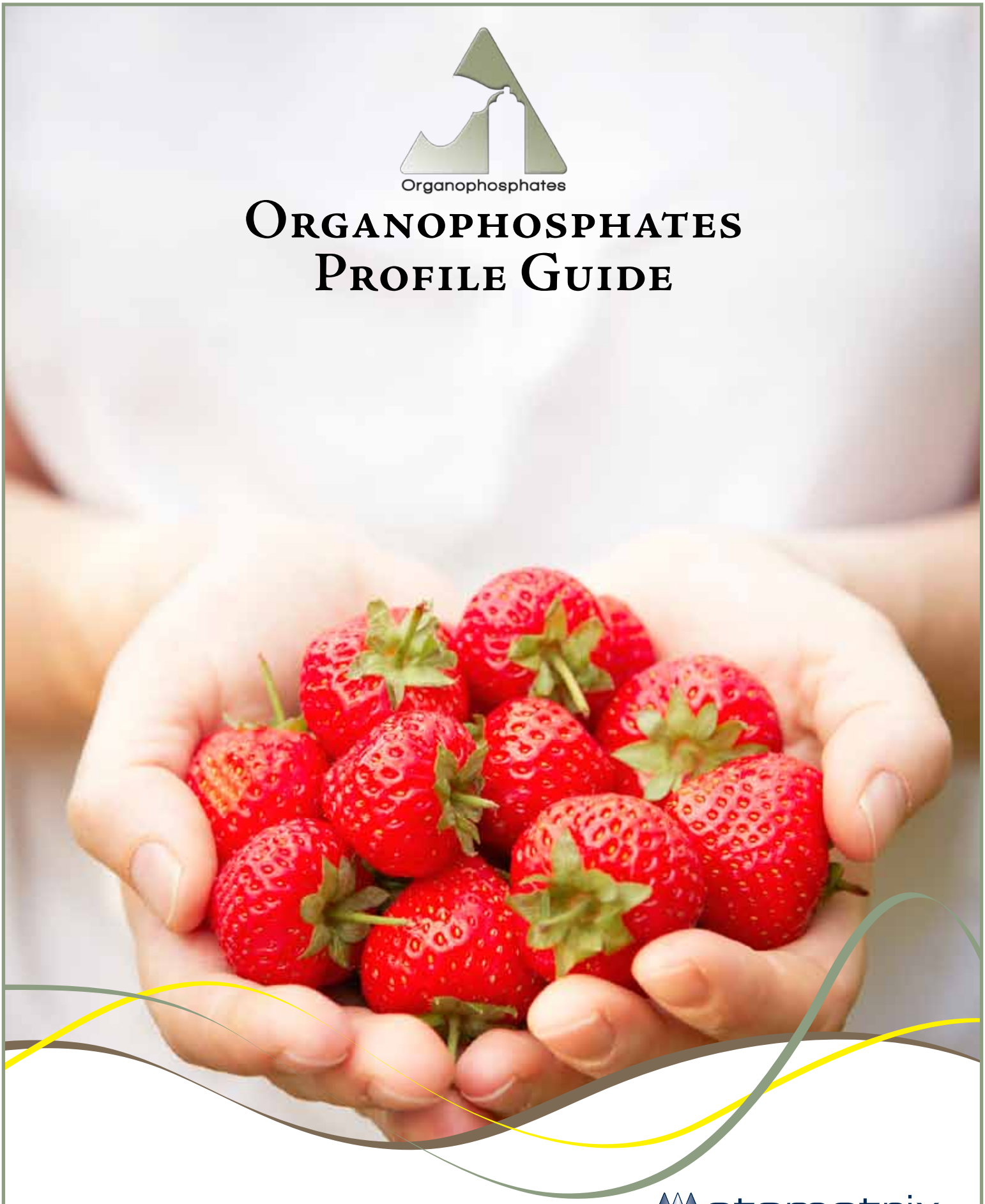
Organophosphates

Organophosphates Profile Guide



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What are organophosphates and why is there concern about human exposure?

Organophosphates (OP) are widely used for insect control on food crops and for pest control in residential and commercial areas. Nearly half of the insecticides used in the United States are OPs; approximately 40 are registered for use by the EPA for uses such as mosquito control, prevention of animal diseases, and insect control on food and vegetable crops. OP exposure may occur by ingestion, inhalation, or dermal contact with insecticides and/or pesticides. Primary exposure to organophosphates in the general population is from ingestion of food products or from residential use. The highest levels of OPs are seen in pesticide applicators, farm workers, and pesticide manufacturers.[1]

Human Toxicity Organophosphates

OPs or their metabolites can inhibit acetylcholinerase in the central and peripheral nervous system leading to excess acetylcholine and a range of neurologic symptoms. Symptoms including nausea, runny nose, dizziness, headache, drowsiness, fatigue, gait disturbance, or numbness and weakness of the extremities may all be exhibited by persons with chronic OP exposure.[2] A survey of health effects of pesticide exposure among agricultural workers revealed, more than half of the workers reported experiencing three or more of the above symptoms.[3]

Because symptoms from chronic low-level exposures to OPs are frequently diverse and insidious in onset, the potential for human toxicity is most readily seen in cases of severe. acute exposure. Detailed descriptions of such a case were developed for a law suit calling for greater tort action as a means for catalyzing improved field protection and compensating victims of pesticide-related injuries. Here is the published description:

"In 1999, a healthy fifteen-year-old migrant farm worker named Jose Casillas left his home in Mexico for the orchards of central Utah hoping to earn enough to support his family in Mexico. A few months after his arrival, Casillas was sprayed by an applicator- tractor with Guthion Solupak, a pesticide similar to Sarin. Earlier that same week, Casillas had been sprayed with other pesticides—which he believed to be only water—while he was working in the field. After the first field exposure, Casillas suffered intense headaches. After the second exposure, Casillas began to vomit, sweat excessively and suffer with diarrhea. Despite being ill, Casillas attempted to ride his bike to work the next morning but lost consciousness and collapsed. By the time medical help arrived, he was dead, 'with foam streaming from his nose.'"[4]

Adverse Health Effects

The effects of mild OP poisoning are recalled using the mnemonic **SLUDGE** (Salivation, Lacrimation, Urination, Defecation, Gastrointestinal motility, Emesis). Symptoms of acute OP poisoning may occur within minutes to hours depending on the method of contact. Exposure by inhalation results in the fastest appearance of toxic symptoms, followed by the gastrointestinal route and finally the dermal route.[5] Early symptoms of OP exposure include nausea, headache, dizziness, excessive salivation, runny nose, and sweating. Patients with prolonged exposure may present with muscle twitching, tremor, poor coordination, vomiting, and diarrhea.

More serious effects have been associated with OP toxicity in children. The following neurodevelopmental problems were associated with prenatal and early childhood exposure.

- Impaired short term memory and mental development
- Increased reaction time & abnormal reflexes
- Mental & emotional problems (adolescent neurodevelopmental problems associated with prenatal and early childhood exposure:
- Impaired short term memory and mental development
- Mental & emotional problems (adolescent exposure)
- Clinical symptoms of exposure in children often present as seizures, lethargy, and comas.[6] A study of 31 children with acute OP exposure through ingestion of agricultural products treated with OPs revealed 71% of the patients presented with coma and/or seizures[7]

Long Term Health Effects

- Studies have shown that children exposed to OP pesticides, both prenatally and during childhood, may have difficulties performing tasks that involve short-term memory, and may show increased reaction time, impaired mental development or pervasive developmental problems.[8] In newborns, the effects of OP exposure are manifested mainly by an increased number of abnormal reflexes, while in adolescents, the

effects manifest as mental and emotional problems.[9,10]

- Impaired T-cell response was observed in adult rats injected with chlorpyrifos as neonates.[11]
- Farmers exposed to chlorpyrifos, malathion, and parathion were observed to have respiratory illnesses including asthma and wheeze; commercial applicators exposed to chlorpyrifos, dichlorvos, and phorate were also found to have wheeze.[12]
- Decreased sperm motility and count were observed in adult male rats treated with chloropyrifos.[13]
- Elevated 8-OhdG was positively correlated with elevated levels of OP insecticides (fenitrothion, dichlorvos, chlorpyrifos, and diazinon) found in urine samples of indoor pesticide sprayers.[14,15]

Laboratory Evaluation of Dialkyl Phosphates to Assess Organophosphate Exposures

Dialkyl phosphates are metabolites that appear in urine, indicating recent (past few days) exposure to OPs. Sometimes it is these compounds that are present in the environment due to breakdown of the OP pesticide in the environmental source. Table 1 shows the six dialkyl phosphates that are measured in the Metametrix organophosphate profile. Hundreds of individual OPs are converted into the dialkyl phosphates, so it is important to identify any possible sources of exposure to the whole range of potential OPs when elevated levels are found. Many of the more common sources for each of the reported metabolites are shown in Table 2.

Atrazine and Atrazine Mercapturate

Atrazine, an herbicide, first went on the market in the United States in 1959 and has become one of the most widely used herbicides in the country.[16] Atrazine, which does not occur naturally, is used to kill pre- and post-emergent weeds, primarily on farms, but has also been used on highways and railways.[17] It is estimated that 76.5 million pounds of atrazine are used in the U.S. each year, with 86% used on corn.[16] Atrazine is one of the most frequently detected contaminants of ground and surface water. The U.S. Geological Survey found that atrazine was detected in streams in agricultural areas about 80% of the time and in groundwater in agricultural areas about 40% of the time.[16] Atrazine has been found to be a persistent pollutant, taking many years to degrade in the soil.[18] Metabolites of atrazine, such as atrazine mercapturate, can be even more persistent than atrazine itself, although they are thought to be less acutely toxic than atrazine. Because atrazine metabolites have been found in greater concentrations in waters, these metabolites should also be included in testing methods.[19]

The major routes of exposure to atrazine are through chemical sprayers used by farm workers, factories that make atrazine, exposure to dirt that has been treated with atrazine, and by drinking water that has been contaminated with atrazine.[20] Human exposure to atrazine is considered harmful at levels higher than 3 parts per billion (the maximum contaminant level, MCL) , according to the US Environmental Protection Agency.[21] Acute exposure levels can cause congestion of heart, lungs and kidneys; hypotension; antidiuresis; muscle spasms; weight loss; and adrenal degeneration.[22]
Chronic exposure to atrazine above the MCL can cause cardiovascular damage, retinal and some muscle degeneration, and reproductive problems. Mammary tumors have been associated with lifetime exposure at levels above the MCL.[22,23]

Table 1: Urinary dialkyl phosphates and the levels below which the 50th,75th, 90th, and 95th percentiles of the U.S. population fall.

OP Metabolite	CDC 50th	CDC 75th	CDC 90th	CDC 95th
Dimethylphosphate (DMP)	<LOD	3.86	9.54	14.6
Dimethylthiophosphate (DMTP)	1.75	5.21	15.7	30.4
Dimethyldithiophosphate (DMDTP)	<LOD	.500	2.14	5.27
Diethylphosphate (DEP)	<LOD	4.42	9.02	13.2
Diethylthiophosphate (DETP)	<LOD	.700	1.47	2.62
Diethyldithiophosphate (DEDTP)	<LOD	<LOD	<LOD	.410

The reference ranges for the Metametrix Organophosphate Profile are values found in the Fourth National Report on Human Exposure to Environmental Chemicals by the CDC and are listed in the table above. Ranges are for survey years 2003-2004.
* All urine concentrations are in units of µg/g of creatinine.

Atrazine has been shown to be an endocrine disruptor, meaning it disturbs the human hormone system. Atrazine increases aromatase production, which ultimately increases estrogen production. It has been linked to prostate and breast cancers in humans, similar to those found in animals exposed to atrazine.[24]

In a study of live births conceived in months when surface water agrichemicals are highest, chronic exposure to atrazine during critical developmental stages increased the odds of 9 of 11 birth defects found to be associated with the exposure period (conception during the months of April-July, the highest usage time for atrazine).[25] One study of pregnant women exposed to atrazine in drinking water during the entire pregnancy showed a higher incidence of small-for-gestational-age infants.[26]

Atrazine exposure has been linked with an increased risk for non-Hodgkin's lymphoma in men who work in a farm environment.[27]

Interpretation of Results

There is no clear single point of demarcation for assuming that toxic effects are present. When levels are in the upper percentiles of the general population, prudent advice for lowering body burden is usually considered to be warranted, especially if symptoms suggestive of OP toxicity are present. Actions to lower levels by simple avoidance of exposure and removal of known sources from the living environment are the obvious place to start. Bioaccumulation of OPs can affect neurological, endocrine, and immune systems and further testing may be useful to determine extent of exposure to these systems.[11,28,29] Elevated OP levels may indicate possible PON1 SNPs and may warrant further evaluation of genetic polymorphisms.

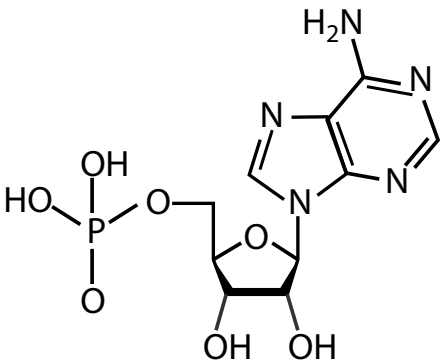
Treatment

Treatment for acute or chronic effects of these toxins includes avoidance, supplementation, and cleansing. After identifying the exposure source individuals should take the necessary precautions to avoid further exposures. Avoidance for individuals in occupations that administer OPs include wearing protective clothing, removing and washing clothes upon entering home and cleansing skin with warm water and soap. Other means of avoidance can include consuming organic foods and checking current dwelling for previous treatment with organophosphate pesticides. Docosahexanoic acid (DHA) is necessary to increase antioxidant activity in the brain and prevent OP induced damage.[30] Antioxidants vitamin E, vitamin C and alpha lipoic acid may also protect against OP induced oxidative stress.[30,31] Supplementation with nutrients to stimulate detoxification (esp. taurine, glycine, and n-acetyl cysteine) may also be useful in reducing body burden of OPs.

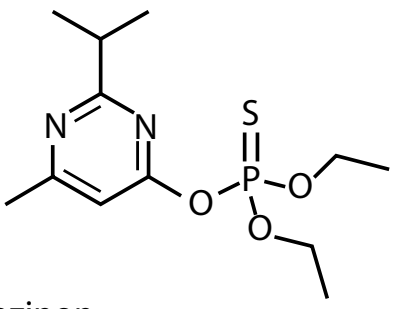
Further Testing

The Metametrix Organix Comprehensive Profile that can reveal concurrent abnormal exposures to ammonia and organic solvents, while providing markers of glutathione status and oxidative stress. That profile also allows assess-ment of deficiencies of specific B-vitamins and nutrients important for mitochondria function. More extensive data on other toxicant body burdens are provided in the Metametrix profiles for Volatile Solvents, Chlorinated pesticides or PCBs in blood, or for Phthalates and Pararbens in urine. These tests can aid in designing appropriate detoxification protocols for individual patients and in monitoring progress in all affected areas.

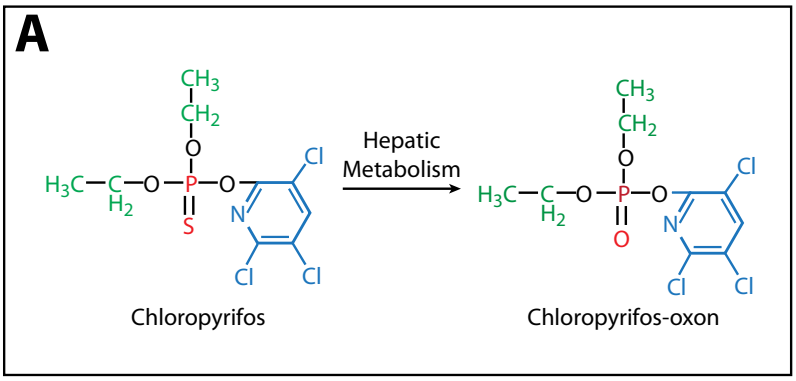
Organophosphate Structures and Metabolism



Adenosine monophosphate



Diazinon



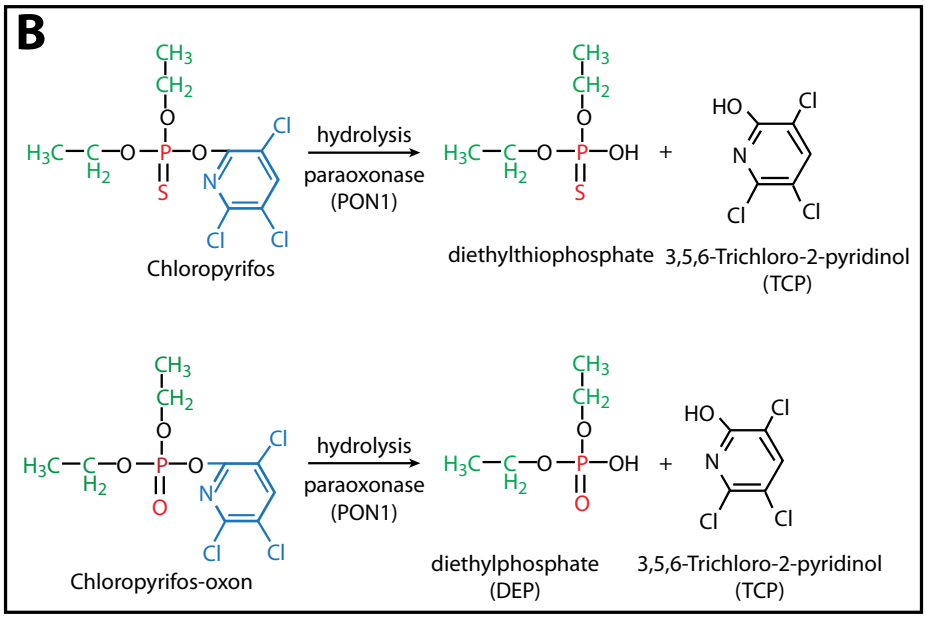


Figure 1:
(A) Activation of OP to acetyl cholinesterase inhibitor;
(B) Hydrolysis of DETP and DEP to dialkyl phosphates.

Table 2: OP pesticides and metabolites[20]

Dialkyl phosphate metabolites	Organophosphate Pesticides	Uses
Dimethylphosphate (DMP)	• Azinphos methyl	• Crops, trees, ornamentals
	• Chloropyrifos methyl	• Stored grain
	• Dichlorvos	• Crops, residential lawns, pet collars, termicide, livestock
	• Diazinon	• Pest strips, residential, food, storage/processing, livestock
	• Dicrotophos	• Crop, lawn/residential/commercial
	• Dimethoate	• Crops, ornamentals
	• Fenitrothion	• Residential/commercial, ant/roach bait
	• Fenthion	• Livestock, mosquito control (Florida)
	• Isazaphos-methyl	• Registrations cancelled
	• Malathion	• Crops, livestock, lawn/turf, mosquitoes
	• Methidathion	• Crops
	• Methyl parathion	• Crops
	• Naled	• Crops, greenhouse, flea collars, mosquitoes
	• Oxydemeton-methyl	• Crops
	• Phosmet	• Crops, ornamental, forestry, livestock
	• Primiphos-methyl	• Stored corn, seed, grain, livestock, bulbs
	• Temephos	• Mosquito larva
	• Tetrachlorvinphos	• Livestock, domestic animals

Dialkyl phosphate metabolites	Organophosphate Pesticides	Uses
Dimethylthiophosphate (DMTP)	• Azinphos methyl • Chloropyrifos methyl • Dimethoate • Fenitrothion • Fenthion • Isazaphos-methyl • Malathion • Methidathion • Methyl parathion • Naled • Oxydemeton-methyl • Phosmet • Primiphos-methyl • Temephos	• Crops, trees, ornamentals • Stored grain • Crops, ornamentals • Residential/commercial, ant/roach bait • Livestock, mosquito control (Florida) • Registrations cancelled • Crops, livestock, lawn/turf, mosquito • Crops • Crops • Crops, greenhouse, flea collars, mosquitoes • Crops • Crops, ornamental, forestry, livestock • Stored corn, seed, grain, livestock, bulbs • Mosquito larva
Dimethyldithiophosphate (DMDTP)	• Azinphos methyl • Dimethoate • Malathion • Methidathion • Phosmet	• Crops, trees, ornamentals • Crops, ornamentals • Crops, livestock, lawn/turf, mosquito • Crops • Crops, ornamental, forestry, livestock
Diethylphosphate (DEP)	• Chlorethoxyphos • Chlorpyrifos • Diazinon • Disulfoton • Ethion • Parathion • Phorate • Sulfotepp • Terbufos	• Crops (corn) • Crop, lawn/turf, residential, termicide, ornamentals, per collars, pasture, livestock • Pest strips, residential, food, storage/processing, livestock • Crops, ornamentals • Crops (citrus), livestock • Crops • Crops • Greenhouses, ornamentals • Crops
Diethylthiophosphate (DETP) • • • • • • •	• Chlorethoxyphos • Chlorpyrifos • Diazinon • Disulfoton • Ethion • Parathion • Phorate • Sulfotepp • Terbufos	• Crops (corn) • Crop, lawn/turf, residential, termicide, ornamentals, per collars, pasture, livestock • Pest strips, residential, food, storage/processing, livestock • Crops, ornamentals • Crops (citrus), livestock • Crops • Crops • Greenhouses, ornamentals • Crops
Diethyldithiophosphate (DEDTP)	• Disulfoton • Ethion • Phorate • Terbufos	• Crops, ornamentals • Crops (citrus), livestock • Crops • Crops

Organophosphate Structures

The most commonly known organophosphate is adenosine triphosphate (ATP). This molecule that functions in all living things to convert chemical energy into biological functions is made up of adenosine as the "organo" group that is linked to phosphate (PO43-). Any compound that mimics the structure of ATP has the potential to disrupt multiple biological functions. Many such compounds have been invented by chemists to kill bugs and increase crop yields. They may be found in any hardware store in packages labeled with names such as Malathoin, Dursban, Diazinon, Sevin Dust and Baygon. The problems with widespread use of these chemicals is that they kill beneficial insects , even worse, they can affect humans, causing allergic reactions or flu-like symptoms for people inadvertently exposed. And there is growing evidence that thy may be linked to non-Hodgkins lymphoma, childhood leukemia, anemia, chromosome damage and weakened immune systems. The full impact of these possibilities is made

by the fact that more than 15 million pounds are applied annually in the U.S. alone.

The structure of Diazinon is juxtaposed with that of adenosine monophosphate above. An oxygen atom in the phosphate ion has been replaced by sulfur and the organic alcohol has some structural differences, but the key organophosphate bond is similar in the two compounds. Predicting toxic effects of such molecules in animal is difficult, and they sometimes become apparent only after sustained use. In 1988 the Environmental Protection Agency prohibited the use of Diazinon on golf courses and sod farms because of decimation of bird flocks that congregated in these areas. Since the toxic effects are insidious, dramatic accounts of severe reactions to very high exposure levels may be required to draw attention to the potential public health threat. The following published account is an example of such effects.

Organophosphate Metabolism

Two chemical changes occur in the body which leads to the production of OP metabolites measured in urine. The first chemical change occurring in the liver is the conversion of sulfur to oxygen producing a more potent acetyl cholinesterase inhibitor. (Figure 1A) The second reaction that occurs in the liver is the hydrolysis of the OP which yields an organophosphate metabolite and the leaving group. (Figure 1B) Hydrolysis of the OP decreases the toxicity of the OP, as the metabolite and leaving group do not inhibit acetyl cholinesterase. Hydrolysis cannot occur without the enzyme paraoxonase (PON1) therefore, individuals homozygous for PON1Q192, are more susceptible to OP toxicity. If, prior to obtaining the genetic data, symptoms indicating sensitivity to OPs are detected, then testing for genetic polymorphisms is warranted.[33-35]

Further information on individual Organophosphate sources and toxicities

- http://www.atsdr.cdc.gov/substances
- http://www.mindfully.org/Pesticide/Organophosphate-Pesticides-CDCMar01.htm

Children & Pesticides

- http://www.panna.org/
- http://wapedia.mobi/en/Organophosphate_poisoning
- http://www.panna.org/resources/specific-pesticides/organophosphates

Other useful sites

- http://www.cdc.gov/exposurereport/results_10.htm
- http://www.idph.state.il.us/Bioterrorism/factsheets/organophosphate.htm
- http://curriculum.toxicology.wikispaces.net/2.2.7.4.5+Organophosphates

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