Chlorpyrifos

Prepared by Meriel Watts, PhD

Contents

Summary

Chlorpyrifos is a chlorinated organophosphate insecticide. It is described as one of the most widely used insecticides in the world, on a wide range of crops and in numerous non-agricultural situations.

However its developer, Dow AgroSciences, stated recently that use has reduced in the last 5 years as growers move to more modern products that fit with 'green' spray programs.

It is still used in domestic situations, in homes and gardens although some countries, such as South Africa and USA, have now discontinued those uses. Dow AgroSciences does not support the use of chlorpyrifos in the home garden or for indoor/outdoor domestic or industrial pest control, because of concerns about exposure to children, pets, wildlife and the environment from this type of use. All uses of chlorpyrifos have been banned in Yemen since 2006.

EMPOWERING PEOPLE FOR CHANGE

PANAP

PESTICIDE ACTION NETWORK ASIA & THE PACIFIC

April 2013

Regulatory risk statements

European Union:

R25 – Toxic if swallowed

R50/53 – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

European Commission: member states must pay particular attention to the protection of birds and aquatic organisms, bees and non-target arthropods.

It is a priority pollutant in the European Water Framework Directive 2000/60/CE.

United States:

Primary environmental concerns are acute and chronic risks to birds, mammals, terrestrial invertebrates, fish, and aquatic invertebrates.

Toxicity

Mode of action

Chlorpyrifos has at least three main modes of action in mammals. It inhibits the enzyme acetylcholinesterase (AChE) causing over-stimulation of the nervous system.

It causes oxidative stress, a process involved in many human diseases, including cancer, Parkinson's disease, Alzheimer's disease, diabetes, and heart failure. It also causes endocrine disruption.

Acute toxicity

It is classified by WHO as Class II, moderately hazardous. Inhibition of AChE leads to increased secretions, sensory and behavioural disturbances, incoordination, depressed motor function, respiratory depression, tremors, convulsions, and death. Seizures, lethargy, and coma are common in children.

Chronic toxicity

Metabolic effects

Early life exposure may predispose a person to obesity, diabetes, and cardiovascular problems later in life.

Liver

Acute and chronic exposure can cause liver damage and disturbance of metabolic function. Chlorpyrifos is a potent inhibitor of the liver CYP450 metabolism of a number of substances including the body's own hormones testosterone and oestrogen, other pesticides, and drugs.

Cancer

US EPA reported no evidence of carcinogenicity in animal studies, but recognised that a number of epidemiological studies indicate chlorpyrifos may be carcinogenic in humans, the association being strongest for lung and rectal cancers. It acknowledged preliminary associations with breast and prostate cancer. Studies also indicate possible associations with non-Hodgkin's lymphoma, lung, kidney, and brain cancer. Chlorpyrifos causes breast cancer cells to grow *in vitro*.

Genotoxicity and mutagenicity

Independent studies have found chlorpyrifos to be mutagenic or genotoxic in human, rat, mouse, Chinese hamster, toad, fish, fruitfly, and plant cells. US EPA stated chlorpyrifos is not mutagenic, but California EPA stated it may be genotoxic.

Endocrine disruption

Chlorpyrifos is an endocrine disruptor; it is antiandrogenic, oestrogenic, and affects thyroid hormones. It inhibits metabolism of testosterone and oestradiol, and testosterone synthesis. It reduces serum levels of cortisol and thyroid hormone T4, induces alterations in thyroid and adrenal glands and differentially affects levels of thyroid-stimulating hormones in men and women. It causes breast cancer cells to grow and is a breast cancer risk through its endocrine actions.

Reproductive and developmental effects

Teratogenic effects observed in rats include skeletal malformations, small hind and fore limbs, lack of spinal development, absence of thoracic vertebrae and cleft palate; in humans, defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples, and genitalia have been associated with gestational exposure to chlorpyrifos. Neuroteratogenicity has also been found in both animal and human studies. Reproductive effects in animals include decreased foetal weight and viability; increased foetal death and early resorption; decreased sperm motility and count; decline in viability and developmental competence of oocytes.

In humans, chlorpyrifos exposure is associated with decreased birth weight and birth length, DNA damage in sperm, and decreased sperm concentration and sperm motility.

Nervous system – Neurodevelopment and behaviour

Chlorpyrifos is a potent developmental neurotoxin at low levels of exposure, below those that trigger foetal AChE inhibition. This is demonstrated in numerous laboratory studies and a number of recent epidemiological studies. Exposures *in utero* and in early childhood can lead to behavioural anomalies in adolescence and adulthood.

Epidemiological studies have found delayed cognitive and psychomotor development, reduced IQ, attention-deficit/hyperactivity disorder (ADHD), and pervasive developmental disorder, smaller head circumference and altered brain structure. It may have long-term consequences for social adjustment and academic achievement. The effects reported are regarded by some scientists as being comparable to those seen with exposures to other neurotoxicants such as lead and tobacco smoke.

Immature organisms are far more sensitive to the effects of chlorpyrifos, in terms of both acute toxicity and developmental and neurobehavioural effects, than mature animals. Chlorpyrifos and its oxon metabolite affect the brain and developing nervous system by interfering at numerous sites and points in time, making the pesticide far more toxic than originally thought when cholinesterase inhibition was assumed to be the sole mechanism of concern.

Chlorpyrifos has a greater adverse effect on neural cell replication and is inherently more toxic to the developing brain than the more acutely toxic organophosphates such as diazinon and parathion. It is toxic to children at doses that are not toxic to adults, and tests using adult animals cannot predict the long-term delayed effects of chlorpyrifos in offspring.

There are sex-related differences in effects on the brain, and subsequent cognitive function in adolescence and adulthood, with females affected more than males by prenatal exposures and vice versa for postnatal exposures.

Nervous system – other effects

Epidemiological studies have shown that both acute and chronic exposures to chlorpyrifos result in a range of long-term neuropsychological effects, including peripheral and central neuropathy, affective disorders, and neurocognitive deficits.

It can cause organophosphate induced delayed polyneuropathy (OPIDP), and organophosphate-induced chronic neuropathy (OPICN), involving degeneration of the peripheral and central nervous systems, which may result in weakness, numbness and paresthesia, and even life-threatening paralysis. It can also cause chronic neuropsychological effects like anxiety, depression and suicide.

There is evidence from laboratory and epidemiological studies of an association with Parkinson's disease.

Immune system

There is evidence from both laboratory and epidemiology studies of immune toxicity, including effects on lymphocytes, thymocytes, T cells, tumour necrosis factor, and autoimmunity.

Exposure

Chlorpyrifos is pervasive in the environment. Adults and children are widely exposed through occupational use, contact with treated surfaces, ingestion or inhalation of contaminated dust, breathing air in treated buildings or near treated fields or orchards, contact with flea collars on pets, and residues in food and drinking water.

It is a widespread contaminant of fruit and vegetables, but is also found in grains, beans, dairy products, meat, fish, tea, and soft drinks. It is even found in processed products such as bread, hamburgers, jam, meat pies, muesli, olive oil, pasta, pizza, sausages, and snack bars. It is a common residue in the dust of rural houses and farmworker vehicles.

Body burdens and poisonings

Chlorpyrifos has been found in cervical fluid, sperm fluid, cord blood, meconium, breast milk, and maternal and infant hair. Biomonitoring in the US showed that 94% of residents had chlorpyrifos in their bodies in 1999-2000.

There are numerous reports of occupational and non-occupational poisonings, and suicides, from a number of countries.

Environmental effects

Aquatic
Chlorpyrifos is very toxic to fish, and moderately to very highly toxic to amphibia and aquatic invertebrates. It can have significant effects on aquatic community structure.

Residues have been found in sea otters, frogs, fish, and oysters. It can accumulate in areas of intense biological productivity, such as littoral zones and river deltas, posing a long-term threat to aquatic ecosystems. It causes endocrine disruption in fish, frogs, and mussels. In fish, it has caused mutagenicity, spinal deformities, and altered swimming behaviour. There have been large fish kills reported in several countries.

Some species of amphibia are very highly sensitive to chlorpyrifos and scientists are concerned about its potential involvement in declining frog populations. Sublethal effects include teratogenicity, genotoxicity, and altered swimming of tadpoles.

Terrestrial
Chlorpyrifos is moderately toxic to earthworms, very toxic to mammals, very highly toxic to some birds, and extremely toxic to bees and beneficial insects, making it completely incompatible with IPM. Sublethal effects in birds include reduced flying ability. There have been a number of reported bird kills.

Chlorpyrifos has an inhibitory effect on soil microbial functional diversity, reducing microbial biomass by as much as 50% after application, inhibiting nitrogen mineralisation, and reducing bacterial, fungal and actinomycete populations.

Environmental fate

Persistence
Chlorpyrifos meets the Stockholm Convention criteria for persistence in soil, sediment and water. Residues are found in soil, groundwater, surface waters and sediments, wastewater, marine sediments, air, rain, snow, and fog.

Bioaccumulation
Bioaccumulation is described as moderate to high. The K_{ow} ranges from 4.7 to 5.11, meeting the Stockholm Convention criteria of 5. Reported bioaccumulation factors vary, but some are higher than the criteria of 5,000.

Long-range transport
Chlorpyrifos volatilises, undergoes long-range transport, and distils out of the air in cold climates far from its site of application.

It has been measured consistently in the Arctic, in ice, snow, fog, air, seawater, lake sediment, fish and vegetation. It is amongst the pollutants with the highest concentrations present in the Arctic, in excess of most legacy POPs pesticides.

Pest resistance
Resistance is now widespread, involving 65 species in at least 47 countries.

Alternatives
Numerous alternatives exist, including biopesticides such as neem, biological controls such as Btk, and predatory and parasitic insects.

There are also numerous agroecological pest management practices that focus on preventing pest build up.

1 Chemical Profile

1.1 Identity

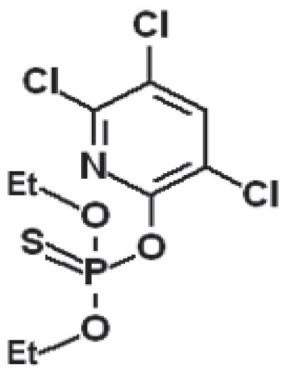
Common name
Chlorpyrifos

Common trade names
Dursban, Lorsban

Chemical names and form
O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate

White to tan coloured crystalline solid. Formulations include gels, emulsifiable concentrates, granules, wettable powders, dry flowable powders, pressurized liquids, dusts, ready-to-use solutions, microencapsulated material, pellets/tablets, soluble concentrates, and impregnated materials such as cattle ear tags and plastic bags.

Molecular formula and structure
$C_9H_{11}Cl_3NO_3PS$



Chemical group
Organophosphate (OP)

Other related chemicals
Chlorpyrifos-methyl

CAS numbers
2921-88-2: chlorpyrifos
5598-13-0: chlorpyrifos-methyl
5598-15-2: chlorpyrifos oxon
5598-52-7: fospirate (chlorpyrifos-methyl oxon)

Other trade names
Ballad, Binachlor, Bonidel, Brodan, Cequisa, Chemiban, Chemicide, Chemitox, Chlorfos, Coroban, Cyren, Dadas, Danusban, Deforce, Dowco 179, Durmet, Dymite, Embark, Empire, Equity, Eradex, Etec, Flypel, Fosban, Govern, Kensban, Killmaster, Languard, Lenfos, Lentrek, Lidcide, Logic, Lyntox, Mas-kill, Milex, Mission, Mortein Roach Bait, Parapet, Paraulod, Pattas, Perri, Pest-Ban 100, Pestgone, Pestox, Piridane, Plasbon, Polaris, Pychlorex, Pyriban, Pyrinex, Pyritilene, Pyrophus, Radar, Rampage, Rentogard, Siga, Spannit, Suscon Green, Terban, Termiban, Termicide, Termifos, Termigard, Termitedown, Termitezap, Termitof, Termitrek, Test, Toppel, Torban, Tracer, Tricel, Vessel, Vexter, Vulcan, Wormgun, X-phos, Xterminate, Zemmiban, Zesban, Zespest.

Chlorpyrifos is also found in mixtures with other insecticides, including abamectin, acetamiprid, buprofezin, cyfluthrin, cypermethrin, diazinon, dichlorvos, emamectin, ethiprole, fenobucarb, hexaflumuron, isoprocarb, permethrin, phoxim, pyretrozine, spinosad, thiram, triazophos, trichlorfon, and fungicides such as mancozeb and carbendazim. Other formulations contain fertilisers, and herbicides such as trifluralin and benfluralin. It is commonly formulated with pyrethroids for use in warehouses, ships, etc.

Trade names of mixtures containing chlorpyrifos and cypermethrin or alpha-cypermethrin include: Accurate ACE, Agent 505, Azudin, Banner, Bisect, Blink, Bombard, Comman, Cychlophos, Cyclone, Dragon, Eclipse, Emrell, Energy, Fighter, Gaya, Invathrin, Kayak, Kenrel, Konsep, Meriphos, Myphos, Naga, Newro, Nurelle, Pazelo, Perforce, Power, Protocol, Safari, Sirelle, Starphos, Strike, Subside, Trend, Twinspan.

1.2 Inerts and contaminants

Contaminants
World Health Organization specifications for maximum levels of contaminants (WHO 2009a):

- sulfotep (*O,O,O',O'*-tetraethyl dithiopyrophosphate) = 3 g/kg
- acetone insolubles = 5 g/kg

1.3 Metabolites

The main degradate in the environment is 3,5,6-trichloro-2-pyridinol (TCP). It is less toxic than chlorpyrifos. A secondary metabolite is 3,5,6-trichloro-2-methoxypyridine (TMP) (EC 2005).

Chlorpyrifos may also be oxidised to an active metabolite, chlorpyrifos oxon (NMFS 2008). The oxon is rapidly formed in chlorinated water, but also degrades rapidly to TCP (Duirk & Collette 2005). Chlorpyrifos oxon is approximately 12 times more toxic than chlorpyrifos (US EPA 2013a).

Six degradation products, including chlorpyrifos oxon, have been identified after electrochemical degradation of chlorpyrifos in wastewater (Robles-Molina et al 2012).

1.4 Mode of action in insects

Chlorpyrifos is a non-systemic organophosphate insecticide, acting as a cholinesterase inhibitor with contact, stomach, and respiratory action (WHO 2009a). It affects the nervous system by binding to the active site of the cholinesterase enzyme, preventing the breakdown of the neurotransmitter acetylcholine in the synaptic cleft. The resulting accumulation of acetylcholine in the synaptic cleft causes overstimulation of the neuronal cells, which leads to neurotoxicity and eventually death (NPIC 2009).

1.5 Uses

Chlorpyrifos is used as an insecticide, acaricide, and nematicide to control Coleoptera, Diptera, Homoptera and Lepidoptera in soil, on foliage, and on animals (WHO 2009a). It is used on nuts, fruit, vegetables, grain, seeds, fodder crops, and Christmas trees; in forestry, nurseries, greenhouses, food processing plants, industrial plants, warehouses, and ships; for disease vector control (mosquito larvicide and adulticide), household pests, fire ants, termites, and pests in animal houses; as a sheep dip for the control of lice, blowfly and ked; on golf courses and turf; as an anti-mildew agent in wood preservatives, and as ant baits; for treating poles, fence posts, railway ties, and railway box cars; in ear tags for cattle which may also contain other insecticides such as diazinon, cypermethrin or permethrin.

In some Latin American countries, chlorpyrifos-treated plastic bags are fixed over bunches of bananas to prevent insect damage (Bellamy 2012).

It is also formulated into paint for controlling insects, in slow release microencapsulated form. One formulation, IGR FITO®, which also contains pyriproxifen, has been trialled as a painted band around citrus trees to prevent ants from foraging in the trees (Juan-Blasco et al 2011), and for preventing infestations of the red palm weevil, *Rhynchophorus ferrugineus,* in palms (Llácer et al 2010). Another insecticidal paint, Inesfly 5A IGR™, which contains diazinon as well as chlorpyrifos and pyriproxifen, has been trialled as an indoor paint in Benin against mosquitoes *Anopheles gambiae* and *Culex quinquefasciatus* (Mosqueira et al 2010); and in Argentina against *Triatoma infestans*, the main vector of Chagas disease (Amelotti et al 2009). One media item reported that approximately 7,000 houses in the Chaco region of Bolivia have been coated with the paint to combat Chagas disease, and that it has been used against scorpions, *Triatoma*, and *Aedes* mosquitos in Mexico, although it has not been evaluated by the World Health Organization for these uses (Friedman-Rudovsky 2012).

In 2010, in Cali, Colombia, urban building owners used chlorpyrifos at an average rate of 2 kg/month/house to control leaf-cutting ants. An urban area with 200 homes was using approximately 4.8 tonnes/year for this one pest (Montoya-Lerma et al 2012).

Chlorpyrifos-methyl is used for post-harvest fumigation of stored grains such as wheat, barley and maize; residues can turn up in animal products, flour and beer (JMPR 2013).

Application

In agriculture, chlorpyrifos is commonly used as a foliar spray, or applied directly to soil and incorporated into it before planting (US EPA 2009a). It may also be applied to bark or seeds. It is applied by aerial spraying, chemigation, ground boom sprayers, tractor-drawn granular spreaders, airblast sprayers, low and high pressure hand wands, backpack sprayers, hydraulic hand-held sprayers, shaker cans, belly grinders, push-type spreaders, large tank sprayers, compressed air sprayers, hose-end sprayers, and aerosol sprayers (US EPA 2006).

Extent of use

Chlorpyrifos is one of the most widely used insecticides in the world. It is one of the main insecticides in countries such as Thailand (Panuwet et al 2009), the Philippines (Lu 2011), Vietnam (Phung et al 2012), Argentina (Jergentz et al 2005), and Brazil where there is an estimated annual usage of 1.8 kt/year (Meire et al 2012). It was ranked as the most common insecticide in 2007 in the US (Alavanja et al 2013). It is the most widely used organophosphate in Chile because it is cheap and easily accessible to the public (Muñoz-Quezada et al 2012). In The Gambia, chlorpyrifos is freely available in local markets for mosquito control (Murphy et al 2012).

China alone has 1,022 registered products containing chlorpyrifos (ICAMA 2012). In 2011, it exported chlorpyrifos to the value of USD 110 million, making it China's 6th highest pesticide export by value. By 2015, China's production capacity is expected to reach 200,000 tonnes, and its output 170,000 tonnes, accounting for over 85% of global capacity and output (AgroNews 2013).

However, Dow AgroSciences, in their submission to the New Zealand Environmental Protection Authority's reassessment of OP and carbamate insecticides, stated that:

- "use has dropped off over the last 20 years and particularly in the last 5 years as growers move to products that fit with 'green' spray programs";
- "in general over the last 20 years, chlorpyrifos has been largely phased out of horticulture and replaced by more modern products"; and
- "Dow AgroSciences does not support the use of chlorpyrifos in the home garden or for indoor/outdoor domestic or industrial pest control. Dow AgroSciences has voluntarily withdrawn its chlorpyrifos products from these uses globally because of concerns about exposure to children, pets, wildlife and the environment from this type of use (Dow AgroSciences 2013).

1.6 Manufacturers

Dow AgroSciences is the original discoverer and developer, but chlorpyrifos is no longer under patent so there are many manufacturers, including Cheminova, Gharda Chemicals, Makhteshim, and SumiAgro.

The main producers in China are Redsun Group, Shandong Tiancheng, Zhejiang Xinnong, Jiangsu Baoling, Zhejiang Dongfeng, Lier Chemical, and Shandong Lvba (AgroNews 2013).

1.7 Regulatory Status

Chlorpyrifos was first registered in 1965 in the US (Cal EPA 2010), and it is now registered in many countries.

Regional and National Bans

In Yemen, chlorpyrifos has been banned from sale and restricted for use since 2006 (El-Zaemey et al 2013).

It is approved in the EU until June 30th 2016, and is authorised in all member countries except Denmark, Finland, Latvia, Lithuania, and Sweden (IUPAC 2012).

Restrictions

USA: Residential uses, uses in indoor areas where children could be exposed such as schools, and use in children's parks, are banned, with the exception of child-resistant ant and roach baits, because of risks to children. All these uses ceased by the end of 2001, and all termite treatments ceased by the end of 2005. It was also prohibited for use on tomatoes (US EPA 2006).

South Africa: Household, home garden and domestic use was banned in 2010 (DAFF 2010).

Reassessments

Chlorpyrifos is being reassessed in a number of countries, including the European Union, New Zealand, and the USA.

1.8 International Standards

PAN International

Chlorpyrifos is on PAN International's list of Highly Hazardous Pesticides for global phase-out (PAN Int 2011).

2 Toxicological & Epidemiological Assessment

2.1 Absorption and metabolism

Chlorpyrifos is absorbed by inhalation, ingestion and skin penetration (Reigart & Roberts 1999). It is completely metabolised to chlorpyrifos oxon and then to 3,5,6-trichloro-2-pyridinol (TCP) in the liver by the cytochrome P450 enzyme system (CYP450) (Hodgson & Rose 2008). CYP450 replaces the sulfur of the P=S group with oxygen in a process known as oxidative desulfuration to form the oxon (Flaskos 2012). The oxon is a more potent inhibitor of acetylcholinesterase than chlorpyrifos itself (Verma et al 2009).

Chlorpyrifos is absorbed rapidly and widely distributed in rats, with 80% excretion in urine within 48 hours (EC 2005). US EPA (2011) gives different figures, stating it is excreted as metabolites, mainly TCP, in urine (84%) and faeces (5%) within 7 hours.

There is some question about the extent of dermal absorption of chlorpyrifos in humans. US EPA (2011) gave a figure of 1-3% dermal absorption based on a 1982 industry (Dow) study. However, the California Environmental Protection Agency (Cal EPA) accepted 9.6% as the appropriate absorption level, stating concerns about the high doses used in the industry study leading to an inadequate characterisation of absorption (Thongsinthusak 1999). An earlier memorandum from Tian Thongsinthusak of Cal EPA, in 1991, shows quite clearly that the higher the dose administered, the lower the dermal absorption, with a dermal dose of 316 $\mu g/cm^2$ resulting in

4.3% dermal absorption and 3 $\mu g/cm^2$ resulting in 11.4 % dermal absorption. A subsequent analysis from the University of Washington, of how dermal absorption figures were arrived at for chlorpyrifos, confirmed Cal EPA's view that 3% is too low and 9.6% more realistic for occupational exposure (Kissel 2011). More recently, Ertl & Butte (2012), in a study on the bioavailability of pesticides in house dust, described it as 93% absorbed in humans, with a dermal penetration ability of 56% and a digestive bioaccessibility of 37% (when food is present in the gut). Epidemiology studies described later in the section on *Human exposure* indicate that there is relatively high dermal exposure occurring under practical conditions of use.

There is a huge variation in the rate of chlorpyrifos detoxification in humans: the enzyme paraoxonase (PON1) plays an important role in this. PON1 is a calcium-activated enzyme distributed in various tissues, including the liver, brain, and blood; and it hydrolyses the oxon before it can reach its target, the acetylcholinesterase enzyme (AChE) (US EPA 2011). Several polymorphisms (variations) of the PON1 gene influence both the level of expression of the enzyme and its catalytic ability, thus determining the rates at which an individual will detoxify a specific pesticide (Cal EPA 2008). PON1 levels vary significantly between people, as much as 14-fold among mothers and as much as 26-fold among newborns (Furlong et al 2006). A 57-fold variation in metabolism was found in a study using human liver microsomes (Croom et al 2010).

Chlorpyrifos also crosses the placenta: in a study on rats, in which dams were fed chlorpyrifos, total residues in foetuses (0.0447 $\mu g/g$) were higher than in the dams (0.0120 $\mu g/g$), with the highest level of residues in the liver (0.053 $\mu g/g$), followed by the brain (0.036 $\mu g/g$), placenta (0.040 $\mu g/g$) and amniotic fluid (0.001 $\mu g/g$) (Akhtar et al 2006).

A study for Dow AgroSciences measured residues in rats milk following chlorpyrifos intake at 0.3 mg/kg/day (US EPA 2011).

2.2 Modes of action in mammals

Chlorpyrifos has at least three main modes of action in mammals: (a) inhibition of the enzyme AChE, (b) oxidative stress, and (c) endocrine disruption. The first two are described below, and endocrine disruption is described later.

Additionally, US EPA (2011) states that the modes of action associated with the effects of chlorpyrifos on the developing brain are still not fully known, but biologically plausible hypotheses include effects on signalling pathways, a morphogenic role of AChE on the structure of the brain, and reduction in axonal transport mediated through impaired tubulin polymerization.

Chlorpyrifos shows a non-monotonic dose response, typical of endocrine disruption, in some circumstances, such as in weight gain in male rats following foetal exposure (Lassiter & Brimijoin 2008).

Inhibition of acetylcholinesterase (AChE)

One of the main actions of chlorpyrifos in humans and insects, as with other organophosphates, is to inhibit the AChE through phosphorylation. This enzyme breaks down the neurotransmitter acetylcholine which activates cholinergic neurons, the nerve cells that control signals in the peripheral nervous system, brain, and spinal cord. If acetylcholine is not inactivated immediately after it has done its job, the neurons become over-stimulated leading to increased secretions, sensory and behavioural disturbances, incoordination, depressed motor function, respiratory depression, tremors, convulsions, and death (Reigart & Roberts 1999; Colborn 2006). Recovery depends on manufacturing more AChE. This effect of chlorpyrifos is said to be caused by the metabolite, chlorpyrifos oxon, rather than the parent compound (Slotkin 2004).

Available data indicates that humans are more sensitive than animals to inhibition of AChE from both oral and dermal exposures (US EPA 2011).

Oxidative stress

Oxidative stress occurs when the production of 'reactive oxygen species', such as free radicals and hydrogen peroxide, exceeds the body's ability to neutralise and eliminate them, overwhelming antioxidant defences such as glutathione, and resulting in DNA damage, and cell and tissue death. Oxidative stress is involved in many human diseases, including Parkinson's disease, cancer, Alzheimer's disease, diabetes, and heart failure. Oxidative stress can also lead to cardiovascular, respiratory and neurological problems as well as advance general aging (Verma et al 2009). Commonly used measures of the extent of oxidative stress in laboratory studies are the levels of glutathione and associated enzymes of the antioxidant system such as glutathione reductase (GR), glucose-6-phosphate dehydrogenase (GPD or G6PD), glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD); and measures of the oxidation of lipids in cell membranes,

lipid peroxidation (LPO), such as levels of malondialdehyde (MDA) and 4-hydroxynonal (4-H). Alterations in the components of the antioxidant system can be used as biomarkers for pesticide poisoning (Mehta et al 2009; Kalender et al 2012).

Oxidative stress, in addition to AChE inhibition, underlies the developmental neurotoxicity of chlorpyrifos (Slotkin & Seidler 2009). Additionally, chlorpyrifos causes damage to the dopaminergic neurons via oxidative stress effects on mitochondria, and this mechanism may lead to neurodegenerative disease such as Parkinson's disease (Lee et al 2012).

A number of studies have demonstrated oxidative stress damage in rodent tissues:

- Chlorpyrifos caused oxidative stress in rat brain, resulting in accumulation of MDA and 4-H in all three regions of the rat brain (fore, mid and hind). It also increased levels of hydrogen peroxide, nitrate and nitrite in brain and liver (Mehta et al 2009; Verma et al 2009).
- At a dose of 5.4 mg/kg (1/25th of the LD_{50}), it caused decreased levels of GPx and GST, but increased activity of MDA, SOD and CAT in rat testis tissue (Kalender et al 2012).
- Another study in rat testis tissue found that 9 mg/kg caused a 179-fold increase in LPO, and significantly decreased CAT, SOD, GPx and GST resulting in oxidative damage to tissue (Attia et al 2012).
- At a dose of 6.75 mg/kg, it increased LPO, and decreased SOD, GST, CAT, and AChE in rat red blood cells (Mansour & Mossa 2009).
- It decreased GPx and GST, but increased the activity of SOD, CAT, and MDA in rat lung tissue (Uzun et al 2010).
- A single oral dose of 63 mg/kg caused oxidative stress in the retina of mice, with increased LPO, and decreased SOD, CAT, and GPx (Yu et al 2008).
- A single dose of 30 mg/kg caused significant increase in LPO and decrease in total antioxidants in rats (Elsharkawy et al 2013).
- Chlorpyrifos decreased SOD and glutathione and increased plasma GPx activity at low doses in rats, but increased it at higher doses (Bebe & Panemangalore 2003).
- An increase in MDA, indicating increased LPO, was observed in plasma, liver, kidney and foetal tissue when pregnant rats were fed chlorpyrifos from the 6th to 15th days of gestation (Zama et al 2007).
- Increase in MDA, SOD and CAT, but decrease in GPx and GST in rats fed a sublethal dose of chlorpyrifos of 5.4 mg/kg per day for 4 weeks (Uzun & Kalender 2013).
- Consistent dose-dependent toxicity to brain cells known as oligodendrocyte progenitors, through oxidative stress (Saulsbury et al 2009).

Chlorpyrifos also causes oxidative stress in fish: it inhibited SOD, CAT, and GR in mosquito fish, *Gambusia affinis* (Kavitha & Rao 2008) and common carp (Xing et al 2012).

2.3 Acute toxicity

Lethal doses

The lethal dose, LD_{50}, is the dose that kills 50% of test animals.

No & Lowest Observed Adverse Effects Levels

The No Observed Adverse Effects Level (NOAEL) is the lowest dose of the chemical given to a test animal at which no harmful effects are observed, and the Lowest Observed Adverse Effects Level (LOAEL) is the lowest dose of the chemical at which a harmful effect is observed.

WHO (2009b) Recommended Classification of Pesticides by Hazard: Class II Moderately hazardous

US EPA (2006) Hazard Classification:

- Acute toxicity by oral, dermal and inhalation = Category II, moderately toxic
- Eye irritation = Category IV, slightly toxic
- Skin irritation = Category IV, mildly toxic

A wide variety of lethal doses have been reported:

Oral LD_{50}:[1]

- rat = 64 mg/kg (IUPAC 2012)
- rat = 66-195 mg/kg (EC 2005)
- rat = 223 mg/kg (US EPA 2011)
- rat = 82-270 mg/kg (Cal EPA 2010)
- rat, female = 144-223 mg/kg (WHO 2009a)
- rat, male = 221-223 mg/kg (WHO 2009a)
- rat = 96 mg/kg (96-480 mg/kg) (NZ EPA 2012)
- chicken = 32-35 mg/kg (ATSDR 1997)

Acute dietary NOAEL = 0.5 mg/kg (US EPA 2009b)

An acute oral study in humans gave the following results (EC 2005):

- LOAEL = 2 mg/kg based on red blood cell AChE inhibition
- NOAEL = 1.0 mg/kg

[1] All values are expressed as mg/kg body weight/day.

The acute oral LD_{50} of sulfotep is 5 mg/kg; at an 'average' oral LD_{50} of 229 mg/kg for chlorpyrifos, the sulfotep contamination at the maximum specification level of 3 mg/kg increases the toxicity of chlorpyrifos by 242% (WHO 2009a).

The acute oral LD_{50} of chlorpyrifos oxon is 100-300 mg/kg bw/day (male and female, respectively) (EC 2005).

Dermal

- LD_{50} rat = 1250-2000 mg/kg (EC 2005)
- LD_{50} rat = >2000 mg/kg (WHO 2009a)
- LD_{50} rabbit = >5000 mg/kg (WHO 2009a)
- LD_{50} mouse = 120 mg/kg (NZ EPA 2012)
- Short-term NOAEL = 5 mg/kg (US EPA 2009b)
- Absorbed dermal NOAEL = 0.15 mg/kg (US EPA 2011)

Inhalation

- LC_{50} rat = 0.1 mg/L (IUPAC 2012)
- LC_{50} rat = >1.0 mg/L (EC 2005)
- LC_{50} rat = >0.2 mg/L (US EPA 2011)
- LC_{50} rabbit = > 200 mg/m^3 (WHO 2009a)
- LC_{50} rat female (4hr) = 2890 mg/m^3 (WHO 2009a)
- NOAEL = 0.1 mg/kg (US EPA 2009b)

Acute sublethal effects in laboratory studies

US EPA (1999a) reported the following symptoms: decreased motor activity and increased incidence of clinical signs consistent with organophosphate intoxication.

Acute effects in humans

The primary effect of acute exposure to chlorpyrifos is on the nervous system. Acute exposure may result in the classic signs and symptoms of organophosphate poisoning in humans (Reigart & Roberts 1999):

Critical symptoms:

- respiratory: bronchospasm and bronchorrhea, producing tightness in the chest, wheezing, productive cough, and pulmonary oedema;
- life threatening severity is indicated by loss of consciousness, incontinence, convulsions, and respiratory depression;
- cardiovascular: bradycardia which may progress to sinus arrest; may be superseded by tachycardia and hypertension; toxic myocardiopathy;
- primary cause of death is respiratory failure and there may be a secondary cardiovascular component.

Early symptoms include:

- headache, nausea, dizziness, hypersecretion including sweating, salivation, lacrimation, and rhinorrhea;
- muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps, and diarrhoea;
- miosis, blurred and/or dark vision;
- anxiety, restlessness, depression, memory loss, confusion, and toxic psychosis manifested as confusion or bizarre behaviour.

Cal EPA (2010) reported, in addition, slurred speech and cardiac arrest.

US EPA (2013a) reported that between 23 and 56% of the cases of chlorpyrifos reported by various US surveillance programmes involved respiratory symptoms.

Children may have slightly different symptoms, less likely to have bradycardia, muscular fasciculations, and lacrimation but seizures, lethargy and coma are common, together with flaccid muscle weakness, constricted pupils and excessive salivation (Reigart & Roberts 1999).

A 9-year-old, who had ingested chlorpyrifos, developed progressive acute respiratory distress syndrome characterised by irreversible fibrosis and obliteration of the lung parenchyma (Nel et al 2002).

Skin and eye irritation

It causes slight irritation to skin, and moderate irritation to eye (WHO 2009a).

2.4 Subchronic / intermediate toxicity

EC (2005):

- lowest relevant NOAEL, oral = 1 mg/kg; 90-day rats, mice and dogs
- lowest relevant NOAEL, inhalation = >0.296 x 10^{-3} mg/L (nose-only)
- lowest relevant NOAEL, dermal = >5 mg/kg; 21-days rats
- peripheral tissue AChE inhibition NOAEL = 1 mg/kg; 6-weeks dietary, dogs
- brain AChE inhibition NOAEL = 2 mg/kg; 6-week dietary, dogs
- red blood cell AChE inhibition NOAEL = <0.5 mg/kg; 6-weeks dietary, dogs

A subacute oral study in humans gave the following results (EC 2005):

- LOAEL= 0.5 mg/kg based on clinical symptoms.

Subchronic effects in laboratory studies
US EPA (2009b) reports the following adverse effects from subchronic toxicity testing:

- inhibition in plasma AChE in rats and dogs at 0.025 to 0.03 mg/kg;
- inhibition in red blood cell AChE in dogs and rats at 0.22 to 0.3 mg/kg;
- higher doses caused increased heart and brain weight, adrenal gland effects, decreased body weight.

Intermediate syndrome
Intermediate syndrome (IMS), lying between acute cholinergic response and long-term neuropathy, is a sequence of neurological signs that appear 24 to 36 hrs after the acute cholinergic effects. Animals generally develop tetraparesis, mydriasis and ventroflexion of the neck several days post exposure. IMS is not a direct effect of AChE inhibition, and the underlying mechanisms are unknown (Idris et al 2012).

A 16-month-old girl developed intermediate syndrome after accidentally ingesting chlorpyrifos. Initially exhibiting lethargy and tachycardia, she developed delayed onset respiratory arrest and flaccid paralysis after an asymptomatic period (Mattingly et al 2003).

IMS was described in a study of 10 patients in Sri Lanka with chlorpyrifos poisoning as a result of intentional ingestion (Jayawardane et al 2008). IMS is a major cause of death from respiratory failure following OP poisoning.

In India, a 14-year-old boy developed both intermediate syndrome and delayed neuropathy after ingesting chlorpyrifos, the later involving wrist drop (Chatterjee & Sarma 2003).

2.5 Chronic toxicity

The chronic NOAELs and LOAELs are:

EC (2005):

- Lowest relevant NOAEL = 1 mg/kg; 2-years rats, mice, dogs; based on AChE inhibition

US EPA (2009b):

- Chronic dietary NOAEL = 0.03 mg/kg
- Chronic RfD = 0.0003 mg/kg
- Long term dermal NOAEL = 0.03 mg/kg
- Long term inhalation NOAEL = 0.03 mg/kg

Systemic effects – laboratory studies
Systemic effects include inhibition of plasma, red blood cell and brain cholinesterase, increased liver weights, decreased body weight gain, ocular effects, adrenal gland effects, altered clinical chemistry and haematological parameters, and increased keratitis and hepatocyte fatty vacuolation (US EPA 2009b).

A single dose of 30 mg/kg caused a significant decrease in haemoglobin concentration, haematocrit percentage, thrombocytic indices, and total protein and albumin levels in rats (Elsharkawy et al 2013).

A sublethal dose of 5.4 mg/kg/day for 4 weeks caused a significant increase in white blood cells and platelets in rats (Uzun & Kalender 2013).

Metabolic effects
A number of studies indicate that exposure to chlorpyrifos, and particularly early life exposure, may predispose a person to obesity, diabetes, and cardiovascular problems later in life. The California EPA (Cal EPA 2010) expressed concern, based on the available limited animal data, about a possible link between “the widespread chlorpyrifos exposure among the general population and the percentage of obesity in the United States”.

Laboratory studies
Developmental exposure to chlorpyrifos can cause long-lasting changes in serotonin receptors and signal transduction, which may result in appetite disorders in adulthood, and consequent increases in obesity and diabetes (Aldridge et al 2004).

Foetal and neonatal male rats exposed to chlorpyrifos experienced excessive weight gain and leptin dysfunction (leptin is a hormone that regulates appetite). The weight gain showed an inverted U-shaped dose-response relationship, typical of endocrine responses (Lassiter & Brimijoin 2008).

Neonatal male rats exposed to sub-toxic levels of chlorpyrifos produced, in adulthood, a “metabolic pattern for plasma lipids and insulin that resembles the major adult risk factors for atherosclerosis and type 2 diabetes mellitus”, i.e. elevated cholesterol and triglycerides, and insulin after eating (Slotkin et al 2005).

In 2011, Slotkin reported on studies in which neonatal rats given chlorpyrifos, in doses devoid of any acute sign of toxicity, developed metabolic dysfunction resembling prediabetes.

Adult exposure to chlorpyrifos can also cause problems: a single acute exposure (50 mg/kg) in adult male rats resulted in hyperglycaemia and

hyperlipidemia, and a corresponding increase in cardiovascular and atherosclerosis risk: there were increases in the levels of glucose, glycogen, corticosterone, triglycerides, and low-density lipo-protein-cholesterol; and a decrease in high-density lipoprotein (Acker & Nogueira 2012). In another study on rats, a single dose of 30 mg/kg induced hyperglycaemia, a significant increase in total cholesterol, and decreases in triglycerides and glycogen (Elsharkawy et al 2013).

In rats fed a sublethal dose of chlorpyrifos of 5.4 mg/kg/day for 4 weeks, there was a significant increase in total cholesterol and decrease in triglyceride levels (Uzun & Kalender 2013).

Liver

Chlorpyrifos is a potent inhibitor of the liver CYP450-dependent metabolism of a number of substances including the body's own hormones testosterone and oestrogen, other pesticides, and drugs such as the antidepressant imipramine. Chlorpyrifos oxon inhibits the metabolism of permethrin (Hodgson & Rose 2008).

Acute exposure can also cause liver damage: a single dose of 30 mg/kg caused liver damage in rats (Elsharkawy et al 2013).

Chronic exposure can cause liver damage and disturbance of metabolic function in the liver. Rats fed a sublethal dose of chlorpyrifos of 5.4 mg/kg/day for 4 weeks suffered liver damage including congestion of the central vein, dilation of sinusoids, diffuse Kupffer cell proliferation, mononuclear infiltration, picnosis, and eosinophilic cytoplasm. They also experienced significant changes to liver function as indicated by an increase in the activity of the enzymes alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), but decreased total protein and albumin levels in blood (Uzun & Kalender 2013).

Ninety-day treatment of rats at doses 1/20th or less of the lethal dose led to increased urinary levels of the metabolites creatinine, glycine, dimethylglycine, dimethylamine, glutamine, succinate, alanine, lactate, and glucose (Wang et al 2011).

Kidneys

Chronic exposure to chlorpyrifos can alter the structural and functional integrity of the kidney, induce oxidative stress, and cause nephrotoxicity, which may lead to renal failure (Wang et al 2011).

Cardiac and haematolymphatic system

One epidemiological study found a statistically significant association between exposure to chlorpyrifos and nonfatal myocardial infarction in farm women, in a small number of cases (9) in the US. The Odds Ratio (OR) was 2.1, i.e. more than double the risk (Dayton et al 2010).

Cancer

US EPA (2011) reported no evidence of carcinogenicity in animal studies, but there are a number of epidemiological studies indicating that chlorpyrifos may be carcinogenic in humans, the association being strongest for lung and rectal cancers, an association recognised by the US EPA (2011) as being consistent and warranting follow-up and further research. US EPA (2011) also acknowledged "preliminary associations with breast and prostate cancer", describing them as weak but warranting further monitoring.

There are several studies on chlorpyrifos showing mutagenicity and genotoxicity (see below), which are strong indicators of potential carcinogenicity. There are also the laboratory studies, referred to below in the section on endocrine disruption, in which chlorpyrifos caused human breast cancer cells to proliferate.

Epidemiology

A case-control study of men with Hodgkin's lymphoma in Canada found a significant association with exposure to chlorpyrifos (Odds Ratio = 5.26), although the number of cases (6) was small (Karunanayake et al 2012).

Case-control studies in 3 US states were pooled to evaluate the risk of non-Hodgkin's lymphoma from exposure to organophosphates. There was an elevated risk from exposure to chlorpyrifos (OR = 3.2) but there were only a small number of cases (7) (Waddell et al 2001).

A number of analyses of exposure to chlorpyrifos and increased risk of various cancers were carried out in the US as part of the Agricultural Health Study, involving more than 50,000 pesticide applicators:

- Lee et al (2004), in a study of 54,383 US male pesticide applicators, with a total of 2,070 malignant neoplasms, found increased risk of lung, kidney, and brain cancer although only the lung was statistically significant (OR = 2.18) for lifetime-exposure days compared with non-exposed individuals. Individuals in the highest category of intensity-weighted exposure-days but not lifetime exposure days, had statistically significant increases in rates of lymphohaematopoietic cancers, leukaemia

and brain cancer compared with non-exposed individuals.

- A further study of the US male pesticide applicators (56,813), found a 2.7-fold increased risk of rectal cancer in the highest exposure category (Lee et al 2007a).
- Alavanja et al (2003) found an increased risk (OR = 1.65) of prostate cancer amongst male applicators exposed to chlorpyrifos, but only in those with a family history of prostate cancer.
- Engel et al (2005) found a slightly increased risk (OR = 1.4) of breast cancer amongst wives of the pesticide applicators who had used chlorpyrifos themselves, and those that had not used it but whose husbands had (OR = 1.3).

Summary

There are a considerable number of epidemiological studies indicating an association between exposure to chlorpyrifos and cancer, particularly lung and rectal cancer. Weaker associations have been found with non-Hodgkin's lymphoma, leukaemia, brain, prostate, and breast cancer. Taken together with the studies showing genotoxicity and mutagenicity, as well as the laboratory studies on endocrine disruption showing that chlorpyrifos caused breast cancer cells to proliferate, there is strong indication that chlorpyrifos is carcinogenic.

Genotoxicity / mutagenicity

One of the main health implications of genotoxicity is cancer. A pesticide is genotoxic if it causes damage to a gene that could result in cell death or changes in the structure or function of the gene. The damage can be mutagenic or non-mutagenic.

Mutagenicity refers to the ability of a toxic agent to induce heritable or transmissible changes in the genetic material of cells or organisms, for example through base-pair substitution (change in amino acid sequence), deletion or addition of gene fragments, chromosomal translocations, sister chromatid exchanges, or some other mechanism. Mechanisms involved include causing damage to the chromosome such as loss, breaks, or rearrangements of chromosomal segments. Mutagenicity tests include the Ames test, mouse lymphoma assay, and micronucleus induction test (increase in the frequency of small fragments formed when chromosomes break).

Genotoxicity also includes interchanges and re-attachments of strands in the chromosome during DNA replication. However, mutagenicity tests are also considered to be genotoxicity tests, and the two terms are often used interchangeably.

US EPA (2011) stated that chlorpyrifos was not mutagenic in bacteria or mammalian cells but did cause slight genetic alterations in yeast and DNA damage to bacteria, that it did not induce chromosome aberrations *in vitro*, was not clastogenic (causing breaks in chromosomes) in mouse micronucleus test, and did not induce unscheduled DNA synthesis in rat hepatocytes, based mainly on studies submitted by the pesticide manufacturer. However, Cal EPA (2010) concluded that some studies suggest chlorpyrifos may be genotoxic, and there is substantial evidence of mutagenicity and genotoxicity from a number of studies, summarised below:

A: Mutagenicity

- Sobti et al (1982) found significantly increased sister chromatid exchange in human lymphoid cells treated with Dursban.
- Amer & Aly (1992) concluded that the chlorpyrifos formulation Dursban was mutagenic, as it induced a high percentage of metaphases with chromosomal aberrations in mouse spleen cell cultures, with sister chromatid exchanges increasing with increasing concentration of the insecticide.
- Yaduvanshi et al (2012) found significant, dose-dependent micronucleus induction in mouse bone marrow.
- Tian & Yamauchi (2003) measured significant dose-dependent micronuclei induction in 3-day mouse embryos following maternal exposure during the early preimplantation period.
- Cui et al (2011) refer to 2 studies, published in Chinese, which found chlorpyrifos induced micronuclei in mouse bone marrow and Chinese hamster lung cells (Li et al 1993; Song et al 1997).
- Lieberman et al (1998) reported DNA damage including chromosomal alterations, chromatid and chromosome breaks, and sister chromatid exchanges in humans exposed to domestic application.
- Yin et al (2009) found increased induction of micronuclei and chromosomal lesions in erythrocytes, and DNA damage in erythrocytes and liver cells of *Bufo bufo gargarizans* tadpoles exposed to the sublethal concentrations of chlorpyrifos.
- Ali et al (2008) found micronucleus induction and DNA damage in the freshwater fish *Channa punctatus* (Bloch).

B: Genotoxicity

- Chlorpyrifos caused an increased ratio of

DNA migration, as assessed by the comet assay, in human lymphocytes at 10 μM (Sandal & Yilmaz 2011).

- Both acute and chronic exposure to chlorpyrifos caused significantly marked DNA damage in rat liver, brain, kidney, and spleen, when measured 24 hours after treatment; the damage was partially repaired at 48 and 72 hours after treatment (Ojha et al 2011).
- Cui et al (2011) found DNA strand breakage and DNA hypomethylation in mouse lymphocytes.
- Rahman et al (2002) found a significant dose-related increase in mean comet tail length, indicating DNA damage in mice leucocytes.
- Chlorpyrifos caused DNA damage in fruit fly (*Drosophila melanogaster*) at 15.0 μg/L, thought to be as a result of reactive oxygen species generation (Gupta et al 2010).
- Patnaik & Tripathy (1992) concluded that the chlorpyrifos formulation Durmet was genotoxic on the basis of induction of mosaic wing spots and sex-linked recessive lethals in *Drosophila*.
- Woodruff et al (1983) found that chlorpyrifos induced a significant amount of ring-X chromosome loss in Drosophila.
- JanakiDevi et al (2013) found significantly higher dose and time-dependent DNA damage in gill, foot and body tissues of the marine bivalve *Donax faba* exposed to chlorpyrifos for 96 hrs in a comet assay.

Chlorpyrifos also shows evidence of genotoxicity in plant cells: Dimitrov & Gadeva (1997) found statistically significant increased frequency of micronuclei in root meristem cells of smooth hawksbeard (*Crepis capillaris* L.), due to partial spindle disturbances leading to anaphase distribution of chromosomes, as a result of exposure to the chlorpyrifos formulation Dursban. The authors also referred to studies showing increased frequency of chromosomal aberrations after exposure to Dursban in fava bean (*Vicia faba*) (Amer & Farah 1983) and barley (*Hordeum vulgare*) (Kaur & Grover 1985).

Chlorpyrifos shows evidence of mutagenicity in the fungus Aspergillus terreus: a concentration of 0.8 ml/L increased mutations in the conidial spores (Sabir 2010).

Additionally, an epidemiological study in India showed that DNA damage is significantly higher in people occupationally exposed to organophosphates (chlorpyrifos, malathion, pirimiphos-methyl, and temephos); and that, amongst those occupationally exposed, damage was even greater in those individuals with certain PON1 genetic polymorphisms, specifically the PON1 Q/Q and M/M genotypes (Singh et al 2011). This indicates that the risk of DNA damage and cancer from exposure to chlorpyrifos is elevated in certain susceptible individuals and subpopulations.

Summary

Independent studies have found chlorpyrifos to be mutagenic or genotoxic in human, rat, mouse, Chinese hamster, toad, fish, fruitfly, and plant cells, although the US EPA (2011) stated that chlorpyrifos is not mutagenic.

Endocrine disruption

There is a considerable amount of evidence that chlorpyrifos causes endocrine disruption, and it is on the US EPA's final list of 60 pesticides for initial Tier 1 screening for endocrine disruption (US EPA 2011).

According to Vandenberg (2012), effects resulting from exposure to chlorpyrifos follow a non-monotonic dose-response curve (NMDRC) in animals, *in vivo*. NMDRCs are now regarded as common phenomena with well-understood mechanisms for endocrine disrupting chemicals (Birnbaum 2012). That means traditionally derived NOAELs and LOAELS very likely are set above the effect level at which the adverse effects are greatest.

Chlorpyrifos is described in a mini review by Hodgson & Rose (2008) as a 'potent inhibitor' of human liver CYP450 metabolism of testosterone and oestradiol (citing Usmani et al 2003, 2006 – see below), thought to be as a result of the interaction of highly reactive sulphur, released during the oxidative desulphuration reaction, with the haeme iron of CYP450.

Pre-incubation of CYP2A4[2] genes with chlorpyrifos (2 μM) followed by testosterone (100 μM) resulted in 98% inhibition of testosterone metabolism (Usmani et al 2003). Pre-incubation of human liver microsomes with chlorpyrifos irreversibly reduced CYP450 metabolism of testosterone by 98% (Usmani et al 2003) and oestrogen by 94% (Usmani et al 2006). Reduced metabolism of oestrogen or testosterone in humans or animals would result in increased exposure of hormone sensitive tissues to these hormones.

Androgenic effects – Laboratory studies

Viswanath et al (2010) described chlorpyrifos as one of the most potent anti-androgenic compounds (along with endosulfan and piperophos) out of the 9 they tested. Chlorpyrifos significantly decreased biosynthesis of testosterone in

[2] Cytochrome P450, family 2, subfamily a

rat Leydig cells; it decreased the expression of key steroidogenic enzymes (cytochrome P450scc, 3ß-HSD, and 17ß-HSD), decreased steroidogenic acute regulatory (StAR) protein expression, and decreased luteinizing hormone receptor stimulated cAMP (cyclic adenosine monophosphate) production.

Androgenic effects - Epidemiology

The androgenic effects of chlorpyrifos demonstrated in laboratory studies are supported by an epidemiological study of 322 male partners in couples presenting to a USA infertility clinic. Their urinary levels of the metabolite TCP were associated with a dose-dependent decrease in oestradiol: an interquartile range increase in TCP was associated with a 1.36 pg/mL decline in oestradiol concentration (Meeker et al 2008). Oestradiol is important in male reproductive health, particularly in germ cell survival. The levels of TCP found in this study were comparable to those found in the Second National Report on Human Exposure to Environmental Chemicals, NHANES 1999-2000, which reported TCP in over 90% of urine samples in the US population. Meeker et al (2008) concluded that this reduction is of potential public health importance on a population level because of widespread exposure.

Oestrogenic effects – laboratory studies

Ventura et al (2012) described chlorpyrifos as a breast cancer risk. They found that low doses (0.05 μM) caused human oestrogen-dependent MCF-7 breast cancer cells to proliferate, mediated by the oestrogen receptor ER-alpha; but high doses (50 μM) induced a decrease in proliferation. However, at 50 μM, chlorpyrifos induced cell cycle arrest; modification of cell cycle progression is a hallmark of tumour cells and is crucial in human cancer progression. Additionally, at 50 μM but not lower concentrations, it induced increases in reactive oxygen species of 58% in MCF-7 cells and 108% in non-hormone dependent breast cancer cells MDA-MB-231. Reactive oxygen species are described as potent mutagens increasing genomic instability. Thus, in this study, chlorpyrifos contributed to breast cancer risk by 2 mechanisms: oestrogenic effect at low doses, and disruption of cell cycle through production of reactive oxygen species (oxidative stress) at high doses, in non-hormone dependent breast cancer cells. The lowest concentration used, 0.05 μM, was described as similar to levels found in water and soil.

In another study on human breast cancer cells, Rich et al (2012) found a non-statistically significant increase in MCF-7 cells at low and medium dose-ranges but not high dose, and not in 2 other breast cell lines that are not oestrogen-responsive (MDA-MB-231 and MCF-10A).

Chlorpyrifos was weakly oestrogenic in 2 *in vitro* assays: MCF-7 human breast cancer cell proliferation assay, and oestrogen receptor transactivation assay (Andersen et al 2002). Kojima et al (2004) also found chlorpyrifos to be oestrogenic in an oestrogen receptor ER-alpha assay using Chinese hamster ovarian cells.

Grünefeld & Bonefeld-Jorgensen (2004) found it to weakly increase mRNA levels in oestrogen receptor ERß in human breast cancer MCF-7BUS cells.

Thyroid effects – Laboratory studies

Thyroid hormones are also affected by chlorpyrifos. Thyroid hormone disruption can result in negative impacts on foetal brain development (Ghisari & Bonefeld-Jorgensen 2005).

Haviland et al (2010) found increased thyroid hormone levels and altered learning behaviour in female mice exposed to 1 and 5 mg/kg chlorpyrifos on gestational days 17-20 (similar effects were not found in males).

Oral chlorpyrifos (12.5 mg/kg twice/week for 43 days) significantly reduced serum concentrations of cortisol and thyroxine (T4) in sheep (Rawlings et al 1998).

Chlorpyrifos exposure, at levels that did not induce brain AChE inhibition or other signs of toxicity (6 mg/kg bw/day), reduced serum T4 in pregnant mice, and their offspring once they had reached adulthood. It also induced alterations in the thyroid gland in both generations and adrenal glands only in the dams. Effects on T4 were more marked in male mice (De Angelis et al 2009).

In another study, chlorpyrifos stimulated the proliferation of thyroid-hormone dependent rat pituitary GH3 cells, the greatest effect being at 10^{-5} M concentration. However, in the presence of thyroid hormone T3, it slightly but insignificantly increased proliferation at 10^{-5}M, but inhibited it at 5 x 10^{-5}M (Ghisari & Bonefeld-Jorgensen 2005).

Thyroid effects - Epidemiology

These laboratory findings of effects on thyroid hormones are supported by the results of an analysis of urinary levels of TCP and thyroid hormones in the U.S. National Health and Nutrition Examination Surveys (NHANES) (Fortenberry et al 2012). An interquartile range increase in urinary TCP was associated with

statistically significant increases in serum T4 of 3.8% in 12-18 year old males, and 3.5% in 18-40 year old males relative to the median T4 levels. It was also associated with decreases in thyroid stimulating hormone of 10.7% among men 18-40 years old, and 20% among men >60 years old, but with increases in the same hormone in women >60 years of age.

Other endocrine effects – Laboratory studies

Gore (2001) showed that vaginal opening and first diestrus both occurred significantly earlier in the offspring of chlorpyrifos-treated vs. control rats (chlorpyrifos was administered in a single dose of 1 mg/kg on gestational day 16). Chlorpyrifos also caused significant increases in gonadotrophin-releasing hormone (GnRH) mRNA levels in adult offspring of treated rats. Pregnant rats received 1 mg/kg chlorpyrifos on gestational day 16.[3]

Chlorpyrifos, at 1 μM, had significant effects on the gene transcription of GnRH neurons, which regulate the reproductive axis, and on levels of GnRH mRNA, in *in vitro* tests. These effects may be mediated by the oestrogen receptors. The effect was biphasic with lower doses stimulating and higher doses inhibiting mRNA levels (Gore 2002).

Slotkin et al (2005) found sex-selective elevated plasma cholesterol and triglycerides in adult rats exposed to 1 mg/kg chlorpyrifos on postnatal days 1-4. The effect was restricted to males, as was postprandial hyperinsulinemia in the face of normal circulating glucose levels.

Both *in utero* and early postnatal exposure of rats to chlorpyrifos resulted in a 50% decrease in the activity of aromatase, the enzyme that catalyses the conversion of androgens to oestrogen (Buratti et al 2011).

Other endocrine effects - Epidemiology

A prospective study of pregnant women in the Rio Negro province of Argentina where OPs, including chlorpyrifos, are used intensively for 6 months of the year, concluded that OP exposure 'very significantly' (by 55%) increased cortisol levels in the first trimester of pregnancy during the spraying period, and that this increase may lead to impaired foetal growth and postnatal development (Cecchi et al 2012).

Summary

Chlorpyrifos is an endocrine disruptor. It is antiandrogenic, oestrogenic, and affects thyroid hormones. It inhibits metabolism of testosterone and oestradiol, and testosterone synthesis. It reduces serum levels of cortisol and thyroid hormone T4, induces alterations in thyroid and adrenal glands and differentially affects levels of thyroid-stimulating hormones in men and women. It causes breast cancer cells to grow and it is a breast cancer risk through its endocrine actions. Chlorpyrifos also causes endocrine disruption in fish, frogs, and mussels (refer section on *Environmental effects*).

Reproductive & developmental effects

The NOAEL and LOAELs for reproductive and developmental toxicity are:

EC (2005):

- Lowest relevant reproductive NOAEL/NOEL = 1 mg/kg, rats; based on decreased body weight and survival of pups at parental toxic doses
- Lowest relevant developmental NOAEL/NOEL = 2.5 mg/kg, rats; based on increased embryo-foetotoxicity (increased post-implantation loss at maternal toxic doses)

Laboratory studies

The California EPA (Cal EPA 2008) reported that there are some studies showing reproductive toxicity at levels of exposure that do not cause excessive maternal toxicity, including resorptions, decreases in foetal weight and long-term effects on brain and behaviour. Additionally, they showed physical abnormalities including small hind and fore limbs, and lack of spinal development amongst litters treated at 0.3 mg/kg/day on gestation day 0-7 (Muto et al 1992).

Farag et al (2003) found chlorpyrifos to be fetotoxic and teratogenic in rats at a maternal dose of 25 mg/kg/day, a dose that also produced some maternal toxicity (depressed body weight and AChE activity). Foetal weight and viability were decreased; foetal death and early resorption were increased; and visceral, skeletal, and external variations also increased. Farag et al (2010) also found a decreased number of live foetuses and increased number of dead foetuses, along with decreased sperm motility and count, when adult male mice were treated with 25 mg/kg/day 4 weeks before mating with untreated females.

A study by Tian et al (2005) indicates that chlorpyrifos is teratogenic and embryotoxic in mice at doses below those that cause maternal toxicity. Pregnant females were given a single intraperitoneal injection (80 mg/kg) of chlorpyrifos on day 10 of gestation and foetuses were evaluated on gestation day 17. No maternal toxicity was observed. There was a significant reduction in the numbers of live foetuses, and increase in resorptions, compared with control

[3] GnRH = gonadotrophin releasing hormone

litters. External and skeletal malformations were observed. Rates of cleft palate increased significantly (5.97%) versus control litters (0.97%). Similarly, the absence of thoracic vertebrae was increased and the number of caudal vertebrae was significantly decreased.

In a study on buffalo ovotoxicity, Nandi et al (2011) found that chlorpyrifos at 0.02 μg/ml reduced oocyte nuclear maturation, and observed a dose-dependent decline in viability and developmental competence of oocytes.

The effect of chlorpyrifos on gonadotrophin-releasing hormone, as reported for rats in the section on *Endocrine disruption*, is likely "to have long-lasting consequences to the fertility of the animal" (Miller et al 2004).

A study of the effects of chlorpyrifos on gene expression in mouse embryonic stem cells found that doses of 100 μM chlorpyrifos and 400 μM of the oxon significantly increased expression of alpha-fetoprotein, a marker gene in the process of stem cell differentiation. These doses were described as only slightly cytotoxic, causing less than 20% reduction in cell viability (Estevan Martínez et al 2011).

Chlorpyrifos and its metabolite chlorpyrifos oxon damage chromatin in human sperm, the oxon more so that the parent compound. Chromatin integrity is essential for proper transmission of paternal genetic information, and hence for sperm fertilising ability (Salazar-Arredondo et al 2008). Late gestational exposure of mice pups to chlorpyrifos at 6 mg/kg, which did not cause systemic toxicity in mothers or inhibit AChE in pups, caused a decrease in body length in male, but not female, pups (Venerosi et al 2009).

Chlorpyrifos, at 5.4 mg/kg, caused necrosis, degeneration, decreasing number of spermatogenic cells in some seminiferous tubules, separating of cells from the basal region of seminiferous tubules, and oedema in interstitial tissue in rat testis tissue (Kalender et al 2012).

When pregnant mice were exposed to sublethal doses of chlorpyrifos (20-80 mg/kg) at day 6 of gestation, the developing embryos had reduced crown-rump length and weight at day 15 (Zubair et al 2010).

A number of animal studies have demonstrated the neurodevelopmental and neurobehavioural teratogenicity of chlorpyrifos. These are discussed further in the following section on the *Nervous system*.

Epidemiology

Sherman (1996) reported 4 cases of birth defects amongst children all exposed *in utero* to the chlorpyrifos formulation Dursban, including defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples, and genitalia. Brain defects were present in the ventricles, corpus callosum, choroid plexus, and septum pellucidum, and genital defects included undescended testes, microphallus, and fused labia. All children had growth retardation, and 3 had hypotonia and profound mental retardation.

Residential chlorpyrifos exposure *in utero*, as measured by levels in umbilical cord blood, was associated with decreased birth weight and birth length in a New York study (Whyatt et al 2004), and significantly poorer mental and motor development at 3 years of age (Rauh et al 2006). This confirmed findings of an earlier study of African-American women, in which high levels of prenatal exposure to chlorpyrifos correlated with reduced birth weight and body length (Perera et al 2003). The PON1 genotype influences the effects of organophosphate exposure on birth outcomes: among pregnant women with measureable levels of chlorpyrifos in their blood, in a New York study, those with lower PON1 levels had children with smaller infant head circumferences at birth. Smaller head size is predictive of subsequent reduced cognitive ability and IQ (Berkowitz et al 2004).

Cal EPA (2008) reported studies showing that exposure to chlorpyrifos has caused DNA damage in sperm, decreased sperm concentration and sperm motility, and decreased testosterone and oestradiol levels in men.

Summary

Teratogenic effects observed in rats include skeletal malformations, small hind and fore limbs, lack of spinal development, absence of thoracic vertebrae and cleft palate; in humans, defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples, and genitalia have been associated with gestational exposure to chlorpyrifos. Neuroteratogenicity has also been found in both animal and human studies. Reproductive effects in animals include decreased foetal weight and viability; increased foetal death and early resorption; decreased sperm motility and count; decline in viability and developmental competence of oocytes. In humans, chlorpyrifos exposure is associated with decreased birth weight and birth length; DNA damage in sperm, and decreased sperm concentration and sperm motility. Additionally, chlorpyrifos has been found in a number of human reproductive tissues including cervical fluid, sperm fluid, cord blood,

meconium, and breast milk (refer sections on *Human exposure, Residues in humans*).

Nervous system – Neurodevelopment and behaviour

Laboratory studies in the early 1990s showed that immature organisms are far more sensitive to the effects of chlorpyrifos, in terms of both acute toxicity and developmental and neurobehavioural effects, than mature animals (Slotkin 2004). Initially, it was assumed that chlorpyrifos' effect on brain development resulted from the same mechanism that underlies general toxicity, i.e. cholinesterase inhibition (Slotkin et al 2006). However, it was subsequently found that chlorpyrifos itself, as well as the oxon metabolite, affect the brain and developing nervous system by other mechanisms and they interfere at numerous sites and points in time, making the pesticide far more toxic than originally thought when cholinesterase inhibition was assumed to be the sole mechanism of concern (Slotkin et al 2006; Flaskos 2012). Recent work by López-Granero et al (2013) on rats indicates that oxidative stress may be another mechanism involved in the deleterious effects of chlorpyrifos on brain cells, causing cognitive and emotional deficits.

Developmental neurotoxicity can result in the death of an embryo, foetus or infant or it can cause severe and permanent neurological defects (Flaskos 2012).

Chlorpyrifos is a potent developmental neurotoxin at low levels of exposure, below those that trigger foetal ChE inhibition. This is demonstrated in numerous laboratory studies and a number of recent epidemiological studies. Exposures *in utero* and in early childhood can lead to behavioural anomalies in adolescence and adulthood. Epidemiological studies have found delayed cognitive and psychomotor development, and reduced IQ.

Chlorpyrifos has a greater adverse effect on neural cell replication and is inherently more toxic to the developing brain than the more acutely toxic organophosphates such as diazinon and parathion (Slotkin et al 2006). It is toxic at doses that are not toxic to adults and tests using adult animals cannot predict the long-term delayed effects of chlorpyrifos in offspring (Colborn 2006).

<u>Laboratory studies: developmental neurotoxicity</u>

A series of studies beginning in the early 1990s showed that foetal and early childhood exposure to low levels of chlorpyrifos (e.g. 1 mg/kg), below the threshold for foetal ChE inhibition (2 mg/kg) (Qiao et al 2002), interfere with the development of the mammalian brain and nervous system, and that these effects may still be apparent in adolescence and adulthood (Qiao et al 2003). These studies showed that it directly targets events specific to the developing brain, disrupting the cellular machinery of most phases of nervous system development, namely neural cell proliferation, differentiation and maturation, the formation and activity of synapses, and the proliferation and differentiation of glia (Whitney et al 1995; Slotkin et al 2006; Flaskos 2012).

Chlorpyrifos inhibits cell membrane function (Barber et al 2001) and is toxic to immature neurons and glia (Monnet-Tschudi et al 2000). Its most critical effects involve interference with the functioning of nuclear transcription factors that control cell fate, including their expression, phosphorylation and ability to bind to their DNA promoter recognition sites (Dam et al 1998; Crumpton et al 2000; Garcia et al 2001; Schuh et al 2002; Slotkin et al 2005).

Initially, chlorpyrifos attacks the neurons that form at the earliest stages of brain and central nervous system development, reducing cell replication and differentiation (by impairing DNA transcription), and reducing neuritic outgrowth including cholinergic projections (Song et al 1998; Dam et al 1999; Das & Barone 1999; Slotkin et al 2001; Qiao et al 2002, 2003; Howard et al 2005). This results in a reduction in neural connections and cell signalling capabilities (Aldridge et al 2003, 2005; Slotkin 2004; Jameson et al 2006). This reduced signalling capacity leads to subsequent deficits in cholinergic synaptic activity and eventually to behavioural anomalies in adolescence and adulthood (Slotkin 1999, 2004; Dam et al 2000; Levin et al 2001; Slotkin et al 2001; Aldridge et al 2004; Slotkin et al 2006). One brief subtoxic dose (1 or 5 mg/kg) can cause behavioural alterations during adolescence and adulthood (Icenogle et al 2004).

Glial cells, which develop later than neurons, are even more susceptible to chlorpyrifos (Qiao et al 2002; Slotkin 2004). Glial cells are critical to normal development, forming a "scaffold" for the migration of cells during tissue construction (Colborn 2006). Other functions include providing nutrition to neurons, formation of the myelin sheath covering nerves, brain homoeostasis, and linking with the immune system (Colborn 2006; Muñoz et al 2010). Chlorpyrifos preferentially targets glial cells (Qiao et al 2002; Garcia et al 2002). Glial cells continue to develop during childhood, so exposures during this period can also cause developmental neurotoxicity (Slotkin 2004). In fact, effects on the rat forebrain, which is rich in cholinergic projections and the development of which peaks *in utero*, are not as severe as effects on the cerebellum which peaks 2 weeks after birth and is non-cholinergic (Campbell et

al 1997; Crumpton et al 2000). This means that the postnatal development period may be even more vulnerable to the effects of chlorpyrifos than the prenatal period (Qiao et al 2002). Neonatal (days 1-4) exposure of rats to chlorpyrifos at levels that cause systemic toxicity (5 mg/kg) also cause severe cell loss in the brainstem in survivors. When exposure occurred at days 11-14, the target shifted to the forebrain and cell loss occurred at levels (1 mg/kg) that did not compromise survival or growth (Campbell et al 1997).

Other studies have demonstrated the diverse effects of chlorpyrifos on the developing brain:

- Doses of 1 mg/kg, below the threshold for inhibiting ChE, caused suppression of fibroblast growth factor *fgf20* in the forebrain and *fgf2* in the brain stem, whilst elevating *fgf4* in the brain stem, in neonatal rats. The *fgfs* play a vital role in neuronal cell differentiation, neurite outgrowth and recovery from neural damage in the striatum and hippocampus (Slotkin et al 2007).
- In cell studies, at concentrations of 0.005-0.1 mM, chlorpyrifos oxon binds to the brain protein tubulin, disrupting tubulin polymerization (which forms microtubles that transport cell components such as mitochondria to nerve axons). Disruption of tubulin has been implicated in neurodegenerative diseases such as Alzheimer's disease (Grigoryan & Lockridge 2009).
- Doses of 1mg/kg fed to pregnant rats on gestational days 17-20 resulted, in the pups, in marked suppression of hemicholinium-3 binding to the presynaptic choline transporter, which is responsive to nerve impulse activity, the difference disappearing at weaning but again becoming apparent in adolescence and adulthood (Qiao et al 2003).
- Subtoxic doses of chlorpyrifos affect the expression of 277 genes in the rat forebrain. Low doses (0.5-5 mg/kg) affected neuroactive ligand-receptor interaction, transmission of nerve impulses, synaptic transmission, regulation of protein metabolism, and DNA-dependent transmission (Stapleton & Chan 2009).
- Finally, US EPA (2011) reports alterations in brain development in offspring of rat mothers exposed at 1mg/kg/day, specifically significant decreases in measurements of the parietal cortex in female offspring at postnatal day 66. The only effect noted in the mothers was plasma and red blood cell AChE inhibition.

As animals mature, damage is evident in a wide variety of brain regions, the most vulnerable being the hippocampus, resulting in behavioural abnormalities (Colborn 2006).

Effect levels in relation to human concentrations

As already stated the effects of chlorpyrifos on the developing brain have been observed at levels of 1 mg/kg, well below the 2 mg/kg (5.7 μM) threshold for effects on AChE. Flaskos (2012), in reviewing the effects of chlorpyrifos oxon on the developing brain, noted that:

- in cell culture studies, the oxon interferes markedly with glial cell differentiation in the concentration range 1-10 μM, impairing the development of extensions by 47% after 24 hr. It also disrupts the microtubule network;
- in cultures of cortical neurons from newborn rats, at concentrations of 20-50 μM, the oxon increased apoptosis (cell death);
- in humans, foetal concentrations of chlorpyrifos commonly reach 8 mg/kg (22.8 μM). The steady state ratio of oxon/chlorpyrifos varies but can be higher than 0.05 in adults. The ratio is expected to be considerably higher in developing organisms, thus levels of the oxon "in the low micromolar range in the developing human can be attainable".

Chlorpyrifos oxon can be 1,000 times more potent than chlorpyrifos in its damage to neurons, and 65% more damaging to glia (Flaskos 2012).

Laboratory studies: effects on behaviour

As well as the effects on the developing brain, listed above, chlorpyrifos also disrupts serotonin, a neurotransmitter that provides essential signals during brain development, and which in turn has been linked to appetite and mood disorders (Aldridge et al 2003, 2004; Garcia et al 2003; Colborn 2006).

Late gestational exposure of mice pups to chlorpyrifos at 6 mg/kg caused significantly less pivoting behaviour and increased immobility (Venerosi et al 2009).

Four-month old female mice that had been exposed prenatally (gestational days 15-18) to 6 mg/kg, and again on postnatal days 11-14 to 1 or 3 mg/kg showed a marked increase in ultrasound vocalisation and increase in frequency but not in duration of social investigation (Venerosi et al 2006).

Repeated post-natal sub-threshold (i.e. with no overt symptoms) exposure to chlorpyrifos can result in persistent cognitive effects in rats, including deficits in learning, memory and sustained attention (Terry et al 2012).

Both acute and chronic postnatal exposure of rats to chlorpyrifos at levels that caused only "negligible acute cholinergic symptoms" resulted in deficits in spatial working memory (Barril et al 2010).

Repeated postnatal (days 4-21) exposure of mice to chlorpyrifos-oxon (0.25 mg/kg) elicited delayed startle response. Other tests carried out, for reflex development, motor coordination, learning and memory in fear conditioning, did not show significant effects. This prompted the authors to conclude that the neurobehavioural consequences of known effects of chlorpyrifos on the developing brain may only be determined by alternative tests, such as those for social interactions, age-dependent effects on learning and memory, or tests designed to assess dopaminergic or noradrenergic function (Cole et al 2012).

Chen et al (2012) found that prenatal exposure of male mice to 5 mg/kg/day induced selective cognitive impairments in adults, with a gradual increase in the lose-shift errors on increased memory loads. There was a weak increase in females. Morphological analysis showed extensive condensed nucleus, enlarged intercellular spaces, and reduced cell count in the CA1 and dentate gyrus sub-regions in the dorsal hippocampus of the males, and the dentate gyrus sub-region of the females.

Exposure of pregnant mice to 3mg/kg/day resulted in visuospatial deficits in adult offspring using performance test in the Morris Maze (Billauer-Haimovitch et al 2009).

Sex-selected effects

To add to the complexity of chlorpyrifos' effects, there are sex-related differences in effects on the brain, and subsequent cognitive function in adolescence and adulthood, with females affected more than males by prenatal exposures and vice versa for postnatal exposures (Slotkin 2004).

Confirming that link, researchers at the University of Wisconsin—Madison found that female mice exposed *in utero* to chlorpyrifos are slow learners, but male mice are not affected (Haviland et al 2010).

Persistent gender-selective behavioural alterations were observed in adolescent and adult rats exposed prenatally to chlorpyrifos at 1 or 5 mg/kg on gestational days 17-20, a peak period of neurogenesis. There was initial hyperactivity in a maze test, and then females but not males showed reduced habituation and memory (Levin et al 2002).

Late gestational exposure of mice pups to chlorpyrifos at 6 mg/kg, which did not cause systemic toxicity in mothers or inhibit AChE in pups, caused a decrease in ultrasonic vocalisation in male but not female pups (Venerosi et al 2009).

Perinatal exposures to ongoing low doses of chlorpyrifos resulted in anxiety in adult female mice (Braquenier et al 2010).

As Venerosi et al (2012) concluded after their review of data on the neurobehavioural effects of developmental exposures to chlorpyrifos, the neurotoxic and endocrine disrupting activities of chlorpyrifos overlap, posing a risk for sex-biased neurodevelopmental disorders in children.

Epidemiology

Epidemiological studies of pregnant mothers exposed to chlorpyrifos through home pesticide use demonstrate a link between *in utero* exposure and low birth weights and/or reduced head circumference of newborns, especially for mothers whose genetic makeup is such that they produce low levels of PON1, the enzyme responsible for detoxifying chlorpyrifos in the body. As stated earlier, reduced head circumference is indicative of subsequent reduced cognitive ability (Whyatt & Barr 2001; Whyatt et al 2004; Berkowitz et al 2004).

Newborn infants in New York, exposed *in utero* to chlorpyrifos from household use, were found to have delayed cognitive and psychomotor development. Those most exposed had significantly more attention problems, attention-deficit/hyperactivity disorder (ADHD) problems, and pervasive developmental disorder problems at 3 years of age (Rauh et al 2006; Gulson 2008). A second study found that these effects were independent of socio-economic factors (Lovasi et al 2011).

"These findings indicate that prenatal exposure to the insecticide chlorpyrifos not only increases the likelihood of developmental delay, but may have long-term consequences for social adjustment and academic achievement" said lead author and investigator on the study [Rauh et al 2006], Virginia Rauh, ScD. "Relatively speaking, the insecticide effects reported here are comparable to what has been seen with exposures to other neurotoxicants such as lead and tobacco smoke." (CCCEH 2006)

In a separate study, Rauh et al (2011) provided evidence that prenatal exposure to chlorpyrifos results in deficits in working memory and IQ scores. As little as 4.6 pg/gm of chlorpyrifos in cord blood during gestation resulted in a drop of 1.4 percent of a 7-year-old child's IQ and 2.8 percent of her/his working memory. Working memory is described as "one of the core

processes of executive function", encompassing ability to memorize new information, hold it in short-term memory, concentrate and manipulate information to produce results. Reduced development of executive functioning has been associated with psychopathology, physical aggression, and lack of school readiness (Horton et al 2012).

A study published in 2012 (Rauh et al 2012), demonstrates that prenatal exposure to chlorpyrifos is altering children's brain structure, the effects being visible at least 11 years after birth. Non-invasive magnetic resonance imaging was used to identify effects of chlorpyrifos exposure as assessed from residues in umbilical cord blood. The authors found significant abnormalities in the cerebral surface, with enlargements there thought to be derived from enlargements in the underlying white matter (glia), at levels of exposure observed with routine non-occupational use and below the threshold for any signs of acute exposure. These abnormalities occurred in regions of the brain associated with attention, receptive language, social cognition, reward, emotion and inhibitory control. They also linked the abnormalities with significant reductions in IQ. Their findings support those from laboratory studies, and previous epidemiological studies linking chlorpyrifos exposure with child cognitive impairment. Higher levels of exposure were associated with a reduction in, or reversal of, the normal sex-related differences in brain development: the right parietal lobe is usually larger in girls than in boys, but in this study, in those with the higher levels of exposure, this was reversed.

This was followed by a study demonstrating the same sex-selectivity observed in laboratory studies on rodents: prenatal exposure to chlorpyrifos (as measured by residues in their cord blood) resulted in a greater decrement in working memory in male than in female children, at 7 years of age (Horton et al 2012).

Other outcomes of developmental exposures

Chlorpyrifos' developmental effects extend beyond those involving neurotoxicity, to involve both heart and liver in ways that can result in the onset of cardiac and metabolic diseases (including diabetes and obesity) long after the end of chlorpyrifos exposure. Again, prenatal exposure to low doses that do not inhibit AChE result in alteration of adult cardiac and liver function. There is a complex dose-response relationship: whereas with acute poisoning a higher dose gives a worse effect, here in some instances effects do not occur at anything but a low dose, and in some cases there were larger alterations at low doses than seen at high doses (Meyer et al 2004).

Summary

US EPA (2011) stated "there is consistency across animal behavior and epidemiology studies such as delays in cognitive achievement, motor control, social behaviour, and intelligence".

Cal EPA (2010) concluded "there is now evidence that chlorpyrifos directly targets events that are specific to the developing brain and that are not related to inhibition of cholinesterase, including: inhibition of DNA synthesis, impairment of cell acquisition and differentiation, interactions with neurotrophic factors, interruption of cell signalling cascades, and alteration in synaptic function… based on cholinesterase inhibitions in dogs and rats and supporting information on cognitive deficiencies in rats".

Cal EPA (2010) concluded that chlorpyrifos:

- affects the developing brain during cell division;
- interferes with RNA synthesis during differentiation;
- interrupts cell signalling;
- interferes with important nuclear transcription factors involved in cell differentiation;
- impairs cholinergic synaptic function during development;
- affects the catecholamine system in the developing brain;
- elicits oxidative stress in the developing brain;
- interferes with gliogenesis and axonogenesis;
- alters levels of neurotrophins in the developing brain; and
- results in behavioural abnormalities.

Together these studies demonstrate that adult models of toxicity do not work for the foetus, and do not predict the vulnerability of the foetus to the effects of chlorpyrifos, and probably other organophosphates (Slotkin 2004; Colborn 2006).

Nervous system - other neurotoxic effects

Laboratory studies

A variety of laboratory studies have demonstrated that adult exposure to chlorpyrifos can cause neurobehavioural changes, reduced cognitive ability, anxiety, and impaired memory and attention, as well as delayed neuropathy.

Adult rats chronically exposed to low levels of

chlorpyrifos (1-5 mg/kg/day) through their diet, with occasional high dose spikes (60, then 45 mg/kg), exhibited neurobehavioural changes and reduced cognitive ability (Moser et al 2005).

Rats injected with chlorpyrifos (1 mg/kg) showed impaired learning months later (Cañadas et al 2005). Adult rats exposed to repeated low doses (1-10 mg/kg) displayed impaired memories, especially in spatial recall, as well as behavioural abnormalities (Yan et al 2012).

High dose acute exposure to chlorpyrifos resulted in elevated anxiety in rats (Sánchez-Amate et al 2001).

Adult rats exposed to repeated doses of chlorpyrifos (18 mg/kg) experienced protracted impairment in sustained attention and increased impulsive behaviour (Middlemore-Risher et al 2010).

Delayed neuropathy in rats was noted at 60-90 mg/kg, which is 4-6 times the LD_{50} (US EPA 2009b).

Epidemiology

Epidemiological studies have shown that both acute and chronic exposures to chlorpyrifos result in a range of long-term neuropsychological effects, including peripheral and central neuropathy, affective disorders, and neurocognitive deficits (Cañadas et al 2005).

Chlorpyrifos, like many other organophosphate compounds, can cause organophosphate induced delayed polyneuropathy (OPIDP). This syndrome is characterised by distal degeneration of axons of both the peripheral and central nervous systems, which may develop after several days or weeks from single or repeated exposure. Weakness, numbness and paresthesia may occur which may be followed by progressive weakness, depression of deep tendon reflexes especially in the lower limbs. In severe cases, quadriplegia with foot and wrist drop and ataxia may develop and the resulting paralysis may be life-threatening (Moretto & Lotti 1998; Lotti & Moretto 2005).

A broader range of neuropathological disorders resulting from organophosphate exposure, which probably overlaps with OPIDP, has been called OPICN or Organophosphate Induced Chronic Neuropathy (Abou-Donia 2003). It has been shown that individuals exposed to a single large toxic dose or to small subclinical doses of organophosphate compounds like chlorpyrifos developed chronic neurotoxicity signs and symptoms that persisted for years after exposure and is distinct from both cholinergic and OPDIP effects. The damaged areas of the Central Nervous System do not regenerate and therefore the signs and symptoms are expected to persist for a long time.

A study which evaluated the neurobehavioral effects of chronic low-level exposure to chlorpyrifos in 22 patients is illustrative of OPICN (Kilburn 1999, cited by Abou-Donia 2003). Kilburn demonstrated an association between chlorpyrifos sprayed inside homes and offices and neurophysiological impairments in balance, visual fields, colour discrimination, hearing reaction time, and grip strength in 22 patients. These patients also had psychological impairment of verbal recall and cognitive function, and two-thirds of them had been prescribed antidepressant drugs. In addition, the patients exhibited severe respiratory symptoms, accompanied by airway obstruction.

People that have been exposed to acute or chronic levels of OP compounds exhibit long-term alterations in neuropsychological performance that mainly affect cognitive processes, such as speed of processing, visual attention, visuoperceptual abilities, memory impairment and problem solving (Moreno et al 2008).

A number of chlorpyrifos-induced chronic neurotoxicity incidents in humans have been reported, for example:

- A 15-year-old female in Sri Lanka, who recovered completely, initially, from ingestion of a large dose of chlorpyrifos, later developed delayed myelopathy and pure motor neuropathy. At 7 weeks, she developed urinary incontinence, followed by progressive spasticity and thoracic cord atrophy (Thivakaran et al 2012).
- A 3 year-old child who accidentally ingested chlorpyrifos suffered life-threatening OPIDP with transient bilateral vocal cord paralysis; recovery was slow (Aiuto et al 1993).
- Permanent paralysis has been reported at sites of dermal exposure to chlorpyrifos (hands) (Meggs 2003).
- Paudyal (2008) reports the development of intermediate syndrome and delayed polyneuropathy following acute poisoning with OPs including chlorpyrifos in Nepal.
- Steenland et al (1994) reported a significant loss of peripheral nerve conduction velocity consistent with delayed-onset neuropathy following poisoning by chlorpyrifos.
- In one attempted suicide case, a 42-year-old year man developed weakness and paresthesia, gait impairment, and loss of tendon reflexes in the legs. The symptoms

appeared 43 days after the poisoning and were unchanged 3 months later (Moretto & Lotti 1998).

- Miranda et al (2002) reported a persistent reduction in grip and pinch strength among patients severely poisoned with chlorpyrifos.
- Exposure to chlorpyrifos was associated with impaired peripheral nervous system function, in a study of pesticide applicators in the US (Starks et al 2012).
- A study of 65 recently exposed chlorpyrifos applicators for termite control found an average level of the metabolite TCP in urine of 629.5 µg/L compared with the general US population level of 4.5 µg/L. The applicators did not perform as well as controls on some neurological tests, and they reported memory problems, emotional states, fatigue and loss of muscle strength (Steenland et al 2000).
- In 1993, Kaplan et al reported 8 cases in the US that developed peripheral neuropathy after exposure to chlorpyrifos in the formulation Dursban, applied by an exterminator; 5 of them also experienced memory loss and cognitive slowing.
- An epidemiological study found an association between exposure to chlorpyrifos and a two-fold increased risk of suicide and non-motor vehicle accidents (Lee et al 2007b). This is supported by findings in animal studies that chlorpyrifos affects changes in the serotonergic system in the brain (Aldridge et al 2005; Moreno et al 2008) and elicits corresponding changes in emotional behaviours (Chen et al 2011). Deficiencies in the serotonergic system are associated with depression, anxiety, and post-traumatic stress disorder (Chen et al 2011). Exposure to organophosphates in general is associated with increased risk of suicide (London et al 2012).
- Rajasekaran et al (2009) reported a case of a 25 year-old male who developed Guillain-Barre syndrome after chlorpyrifos exposure.

Ziem & McTamney (1997) reported that exposure to chlorpyrifos has been associated with, and suspected of causing the onset of, multiple chemical sensitivity with chronic illness.

Other studies have associated OPs in general with a range of neuropsychological effects, including:

- 2 cases in South Africa developed choreiform dyskinesias (a type of involuntary movement), with one experiencing severe depression and emotional lability (Joubert & Joubert 1988).
- In 1997, Jamal referred to evidence of chronic psychiatric effects of OPs from case studies.
- Commercial sprayers exposed to OPs showed elevated levels of anxiety (Levin et al 1976).

Nervous system - neurodegenerative diseases

Exposure to OPs, including chlorpyrifos, results in oxidative stress, one of the factors implicated in neurodegenerative diseases such as Parkinson's and Alzheimer's.

Laboratory studies

Animal and cell studies that have shown chlorpyrifos induces Parkinson's disease-associated changes in the dopaminergic nigrostriatal pathway in the brain:

- Xu et al (2012) showed chlorpyrifos causes inhibition of gene and protein expression of monoamine oxidase *in vitro*, with decreased PC12 cell viability and increased dopamine concentrations.
- Torres-Altoro et al (2011) showed that chlorpyrifos dysregulates dopamine signalling and glutamate neurotransmission, and induces neuronal injury in the striatum of mouse brain *in vitro*.
- Lee et al (2012) found that chlorpyrifos causes damage to the dopaminergic neurons via oxidative stress effects on mitochondria.
- Montes de Oca et al (2013) showed that acute exposure to 250 mg/kg caused increased levels of dopamine metabolism in the hippocampus and decreased gamma-aminobutyric acid (GABA) and glutamate in the striatum of the brain, measured 7 months after exposure, as well as displaying long-term compulsive behaviour.

Epidemiology

Few epidemiological studies have been carried out to explore this association, but several have shown increased risk of Parkinson's (Dhillon et al 2008) and Alzheimer's diseases (Hayden et al 2010) after exposure to OPs. Additionally studies with mice have shown an increase in levels of amyloid ß in the brains of mice 8 months after acute exposure to chlorpyrifos. Deposits of amyloid ß, together with reduced synthesis of acetylcholine are associated with Alzheimer's disease (Salazar et al 2011).

Dhillon et al (2008) found a two-fold increase in risk (OR = 2.0) of Parkinson's disease amongst users of chlorpyrifos in a case-control study in Texas. An investigation of Parkinson's disease associated with contaminated well water in California, USA, found an increased risk (OR = 1.87) with high levels of chlorpyrifos contamination (Gatto et al 2009).

Manthripragada et al (2010) found increased risk of Parkinson's disease when exposed to chlorpyrifos (OR = 1.56, increasing to 2.61 for those carrying the PON1-55 genetic variation). A further study found that the association between chlorpyrifos and Parkinson's was strengthened, on average, 260% in people with the PON1 55MM variant genotype (Manthripragada et al 2010).

Immune system

US EPA (2009b) states that there is now a new data requirement for immunotoxicity, supported by reports in open literature of immunologic abnormalities in workers (Thrasher et al 1993; Gotoh et al 2001) and laboratory rats (Blakely et al 1999; Navarro et al 2001). US EPA also draws attention to the review by Galloway & Handy (2003) of the immunotoxicity of organophosphates in general.

Laboratory studies

A study published in 2001 demonstrated that development exposure to chlorpyrifos results in long-term deficits in immune competence. Exposure of neonatal rats to 1 mg/kg on postnatal days 1-4 had no immediate effect on T-cell mitogenic responses to concanavalin A challenge.[4] However, once the animals reached adulthood, T-cell responses were significantly impaired. There were no deficits in basal T-cell replication rates, implying that the adverse effect of chlorpyrifos exposure was specific to mitogenic activation. Treatment during a later neonatal period (days 11-14) elicited similar deficits in adulthood (Navarro et al 2001).

In an earlier study, a commercial formulation of chlorpyrifos induced immune alterations in rats associated with lymphocyte subpopulations, demonstrated by the presence of normal antibody and phagocytic responses in association with reduced T-lymphocyte blastogenesis and enhanced expression of specific cell surface antigens (Blakely et al 1999).

A study by Rowsey & Gordon (1999) indicated that hypothermia and fever resulting from exposure to chlorpyrifos in rats is mediated by an endogenously produced cytokine, tumour necrosis factor.

In investigating the mechanisms of immunotoxicity of chlorpyrifos, Prakash et al (2009) found that it can induce apoptosis (programmed cell death) in murine thymocytes, possibly mediated through generation of reactive oxygen species.

Li et al (2009) found chlorpyrifos, at very low doses (0-100 ppm), induced apoptosis in human Jurkat T cells in a dose- and time-dependent manner. Doses of 50 and 100 ppm also caused DNA fragmentation.

Epidemiology

An analysis of periodic medical examinations of 64 termite control operators using chlorpyrifos revealed abnormal white blood cells, as well as severely depressed serum butyl cholinesterase activity, depressed erythrocyte AChE, and abnormal blood urine nitrogen (Gotoh et al 2001).

A study of 12 people exposed to chlorpyrifos found a high rate of atopy and antibiotic sensitivities, elevated CD26 cells (T cell activation antigen, a key modulator of immune response), and a higher rate of autoimmunity, compared with two control groups.

Autoantibodies were directed toward smooth muscle, parietal cell, brush border, thyroid gland, myelin, and antinuclear antibodies (Thrasher et al 1993). In a further study of 29 people chronically exposed to chlorpyrifos, Thrasher et al (2002) again found elevated CD26 cells and increased frequency of autoantibodies, together with decreased CD5 phenotype, and decreased mitogenesis in response to phytohemagglutinin and concanavalin.

Summary

There is evidence from both laboratory and epidemiology studies of immune toxicity, including effects on lymphocytes, thymocytes, T cells, tumour necrosis factor, and autoimmunity.

Respiratory effects

A cross-sectional study of indigenous women in Costa Rica exposed to pesticides on plantain plantations found a strong association between exposure to chlorpyrifos and respiratory wheeze (OR = 6.7) (Fieten et al 2009).

2.6 Toxic interactions

Chlorpyrifos interacts with a number of other pesticides to increase toxic effects (Hernández et al 2012):

- A mixture of 5 OPs (chlorpyrifos, diazinon, dimethoate, acephate and malathion) produces greater than additive effects in laboratory animals, showing a clear pattern of synergism.
- Co-exposure to chlorpyrifos and alpha-cypermethrin increases the tissue concentration of cypermethrin.
- Chlorpyrifos oxon strongly inhibits the breakdown of permethrin by hydrolysis.
- Chlorpyrifos increases sensitivity to the toxic effects of carbaryl.

[4] Concanavalin is a lectin (carbohydrate-binding protein) originally extracted from the jack bean, *Canavalia ensiformis*, and known to induce mitosis.

2.7 People at heightened risk

Newborn children can be 65-164 times more vulnerable than adults to the OPs chlorpyrifos, diazinon, and parathion (Furlong et al 2006). This is because the PON1 enzyme responsible for detoxifying chlorpyrifos is present at very low levels in children under the age of 2 (Furlong et al 2005), 3-to-4 fold lower than those of their mothers (Holland et al 2006).

Activity of PON1 increases up until the age of 7, so it is not until this age that children have the same ability as adults to detoxify OPs. PON1 levels are even lower in the unborn foetus (Huen et al 2009).

There is also a huge variation in the levels of PON1 between people because of genetic polymorphisms and, as a result, the range for chlorpyrifos sensitivity can be as much as 14-fold among mothers and as much as 26-fold among newborns (Furlong et al 2006).

Studies using human liver microsomes showed a variation of up to 57-fold in the metabolism of chlorpyrifos to chlorpyrifos oxon (Croom et al 2010).

US EPA (2011) states that pregnant women may be more sensitive to chlorpyrifos than non-pregnant people, because of a reduced capacity of the detoxifying enzymes (e.g. PON1, CYP450) – pregnant rats are 2 to12 fold more sensitive than non-pregnant female rats for ChE inhibition.

Yet, the US EPA applies only a 10-fold uncertainty factor for interspecies variation (US EPA 2011).

3 Human Exposure

3.1 Exposure guidelines

- Acceptable Daily Intake (ADI) = 0.01 mg/kg/day (EC 2005)
- Acute Reference Dose (ARfD) = 0.1 mg/kg/day (EC 2005)
- Child specific RfD = 0.0001 mg/kg/day (Cal EPA 2010)
- Acceptable Operator Exposure Level (AOEL) (US) = 0.0015 mg/kg/day (Fenske et al 2012)
- AOEL systemic = 0.01 mg/kg/day (IUPAC 2012)
- Acute dietary RfD = 0.0036 mg/kg/day (US EPA 2011)
- Chronic dietary RfD = 0.0003 mg/kg/day (US EPA 2011)

Chlorpyrifos oxon:

- Acute dietary RfD = 0.0005 mg/kg/day (US EPA 2011)
- Chronic dietary RfD = 0.00011 mg/kg/day (US EPA 2011)

Chlorpyrifos-methyl:

- ADI = 0-0.01 mg/kg/day (JMPR 2013)

The California EPA established a child-specific reference dose (chRfD) of 0.0001 mg/kg/day on the grounds that "there is now evidence that chlorpyrifos directly targets events that are specific to the developing brain and that are not related to inhibition of cholinesterase, including: inhibition of DNA synthesis, impairment of cell acquisition and differentiation, interactions with neurotrophic factors, interruption of cell signalling cascades, and alteration in synaptic function … based on both cholinesterase inhibitions in dogs and rats and supporting information on cognitive deficiencies in rats" (Cal EPA 2010).

3.2 Occupational exposure

Chlorpyrifos has high potential for adverse effects in occupational applications, especially in developing countries (Phung et al 2012).

Using epidemiological data and a variety of probabilistic risk assessment techniques, Phung et al (2013) concluded that single-event spraying of chlorpyrifos in Vietnam is likely to have adverse effects on Vietnamese rice farmers, with 29-33% affected.

Measurements of chlorpyrifos levels in ambient air breathed by farmers in Tambon Bang Rieng, Thailand, found that farmers were inhaling concentrations up to 0.61 mg/m^3, more than twice the ADI for all routes of exposure (Jirachaiyabhas et al 2004).

In Vietnam, exposure levels for farmers using chlorpyrifos on rice, measured post application, ranged from 0.35 to 94 μg/kg/day, exceeding "most of the acute guidelines", and were significantly higher than in a similar study in Sri Lanka, (highest level there was 8.4 μg/kg/day). Urinary TCP levels ranged from 0.7-14.7 μg/g creatinine, with the highest levels reached 25 hrs after application (Phung et al 2012).

However, much higher levels of exposure have been recorded amongst pesticide applicators in Egyptian cotton fields using backpack mistblowers: TCP levels measured during the 1-2 week period of application were up to

6,437 µg/g creatinine in applicators, 184 µg/g in technicians, and 157 µg/g in engineers, the latter 2 categories supervising the applications. Adverse effects on red blood cell AChE activity were recorded at TCP levels above 3,161 µg/g, and on plasma butyrylcholinesterase above 114 µg/g. These applicators had previously been shown to suffer a range of neurobehavioural deficits (Farahat et al 2010, 2011). A subsequent study found lower levels of TCP in applicators urine (mean 719 µg/g) (Crane et al 2013). In Egypt, most of the pesticide applicators used, by the Ministry of Agriculture, in the cotton fields are adolescents (12-21 years) (Crane et al 2013).

Dermal exposure, as applicators and technicians walked through the cotton, is the main source of exposure. Fenske et al (2012) determined that 94-96% of internal doses in these workers comes from dermal exposure, and that all workers exceeded the US AOEL of 1.5 µg/kg/day.

Both adults and children, from the age of 10, work in the banana and plantain plantations in Costa Rica, placing chlorpyrifos-treated blue plastic bags around bunches of plantain. Middlemen reportedly put considerable pressure on producers to use these bags. Many of them end up in the villages and streams when it rains (Barraza et al 2011). Elevated levels of chlorpyrifos metabolites have been found in the urine of both adults and children involved in banana plantation work and small-scale farming in Nicaragua (Rodríquez et al 2006).

Protective clothing

US EPA (2009a) stated that, even when all feasible PPE or engineering controls are used, there are still occupational exposures of concern. There were concerns about mixing/loading liquids, mixing wettable powder, aerial application, backpack sprayers, high-pressure wands, hand-held sprayers or dusters, and re-entry intervals especially for activities such as pruning, transplanting and burlap/balling (US EPA 2009b).

Many farmers in developing countries do not use PPE, let alone the engineering controls referred to above for the USA. Few workers in the Egyptian cotton fields report using PPE (Lein et al 2012), none of them wearing respiratory, eye, face or hand protection (Fenske et al 2012). In a study of chlorpyrifos exposure in Vietnamese rice fields, no applicators used gloves, most wearing only normal long-sleeve shirt and pants, hat and mask, with the proportion of body surface exposed being 63.5-84.8% (Phung et al 2012).

3.3 Non-occupational exposure

Non-occupational exposure to chlorpyrifos is widespread in many countries, particularly amongst rural populations, or where it is used for household pest control. People are exposed by contact with treated surfaces, ingestion or inhalation of contaminated dust, breathing air in treated buildings or near treated fields or orchards where it has been applied, contact with flea collars on pets, and eating food containing residues of chlorpyrifos.

Children's exposure to chlorpyrifos is of the greatest concern, because of their greater sensitivity to it, and because of its developmental effects. It has been found in umbilical cord blood, the meconium of newborns, breast milk, and children's urine, indicating considerable prenatal and neonatal exposure (refer section *Residues in humans* for details). It has been found in indoor air samplers of pregnant mothers in urban USA, rural house and vehicle dust, on the hands of toddlers, and in rural air monitoring.

Indoor air, dust and surfaces

Chlorpyrifos was phased out from household use in the USA in 2001. Prior to, and around the time of phase-out, its presence as residues in dust, floor wipes, and air in houses, childcare facilities and schools was almost ubiquitous (US EPA 2013b). It continues to persist in many homes. For example in 2011, residues were found in 40% of indoor air samples taken in Boston, USA, at an average concentration of 0.33 ng/m^3 (Lu et al 2013). Although these levels and the rate of detection are lower than in previous studies, the authors noted that all recent studies continued to measure chlorpyrifos in the indoor environment and proposed that a lack of significant degradation pathways in the indoor environment contributes to its persistence there. This proposal is supported by the findings published in 1994 that chlorpyrifos was still present in the air in houses, measured at levels of 0.1-0.7 µg/m^3 8 years after its application for termite control (Wright et al 1994). Semi-volatile pesticides such as chlorpyrifos have long persistence on rugs, furniture, soft toys, pillows and other absorbent surfaces particularly in closed apartments (Landrigan et al 1999).

Another study in the US also found that chlorpyrifos was one of the most frequently detected pesticide contaminants in house dust, with frequency of detection in rural homes being 57% (at up to 200 ng/gm) and in urban homes 39% (at up to 56 ng/g) (Quirós-Alcalá et al 2012).

In an earlier study, carried out in North Carolina, USA in 2000-2001, the metabolite TCP was detected in 100% of indoor floor dust (max 391 ng/m^3) and air (max 29.4 ng/m^3) in homes and day care centres, 97% of solid food and 95% of indoor air samples (Morgan et al 2005).

Residues (0.1-0.63 mg/kg dust) have recently been found in house dust in Germany, where it is one of the most commonly found residues, along with the POPs lindane and DDT, potential POPs methoxychlor and propoxur, and permethrin and piperonyl butoxide (Ertl & Butte 2012).

During 2001-2004, nearly 100% of indoor air samplers in the homes of pregnant women in New York contained chlorpyrifos (Whyatt et al 2007).

Levels of chlorpyrifos in the air following indoor household use in the US were significantly higher in the infant breathing zone than in the adult sitting zone (Fenske et al 1990).

Chlorpyrifos has been found in the air, but not dust, in daycare centres, kindergarten classrooms and homes in South Korea (Kim et al 2013).

Pets

Family pets can be another source of exposure: one study found up to 7,000 μg of chlorpyrifos on hair collected 4 hours after a dog had been treated with a commercial flea product, with 26.63 μg measured 3 weeks after treatment (Boone et al 2001).

Rural ambient exposures

Recently, the US EPA (2013a) released a preliminary assessment of the volatilisation of chlorpyrifos and chlorpyrifos oxon from sprayed crops. It concluded that there is a risk to bystanders from the vapour emitted from some crops sprayed with chlorpyrifos. The National Pesticide Information Center recorded 10 cases of poisoning resulting from spray drift from 2002 to 2010. The California Pesticide Illness Surveillance Program reported 61 incidents involving spray drift or volatilisation from 2002 to 2009 (US EPA 2013a).

Air monitoring in the US in 1996 identified a maximum 6-hour air concentration of 28 μg/m^3 at 57 feet from the edge of a chlorpyrifos-sprayed field (US EPA 2013a)

Chlorpyrifos has also been detected in the house dust of 100% of applicator houses that were tested in the US (Fenske et al 2002), and in up to 90% of dust samples in farmworker houses (Bradman et al 2007). Chlorpyrifos was also found in farmworker vehicles (Curl et al 2002), and in the urine of farmworkers' children (Curwin et al 2007).

Another, more recent, study of US farmworker children found chlorpyrifos in 100% of household air and dust samples even though it was not used in the homes, and calculated that non-dietary ingestion was the main route of exposure for these children (Beamer et al 2012).

Soil from outdoor play areas in homes in an agricultural area of Washington State, USA, contained residues of chlorpyrifos and other pesticides (Simcox et al 1995).

Ambient community (i.e. away from the fields) air monitoring data from agricultural regions of California showed that short-term chlorpyrifos exposure estimates exceeded the 'acute reference dose' ARfD for 50% of children; and non-cancer risks were higher for children than adults (Lee et al 2002).

A recent study in Australia found that there was widespread chronic exposure of preschool children to OP and pyrethroid insecticides and that, although most exposures were higher in the rural area, urban children's exposure to chlorpyrifos (and bifenthrin) was just as great, probably because they are used widely in the domestic setting, as well as in agriculture (Babina et al 2012).

In the Egyptian cotton fields referred to earlier, elevated levels of urinary TCP were found in residents from the same villagers as the applicators, although at lower levels (Crane et al 2013). The mean level was 44.9 μg/g, extremely high compared with the mean level of 2.09 μg/g in the general USA adolescent population (Crane et al 2013).

Children living near banana and plantain plantations in Costa Rica have elevated levels of urinary TCP, double that of children from other areas, and for many at levels exceeding both (US) acute and chronic reference doses (van Wendel de Joode et al 2012).

An assessment of risks from chlorpyrifos applied to citrus trees in Spain with airblast sprayers concluded there is a significant risk to bystanders from spray drift, and that risk is magnified 3-fold for children (Cunha et al 2012).

Food residues

Children's exposure continues with their food: when urban children in a US study changed to organic fruit and vegetables, their urinary levels of chlorpyrifos metabolites fell to undetectable

almost immediately (Lu et al 2006, 2008), indicating that their previous exposure was solely dietary. In Chiang Mai province in Thailand, residues of chlorpyrifos in the urine of schoolchildren were surmised by the authors of the study to have come from dietary exposure (Panuwet et al 2009).

A study of 129 preschool children in the US, which found TCP in 100% of the indoor floor dust and hard surface wipes of their homes and daycare centres, also found it in 97% of their solid food, and 95% of indoor air samples. Levels up to 104 ng/ml were found in preschool children's urine, and dietary intake was considered to be the main source for this (Morgan et al 2005).

An analysis of food intake and residue studies in the USA, showed that preschoolers are significantly more exposed to chlorpyrifos through residues in food than are parents, with a mean daily intake of 7.45 x 10^{-5} mg/kg/day (more than 3 times that of adults). The main contributors to this intake were grapes, apples, peaches, dairy, and tomatoes (in descending order). Dairy residues were thought to have originated from grazing fields after chlorpyrifos application, or in feed given to cows (Vogt et al 2012). Use of chlorpyrifos-impregnated ear tags to control parasites on cattle also results in residues of the insecticides in fat, muscle and organ tissue (Byford et al 1986).

In the US, chlorpyrifos has also been found in orange juice and a composite cherry/nectarine/apple juice (Riederer & Lu 2012), cranberries (Putnam et al 2003), peaches, nectarines, kale greens, collard greens, broccoli, corn, summer squash, almonds (NPIC 2009).

In a study on persistence in a cranberry bog, Putnam et al (2003) found that, although the half-life of chlorpyrifos was found to be 3.5 days in cranberries, residues were still detectable at harvest, 62 days after the chlorpyrifos application.

Chlorpyrifos has been found to be persistent in cotton gin trash, with a half-life of 133 days, hence trash from cotton plants treated with chlorpyrifos may result in residues in cattle (Crossan & Kennedy 2008).

Australian children have a much higher intake of chlorpyrifos, the most frequently found OP residue, than children in USA or Japan: the Australian estimated dietary intake for 2-5 years-olds is 0.6 μg/kg/day, compared with children aged 3-6 in Japan (0.007 μg/kg/day) and in the US (age not given) of 0.03 μg/kg/day (Babina et al 2012).

A survey of schoolchildren in Chile found that 80% of them had metabolites of chlorpyrifos in their urine; and this was associated with eating fruits and vegetables, prompting the authors of the study to suggest "the need for a review of policies to regulate the sale and application of chlorpyrifos in Chile" (Muñoz-Quezada et al 2012). Chlorpyrifos was detected in 50% of samples of fruit and vegetables collected in December 2010.

Potatoes can take up chlorpyrifos from the soil and remain in the harvested crop, and still be largely present after cooking. Boiling reduced residues by only 14%; storage for 17 days at 20°C reduced residues by 50% (Juraske et al 2011).

Residues have been found in a wide variety of foods in many different countries, including fruit, vegetables, grains, fish and processed foods:

- Pakistan: cottonseed, apples, citrus fruit (Tariq et al 2007); imported wheat (Riazuddin et al 2011); apple gourd, bitter gourd, cauliflower, chilli, eggplant, peas, spinach, and tomato with many residues exceeding the MRL, and up to 0.96 mg/kg found in bitter gourd, prompting Latif et al (2011) to identify "an urgent need to control the use of some excessively applied and potentially persistent pesticides, such as….chlorpyrifos" (Latif et al 2011).
- India: beans, brinjal, cabbage, carrots, cauliflower, chilli, ladyfinger, leeks, mustard, okra, and tomato, at up to 0.179 mg/kg mean concentration in the latter (Mukherjee 2003; Sinha et al 2012; Ananda Gowda & Somashekar 2012); also in 'made' tea at 0.43 mg/kg and fresh tea leaves at 0.73 mg/kg (Bishnu et al 2009);
- China: at high levels in rice (mean = 0.174 mg/kg, and in fish (mean = 0.021 mg/kg) (Wang et al 2012c); vegetables such as Shanghai greens (94% of samples), Chinese cabbage (85%), carrot (64%), and spinach (Wang et al 2008); according to a media report residues have been found on peanuts imported into Australia from China (Kretowicz 2012);
- Thailand: one media item reports levels of 0.84 mg/kg in parsley (Sarnsamak 2012);
- Columbia: tomatoes (Uribe et al 2012);
- Mexico: maize, chickpeas and wheat (Aldana-Madrid et al 2008);
- Brazil: apples, beans, carrots, oranges, peaches, pears, potatoes, strawberries, and tomatoes (Gebara et al 2011);
- Nigeria: maize (0.062 mg/kg) (Ogah & Coker 2012);
- Turkey: in grapefruit (0.04 mg/kg); lemon (0.005 mg/kg) (Sungur & Tunur 2012);
- Serbia: potatoes and onions, at 1.18 mg/kg in the latter, which is 20 times the MRL (Marković et

al 2010);

- Egypt: fish from the River Nile tributaries (at 9.38 μg/kg) (Malhat & Nasr 2011).
- Ghana: tomato, eggplant and pepper (Botwe et al 2012); and papaya, watermelon, banana, mango, pear, pineapple, lettuce, cabbage, carrot, and onion (Bempah et al 2012); waakye (rice and beans) and fufu (cassava and plantain dough) (Amuzu 2012);
- Tanzania: spinach (0.02 μg/kg) and rice (0.02 μg/kg) (Ndengerio-Ndossi & Cram 2005);
- New Zealand: apples, apricots, bananas, feijoas, grapes, kiwifruit, lemons, mandarins, oranges, peaches; bok choi, silver beet, spinach, spring onions, tomatoes; bran cereal, bread, hamburgers, jam, meat pies, muesli, olive oil, pasta, pizza, raisins, rice, sausages, and snack bars (MPI 2012a,b);
- EU: in one report from the European Union, it was one of the most commonly found residues, including in beans, carrots, cucumbers, mandarins, oranges, pears, potatoes, rice, and spinach, up to 3.7 mg/kg in potatoes (EFSA 2010);
- France: the most frequently detected pesticides included chlorpyrifos particularly in peaches, pears, apples, and grapes; and chlorpyrifos-methyl, particularly in wheat-based products (Nougadère et al 2012).

Drinking water

Residues of chlorpyrifos and chlorpyrifos oxon in drinking water are of concern. The US EPA (2011) estimates that chlorpyrifos used at an average typical application rate on sugar beet may result in infants aged <1 yr old consuming residues of chlorpyrifos (in drinking water) at 3.4 times higher than the acceptable level (the 'Acute Population Adjusted Dose'), and that maximum application rates on grapes would result in an estimated 27 times higher level than the acceptable, in the same infants.

A review of water monitoring in Australia reported chlorpyrifos in the state of Victoria's domestic water supplies, with residues having been found in the Mitchell River, Gippsland surface waters, Goulburn Murray Water, Katamatite water supply channel (at 0.089 μg/L), and Yarra River (0.04 μg/L) (Amis 2008, 2012).

It has been detected in drinking water reservoirs in Canada's Northern Great Plains, at 0.020 μg/L (Donald et al 2007). In India, chlorpyrifos has been found at levels of 4.8 μg/L in soft drinks, 47 times higher than the permissible limit recommend by the Bureau of Indian Standards (Ali et al 2008).

Chlorpyrifos has also been found in soft drinks: in India, it was found (along with a number of other pesticides) in 100% of samples of drinks such as Pepsi, Coca-Cola, Fanta, Sprite, Mountain Dew and 7 other bottled drinks all made by two American companies. The maximum concentration found was 7.2 μg/L, 72 times higher than the EU limit of 0.1 μg/L for water.[5] The average concentration was 42 times higher than the EU limit (Mathur et al 2003). A parliamentary investigation corroborated the findings, causing the parliament to ban its cafeterias from serving Pepsi and Coke and the defence ministry issued a circular ordering its clubs to stop selling the drinks (Singh 2004). A repeat analysis published in 2006 again found chlorpyrifos in 100% of samples, this time with a maximum concentration of 20.43 μg/L in Coca-Cola, and an average of 4.71 μg/L (Johnson et al 2006).

Other exposures

In South Africa, poverty drives many youths, even as young as 12-14 years of age, to sell pesticides illegally on the streets, at rail stations and even door-to-door. Chlorpyrifos, and other highly hazardous pesticides, are decanted into drink and medicine bottles and sold unlabelled for unregistered, mainly domestic, uses. The youths are at risk from spillage and contamination. Children also purchase these pesticides for parents and use them at home. This problem has also been documented in Zimbabwe, Tanzania, Mozambique, United States, Brazil, the Dominican Republic and Israel, although it is not stated whether chlorpyrifos is involved in all these countries (Rother 2010).

4 Body burdens and poisonings

4.1 Residues in humans

Biomonitoring in the US showed that 94% of residents had chlorpyrifos in their bodies in 1999-2000. Children aged 6-11 years had almost twice the levels of adults. Chronic exposure levels were 4.6 times higher than the 'acceptable' level for children, and 3 times for youth aged 12-19 years (Schafer et al 2004). A chlorpyrifos metabolite was found in the urine of over 80% of adults and 90% of children from representative population samples (Schettler et al 2000).

One study in Minnesota, USA, found that over a 5-day period metabolites of chlorpyrifos were detected in the urine of 98% of the urban children tested (Adgate et al 2001).

[5] EU limit = 0.1 μg/L for individual pesticides; 0.50 for total pesticides (COUNCIL DIRECTIVE 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Official Journal of the European Communities L330/32. http://eur-lex.europa eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF).

Chlorpyrifos is capable of crossing the placenta so foetal exposure occurs following the exposure of pregnant women. Chlorpyrifos has been found in the blood of pregnant women in South Africa (Naik 2012). One US study found chlorpyrifos in 63% of cord blood samples (Barr et al 2010). In another US study, it was found in 70.5% of samples of maternal blood and 87.5% of cord blood, the difference thought to be because of mothers' greater levels of the detoxifying enzyme PON1 (Huen et al 2012).

It has also been found in the meconium (first faeces) of newborn infants in the Philippines (Ostrea et al 2006) and USA (Whyatt et al 2009).

Exposure then continues with the newborn's first feed: chlorpyrifos has been found in breast milk in India and USA.

In Bhopal, India, chlorpyrifos was found at levels of 85-355 μg/L, which resulted in infant intake of 41 μg/kg per day, 41 times higher than the level recommended by the WHO (Sanghi et al 2003).

Casey (2005) found chlorpyrifos in samples of breast milk from 25 of 26 lactating women in the USA, with milk concentrations (0.32 to 2.29 μg/L) significantly higher than plasma or saliva concentrations. This is because chlorpyrifos' high lipid solubility coefficient of 4.7-5.3 renders it capable of concentrating in milk fat.

A recent breast milk biomonitoring programme in the US reported median concentrations of 0.024 μg/kg and 0.028 μg/kg of milk for urban and agricultural women respectively in California; and 0.004 μg/kg of chlorpyrifos-methyl in urban women. The detection frequency was 100% for chlorpyrifos, and 67% for chlorpyrifos-methyl in urban women (Weldon et al 2011). In other studies, chlorpyrifos has been detected in breast milk at 0.436 μg/kg (Cal EPA 2008).

It has also been detected in cervical fluid (6.83 μg/kg), sperm fluid (0.50 μg/kg) (Cal EPA 2008), and maternal and infant hair (Ostrea et al 2009).

Residues in humans have been measured in a number of countries including China (cord blood - Wickerham et al 2012), the Philippines (maternal, foetal and infant samples - Ostrea 2002, 2009), Malaysia (schoolchildren - Mathur et al 2005), India (villagers, 85% of samples, up to 0.497 mg/L whole blood - Mathur et al 2005), US (maternal and cord blood, meconium - Whyatt et al 2009; Huen et al 2012).

4.2 Occupational poisonings

In a study of acute pesticide poisonings from 1995 to 2006 amongst working children in Nicaragua, aged 5 to 14 years, 47% were caused by organophosphates, mainly methamidophos and chlorpyrifos (Corriols & Aragón 2010).

Chlorpyrifos has been involved in acute poisonings in cashew nut peeling sheds in Kerala, India. Between February 2000 and January 2003, there were at least 10 such incidents involving the pesticides chlorpyrifos, malathion or methyl parathion, with in one case 227 women hospitalised (Thanal 2003).

An epidemiological study of pesticide applicators in the US found that there was a two-fold increased risk of accidents (non-motor vehicle) and suicide amongst users of chlorpyrifos, possibly reflecting a link between exposure and depression (Lee et al 2007b).

From Jan 2002 to Feb 2011, there were 141 poisoning incidents with chlorpyrifos recorded in the US, although some of these may have been from non-agricultural use. Of these, 37% reported respiratory problems. There was one fatality, described as follows: "A 58 year old male was reportedly exposed to a ULV product five to six times. Each time he was taken to the emergency room with difficulty breathing and an upset stomach. He was diagnosed with and treated for COPD[6]. The last time he was exposed to the ULV product, he fell while taking a shower after the exposure. He was subsequently hospitalized and died about 10 days later. He also suffered from peeling skin" (US EPA 2013a).

Other occupational poisoning cases were described in the section *Nervous system - other neurotoxic effects*.

4.3 Suicides

Cases of attempted or successful suicide have been reported in a number of countries including India (Srinivas Rao et al 2005), Iran (Soltaninejad et al 2007), Israel (Kventsel et al 2005), Italy (Moretto & Lotti 1998), Nepal (Paudyal 2008), Nicaragua (Miranda et al 2002), Spain (Martínez et al 2004), Sri Lanka (Wickramasinghe et al 2009), Taiwan (Lee & Lin 2006), Turkey (Daglioglu et al 2011), USA (US EPA 1999a; Arroyo Plasencia et al 2012), Venezuela (Guadarrama-Naveda et al 2001), and a subcutaneous self-injection case in France (Soummer et al 2011).

[6] Chronic obstructive pulmonary disease.

In the Central province of Sri Lanka, of 78 patients with organophosphate poisoning, 59 had ingested chlorpyrifos (Jayawardane et al 2008).

Chlorpyrifos is reported of have a global case fatality rate of 8% for self-poisoning (Gunnell et al 2007).

A newborn baby died in South Africa soon after birth, following its mothers attempted suicide with chlorpyrifos. The mother experienced tonic-clonic seizures, vomiting, diarrhoea, a garlic odour, faecal incontinence, pinpoint pupils, and muscle weakness and fasciculations. The mother survived, but the baby born prematurely died 2 days after birth (Solomon & Moodley 2007).

Foetal death following maternal ingestion of chlorpyrifos has been reported in Turkey (Sebe et al 2005).

4.4 Accidental poisonings

In Nicaragua, children living in a community in the path of rainwater run-off from a large crop-dusting airfield had depressed cholinesterase activity, thought to be caused by playing barefoot in puddles of water. Pesticides found in their well-water included chlorpyrifos (McConnell et al 1999). Additionally, acute and chronic symptoms have been recorded both in the workers that manufacture chlorpyrifos-treated bags used in plantations, and in workers that put the bags on the fruit (Wesseling et al 2006, 2007).

In the USA, 2,593 people, mainly children, were identified with acute pesticide exposure to chlorpyrifos at school between 1998 and 2002. Sixty nine percent of 406 cases with detailed information arose from application of pesticides on the school grounds – diazinon, chlorpyrifos and malathion were commonly implicated; 13% arose from spray drift from neighbouring operations – chlorpyrifos was one of the main pesticides involved (Alarcon et al 2005).

Also in the US, between 2002 and 2008, there were 126 incidents involving chlorpyrifos, with more than 150 people affected (US EPA 2009a). US EPA (2013a) reported 141 incidents between 2002 and 2011 that involved chlorpyrifos alone but many more than involved other chemicals as well as chlorpyrifos. California alone reported 100 cases from 2002 to 2009 involving chlorpyrifos, of which 61 were associated with drift or volatilisation. Another database, NIOSH-SENSOR-Pesticides gives a figure of 204 cases of suspected chlorpyrifos poisoning, of which 21% were attributable to drift and volatilisation (6 were bystanders, 13 work-related, 1 residential application).

In November 2000, a cloud of chlorpyrifos drifted onto the grounds of Mound Elementary School in Ventura County, California (USA), from a lemon grove across the street. Dozens of students and teachers complained of dizziness, headaches, and nausea following the early morning application. The grower made a second application later that week that also drifted onto the school grounds. Samples from the kindergarten room (14 m from the grove), desks and play areas (hundreds of metres distant), and other campus locations tested positive for OPs (Kegley et al 2003).

In 2007, 26 vineyard workers reported effects from drift/volatilisation from an adjacent almond orchard; 12 had respiratory problems including difficulty breathing, shortness of breath, cough, sore throat, and chest tightness (US EPA 2013a).

A 61-year-old man sprayed a nest of termites with chlorpyrifos, without any protective clothing. After 30 minutes, he suffered nausea, abdominal cramps, arm and leg weakness, shoulder and chest pain, and numbness in left hand and arm. Clinical signs included urinary retention, left peritoneal palsy, and loss of strength. Widespread neuropathy was progressive, and paralysis of hands persisted. He never regained use of his hands, continued to have a disturbed gait with inability to clear his left foot when walking, and continued to suffer urinary retention which required catherization (Meggs 2003).

There have been cases in the USA of children ingesting household formulations of chlorpyrifos (0.5%), including the fatality of a 22 month-old boy (US EPA 1999a).

A church in Harper Kansas, USA, was treated for termites with chlorpyrifos in July 1995. One year later chlorpyrifos was still being detected in the air, and people who worked at the church reported symptoms of “chronic neurobehavioural poisoning” (US EPA 1999a).

A man in his 30s suffered symptoms of OP poisoning after mowing a hospital grounds lawn that had been treated with fertilizer containing chlorpyrifos (US EPA 1999a).

There have been a number of media reports linking several incidents involving the deaths of young female tourists in Thailand and Vietnam with exposure to chlorpyrifos used in hotels (Daily Mail Reporter 2011; Hopper 2012; Thanh Nien News 2012).

In Jamaica, a hotel employee was reported to be still suffering respiratory complications a year after 3 employees were poisoned when chlorpyrifos was sprayed in their dining room to control cockroaches, according to a media report (Serju 2012). Another report from Jamaica refers to "many children" who fell ill after chlorpyrifos was used in two schools (The Gleaner 2012). Other accidental poisoning cases have been described under the section *Nervous system - other neurotoxic effects*.

5 Environmental Effects

5.1 Aquatic toxicity

GHS classification and labelling:

Category	Hazard Phrase
Aquatic Acute Tox 1	H400 – very toxic to aquatic life
Aquatic Chronic Tox 1	H410 – very toxic to aquatic life with long lasting effects

Transport to surface water via spray drift poses a risk to aquatic species (WHO 2009a).

Fish

Very ecotoxic to fish (NZ EPA 2012):

- LC_{50} (96hr) = 0.00054-520 mg/L (EC 2005)
- Chronic NOEC = 0.00014 mg/L (EC 2005)

Reproductive NOAEC:

- Freshwater fish (fathead minnow) = 0.57 ppb (US EPA 2006)
- Estuarine fish (Atlantic silverside) = 0.28 ppb (US EPA 2006)

Chlorpyrifos causes inhibition of AChE in fish (Assis et al 2012; Oruc 2012).

Exposure of Australian catfish (*Tandanus tandanus*) to a short pulse of chlorpyrifos at 2 µg/L resulted in reduced growth, although there was no difference in food intake (Huynh & Nugegoda 2012).

Sublethal exposure to chlorpyrifos results in oxidative stress in fish. For example, 40-day exposure to environmentally relevant doses of chlorpyrifos (116 µg/L) decreased the activity of antioxidant enzymes in common carp (*Cyprinus carpio* L.) (Xing et al 2012); and exposure to 5, 10 and 15 ppb increased MDA and SOD, but decreased GST and CAT in the Nile tilapia (*Oreochromis niloticus*) (Oruc 2012). Wu et al (2011) found that activitiy of SOD and CAT increased at lower concentrations of chlorpyrifos, but decreased at higher concentrations.

Chlorpyrifos has been shown to be mutagenic in fish: Ali et al (2008) found micronucleus induction and DNA damage in the freshwater fish *Channa punctatus* (Bloch).

Chlorpyrifos has also been observed to cause endocrine disruption in fish, the Nile tilapia (*Oreochromis niloticus*), in particular lowering serum cortisol, oestradiol, and testosterone levels, without change to gonad somatic indices (Oruc 2010).

Developmental subchronic exposure to chlorpyrifos can result in neurobehaviour effects: exposure of zebrafish (*Danio rerio*) larvae to 0.01 or 0.1 µM during development induced specific behavioural deficits in 7-day old fish, including decreased swim speed and thigmotaxis (preference for the edge, an anxiety-related disorder), but no change in avoidance behaviour. The authors described the thigmotaxis effect as interference in the development of anxiety-related behaviours (Richendrfer et al 2012).

Reduction in swimming activity has also been recorded in coho salmon (*Oncorhynchus kisutch*) at 0.6 µg/L; reduction in feeding occurred at 1.2 µg/L (Sandahl et al 2005).

Effects on schooling behaviour (e.g. location, orientation, grouping pattern) in fathead minnows (*Pimephales promelas*) has been observed at exposure to > 47 µg/L of chlorpyrifos in the formulation Dursban (Holcombe et al 1982).

Spinal deformities occurred in rainbow trout (*Salmo gairdneri*) after 48 hours exposure to concentrations of chlorpyrifos > 47 µg/L in the formulation Dursban (Holcombe et al 1982).

Residues have been found in fish in a number of countries, including:

- China (mean = 21.4 µg/kg) (Wang et al 2012c);
- Egypt, in River Nile tributaries at 9.38 µg/kg (Malhat & Nasr 2011); and in a drainage canal surrounding a pesticide factory at 31.6 µg/kg (Abdel-Halim et al 2006);
- USA, at 3.1 µg/kg in liver tissue (Sapozhnikova et al 2004);
- Taiwan, in both wild fish (64 µg/kg) and farmed fish (463 µg/kg); in the latter, the chlorpyrifos came from the fish feed (Sun & Chen 2008);
- India, in Kolleru Lake, at 88,600 µg/kg (Amaraneni & Pillala 2001); in the sub-Himalayan Dal Lakes, at 54% frequency and up to 3 µg/kg (Muddasir et al 2012);

- Ghana, in lagoons, at 0.3 µg/kg (Essumang et al 2009);
- Ethiopia, Lake Koka, in 23% of *Clarias gariepinus* and 10% of *Oreochromis niloticus*, at up to 1.12 µg/kg (Deribe et al 2011).

Climate change may increase the toxicity of chlorpyrifos to fish: Patra et al (2007) found that sublethal exposures to chlorpyrifos reduced upper temperature tolerance limits in freshwater fish species by 3.8°C for silver perch (*Bidyanus bidyanus*) and 5.8°C for rainbow trout (*Oncorhynchus mykiss*).

Between 1974 and 2005, chlorpyrifos was reported as the probable causative agent of 108 aquatic incidents, e.g. fish kills (US EPA 2009a). In 2001, chlorpyrifos killed hundreds of fish in the River Ouse, UK (PAN UK 2001). Fish kills have also been reported in Australia (NRA 2000a).

Amphibia

Chlorpyrifos is moderately to very highly toxic to amphibia depending on the species. In the US EPA's ECOTOX database, LC_{50}s for amphibia range from 66.2 to 5,471 µg/L (Davidson et al 2012). Exposure to chlorpyrifos inhibits AChE activity (Colombo et al 2005). Chlorpyrifos oxon is significantly more toxic to amphibia than the parent compound (Sparling & Fellers 2007).

Two formulations of chlorpyrifos, Dursban and Lorsban, were more neurotoxic to frogs that the active ingredient in *in vitro* tests (Swann et al 1996). They also caused swelling of mitochondria.

There is concern that contamination by pesticides, including chlorpyrifos, from sources at a distance from some frog populations may be contributing to their decline, particularly in the Sierra Nevada Mountains in California, USA, which are downwind of the intensely cultivated San Joaquin Valley (Sparling et al 2001). The authors found chlorpyrifos or diazinon in 50% of the Pacific tree frog (*Hyla regilla*) at the Yosemite National Park, compared with 9% at the coast. Mean tissue concentration of chlorpyrifos was 15 µg/kg.

This view is supported by the Sparling & Fellers (2009) study, which established an LC_{50} for chlorpyrifos of 365 µg/L for larval Pacific tree frogs (*Pseudacris regilla*) and 66.5 µg/L for foothill yellow-legged frogs (*Rana boylii*), the first an abundant species, and the second in severe decline. Time to metamorphosis increased in both species, and mean body size was reduced in *R boylii*.

In another survey in California, chlorpyrifos was the 3rd most frequently found contaminant (after endosulfan and dacthal) in Cascade frogs (*Rana cascadae*) and Pacific chorus frogs (*Pseudacris regilla*). It was detected in 48.9% of samples, at a mean tissue weight of 0.484 µg/kg, although they found no difference in levels between sites of frog decline and sites where no decline was evident. It was also found in the sediment in the frog sites, at 62.9% frequency and 0.754 µg/kg mean sediment weight (Davidson et al 2012).

Residues of chlorpyrifos have also been found in Pacific tree frog tadpoles at 17.4 µg/kg in California (Datta et al 1998).

In a study in Sri Lanka (Jayawardena et al 2010) of chronic exposure to concentrations similar to those found in the environment there (50 to 500 µg/kg), chlorpyrifos was found to have a profound effect on amphibia even at the lowest concentrations. The following effects were found on the common hourglass tree frog (*Polypedates cruciger*):

- survival of the tadpole was reduced to 80% at 500 µg/kg; and was still significantly reduced at 50 µg/kg;
- growth of tadpoles was significantly reduced;
- tadpoles took longer to develop;
- malformations in 60% of tadpoles, mainly in the spine, including hunched back (kyphosis), and curvature (scoliosis), as well as skin ulcers and oedemas. The oedemas later resulted in twisting of the body axis and consequent effects on swimming behaviour (such as swimming upside down, inability to balance); they were often fatal upon rupture. Even at 50 µg/kg, 35% malformations occurred.

Amphibia are sensitive to endocrine disrupting effects of chlorpyrifos. Bernabò et al (2011a) exposed tadpoles of the frog *Rana dalmatina* to either 0.025 mg/L or 0.05 mg/L chlorpyrifos (both ecologically relevant doses). At 1 month of metamorphosis, 20-25% of those exposed were classified as 'intersex' due to the presence of testicular oocytes (compared to none in the control group).

Other effects of chlorpyrifos that have been recorded in amphibia include:

- damage to muscles (Colombo et al 2005);
- reduced swim speed and activity in tadpoles, swimming in a spiral orbit, and swimming upside down (Widder & Bidwell 2006; Wijesinghe et al 2011);
- reduced body length at 0.001 mg/L and mass at 0.1 mg/L (Richards & Kendall 2003);

- genotoxicity: increased induction of micronuclei and chromosomal lesions in erythrocytes, and DNA damage in erythrocytes and liver cells of *Bufo bufo gargarizans* tadpoles exposed to sublethal concentrations of chlorpyrifos (Yin et al 2009);
- teratogenic effects such as abnormalities in tail flexure, skeleton, and muscle development (Bernabò et al 2011b), and abnormal gut coiling (Bonfanti et al 2004);
- gill alteration including mucous secretion, and epithelium detachment and degeneration (Bernabò et al 2011b).

Exposure to environmentally relevant concentrations of chlorpyrifos (2-200 µg/L) increased the sensitivity of the tiger salamander to a pathogen, *Ambystoma tigrinum* virus (ATV), another mechanism by which chlorpyrifos may be contributing to the global decline in amphibia (Kerby & Storfer 2009).

Aquatic mammals

Chlorpyrifos residues have been measured in the blood of free-ranging sea otters in Alaska and California (Jessup et al 2010).

Aquatic Invertebrates

Moderate to very high toxicity. Very ecotoxic to aquatic crustaceans (NZ EPA 2012).

Freshwater:

- Acute LC_{50} (*Daphnia magna*) = 0.1 ppb (US EPA 2006)
- Acute LC_{50} (stonefly) = 50 ppb (US EPA 2006)
- Reproductive NOAEC (*Daphnia magna*) = 0.04 ppb (US EPA 2006)
- Chronic NOEC (*Daphnia magna*) = 0.000056 mg/L formulation, 21 days (EC 2005)

Crustaceans:

- Acute LC_{50} (mysid shrimp) = 0.035 ppb (US EPA 2006)
- Reproductive NOAEC (mysid shrimp) = <0.0046 ppb (US EPA 2006)
- Chronic NOEC (mysid shrimp) = 0.0046 mg/L (EC 2005)

Chlorpyrifos can have significant effects on aquatic community structure. A single pulse of chlorpyrifos at 1 µg/L had long lasting effects on the macroinvertebrate community structure of a coastal stream mesocosm system in Australia. Significant community level effects were detected with no evidence of recovery after 124 days. The mayflies *Atalophlebia* sp. and *Koorrnonga* sp, were particularly sensitive to chlorpyrifos and decreased in abundance after dosing (Colville et al 2008).

In a previous study on the effects of chlorpyrifos on a freshwater ecosystem, van Wijngaarden et al (2005) established a NOEC of 0.1 µg/L, noting that microcrustaceans (cladocerans and copepod nauplii) are amongst the most sensitive organisms. Under simulated Mediterranean conditions, algal blooms were experienced as an indirect effect of chlorpyrifos on grazing organisms.

Synergistic effects on toxicity have occurred when larvae of the aquatic midge *Chironomus tentans* have been exposed to mixtures of chlorpyrifos and the herbicides atrazine or cyanazine. The toxicity of chlorpyrifos was enhanced 1.8-fold by atrazine and 2.2-fold by cyanazine, the effect being associated with inhibition of AChE even though the herbicides are not inhibitors of AChE (Jin-Clark et al 2002). Synergism was also noted in a mixture of chlorpyrifos, imidacloprid and dimethoate, in terms of toxicity to *Chironomus dilutus* larvae (LeBlanc et al 2012).

Chlorpyrifos was found in prawns from Kolleru lake wetland in India, at a maximum concentration of 27.8 µg/L (Amaraneni 2006).

Echinoderms

Chlorpyrifos is very toxic to sea urchins. Exposure of the sea urchin *Paracentrotus lividus* to concentrations of 10^{-4} M, 10^{-5} M, and 10^{-6} M during the mating stage caused irreversible damage resulting in death in the embryonic stage. Concentrations of 10^{-4} M caused the death of all gastrulas, with the other concentrations leaving some larvae to metamorphose.

These survivors metamorphosed into immature sea urchins faster, but lacked certain skeletal components and spines and sometimes pedicles. Those exposed to 10^{-5} M died within a few days, and many of those exposed to 10^{-6} M developed but with elongated spines or other skeletal components (Amaroli et al 2013).

Aluigi et al (2010) found that the same doses, 10^{-4} M to 10^{-6} M, from 2 days after fertilisation prevented larval growth and fertilisation in *P lividus*. Exposures to low doses, 10^{-7} M to 10^{-10} M, from 2 days after fertilization did not prevent metamorphosis but did alter size and shape.

Exposures at later stages caused reabsorption of larval structures and precocious release of the immature rudiments, followed by death of juveniles.

Molluscs

Moderate to very high toxicity (Kegley et al 2011).

- Acute LC_{50} (oyster embryo-larva) = 2,000 ppb (US EPA 2006)

Chlorpyrifos causes endocrine disruption in molluscs. Studies on marine mussels *Mytilus galloprovincialis* showed complex interactions between chlorpyrifos and 17ß-oestradiol in the digestive gland (Canesi et al 2011).

It was found in all samples of oysters in Chesapeake Bay, USA, at levels up to 0.42 µg/kg wet weight (Lehotay et al 1998).

Plankton

Phytoplankton: Moderate toxicity (Kegley et al 2011)
Zooplankton: Slight to very high toxicity (Kegley et al 2011)
Very ecotoxic to algae (NZ EPA 2012).

- Algal acute LC_{50} 72 hrs = 1.2 mg/L technical (EC 2005)
- Algal acute LC_{50} = 0.140-0.300 mg/L (US EPA 2006)
- Algal acute NOEC = 0.1-0.001 mg/L (EC 2005)
- Algal chronic NOEC = 0.027-0.063 mg/L formulation (EC 2005)

Chlorpyrifos, at a concentration of 0.1 µg/L, significantly changed the composition of the plankton community in seawater, particularly reducing arthropods (Tagatz et al 1982).

Chlorpyrifos was one of the most frequently detected pesticides in zooplankton, along with endosulfan, at 10 remote inland lakes in Ontario, at a maximum concentration of 0.08 ng/g (Kurt-Karakus et al 2011).

5.2 Terrestrial toxicity

Mammals

Chlorpyrifos is described as very ecotoxic to terrestrial vertebrates (NZ EPA 2012).

Acute toxicity – LD_{50}:

- Female mouse = 64 mg/kg (EC 2005)
- Rabbit = 1,000-2,000 mg/kg (NPIC 2009)
- Guinea pigs = 500 mg/kg (NPIC 2009)
- Sheep = 800 mg/kg (NPIC 2009)

Pets treated with products containing chlorpyrifos are at risk: dogs treated with a commercial flea product suffered depressed cholinesterase activity which did not return to pre-treatment levels even after 3 weeks (Boone et al 2001).

Birds

Chlorpyrifos is described as very highly toxic to some birds, such as pheasant; highly toxic to common pigeons, house sparrows, and chickens; and moderately toxic to mallard ducks (NPIC 2009).

Acute toxicity – LD_{50}:

- common quail = 13.3 mg/kg (EC 2005)
- house sparrow = 10 mg/kg (US EPA 2006)
- pheasant = 8.41 mg/kg of formulation (EC 2005)

Dietary toxicity – LC_{50}:

- Mallard duck = 203 ppm (EC 2005)
- Mallard duck = 136 ppm (US EPA 2006)

Reproductive toxicity – NOEC/NOAEL:

- Mallard duck = 25 ppm (EC 2005; US EPA 2006)

There is growing concern that sublethal exposure to OPs might reduce bird populations by negatively affecting physiological and behavioural responses. Reduction in flying ability can affect migratory success. For example, exposure to chlorpyrifos at "environmentally relevant concentrations" (3 mg/kg), caused a significant increase in flight times in homing pigeons (*Columba livia*), indicating reduced flying ability (Moye & Pritsos 2010).

In 1995, chlorpyrifos was responsible for a "major incident" in Australia, at Macquarie Marshes. About 400-500 nestling ibis were killed. They had been feeding on grasshoppers, and chlopryrifos was found in their liver (0.026 mg/kg) and intestinal tissue (0.167 mg/kg) (NRA 2000b).

Between 1974 and 2005, chlorpyrifos was reported as the probable causative agent of 79 terrestrial incidents, mainly bird and honey bee kills (US EPA 2009a).

The American robin (*Turdus migratorius*) is the most frequently reported bird species killed in field incidents involving chlorpyrifos in the US (NPIC 2009).

Bees

Chlorpyrifos is extremely toxic to honey bees (WHO 2009a).

Acute toxicity to honey bees (*Apis mellifera*):

- oral LD_{50} = 0.25 µg/bee (EC 2005)

- oral LD_{50} = 0.36 µg/bee (WHO 2009a)
- contact LD_{50} = 0.059 µg/bee (EC 2005)
- contact LD_{50} = 0.07 µg/bee (WHO 2009a)

According to Carrasco-Letelier (2012), the maximum recommended dose for the formulation Lorsban 48E for soybean crops in Uruguay is 23 times the formulation's contact LD_{50} of 0.059 µg/bee.

Chlorpyrifos is also highly toxic to bumblebees. In an experiment in which *Bombus impatiens* were exposed for 2 weeks to white clover plots sprayed 24 hours previously with label rates of chlorpyrifos, half of the colonies had no live brood or adults and, overall, worker numbers were reduced by 57%, honey pots by 87%, and brood chambers by 94% (Gels et al 2002).

It is clear that honeybees are widely exposed to chlorpyrifos despite regulatory statements that risks to bees are minimised by label restrictions on time of application (e.g. WHO 2009). Chlorpyrifos was the most frequently detected insecticide in honey in Uruguay (42% of samples at up to 80 µg/kg), and propolis (78% at up to 111 µg/kg) (Pareja et al 2011). In North America, it was found in wax in 63.2% of colonies (at up to 890 µg/kg), in 43.7% of pollen samples (at up to 830 µg/kg), in 8.6% of bees (at up to 10.7 µg/kg) (Mullin et al 2010). The authors state the LD_{50} as 1,220 µg/kg, but note that although these exposures are sublethal, sublethal exposures can reduce honeybee fitness especially that of the queen, and pesticides can interact synergistically to cause mortality. In Spain, chlorpyrifos was found in 5.6% of beeswax samples at 172 µg/kg (Serra-Bonvehí & Orantes-Bermejo 2010).

Beneficial insects

Chlorpyrifos is extremely toxic to beneficial insects (WHO 2009a), and is completely incompatible with IPM. A review from the University of Melbourne classified chlorpyrifos as in the highest class of toxicity to all groups of parasitoids and predators considered (beetles, ladybirds, predatory bugs, predatory mites, lacewings, and spiders (Thomson 2012).

The following LC_{50}s have been established:

- 0.058 µg/ml (range 0.039-0.081) for *Trichogramma ostriniae* (Wang et al 2012a)
- 0.0008 µg/ml for *Aphytis melinus* (Prabhaker et al 2007)
- 0.006 µg/ml for *Gonatocerus ashmeadi* (Prabhaker et al 2007)
- 0.012 µg/ml for *Eretmocerus eremicus* (Prabhaker et al 2007)
- 0.017 µg/ml for *Encarsia formosa* (Prabhaker et al 2007).

Frampton & van den Brink (2007) found that application of chlorpyrifos (at 0.48 kg/ha) in wheat fields in summer had a dramatic negative effect on arthropod abundance and taxonomic richness. There was a substantial reduction in Collembola (springtails) that had not recovered 44 days after application. Abundance of most macroarthropods was reduced, with the parasitic wasps, Hymenoptera, being most strongly affected.

Application of chlorpyrifos to soils at recommended field rates resulted in significant avoidance in the springtails *Folsomia candida*, and a significant drop in the number of juveniles produced (Santos et al 2012). Springtails play a key role in the soil food web through the breakdown of leaf litter in the soil, the release of nutrients, and the support of soil microorganisms (which feed on their faecal pellets).

Chlorpyrifos is highly toxic to the parasitic wasp *Trichogramma* including *Trichogramma ostriniae*, which is a major natural enemy of lepidopteran pests, and particularly the Asian corn borer (*Ostrinia furnacalis*) (Wang et al 2012a). Further, chlorpyrifos has significant effects on parasitisation and reproduction of *Trichogramma brassicae* at LD_{20}, a dose that kills 20% of the parasitoid. Following exposure, there was a significant decrease in egg parasitisation and therefore also a significant reduction in their progeny, especially of female progeny (Delpuech & Meyet 2003).

Chlorpyrifos, at a rate of 0.73 kg/ha, had severe adverse effects on the multicoloured Asian lady beetle, *Harmonia axyridis* (Pallas). It significantly reduced egg hatch and survival of first instar larvae, and caused 100% mortality of third instars and adults (Galvan et al 2005).

The recommended field rate of chlorpyrifos for European corn borer on maize (375 g/ha) is 7,982 times higher than its LD_{50} for the parasitic wasp *Aphidius ervi*, according to Desneux et al (2004). Sublethal effects include alteration of orientation behaviour, with some females permanently bending their abdomens forward as if attacking aphids.

Chlorpyrifos inhibited the activity of ChE in the garden wolf spider *Anoteropsis hilaris* (Pekár 2012).

Earthworms

Chlorpyrifos is moderately toxic to earthworms.

Acute toxicity:

- 14 days LC_{50} = 129 mg/kg (species not included) (EC 2005)
- 14 days LC50 = 9.5 mg/kg for *Lumbricus rubellus* (NZ EPA 2012)
- 96 hr LC50 = 7.3 mg/kg for *Perionyx excavatus* (Das Gupta et al 2010)

Acute toxicity of metabolites:

- TCP - 14 days LC_{50} = 9.8 mg/kg (species not included) (EC 2005)

Reproductive toxicity:

- 56 days NOEC = 9.5 kg/ha (EC 2005)
- TCP 56-day NOEC = 4.60 mg/kg dry soil (EC 2005)

A number of sublethal effects on earthworms have been reported. For example, application of chlorpyrifos to soils at recommended field rates resulted in avoidance behaviour, and a significant (43%) drop in number of juveniles produced by earthworms *Eisenia andrei* (Santos et al 2012). It also resulted in a significant reduction in total number of adults and juvenile earthworms (10 species) in Sri Lanka, which together with a decrease in termite numbers was claimed to have resulted in reduced leaf litter degradation (De Silva et al 2010).

Chlorpyrifos affects the immune system of earthworms: it is reported to have decreased immunocyte viability in *Eisenia andrei* (Galloway & Handy 2003).

Oxidative stress, as a result of exposure to chlorpyrifos (10-40 mg/kg dry soil), was demonstrated in *Eisenia foetida*, with inhibition in SOD, followed by a strong stimulation; CAT activity also increased (Wang et al 2012d).

A study of earthworms in an orcharding area of South Africa revealed that the persistence of chlorpyrifos in the soil following spraying resulted in chronic exposure of earthworms (*Aporrectodea caliginosa*) with a resultant loss of weight and decrease in AChE activity (Reinecke & Reinecke 2007).

A mixture of chlorpyrifos and cypermethrin showed increased toxicity over chlorpyrifos by itself, with 5 mg/kg causing significant reductions in growth and reproduction (Zhou et al 2011).

Plants

Chlorpyrifos is phytotoxic and has killed plants (US EPA 2009a).

Microorganisms

Chlorpyrifos has an inhibitory effect on soil microbial functional diversity, reducing microbial biomass by as much as 50% after application, inhibiting nitrogen mineralisation, and reducing bacterial, fungal and actinomycete populations. Microbial functional diversity is an important indicator of soil health (Hua et al 2009). It inhibits the saprotrophic bacterium *Pseudomonas putida* (Chen et al 2010). *P putida* assists plant growth and protects it from pathogens.

6 Environmental Fate

The half-life of chlorpyrifos indoors is estimated to be 30 days but some studies show it is still present in ambient air up to 8 years after application (Cal EPA 2010).

6.1 Soil

Degradation

Both biotic and abiotic processes contribute to the degradation of chlorpyrifos. One key process is enzymatic or clay-/metal-catalysed hydrolysis, the rate of which increases with pH and temperature. It also undergoes photolytic degradation in sunlight (Gebremariam et al 2012).

However, the main route of degradation appears to be via aerobic and anaerobic microbial metabolism. Chlorpyrifos degrades slowly in soil under both aerobic and anaerobic conditions. The major degradate of chlorpyrifos in the environment, under most conditions, is 3,5,6-trichloro-2-pyridinol (TCP).

Hydrolytic degradation becomes the major mechanism in alkaline soils under low moisture conditions, but it is inhibited at high concentrations of chlorpyrifos (1,000 µg/g) (Racke et al 1996).

Chlorpyrifos has a strong tendency to sorb to organic matter and soil (Gebremariam et al 2012); it has a high soil sorption coefficient - average K_{oc} = 8,498 ml/g (Liu et al 2001), range = 652-30,381 ml/g (Gebremariam et al 2012). The dissipative half-life is significantly longer in organic soils than mineral soils (Gebremariam et al 2012).

Chlorpyrifos reduces the availability of nitrogen and phosphate in the soil (Sardar & Kole 2005).

Persistence

Chlorpyrifos is persistent in soils under some conditions. There is a wide range of half-

lives (DT_{50}) reported in the literature for soil persistence, ranging from a few days to 4 years, depending on application rate, ecosystem type, and various environmental factors. The persistence of chlorpyrifos on soil, foliage, and fruit has also been found to vary considerably with different formulations containing different inert ingredients, with a microencapsulated formulation being the most persistent (Montemurro et al 2002).

US EPA (2006) described chlorpyrifos as persistent in the absence of light, and the US submission to the Stockholm Convention POPs Review Committee in 2012 gave a half-life in soil of 180 days.[7]

Racke et al (1994), of Dow Chemical Company, the manufacturer of chlorpyrifos, found half-lives of 175, 214, 230, 335, and 1,576 days in five soils from different US states, in laboratory dissipation studies under standard laboratory conditions (25°C, darkness, field moisture capacity). These were termiticide treatments, with application rates of 738-897 *µ*g/g. Termiticide application rates are much higher than in agricultural usage, and higher rates of application result in slower dissipation.

Baskaran et al (1999) determined a half-life of chlorpyrifos of 462 days in Australian red-brown soil under laboratory conditions of constant temperature at 25°C and moisture (60% maximum water holding capacity), and termiticide application rates of 1000 mg/kg. This study also found that hydrolytic breakdown of chlorpyrifos is more rapid in alkaline conditions.

In an evaluation of insecticides for soil treatment of termites in Arizona, 22% of chlorpyrifos applied at 1% active ingredient was still present in the soil 1 year after application: the initial concentration was 1,420 ± 214 ppm, and the residual amount after 1 year was 315 ± 48 ppm. Where the soil was covered by a slab, the mean residual level of chlorpyrifos after 1 year was 51% of initial concentration (1,601 ± 36 ppm falling to 813 ± 199 ppm), i.e. DT_{50} > 365 days (Baker & Bellamy 2006).

Another study, on the efficiency of insecticides as soil termiticides, found a DT_{50} of 8.2 months for chlorpyrifos at 0-2.5 cm depth. Chlorpyrifos was added to soil beneath a concrete slab, a common preconstruction technique in the USA before this use was prohibited in 2005 (Mulrooney et al 2006).

Zhong et al (2012) reported that such is chlorpyrifos' persistence, that when it has been used as a soil termiticide, summertime levels in indoor air did not decline over a period of 7 years after initial application.[8]

In an experiment to determine the persistence of the toxicity of chlorpyrifos to the amphipod *Hyalella curvispina* and the fish *Cnesterodon decemmaculatus*, after application in experimental soybean crops in Argentina, Mugni et al (2012) found that toxicity persistence in the runoff from the soil remained at 100% for *H. curvispina* for 42 days, then decreased slowly to 30% after 140 days. In late season applications, chlorpyrifos mortality in the soil remained at 100% until 84 days after spraying, remaining still at 80% at the end of the experiment (140 days). Early- and mid-season applications resulted in more rapid decay of toxicity, showing that prevailing environmental conditions alter the rate of decay of chlorpyrifos toxicity. Temperatures were lower in the late season, suggesting a decreased loss of chlorpyrifos from the soil through vaporisation and photodegradation. The persistence of chlorpyrifos toxicity in soil to 80% after 140 days is indicative of the chemical's persistence in the soil: a half life was not identified but it is reasonable to assume it would exceed 180 days.

Chlorpyrifos dissipation from soil is faster under tropical conditions; in one study where it was applied to a mustard crop, there were negligible amounts left after 70 days; half-life was 3.6-9.4 days. In other studies where chlorpyrifos has been applied to bare fields in tropical conditions, the half-life ranges from 0.6-5.4 days (Chai et al 2009).

Whilst EC (2005) gave a half-life in soil for the metabolite TCP as ranging from 8 to 96 days, the US EPA (2006) describes TCP as mobile in soils but persistent when not exposed to light, with "substantial amounts" remaining 365 days after application.

Factors affecting persistence

The dissipative half-life is significantly longer in organic soils than mineral soils. Hydrolysis is slower in water containing clay minerals, humate, dissolved organic matter, and suspended sediment (Gebremariam et al 2012). The addition of organic matter to soil, in the form of biochar, increased persistence from a DT_{50} of 21.3 days to 55.5 days, and to 158 days in sterilised soil (Yang et al 2010).

---

[7] UNEP-POPS-POPRC7CO-SUBM-ENDOSU-DDT-US_2-120623.En.

[8] Zhong et al (2012) cite the following reference which has not been located: Yoshida S, Taguchi S, Hori S. 2004. Chlorpyrifos and S-421 residues in indoor air and polished rice around nine years after application for termite control. *J Soc Indoor Environ Japan* 7:7-15

Degradation rates of chlorpyrifos are modulated by soil pH, moisture, and temperature, as well as formulation and application rates. In one experiment, degradation rates doubled with each increase of 10°C (Racke et al 1994).

Hydrolytic breakdown of chlorpyrifos is more rapid in alkaline conditions (Baskaran et al 1999).

Shading appears to reduce photodegradation (Chai et al 2009).

Hence, persistence of chlorpyrifos increases with increased soil organic matter, decreased temperature, decreased pH, and decreased ultraviolet light.

Muir et al (2004), using BIOWIN and a procedure described by Gouin (2003), calculated the following half-life for Arctic conditons:

- Soil DT_{50} = 435 days

Residues

Chlorpyrifos has been measured in soils in a number of countries, including:

- Philippines: in 27.4% of soil samples with a mean concentration of 0.01 mg/kg in Benguet, a vegetable producing region in the Philippines (Del Prado Lu 2010);
- India: in the soil of tea ecosystems in West Bengal at a level of 0.53 mg/kg (Bishnu et al 2009);
- New Zealand: in cropping soils in the Auckland region, at 0.4 mg/kg (Gaw 2002);
- Argentina: in the orcharding area of Neuquen River Valley, at maximum concentrations of 60.5 µg/kg; levels were found to increase in concentration during the growing season (Loewy et al 2011);
- Ghana: in the vegtable production areas of Opeibea and Dzorwulu, Accra (Amuzu 2012);
- South Africa: in an orcharding area, a low but persistent level of chlorpyrifos in the soil prior to the start of the spray season (0.2-2.7 µg/kg), with that increasing up to a mean of 6.7 µg/kg in the orchard area, 3.98 µg/kg in the spray drift area adjacent to the orchards, 1.97 µg/kg in the far spray drift area (500m), and 8.68 µg/kg in the runoff area. Chlorpyrifos was persistent in the soil for up to 6 months after the last spraying event (Reinecke & Reinecke 2007);
- Serbia: at 47.4 µg/kg in the agricultural soils in the Belgrade area (Marković et al 2010).

6.2 Water and sediment

Chlorpyrifos is a priority pollutant in the European Water Framework Directive 2000/60/CE (Robles-Molina et al 2012).

Degradation and partitioning

Chlorpyrifos breaks down in water by microbial action, hydrolysis, and photolysis (Racke 1993).

- Solubility in distilled water = 0.39 mg/L (Liu et al 2001)
- Solubility in seawater = 0.073 mg/L (Liu et al 2001)
- Median aquatic sediment sorption, K_{oc} = 15,500 L/kg (Gebremariam et al 2012)

It has low water solubility, and is moderately hydrophobic (Gebremariam et al 2012). Based on its sorption coefficient (K_{oc}), chlorpyrifos is expected to be adsorbed to suspended solids and sediment (Gebremariam et al 2012). This makes it susceptible to movement to waterways via surface runoff (Wightwick & Allinson 2007). Chlorpyrifos has a relatively higher affinity for aquatic sediments than soils (Gebremariam et al 2012).

Volatilisation from water surfaces is expected to be an important fate process based on the Henry's Law constant (HSDB 2008). Degradation of chlorpyrifos is primarily due to microbial action and therefore is reduced by lower temperature, anaerobic conditions, and strong sorption to sediment.

Persistence

- Estimated volatilisation half-lives for a model river = 24 days; and for a model lake = 178 days (HSDB 2008)
- Hydrolysis DT_{50} in distilled water at 25°C was 62 days (pH 4.7), 35 days (pH 6.9), and 22 days (pH 8.1) (HSDB 2008)
- DT_{50} water sediment/whole system = 22-51 days (EC 2005)
- DT_{50} water sediment/whole system = 36.5 days (IUPAC 2012)

However, a number of studies have shown much higher persistent under 'field' conditions, in some cases exceeding the Stockholm Convention criteria for persistence of 2 months [60 days] in water or 6 months [180 days] in sediment.

An environmental fate review from Dow Chemical Company (Racke 1993) gives a DT_{50} of 150-200 days in anaerobic pond sediments. The Australian government review (NRA 2000a) refers to pond studies that give a DT_{50} in sediment of

200 days, exceeding the Stockholm Convention persistence criteria.

In a study in California, the persistence of chlorpyrifos in sediment from a San Diego creek was found to increase significantly under anaerobic conditions: the DT_{50} for aerobic conditions was 20.3 days but for anaerobic conditions it was 223 days, although only 57.6 days in sediment from Bonita Creek (Bondarenko & Gan 2004).

Chlorpyrifos had a half-life of 126 days in water of the Susquehanna River, Chesapeake Bay, USA (Liu et al 2001).

Using constructed wetlands to explore removal of chlorpyrifos and pyrethroids from agricultural runoff water in California, Budd et al (2011) demonstrated that the average DT_{50} for chlorpyrifos in sediment under wetland and anaerobic conditions was 106 ± 54 days.

Chlorpyrifos degradation is significantly slower in seawater than it is in fresh water. One study in California found a DT_{50} for seawater of 49.4 days at 10°C, compared with 18.7 days in freshwater. At 21°C, the DT_{50} for seawater was 15.2 days, so temperature has a significant effect on seawater degradation (Bondarenko et al 2004).

Chlorpyrifos, at a concentration of 16.2 ng/L, was found in a section of an ice core sample from the largest icecap in Eurasia – Austfonna, Svalbard, Norway – believed to have been deposited in the early to mid 1980s, indicating considerable persistence under Arctic conditions (Hermanson et al 2005).

As in soil, the persistence of chlorpyrifos in water and sediment increases with decreased temperature, decreased pH, and decreased ultraviolet light. Muir et al (2007) concluded that low temperatures may preserve chlorpyrifos, particularly in icecaps and cold, oligotrophic lakes. It is therefore reasonable to assume that persistence will be significantly greater in the cold and often dark conditions of the Arctic than indicated by the half-lives derived from tropical or temperate regions. Muir et al (2004), using BIOWIN and a procedure described by Gouin (2003), calculated the following half-lives for Arctic conditions:

- Water DT_{50} = 218 days
- Sediment DT_{50} = 1,414 days

Residues - groundwater

Chlorpyrifos has been detected in groundwater in a number of countries, for example:

- Pakistan: in 58.3% of samples in the tobacco growing area of Mardan (0.03 µg/L) (Tariq et al 2007);
- New Zealand: in wells in Southland, at 0.56 µg/L, and in Waikato (Close & Skinner 2012);
- Argentina: in wells in the Neuquen River Valley (Loewy et al 2011);
- Brazil: in 75% of well water samples at up to 0.22 µg/L in the Cristal basin, after application to tobacco crops (Bortoluzzi et al 2007);
- Turkey: in 57% of samples taken along the Mediterranean coast (Tuncel et al 2008);
- Australia: in the State of Victoria it has been found in Bacchus Marsh (0.19 µg/L), Gippsland (0.09 µg/L), Goulburn-Murray (2.4 µg/L), Ovens/King (0.01 µg/L), and Werribee (0.2 µg/L) (Wightwick & Allinson 2007);
- EU: in Spain - Barcelona (0.021 µg/L) (Teijon et al 2010), and in a volcanic aquifer in the NE of Gran Canaria Island (0.294 µg/L) (Estévez et al 2012); in Greece (Vryzas et al 2012); in a vineyard area in the Alentejo region of South Portugal in 2004-6, at low levels (<0.05 µg/L) (Silva et al 2011);
- US: 'infrequently' in ground water in the US between 1992 and 2001 (Gilliom et al 2006).

Residues - surface water and sediment

The European Union maximum allowable level for drinking water is 0.1 µg/L, and the general water quality criterion for protecting freshwater organisms is 0.083 µg/L (Otieno et al 2012). The chronic US benchmark for aquatic invertebrates is 0.04 µg/L (Zhang et al 2012).

Chlorpyrifos has been found in surface waters and sediments in many countries, frequently exceeding these criteria, including:

- USA: in 15% of agricultural streams, and 65% of urban streams in the states of Georgia, Alabama and Florida in 1994 (US EPA 2006). In California, chlorpyrifos exceeded regulatory limits in 44 water bodies, 610.3 miles of rivers or streams, and 43,614.0 acres of estuary (NMFS 2008). Levels found in US streams are up to 5.8 µg/L. There have been 1,131 detections of chlorpyrifos in streams in just 4 states. Sediment concentrations have been found as high as 455.560 µg/kg dry weight in agricultural drains and 17.373 µg/kg in rivers (NMFS 2008). More recent monitoring, over the 5 years from 2006-2010, in California found chlorpyrifos in 17.7% of samples, at levels exceeding water quality criteria in 9.9%, with the highest level found being 3.7 µg/L. In one area, Santa Maria Valley, where the main uses are on vegetables, strawberries and wine grapes, the levels exceeded the

criteria in 57% of the samples (Zhang et al 2012). It has been measured in tributaries and rivers running into Chesapeake Bay, at up to 0.190 µg/L (Harman-Fetcho et al 1999; Lehotay et al 1998; Liu et al 2001). Residues of 0.0042 µg/L have been found in Lake Tahoe in the Sierra Nevada mountains in USA; residues were found in 100% of lake water samples, with the highest concentration at 25-m depth (McConnell et al 1998). Residues at 0.220 µg/L have been found in the San Joaquin River, USA (McConnell et al 1998). Levels of chlorpyrifos in Beasley Lake in the Mississippi Delta, USA, were highest of all current use insecticides, at up to 0.039 µg/L; it was also found in leaf litter at 23 µg/kg (Lizotte et al 2010). Chlorpyrifos was found in the sediments of 9 of 16 stormwater ponds tested including those draining from golf courses (up to 7 µg/g), residential areas (up to 13.84 µg/g), and commercial areas (up to 10.08 µg/g) in South Carolina in 2007 (Crawford et al 2010). Recently, it was found in 49% of sediment samples from streams in Central Valley, California, at levels up to 98.6 µg/kg (Weston et al 2013);

- Canada: at all rural and urban surface water sites monitored in the Lower Fraser Valley, British Columbia, with levels in urban water reaching 0.38 µg/L (Woudneh et al 2009). Residues were also found in a 13% of samples from a wetland in Quebec, at an average of 0.06 µg/L, exceeding by 17 times the water quality criteria (Poissant et al 2008); it was one of the most frequently detected pesticides in the water at 10 remote inland lakes in Ontario, at a maximum concentration of 0.5 ng/L (Kurt-Karakus et al 2011);
- China: in sediment of urban waterways in the Pearl River Delta (Zhong et al 2012). It was also found in the water (max 1.89 ng/L) and sediment (max 0.165 µg/kg) of Beijing Guanting reservoir (Xue et al 2005); in 97% of sediment samples from Chaohu Lake at a maximum concentration of 0.46 µg/kg dry weight (Wang et al 2012b); in the sediment of an urban stream in Guangzhou at up to 17.8 µg/kg dry weight (Li et al 2013); in the sediment of wetlands in northern Beijing at up to 0.237 µg/kg (Xue et al 2008);
- Bangladesh: in paddy field water (1.12 µg/L) and in lakes (0.98 µg/L) (Chowdhury et al 2012); and 0.12 µg/L in the Kaligonga river (Bhattacharjee et al 2012);
- Philippines: in 1 water sample (70 µg/L) in Benguet, a vegetable-producing region in the Philippines (Del Prado Lu 2010);
- Japan: at low levels in river sediment in both urban and rural areas, the urban contamination thought to have come from previously permitted termiticide treatments, banned in 2003 (Kitada et al 2008); in river water in Okinawa (Zhong et al 2012).
- India: residues of 0.103 µg/L were found in water and up to 238,000 µg/kg in sediment from Kolleru lake wetland (Amaraneni 2006); in 27% samples of water from rice fields and canals in Haryana, Uttar Pradesh and Uttarkhand, at up to 0.006 µg/L (Mukherjee & Arora 2011);
- Iran: at 22,430 µg/L in spring water (Dehghani et al 2012);
- Israel: during the first significant rainfall following dry season pesticide application in the Hula valley in 2009, the daily average levels in the upper Jordan River reached 4.5 µg/L for chlorpyrifos, 18.6 µg/L for the oxon, and 2.2 µg/L for TCP; the load reaching one measuring station during the first 2 days was 1,785 g chorpyrifos, 1,377 g oxon, and 161 g TCP. The levels observed exceeded acute toxicity levels for freshwater invertebrates and fish (Olsson et al 2013);
- Malaysia: in the Selangor River at up to 0.1952 µg/L; wetlands that are habitat for fireflies could be threatened by chlorpyrifos levels of up to 0.1486 µg/L which is above the ambient water quality level of 0.083 µg/L for acute toxcity to aquatic organisms (Leong et al 2007);
- Argentina: one of the most frequently detected pesticides in surface water and sub-surface drains in the pome-fruit growing region of Neuquen River Valley. It was detected in 73% of samples at a maximum concentration of 1.16 µg/L (Loewy et al 2011). It was also found along the Suquía River at levels up to 5.5 ng/L, reported as surpassing the Canadian Water Quality Guideline of 3.5 ng/L established to protect freshwater biota (Bonansea et al 2013). It was measured in 2 streams in a soybean production area: in the Brown stream, at 226 µg/kg in the suspended particles, at 0.45 µg/L in floodwater, 13.5 µg/kg in bottom sediment, and at 30.3 µg/kg in runoff sediment; and in the Horqueta stream, it was measured at 64 µg/kg in the suspended particles and at 30.3 µg/kg in runoff sediment (Jergentz et al 2005). Residues of chlorpyrifos in runoff and floodwater exceeded the water quality criteria on 5 occasions;
- Mexico: in the sediment of agricultural drains in the Culiacan Valley, Sinaloa, at 0.9 µg/kg dry weight (García-de la Parra et al 2012);
- Brazil: at 0.54 µg/L (Nogueira et al 2012); in 75% of surface water samples, at up to 0.29 µg/L, in

the Arvorezinha basin following application to tobacco crops (Bortoluzzi et al 2007);

- Costa Rica: at 26 ng/L in the Jiménez River as a result of pineapple production in the river's watershed (Echeverría-Sáenz et al 2012);
- Kenya: widely distributed in Lake Naivasha at levels up to 26.6 μg/L in water and 30 μg/kg dry weight in sediment, as a result of horticultural use on surrounding farmland (Otieno et al 2012);
- Ghana: at a mean level of 10.77 μg/kg in sediment of the Oyansia stream in the vegetable production areas of Opeibea and Dzorwulu in Accra (Amuzu 2012);
- Egypt: both chlorpyrifos and chlorpyrifos-methyl were found in water and sediment of a drainage canal surrounding a pesticide factory at Damietta Governorate in Egypt. Chlorpyrifos was present in water up to 303.8 μg/L and sediment up to 303.8 μg/kg; and chlorpyrifos-methyl at up to 41 μg/L in water and 61.3 μg/kg in sediment. Additionally chlorpyrifos, but not chlorpyrifos-methyl, was found in fish, at up to 31.6 μg/kg (Abdel-Halim et al 2006).
- Australia: in 39% of sediment samples from irrigation channels and drains in the cotton growing area of Queensland, at a maximum concentration of 94 μg/kg dry weight (Müller et al 2000); in the state of Victoria, it has been found in Gippsland (70 μg/kg of sediment and 0.002 μg/L water), and Goulburn-Murray irrigation supply channels (0.089 μg/L) (Wightwick & Allinson 2007); in New South Wales at 17 μg/L, Tasmania at 0.15 μg/L mean), and Onkaparinga South Australia (Wightwick & Allinson 2007);
- Turkey: in 75% of samples of surface water taken along the Mediterranean Coast (Tuncel et al 2008);
- EU: in Italy at 0.275 μg/L (EC 2005); Spain at 0.312 μg/L (Claver et al 2006);
- South Africa: 344 μg/kg in suspended sediment in the Lourens River (Schulz et al 2001).

Residues - wastewater

It is described as being "often present in wastewater" in Spain (Robles-Molina et al 2012), for example it was found at 0.01838 μg/L in the wastewater treatment plant in Barcelona by Teijon et al (2010).

Chlorpyrifos was detected in secondary treated effluent, water being recycled for use as drinking water in Perth, Australia, but was not found after the water was further treated with reverse osmosis (Rodríguez et al 2012).

Residues - marine

Chlorpyrifos has been found in the marine environment in a number of countries, including frequent detections in the sediments of coastal areas of Mexico, Costa Rica, Nicaragua, and Panama, as a result of riverine discharge of suspended sediment from agricultural drainage (Gebremariam et al 2012):

- Indonesia: in samples of coral taken from coastal waters (Sabdono et al 2007);
- Costa Rica: it was measured at 34.2 μg/kg in the costal sediments around Rio Parismina (Galloway & Handy 2003);
- Ghana: in lagoons, at 1,580 μg/L (Essumang et al 2009);
- Mexico: widespread distribution in sediment of the Altata-Ensenada del Pabellon coastal lagoon at up to 8 μg/kg dry weight (Carvalho et al 2002);
- USA: in sediment in California at 9.5 μg/kg dry wt (Sapozhnikova et al 2004).

Chlorpyrifos can accumulate in areas of intense biological productivity, such as littoral zones and river deltas, posing a long-term threat to aquatic ecosystems (Gebremariam et al 2012).

6.3 Air

Chlorpyrifos is described as having intermediate vapour pressure (Gebremariam et al 2012), and as being volatile (IUPAC 2012).

- 3.35×10^{-3} Pa at 25°C (EC 2005)
- 2.546×10^{-3} Pa at 25°C (WHO 2009a)
- 1.43×10^{-3} Pa at 25°C (IUPAC 2012)

This indicates that chlorpyrifos will exist in both vapour and particulate phases in the atmosphere. Vapour-phase chlorpyrifos is degraded by reaction with photochemically-produced hydroxyl radicals, with the half-life for this reaction estimated to be 4.2 hours. Particulate-phase chlorpyrifos will be removed by wet or dry deposition (HSDB 2008).

Volatilisation from moist soil surfaces may be an important fate process (HSDB 2008). In a study of volatilisation from a rice paddy in Italy, 3.3% of the initially applied chlorpyrifos had volatilized after 6 days, but volatilisation was still continuing when the testing was stopped (Ferrari et al 2005).

Chlorpyrifos can be converted to chlorpyrifos oxon in the air via direct or indirect photolysis (US EPA 2013a).

Although the estimated atmospheric half-life of chlorpyrifos, given as 4.2 hrs in HSDB (2008) and PUBCHEM[9], indicates that chlorpyrifos is not expected to undergo long-range transport, it has been found extensively in Arctic media indicating that long-range transport is occurring and has been occurring for many years. Ruggirello et al (2010) suggest this is likely to be a result of lack of ultraviolet radiation during the polar darkness lowering concentrations of hydroxyl radicals in the air and preventing atmospheric photolysis. The lack of chlorpyrifos oxon in the Austfonna ice core further suggests low levels of oxidation of chlorpyrifos in the Arctic region. A lack of atmospheric moisture may reduce water solubility, increasing the air-water partition coefficient, K_{aw}, increasing the time chlorpyrifos remains in the gas phase and further assisting its long-range transport (Hermanson et al 2005).

Residues – short to medium range transport
Chlorpyrifos was found in 100% of air samples, at a maximum concentration of 2,000 pg/m^3 in the Chesapeake Bay area, USA. Calculated air-water gas exchange fluxes ranged from -20 to +68 ng/m^2/day, the negative value indicating net absorption in the air. The major equilibrium transfer direction was from water to air (Harman-Fetcho et al 2000). Net volatile loss of chlorpyrifos from the surface waters of Chesapeake Bay was calculated to be 147 g/day in March, and net deposition to be 85 g/day in June (one of the main months of usage) (McConnell et al 1997).

It was one of the 2 most frequently detected pesticides in air in Iowa, in 19% of samples, at a maximum of 2.9 ng/m^3 (Peck & Hornbuckle 2005).

Chlopryrfios was found in 84% of samples taken in the citrus growing area of Tulare, in California's Central Valley, with a median concentration of 33 ng/m^3 (Harnly et al 2005).

Air monitoring studies in the US demonstrated the presence of chlorpyrifos in the air near homes in agricultural communities in 75% of the air samples collected. Eleven percent of the samples had levels above those determined by regulators to be 'acceptable' for 24-hour exposure of children, with the highest concentration nearly 8 times the 'acceptable' level (Mills & Kegley 2006). Other studies carried out by the California Air Resources Board confirmed the potential for high exposure in areas near application sites (ARB 1998).

In the spring of 2006, the Farm Worker Project and PAN North America carried out air monitoring for chlorpyrifos in the Yakima Valley, California, at two homes near orchards. At both locations, chlorpyrifos was measured on each day of a 3-week period. At one home, the levels exceeded regulatory 'acceptable' levels 29% of the time and at the other location 38% of the time. The highest concentration was 475 ng/m^3, 2.8 times the 24-hour acute child Reference Exposure Level (REL) (Dansereau et al 2006).

PAN North America again carried out air monitoring, between June 2006 and August 2009, this time in Central Minnesota. Chlorpyrifos was found near Browerville in 2006 and Perham in 2009, with 33% of 40 field samples containing measurable levels of chlorpyrifos, the maximum concentration being 47 ng/m^3 (Tupper et al 2012).

Chlorpyrifos undergoes regional air transport in the US, with an estimated annual loading of 24-31 kg/year in the Sierra Nevada mountains in California (McConnell et al 1998). It was found in air at up to 220 pg/gm in national parks in Washington and California (Landers et al 2008).

In a further demonstration of the regional transport of chlorpyrifos, Mast et al (2012) measured chlorpyrifos in the snow, rain, lichen, and lake sediment in Yosemite National Park, USA. It was detected in 100% of snow samples, at up to 4.9 ng/L, and was one of the most commonly detected current-use pesticides in rain, with an overall deposition rate of 1.14 μg/m^2, similar to that of endosulfan (1.55); and it was found in 70% of lichen samples, at an average concentration of 1.7 ng/g, and in 2 out of 19 sediment samples.

It has been found in the air in many other countries, including:

- Turkey: highest levels in the air of all pesticides measured (along with endosulfan); levels of 0.143 ng/m^3 of chlorpyrifos have been measured in summer, and 121 pg/m^3 in winter (Bozlaker et al 2009);
- Algeria: at 2.2 ng/m^3 at Lake Baraki, and 1.9 ng/m^3 at Lake Reghaia (Moussaoui et al 2012);
- Brazil: at up to 0.100 ng/m^3 in the National Parks of Serra dos Órgãos and São Joaquim, the highest level of any pesticide except endosulfan (Meire et al 2012);
- Costa Rica: at up to 1.266 ng/m^3 in the central valley, thought to have originated in the nearby coffee plantations at Belen (Gouin et al 2008);
- New Zealand: at up to 0.012 ng/m^3 at Temple Basin in the Southern Alps, thought to have originated from the Canterbury Plains (Lavin et al 2012);

[9] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2730#x321.

- Australia: chlorpyrifos was the most commonly detected pesticide in the air at the coastal town of Coffs Harbour, associated with domestic use and use on banana plantations, at a maximum of 208 ng/m^3 (Beard et al 1995);
- Canada: chlorpyrifos was one of the most frequently detected pesticides in the air at 10 remote inland lakes in Ontario, at a maximum concentration of 0.06 ng/m^3 (Kurt-Karakus et al 2011); it was one of the most frequently detected at Bratt's Lake, Saskatchewan, at up to 1,380 pg/m^3, and 3,900 pg/m^3 for the oxon, thought to come from use against grasshoppers on the Prairies (Raina et al 2010); it was found in 66% of samples taken at St Damase, an agricultural site located in the Yamaska basin in Québec, at up to 868 pg/m^3 (Aulagnier et al 2008).

Rain

The oxon degradate was detected in 79% of rainwater samples in California at a maximum concentration of 100 ng/L (NMFS 2008).

Chlorpyrifos was found in 100% of rain samples in the Chesapeake Bay study referred to above, at maximum concentration of 0.081 ng/L (Harman-Fetcho et al 2000). It was detected more frequently in rain at urban sites than agricultural sites in the Mississippi River Valley (Majewski et al 2000).

Chlorpyrifos was one of the 10 most commonly detected compounds in rain across Maryland, Indian, Nebraska and California in the US in 2003-4, detected in 66% of samples, and at up to 1.84 μg/L, and 0.1 μg/L for the oxon (Vogel et al 2008).

It has been measured in rain in the Sierra Nevada mountains, USA, at 13 ng/L; and at 189 ng/L in Lindcove, California (McConnell et al 1998).

In one US study, the average levels of chlorpyrifos in rainwater in San Joaquin River basin, California, were higher than those in storm runoff by a factor of 2.5 (Zamora et al 2003).

Chlorpyrifos has been detected at low levels in rain in Brazil (Nogueira et al 2012).

Chlorpyrifos was one of the most frequently detected pesticides in the rain at 10 remote inland lakes in Ontario, Canada, at a maximum concentration of 43 ng/L (Kurt-Karakus et al 2011).

Snow

It is one of the most commonly detected pesticides in snow in Mt Rainier National Park, Washington (NMFS 2008).

It has been detected in snow in California's Sierra Nevada mountains at up to 4.4 ng/L (McConnell et al 1998).

Fog

Chlorpyrifos has been found in fog water in California at up to 14,200 ng/L in the Central Valley (McConnell et al 1998).

Residues – long-range tranpsort

Residues in the Arctic are likely to have resulted from long-range atmospheric transport, so are reported here under the section on air.

The Arctic Monitoring and Assessment Programme (AMAP) reported that chlorpyrifos has been identified in fish, surface water, ice and fog from the Bering and Chukchi Seas, air in the eastern Canadian archipelago, and subarctic and arctic lakes in Canada (Hoferkamp et al 2010). Other studies have consistently found it in Arctic media, including air, snow, seawater, lake sediment, and vegetation.

In 1993, the BERPAC programme carried out sampling in the Bering and Chukchi marine ecosystems, identifying chlorpyrifos in seawater, marine ice, and marine fog (1-5 ng/L). It was one of the most frequently detected contaminants in the seawater (6 of 9 samples) and ice (1 integrated sample). Concentrations were highest in the marine ice (170 ng/L) and seawater (19-67 ng/L) at locations closest to the ice edge, or polynya. The polynya ecosystem is the most biologically productive zone in the Arctic marine environment, with high concentrations of Arctic marine mammals and birds, and consequently important areas where northern Indigenous Peoples focus their traditional hunting and fishing. During melt periods, chlorpyrifos is likely to be released into the adjacent marine waters when biological spring is beginning. The authors of this study expressed the view that the measured levels of chlorpyrifos might have detrimental effects on the biota, especially aquatic organisms (Chernyak et al 1996).

Chlorpyrifos was not found in air samples in the above study, but it was found in air in a separate study, in interstitial air sampled concurrently with fog sampling in the same area, in 1993. It was also found in the fog by Rice & Chernyak (1997):

Chlorpyrifos in Arctic fog and air

Fog sample – water fraction	Air sample - vapour fraction	Air sample - particulates
0.08 ng/L	0.76 ng/L	0.08 ng/L

Fogs are common over much of the Bering and Chukchi Sea area, occurring up to 80% of the year in the Aleutian Islands, so exchanges at the interface between fog with snow, ice and seawater may be a common occurrence. Rice & Chernyak (1997) proposed that once chlorpyrifos and other contaminants are in the Arctic atmosphere, fog plays a major role in recycling them within the ecosystem.

Jantunen et al (2007) also found chlorpyrifos in Arctic air samples taken over the Labrador Sea, at 0.36-30.4 pg/m^3.

In 2010, chlorpyrifos was again found in all oceanic air samples taken over the Sea of Japan, the East China Sea, and the Bering and Chukchi Seas, the concentration decreasing from Asia to the Arctic (Zhong et al 2012). Air-sea gas exchange varied from net volatilisation in East Asia (<40°N) to net deposition in the Arctic. Chlorpyrifos (along with endosulfan and dicofol) was one of the most abundant pesticides found in air and in the seawater. Chlorpyrifos levels in Arctic seawater were <1 pg/L, lower than in previous studies, perhaps reflecting lower releases following the restrictions on residential and termiticide uses in the USA. However, this study showing declining gradients from Asia to the Arctic indicates that Asia continues to be a significant source of long-range transport of chlorpyrifos to the Arctic.

The upper 40 m of an ice core taken from Svalbard, Norway in 1998 was analysed for the presence of a number of pesticides and metabolites. Nine compounds were not detected, including chlorpyrifos oxon. Twenty compounds were found in discontinuous layers, including many of the POPs pesticides. Eight compounds were found to have continuous profiles and these included chlorpyrifos, indicating historic deposition. Chlorpyrifos first appeared in 1972, peaked in 1980 at a concentration of 16.2 ng/L, and began to decline in the 1990s. Chlorpyrifos was not found in the 1992-1998 layer (Hermanson et al 2005).

Garbarino et al (2002) found high concentrations of chlorpyrifos (70-80 ng/L) in snow collected from sea ice at 3 sites in northwest Alaskan Arctic estuaries in the Chukchi and Beaufort Seas during 1995-96. These concentrations were higher than those of any POP or other current use pesticide tested, including endosulfan, DDT, chlordane, dieldrin, HCH, and PCBs.

Ice core segments on Holtedahlfonna in Svalbard, Norway were compared with segments taken at Austfonna, also in Svalbard. Back trajection calculations show that Eurasia is the source of the chlorpyrifos 74% of the time for Austfonna, and 45% of the time for Holtedahlfonna. They found the peak flux of chlorpyrifos to be 809 pg/cm^2/yr and calculated the contaminant burden for the years 1952 - 2005 to be 776 ng, well in excess of any other pesticide (the next highest burdens were gamma-HCH at 520 ng and alpha-HCH at 402). They also calculated that the chlorpyrifos burden is higher at Austfonna by a factor of about 13. These figures indicate that chlorpyrifos has had the greatest historical impact on Svalbard of all pesticides; and the input and burden is still growing. It was first detected in 1971-80 with a comparatively low input of 64.8 pg/cm^2/yr but that had increased to 808 pg/cm^2/yr by 2005. Chlorpyrifos was the only currently used pesticide (including endosulfan) detected continuously in the Holtedahlfonna ice core (Ruggirello et al 2010).

In a study of U.S. western parks, chlorpyrifos was found in all parks sampled including 2 in the Alaskan Arctic, and in more than 50% of the fish samples (up to 1.2 ng/g wet weight) (Hageman et al 2006; Landers et al 2008). It was found in snow, sediment, lichen, conifer needles, and fish. The authors noted that chlorpyrifos was better accumulated in plant material than in fish. Concentrations of chlorpyrifos in vegetation ranged up to 31 ng/g in conifers (higher than DDT, PCB, and chlordane). Levels in lichen were at or below detection limits. Chlorpyrifos and endosulfan were the most commonly detected current use pesticides. Levels found in snow were up to 2.8 ng/L (Hageman et al 2006). The study reports the flux in snow and ice cores as 204 ng/m^2/yr at Lakes Burial, Matcharak and Kangilipack; and 0.5-32 ng/m^2/yr at Lakes Wonder, McLeod and Kahiltna base camp. The authors stated that chlorpyrifos was identified as a potential concern because of comparatively high concentrations in vegetation, and because concentrations in sediment are increasing over time, and it is still in current use (Landers et al 2008).

Muir et al (2007) detected chlorpyrifos in water samples from 2 Canadian Arctic lakes at up to 1.6 ng/L.

6.4 Bioaccumulation

Moderate to high (HSDB 2008).

Bioaccumulation potential - Log K_{ow}
Values for log K_{ow} (octanol-water partition coefficient) vary from 4.7 to 5.11, all either close to, or exceeding, the bioaccumulation criteria for the Stockholm Convention of 5.

Values of log K_{ow}:

- 4.7 (EC 2005)
- 4.96 – 5.11 (Gebremariam et al 2012)
- 4.7; 4.82; 4.96, 5.11; 5.2; 5.27 (experimental) (Racke 1993)

Bioconcentration and bioaccumulation factors

Bioaccumulation studies were not required for registration in the US, although there is acknowledgement that it has been detected in fish tissue (US EPA 2006). Additionally, the US EPA (2006) stated "at maximum application rates chlorpyrifos may bioconcentrate in the tissues of fish and aquatic invertebrates to levels that exceed acute LC_{50} values for sensitive bird species and reproductive NOAELs for birds and small mammalian species". "Bioconcentration of chlorpyrifos in ponds and estuarine areas may pose acute and/or reproductive risks to aquatic birds and mammals feeding adjacent to treated areas."

The NZ EPA's webpage[10] on classification of chlorpyrifos describes it as bioaccumulative in the fish *Gasterosteus aculeatus*, threespine stickleback, with a BCF = 20,860, based on a study by Deneer (1994). Deneer (1994) also refers to lipid-based BCFs of 12,000 in bluegills, 21,000 in fathead minnow, and 17,500 in guppy.

The US government Hazardous Substances Data Bank (HSDB 2008) identified the following studies:

- A measured log BCF value for chlorpyrifos of 2.67 was determined from a 35-day flowing-water study using mosquito fish (Veith et al 1979). Log BCF relates the bioconcentration factor to the partition coefficient log K_{ow};
- An experimental log BCF value of 2.50 was determined by Dow Chemical Company from a static ecosystem study using mosquito fish (Kenaga 1980);
- In a review of the environmental fate of chlorpyrifos by Dow Chemical Company, BCF values of 100-4,667 were reported in a variety of fish under field conditions. BCF values of 58-1,000 were reported in a variety of fish using flow-through aquariums (Racke 1993). According to a classification scheme, this BCF suggests the potential for bioconcentration in aquatic organisms is moderate to high, provided the compound is not metabolized by the organism (Franke et al 1994).

In addition, the 1993 review from Dow Chemical Company reported aquatic bioconcentration factors of 100-5,100 in fish (Racke 1993). Marshall & Roberts (1978), in their review of the ecotoxicology of chlorpyrifos, reported BCFs up to 6,000 in fish species; however it is unclear if equilibrium was reached.

Hansen et al (1986) of US EPA reported a bioconcentration factor of 5,100 in gulf toadfish (*Opsanus beta*). Mulla et al (1973) measured a BCF range of 1,200-4,677 in fish in a small warm-water lake in southern California.

Log BCF values reported are 3.84 in zebrafish (El-Amrani et al 2012), and the authors of this study report other studies finding log BCFs in fish between 1.69 and 3.45.

Other measured bioconcentration factors include 1,400 in oysters (Woodburn et al 2003); 2,665 in red hybrid *Tilapia* (Thomas & Mansingh 2002); 1,700 in guppies (*Poecilia reticulata*) (Welling & de Vries 1992); and 400 in Mediterranean mussel (*Mytilus galloprovincialis*) (Serrano et al 1997).

A bioconcentration factor of 1,600 was measured in the freshwater amphipod *Gammarus pulex*. The authors of this study, based on this measurement, estimated a BCF of 4,658 in females at their maximum lipid content (lipid content varies seasonally). They also noted that the QSAR prediction using a log K_{ow} of 4.7 under-predicts BCFs compared to the measured valued (Ashauer et al 2006). This gives weight to the higher values for log K_{ow} reported.

There are several studies showing bioaccumulation in plants, including duckweed *Lemna minor* L. and water lettuce *Pistia straiotes* L. (Prasertsup & Ariyakanon 2011), and blue-green algae (Lal et al 1987). Racke (1993) reports BCFs for aquatic plants of 600-1900. Measurements taken in US Western National Parks found bioaccumulation occurring in conifer needles. The concentration of chlorpyrifos in 2 year-old needles was almost double that of first year needles (yr 1 = 11.6 ng/g; yr 2 = 20.5 ng/g) (Landers et al 2008).

Earthworms bioaccumulate chlorpyrifos to a limited degree (BCF = 0.73), especially in soils with high organic matter (Yu et al 2006).

7 Pest Resistance

Pest resistance to chlorpyrifos is now widespread, involving 65 species in at least 47 countries (MSU 2013).

[10] http://www.epa.govt.nz/search-databases/Pages/ccid-details.aspx?SubstanceID=2401.

Species	Common name	Host	Countries
Aedes aegypti	yellow fever mosquito	human	11 countries
Aedes albopictus	Asian tiger mosquito	human	Pakistan
Aedes canadensis	woodland pool mosquito		USA
Aedes melanimon	medium-sized saltmarsh mos.		USA
Aedes nigromaculis	pasture floodwater mos.		USA
Aedes togoi			S Korea
Anopheles (6 species)	anopheles mosquito		UAE, Egypt, Turkey, El Salvador, Dijbouti
Aonidiella aurantii	California red scale	citrus	USA, South Africa
Aonidiella citrina	yellow scale		USA
Aphis gossypii	melon and cotton aphid	cotton, vegetables	China, USA
Bemisia argentifolii	silverleaf whitefly		USA
Bemisia tabaci	sweetpotato whitefly	cotton	Pakistan, USA
Blatella germanica	German cockroach		USA, Cuba, Panama, Denmark, Malaysia
Blissus insularis	southern cinch bug	grasses	USA
Boophilus microplus / *Rhipicephalus microplus*	southern/ tropical cattle tick	cattle	Brazil, France, Australia
Cacopsylla pyri	pear psylla, European pear sucker		France
Chaoborus astictopus	clear lake gnat		USA
Chilo suppressalis	Asiatic rice borer	rice	China
Choristoneura rosaceana	oblique banded leafroller		USA
Chrysoperla carnea	common green lacewing		Pakistan

Species	Common name	Host	Countries
Culex (9 species)	house mosquito	houses; humans, birds	20 countries
Culiseta inornata	winter mosquito		USA
Cydia pomonella	codling moth	fruit trees, walnut	France, Spain
Delia antiqua	onion maggot	vegetables	USA
Diaphorina citri	Asian citrus psyllid	citrus	USA
Drosophila melanogaster	common fruitfly		Israel
Earias vittella	spotted bollworm	cotton	Pakistan
Frankliniella occidentalis	western flower thrips	cotton	USA, Australia
Helicoverpa armigera	cotton bollworm	cotton, corn, sorghum, tomato	India, Pakistan
Helicoverpa zea	corn earworm		Nicaragua
Laodelphax striatellus	small brown planthopper	rice	China
Leptinotarsa decemlineata	Colorado potato beetle	eggplant, pepper, potato, tomato	Serbia
Leucoptera (2 species)	coffee leaf miner	coffee	Brazil, Tanzania
Liriomyza trifolii	American serpentine leaf miner	chrysanthemum, celery	USA, Canada
Musca domestica	house fly		USA
Myzus persicae	green peach aphid	flowers, crops, fruit, trees, grains, tobacco, vegetables	Australia
Oxya chinensis	grasshopper		China
Panonychus ulmi	European red mite	fruit trees	Turkey
Pectinophora gossypiella	pink bollworm	cotton	India
Phyllonorycter blancardella	spotted tentiform leaf miner	apple	USA
Plutella xylostella	diamondback moth	crucifers, nastrurium	USA Pakistan Australia
Popilla japonica	Japanese beetle	turf	USA
Schizaphis graminum	greenbug	sorghum	USA

Species	Common name	Host	Countries
Spodoptera exigua	beet army worm, lesser army worm	cotton, celery, tomato, lettuce, cabbage, alfalfa	Pakistan Nicaragua USA
Spodoptera frugiperda	fall armyworm	cotton, grasses, grains, sugarcane	USA
Spodoptera littoralis	Egyptian cotton leafworm, army worm	alfalfa, cotton, potato, vegetables	Egypt Israel
Spodoptera litura	Mediterranean climbing cutworm	tobacco	Pakistan India
Tetranychus urticae	twospotted spider mite	cotton, fruits, vegetables, walnut, ornamentals	6 countries
Tribolium castaneum	red flour beetle	stored grain, peanuts, sorghum	Australia
Typhlodromus = Galenod pyri	predatory mite mites		UK, France

8 Alternatives to chlorpyrifos

8.1 Alternative insecticides

There are many other synthetic chemical insecticides on the market, but most of these also have a range of adverse health and environmental effects, such as endocrine disruption, cancer, neurological damage, groundwater contamination, persistence, etc. Hence, their use is not recommended to replace chlorpyrifos.

There are some insecticides derived from natural plant extracts that can kill or repel insects; some deter insects feeding, or inhibit their growth. Natural soaps and minerals can also be used, as can naturally occurring pathogens like *Bacillus thuringiensis* (Bt) used as a spray—NOT as a genetically engineered part of the crop itself.

Care must be taken even with natural plant extracts as some, such as pyrethrum, can have toxic effects on beneficial insects, animals, and humans. Other plant extracts that can be used to replace chlorpyrifos include neem, lemon grass, garlic, ginger, marigold, quassia, turmeric, and many more.

Generally an insecticide, even a natural one, should be regarded as the choice of last resort, with the primary focus being placed on alternative pest management practices that prevent the need for a spray.

8.2 Agroecological pest management

There is now widespread support for agroecological, or ecosystem-based, approaches to pest management at the highest international levels, as well as among many farmers worldwide. Major improvements in crop yields and farmers' incomes have been achieved, as well as reversing the trend towards species loss and genetic erosion, and assisting adaption to climate change (UNEP 2012).

Agroecological pest management focuses on sustainable ecological solutions that prevent pest build up. It takes a holistic approach to crop management that recognises pests as an integral part of the whole agroecosystem, forming a complex with beneficial insects, weeds, diseases and crops. The self-regulatory mechanisms of a highly biodiverse farming system help keep pest species in balance. A healthy soil with a rich diversity of biota and a high content of organic matter is key to sustainable management of pests and diseases.

Elements of alternative or ecological pest management:

- designing a farm ecosystem that encourages biodiversity, providing habitats for beneficial insects;
- using resistant, often indigenous, crop varieties;
- diversifying crops by intercropping, rotation, and use of multiple varieties;
- cultural practices that encourage healthy soils and hence healthy plants, such as fallowing, appropriate tillage, water management, mulching, and use of animal manures, green manures, vermicasts, composts, liquid bio-fertilisers, and enhanced indigenous micro-organisms;
- cultural practices that contribute to the suppression of pest populations, such as varying times of sowing, planting and harvesting, adjusting row width, use of trap crops, and appropriate pruning;
- companion planting to deter pests;
- accurate identification of both pests and beneficial insects and knowledge of their life cycles, habitats, and periods of population expansion and vulnerability;
- enhancing the habitats and hence populations of (or introducing) natural enemies such as parasitoids like the *Encarsia* wasp and

predators like the damselfly and spiders, as well as birds where appropriate; other beneficial insects that control pests for which chlorpyrifos is used include Braconid, *Cotesia* wasp, damsel bug, *Diadegma* wasp, carabid beetle, hoverfly, lacewing, ladybird beetles, minute pirate bug, praying mantis, predatory mites, rove beetles, spiders, tachinid flies, *Tiphia* wasp, and *Trichogramma* – see below for more details on some of these.

- field sanitation, removing infested plant material including crop residues to reduce carryover of pests from one planting to the next;
- systematic scouting of crops for pests and natural enemies, either regularly or at susceptible times, sometimes involving the use of sweep nets, sticky traps, and pheromone traps;
- use of mechanical methods such as light traps, fruit fly traps, trenches (e.g. to prevent migration of rice molluscs into paddy fields), nets, reflective ribbon, bird perches, pheromone traps, sticky board traps, soil baits, soil traps, bagging of fruit, and plant ash; and
- use of pheromone traps to trap insects and pheromone dispensers to disrupt mating.

(SIBAT 1999a, 1999b; OISAT 2004; UNEP 2012)

The Online Information Service for Pesticide Management in the Tropics (OISAT), established by PAN Germany, contains extensive information on managing particular pests in specific crops without the use of chlorpyrifos.

Some specific examples of biological controls

(UNEP 2012)

1. Biological preparations

- *Neem/azadirachtin* - effective on over 200 pests including some species of whiteflies, thrips, leaf miners, caterpillars, aphids, scales, beetles, true bugs, and mealybugs; best used on immature stages of pests, before pest levels are high, and with repeated applications.

2. Pathogens

- *Bacillus thuringiensis*[11] Israeli - effective against mosquito larvae and is widely used as a larvicide in mosquito control programmes.
- *Bacillus thuringiensis* var *kurstaki* (Btk) - effective against larvae of members of the Lepidopteran family, i.e. moth and butterfly caterpillars, such as bollworms, leafminer, leafroller, diamondback moth, borers, budworms, army worm, cutworm, etc.
- *Beauveria bassiana*[12] – effective against aphids, boll weevil, stem weevil, caterpillars, codling moth, coffee berry borer, Colorado potato beetle, diamondback moth, European corn borer, fire ants, flies, grasshoppers, Japanese beetle, leafhoppers, leaf-feeding insects, mealybug, Mexican bean beetle, mites, psyllids (lygus bugs and chinch bugs), thrips, whiteflies, and some scales.
- *Metarhizium anisopliae*[13] - effective against aphids, thrips, leaf hopper, whiteflies, scarabs, weevils, mites, gnats, ticks, locusts, termites, cockroaches, flies, and mosquito larvae.
- *Nomuraea riley* - attacks the larvae of stem borers, leaf folders, army worms and case worms; also used against pod bore and cotton bollworm.
- *Helicoverpa armigera* nuclear polyhedrosis virus - against podborer, cotton bollworm, pink bollworm, fruit and shoot borer.

3. Predators

- *Chrysoperla carnea*, common green lacewing - the larvae prey on the nymphs and adults of aphids, bollworms, spider mites, jassids, thrips, whiteflies, leafhopper eggs, leaf miners, small caterpillars, beetle larvae, tobacco budworm, and others.
- *Coccinella septempunctata*, seven-spotted ladybird beetle - prey on aphids, whiteflies, and bollworms, attacking eggs, nymphs and adults; other ladybirds also prey on jassids, mealybugs, scale, mites, psyllids, timgids, planthoppers, and leafhoppers.
- *Orius* spp - thrips, spider mites, insect eggs, aphids, mites, psyllids, whiteflies, small caterpillars, corn earworm eggs, European corn borer, potato leafhopper nymphs, and leafminer.

4. Parasitoids

- *Trichogramma* sp - extremely tiny wasps that parasitize the eggs of hundreds of pests, including bollworms, borers, thrips, jassids, caterpillars, leaf miner, etc.
- Braconid wasps – parasitize larvae including aphids, beetles, bollworm, caterpillars, flies, and sawflies, etc.
- Ichneumonid wasps – parasitize larvae of diamondback moth, bollworm, caterpillars, pod borers, etc.

---

11 *Bacillus thuringiensis* (Bt) is a naturally occurring bacteria used as a biological pesticide. There are a number of different strains that are active against different insect species.

12 *Beauveria bassiana* is a naturally occurring entomopathogenic fungus, causing white muscadine disease in foliar pests

13 *Metarhizium anisopliae* is a widely distributed natural soil fungus that attacks a variety of insects, causing green muscadine disease.

References

Abdel-Halim KY, Salama AK, El-Khateeb EN, Bakry NM. 2006. Organophosphorus pollutants (OPP) in aquatic environment at Damietta Governorate, Egypt: implications for monitoring and biomarker responses. *Chemosphere* 63(9):1491-8.

Abou-Donia MB. 2003. Organophosphate ester-induced chronic neurotoxicity. *Arch Environ Health* 58(8):484-97.

Acker CI, Nogueira CW. 2012. Chlorpyrifos acute exposure induces hyperglycemia and hyperlipidemia in rats. *Chemosphere* 89(5):602-8.

Adgate JL, Barr DB, Clayton CA, Eberly LE, Freeman NC, Lioy PJ, Needham LL, Pellizzari ED, Quackenboss JJ, Roy A, Sexton K. 2001. Measurement of children's exposure to pesticides: analysis of urinary metabolite levels in probability-based sample. *Environ Health Perspect* 109(6):583-90.

AgroNews. 2013. 2012 China's major pesticides varieties tracking – chlorpyrifos. Agropages.com. http://news.agropages.com/News/NewsDetail---8993.htm.

Aiuto LA, Pavlakis SG, Boxer RA. 1993. Life-threatening organophosphate-induced delayed polyneuropathy in a child after accidental chlorpyrifos ingestion. *J Pediatr* 122(4):658-60.

Akhtar N, Srivastava MK, Raizada RB. 2006. Transplacental disposition and teratogenic effects of chlorpyrifos in rats. *J Toxicol Sci* 31(5):521-7.

Alarcon WA, Calvert GM, Blondell JM, Mehler LN, Sievert J, Propeck M, Tibbetts DS, Becker A, Lackovic M, Soileau SB, Das R, Beckman J, Male DP, Thomsen CL, Stanbury M. 2005. Acute illness associated with pesticide exposure at schools. *JAMA* 294(4):455-65.

Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J, Coble J, Sandler DP, Blair A. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol* 157(9):800-14.

Alavanja MC, Ross MK, Bonner MR. 2013. Increased cancer burden among pesticide applicators and others due to pesticide exposure. *CA Cancer J Clin* 63(2):120-42.

Aldana-Madrid ML, Valdez-Hurtado S, Vargas-Valdez ND, Salazar-Lopez NJ, Silveira-Gramont MI, Loarca-Piña FG, Rodríguez-Olibarria G, Wong-Corral FJ, Borboa-Flores J, Burgos-Hernández A. 2008. Insecticide residues in stored grain in Sonora, Mexico: quantification and toxicity testing. *Bull Environ Contam Toxicol* 80(2):93-6.

Aldridge JE, Seidler FJ, Meyer A, Thillai I, Slotkin TA. 2003. Serotonergic systems targeted by developmental exposure to chlorpyrifos: effects during different critical periods. *Environ Health Perspect* 111(14):1736-43.

Aldridge JE, Seidler FJ, Slotkin TA. 2004. Developmental exposure to chlorpyrifos elicits sex-selective alterations of serotonergic synaptic function in adulthood: critical periods and regional selectivity for effects on the serotonin transporter, receptor subtypes, and cell signaling. *Environ Health Perspect* 112(2):148-55.

Aldridge JE, Levin ED, Seidler FJ, Slotkin TA. 2005. Developmental exposure of rats to chlorpyrifos leads to behavioral alterations in adulthood, involving serotonergic mechanisms and resembling animal models of depression. *Environ Health Perspect* 113(5):527-31.

Ali D, Nagpure NS, Kumar S, Kumar R, Kushwaha B. 2008. Genotoxicity assessment of acute exposure of chlorpyrifos to freshwater fish *Channa punctatus* (Bloch) using micronucleus assay and alkaline single-cell electrophoresis. *Chemosphere* 71(10):1823-31.

Aluigi MG, Falugi C, Mugno MG, Privitera D, Chiantore M. 2010. Dose-dependent effects of chlorpyriphos, an organophosphate pesticide, on metamorphosis of the sea urchin, *Paracentrotus lividus*. *Ecotoxicology* 19(3):520-9.

Amaraneni SR. 2006. Distribution of pesticides, PAHs and heavy metals in prawn ponds near Kolleru lake wetland, India. *Environ Int* 32(3):294-302.

Amaraneni SR, Pillala RR. 2001. Concentrations of pesticide residues in tissues of fish from Kolleru Lake in India. *Environ Toxicol* 16(6):550-6.

Amaroli A, Aluigi MG, Falugi C, Chessa MG. 2013. Effects of the neurotoxic thionophosphate pesticide chlorpyrifos on differentiating alternative models. *Chemosphere* 90(7):2115-22.

Amelotti I, Catalá SS, Gorla DE. 2009. Experimental evaluation of insecticidal paints against *Triatoma infestans* (Hemiptera: Reduviidae), under natural climatic conditions. *Parasit Vectors* 2:30.

Amer SM, Farah OR. 1983. Cytological effects of pesticides. XII. Effects of the phosphorothioate insecticide dursban on the mitosis of *Vicia faba*. *Cytologia* 48(1):27-33.

Amer SM, Aly FAE. 1992. Cytogenic effects of pesticides. IV. Cytogenic effects of the insecticides Gardona and Dursban. *Mutat Res* 279(3):165-70.

Amis A. 2008. Survey of Pesticides in Surface Waters of Domestic Water Supplies – Victorian Water Authorities 1998-2007. Friends of the Earth, National Toxics Network, Melbourne.

Amis A. 2012. Issues Regarding Melbourne Drinking Water & Pesticides. Friends of the Earth, Melbourne. http://www.foe.org.au/sites/default/files/Melbourne%20Water%20Supply%20Pesticides%20June%202012.pdf.

Amuzu KK. 2012. Organochlorine Pesticides Residues Levels in Cabbage, Soil and Irrigation Water in Some Farming Communities in Accra. Thesis, Kwame Nkrumah University of Science and Technology, Kumasi College of Engineering. http://dspace.knust.edu.gh:8080/xmlui/handle/123456789/4595.

Ananda Gowda SR, Somashekar RK. 2012. Evaluation of pesticide residues in farmgate samples of vegetables in Karnataka, India. *Bull Environ Contam Toxicol* 89(3):626-32.

Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, Bonefeld-Jørgensen EC. 2002. Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity *in vitro*. *Toxicol Appl Pharmacol* 179(1):1-12.

ARB. 1998. Report for the Application and Ambient Air Monitoring of Chlorpyrifos (and the Oxon Analogue) in Tulare County during Spring/Summer, 1996. Air Resources Board, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/chlrpfs.pdf.

Arroyo Plasencia AM, Halcomb SE, Dribben W, Schwarz ES, Mullins M. 2012. Chlorpyrifos. 319. Abstracts of the 2012 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, 25 May – 1 June 2012, London, UK. *Clin Toxicol* 50(4):357.

Ashauer R, Boxall A, Brown C. 2006. Uptake and elimination of chlorpyrifos and pentachlorophenol into the freshwater amphipod *Gammarus pulex*. *Arch Environ Contam Toxicol* 51(4):542-8.

Assis CR, Linhares AG, Oliveira VM, França RC, Carvalho EV, Bezerra RS, de Carvalho LB Jr. 2012. Comparative effect of pesticides on brain acetylcholinesterase in tropical fish. *Sci Total Environ* 441:141-50.

ATSDR. 1997. Toxicological Profile for Chlorpyrifos. Agency for Toxic Substances and Disease Registry, United States Department of Health and Human Services, Atlanta. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=495&tid=88.

Attia AA, ElMazoudy RH, El-Shenawy NS. 2012. Antioxidant role of propolis extract against oxidative damage of testicular tissue induced by insecticide chlorpyrifos in rats. *Pestic Biochem Physiol* 103:87-93.

Aulagnier F, Poissant L, Brunet D, Beauvais C, Pilote M, Deblois C, Dassylva N. 2008. Pesticides measured in air and precipitation in the Yamaska Basin (Québec): occurrence and concentrations in 2004. *Sci Total Environ* 394(2-3):338-48.

Babina K, Dollard M, Pilotto L, Edwards JW. 2012. Environmental exposure to organophosphorus and pyrethroid pesticides in South Australian preschool children: a cross sectional study. *Environ Int* 48:109-20.

Baker PB, Bellamy DE. 2006. Field and laboratory evaluation of persistence and bioavailability of soil termiticides to desert subterranean termite *Heterotermes aureus* (Isoptera: Rhinotermitidae). *J Econ Entomol* 99(4):1345-53.

Barber D, Hunt J, Ehrich M. 2001. Inhibition of calcium-stimulated ATPase in the hen brain P2 synaptosomal fraction by organophosphorus esters: relevance to delayed neuropathy. *J Toxicol Environ Health A* 63(2):101-13.

Barr DB, Ananth CV, Yan X, Lashley S, Smulian JC, Ledoux TA, Hore P, Robson MG. 2010. Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey. *Sci Total Environ* 408(4):790-5.

Barraza D, Jansen K, van Wendel de Joode B, Wesseling C. 2011. Pesticide use in banana and plantain production and risk perception among local actors in Talamanca, Costa Rica. *Environ Res* 111(5):708-17.

Barril J, López-Granero C, Cardona D, Giménez E, Sánchez-Santed F, Pellín MDLC, Esteban J, Cañadas F. 2010. Chronic dietary and acute exposure in rats: neurobehavioural and neurochemical correlates. *Toxicol Lett* 196S(P207-08): S225-6.

Baskaran S, Kookana RS, Naidu R. 1999. Degradation of bifenthrin, chlorpyrifos and imidacloprid in soil and bedding materials at termiticidal application rates. *Pestic Manag Sci* 55(12):1222-8.

Beamer PI, Canales RA, Ferguson AC, Leckie JO, Bradman A. 2012. Relative pesticide and exposure route contribution to aggregate and cumulative dose in young farmworker children. *Int J Environ Res Public Health* 9(1):73-96.

Beard J, Westley-Wise V, Sullivan G. 1995. Exposure to pesticides in ambient air. *Aust J Public Health* 19(4):357-62.

Bebe FN, Panemangalore M. 2003. Exposure to low doses of endosulfan and chlorpyrifos modifies endogenous antioxidants in tissues of rats. *J Environ Sci Health B* 38(3):349-63.

Bellamy AS. 2012. Banana production systems: Identification of alternative systems. *Ambio* [Epub Sept 29].

Bempah CK, Asomaning J, Boateng J. 2012. Market basket survey for some pesticides residues in fruits and vegetables from Ghana. *J Microbiol Biotech Food Sci* 2(3):850-71.

Berkowitz GS, Wetmur JG, Birman-Deych E, Obel J, Lapinski RH, Godbold JH, Holzman IR, Wolff MS. 2004. *In utero* pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ Health Perspect* 112(3):388-91.

Bernabò I, Gallo L, Sperone E, Tripepi S, Brunelli E. 2011a. Survival, development, and gonadal differentiation in *Rana dalmatina* chronically exposed to chlorpyrifos. *J Exp Zool A Ecol Genet Physiol* 315(5):314-27.

Bernabò I, Sperone E, Tripepi S, Brunelli E. 2011b. Toxicity of chlorpyrifos to larval *Rana dalmatina*: acute and chronic effects on survival, development, growth and gill apparatus. *Arch Environ Contam Toxicol* 61(4):704-18.

Bhattacharjee S, Fakhruddin AN, Chowdhury MA, Rahman MA, Alam MK. 2012. Monitoring of selected pesticides residue levels in water samples of paddy fields and removal of cypermethrin and chlorpyrifos residues from water using rice barn. *Bull Environ Contam Toxicol* 89(2):348-53.

Billauer-Haimovitch H, Slotkin TA, Dotan S, Langford R, Pinkas A, Yanai J. 2009. Reversal of chlorpyrifos neurobehavioral teratogenicity in mice by nicotine administration and neural stem cell transplantation. *Behav Brain Res* 205(2):499-504.

Birnbaum L. 2012. Environmental chemicals: evaluating low-dose effects. *Environ Health Perspect* 120(4):a143-4.

Bishnu A, Chakrabarti K, Chakraborty A, Saha T. 2009. Pesticide residue level in tea ecosystems of Hill and Dooars regions of West Bengal, India. *Environ Monit Assess* 149(1-4):457-64.

Blakely BR, Yole MJ, Brousseau P, Boermans H, Fournier M. 1999. Effect of chlorpyrifos on immune function in rats. *Vet Hum Toxicol* 41(3):140-4.

Bonansea RI, Amé MV, Wunderlin DA. 2013. Determination of priority pesticides in water samples combining SPE ad SPME coupled to GC-MS. A case study: Suquía River basin (Argentina). *Chemosphere* 90(6):1860-9.

Bondarenko S, Gan J. 2004. Degradation and sorption of selected organophosphate and carbamate insecticides in urban stream sediments. *Environ Toxicol Chem* 23(8):1809-14.

Bondarenko S, Gan J, Haver DL, Kabashima JN. 2004. Persistence of selected organophosphate and carbamate insecticides in waters from a coastal watershed. *Environ Toxicol Chem* 23(11):2649-54.

Bonfanti P, Colombo A, Orsi F, Nizzetto I, Andrioletti M, Bacchetta R, Mantecca P, Fascio U, Vailati G, Vismara C. 2004. Comparative teratogenicity of chlorpyrifos and malathion on *Xenopus laevis* development. *Aquatic Toxicol* 70(3):189-200.

Boone JS, Tyler JW, Chambers JE. 2001. Transferable residues from dog fur and plasma cholinesterase inhibition in dogs treated with a flea control dip containing chlorpyrifos. *Environ Health Perspect* 109(11):1109-14.

Bortoluzzi EC, Rheinheimer DS, Gonçalves CS, Pellegrini JB, Maroneze AM, Kurz MH, Bacar NM, Zanella R. 2007. Investigation of the occurrence of pesticide residues in rural wells and surface water following application to tobacco. *Química Nova* 30(8):1872-6.

Botwe BO, Ntow WJ, Nyarko E, Kelderman P. 2012. Evaluation of occupational and vegetable dietary exposures to current-use agricultural pesticides in Ghana. In: Soundararajan RP (Ed.). *Pesticides – Recent Trends in Pesticide Residue Assay*. InTech. http://www.intechopen.com/books/pesticides-recent-trends-in-pesticide-residue-assay.

Bozlaker A, Muezzinoglu A, Odabasi M. 2009. Processes affecting the movement of organochlorine pesticides (OCPs) between soil and air in an industrial site in Turkey. *Chemosphere* 77(9):1168-76.

Bradman A, Whitaker D, Quirós L, Castorina R, Claus Henn B, Nishioka M, Morgan J, Barr DB, Harnly M, Brisbin JA, Sheldon LS, McKone TE, Eskenazi B. 2007. Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. *J Expo Sci Environ Epidemiol* 17(4):331-49.

Braquenier JB, Quertemont E, Tirelli E, Plumier JC. 2010. Anxiety in adult female mice following perinatal exposure to chlorpyrifos. *Neurotoxicol Teratol* 32(2):234-9.

Budd R, O'geen A, Goh KS, Bondarenko S, Gan J. 2011. Removal mechanisms and fate of insecticides in constructed wetlands. *Chemosphere* 83(11):1581-7.

Buratti FM, De Angelis G, Ricceri L, Venerosi A, Calamandrei G, Testai E. 2011. Foetal and neonatal exposure to chlorpyrifos: biochemical and metabolic alterations in the mouse liver at different developmental stages. *Toxicology* 280(3):98-108.

Byford RL, Lockwood JA, Smith SM, Harmon CW, Johnson CC, Luther DG, Morris HF Jr, Penny AJ. 1986. Insecticide residues in cattle treated with a cypermethrin, chlorpyrifos, piperonyl butoxide-impregnated ear tag. *Bull Environ Contam Toxicol* 37(5):692-7.

Cal EPA. 2008. Evidence on the Developmental and Reproductive Toxicity of Chlorpyrifos. Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/ChlorpyrifosHID0908.pdf.

Cal EPA. 2010. Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901 (g): Child-Specific Reference Dose (chRD) for School Site Risk Assessment – Chlorpyrifos. Integrated Risk Assessment Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. http://oehha.ca.gov/public_info/public/kids/pdf/061710Chlorpyrifos.pdf.

Campbell CG, Seidler FJ, Slotkin TA. 1997. Chlorpyrifos interferes with cell development in rat brain regions. *Brain Res Bull* 43(2):179-89.

Cañadas F, Cardona D, Dávila E, Sánchez-Santed F. 2005. Long-term neurotoxicity of chlorpyrifos: spatial learning impairment on repeated acquisition in a water maze. *Toxicol Sci* 85(2):944-51

Canesi L, Negri A, Barmo C, Banni M, Gallo G, Viarengo A, Dondero F. 2011. The organophosphate chlorpyrifos interferes with the responses to 17ß-estradiol in the digestive gland of marine mussel *Mytilus galloprovincialis*. *PLoS ONE* 6(5):e19803.

Carrasco-Letelier L, Mendoza-Spina Y, Branchiccela MB. 2012. Acute contact toxicity test of insecticides (Cipermetrina 25, Lorsban 48E, Thionex 35) on honeybees in the southwestern zone of Uruguay. *Chemosphere* 88(4):439-444.

Carvalho FP, Gonzalez-Farias F, Villeneuve JP, Cattini C, Hernandez-Garza M, Mee LD, Fowler SW. 2002. Distribution, fate and effects of pesticide residues in tropical coastal lagoons of northwestern Mexico. *Environ Technol* 23(11):1257-70.

Casey KA. 2005. Chlorpyrifos in breast milk? Dissertation. The University of Tennessee, AAT 3205781. http://proquest.umi.com/pqdlink?Ver=1&Exp=04-17-2017&FMT=7&DID=1092085911&RQT=309&attempt=1&cfc=1.

CCCEH. 2006. Exposures to the insecticide chlorpyrifos in pregnancy adversely affect child development. Press release, Dec 4. Columbia University's Mailman School of Public Health. http://www.world-wire.com/news/0612040001.html.

Cecchi A, Rovedatti MG, Sabino G, Magnarelli GG. 2012. Environmental exposure to organophosphate pesticides: assessment of endocrine disruption and hepatoxicity in pregnant women. *Ecotoxicol Environ Saf* 80:280-7.

Chai L-K, Mohd-Tahir N, Bruun Hansen HC. 2009. Dissipation of acephate, chlorpyrifos, cypermethrin and their metabolites in a humid-tropical vegetable production system. *Pest Manag Sci* 65(2):189-96.

Chatterjee M, Sarma PS. 2003. Unusual neurological complications in a case of organophosphate poisoning. *Neurol India* 51(2):290-1.

Chen H, Yao J, Wang F, Zhou Y, Chen K, Zhuang R, Zaray G. 2010. Investigation of the acute toxic effect of chlorpyrifos on *Pseudomonas putida* in a sterilized soil environment monitored by microcalorimetry. *Arch Environ Contam Toxicol* 58(3):587-93.

Chen WQ, Yuan L, Xue R, Li YF, Su RB, Zhang YZ, Li J. 2011. Repeated exposure to chlorpyrifos alters the performance of adolescent male rats in animal models of depression and anxiety. *Neurotoxicol* 32(4):355-61.

Chen XP, Chen WZ, Wang FS, Liu JX. 2012. Selective cognitive impairments are related to selective hippocampus and prefrontal cortex deficits after prenatal chlorpyrifos exposure. *Brain Res* 1474:19-28.

Chernyak SM, Rice CP, McConnell LL. 1996. Evidence of currently-used pesticides in air, ice, fog, seawater and surface microlayer in the Bering and Chukchi seas. *Mar Pollut Bull* 32(5):410-9.

Chowdhury AZ, Jahan SA, Islam MN, Moniruzzaman M, Alam MK, Zaman MA, Karim N, Gan SH. 2012. Occurrence of organophosphorus and carbamate pesticide residues in surface water samples from the Rangpur district of Bangladesh. *Bull Environ Contam Toxicol* 89(1):202-7.

Claver A, Ormad P, Rodríguez L, Ovelleiro JL. 2006. Study of the presence of pesticides in surface waters in the Ebro river basin (Spain). *Chemosphere* 64(9):1437-43.

Close ME, Skinner A. 2012. Sixth national survey of pesticides in groundwater in New Zealand. *NZ J Mar Freshwater Res* 46(4):443-57.

Colborn T. 2006. A case for revisiting the safety of pesticides: a closer look at neurodevelopment. *Environ Health Perspect* 114(1):10-17.

Cole TB, Fisher JC, Burbacher TM, Costa LG, Furlong CE. 2012. Neurobehavioural assessment of mice following repeated postnatal exposure to chlorpyrifos-oxon. *Neurotoxicol Teratol* 34(3):311-22.

Colombo A, Orsi F, Bonfanti P. 2005. Exposure to the organophosphorus pesticide chlorpyrifos inhibits acetylcholinesterase activity and affects muscular integrity in *Xenopus laevis* larvae. *Chemosphere* 61(11):1665-71.

Colville A, Jones P, Pablo F, Krassoi F, Hose G, Lim R. 2008. Effects of chlorpyrifos on macroinvertebrate communities in coastal stream mesocosms. *Ecotoxicol* 17(3):173-80.

Corriols M, Aragón A. 2010. Child labour and acute pesticide poisoning in Nicaragua: failure to comply with children's rights. *Int J Occup Environ Health* 16(2):193-200.

Crane AL, Abdel Rasoul G, Ismail AA, Hendy O, Bonner MR, Lasarev MR, Al-Batanony M, Singleton ST, Khan K, Olson JR, Rohlman DS. 2013. Longitudinal assessment of chlorpyrifos exposure and effect biomarkers in adolescent Egyptian agricultural workers. *J Expo Sci Environ Epidemiol* [Epub Jan 16].

Crawford KD, Weinstein JE, Hemingway RE, Garner TR, Globensky G. 2010. A survey of metal and pesticide levels in stormwater retention pond sediments in coastal South Carolina. *Arch Environ Contam Toxicol* 58(1):9-23.

Croom EL, Wallace AD, Hodgson E. 2010. Human variation in CYP-specific chlorpyrifos metabolism. *Toxicology* 276(3):184-91.

Crossan AN, Kennedy IR. 2008. Calculation of pesticide degradation in decaying cotton gin trash. *Bull Environ Contam Toxicol* 81(4):355-9.

Crumpton TL, Seidler FJ, Slotkin TA. 2000. Developmental neurotoxicity of chlorpyrifos *in vivo* and *in vitro*: effects on nuclear transcription factors involved in cell replication and differentiation. *Brain Res* 857(1-2):87–98.

Cui Y, Guo J, Xu B, Chen Z. 2011. Genotoxicity of chlorpyrifos and cypermethrin in ICR mouse hepatocytes. *Toxicol Mech Methods* 21(1):70-4.

Cunha JP, Chueca P, Garcerá C, Moltó E. 2012. Risk assessment of pesticide spray drift from citrus applications with air-blast sprayers in Spain. *Crop Protect* 42:116-23.

Curl CL, Fenske RA, Kissel JC, Shirai JH, Moate TF, Griffith W, Coronado G, Thompson B. 2002. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environ Health Perspect* 110(12):A787-92.

Curwin BD, Hein MJ, Sanderson WT, Striley C, Heederik D, Kromhout H, Reynolds SJ, Alavanja MC. 2007. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. *Ann Occup Hyg* 51(1):53-65.

DAFF. 2010. Prohibition notice regarding the use of certain agricultural remedy. Government Notices. Department of Agriculture, Forestry and Fisheries No. R. 375. Government Gazette, 14 May 2010. http://www.nda.agric.za/doaDev/sideMenu/ActNo36_1947/gg33171_nn375_Fert.pdf.

Daglioglu N, Akcan R, Gulmen MK, Yener F, Efeoglu P. 2011. Pesticide intoxications in Cukurova, Turkey: three year analysis. *Hum Exp Toxicol* 30(12):1892-5.

Daily Mail Reporter. 2011. 'Bed bug pesticide poisoning' killed Californian woman and six other tourists in Thailand. *Mail Online*. May 10th. http://www.dailymail.co.uk/news/article-1385518/Bed-bug-pesticide-poisoning-caused-death-California-woman-tourists-Thailand.html#ixzz1NztCOKQX.

Dam K, Seidler FJ, Slotkin TA. 1998. Developmental neurotoxicity of chlorpyrifos: delayed targeting of DNA synthesis after repeated administration. *Brain Res Dev Brain Res* 108(1-2):39-45.

Dam K, Garcia SJ, Seidler FJ, Slotkin TA. 1999. Neonatal chlorpyrifos exposure alters synaptic development and neuronal activity in cholinergic and catecholaminergic pathways. *Brain Res Dev Brain Res* 116(1):9-20.

Dam K, Seidler FJ, Slotkin TA. 2000. Chlorpyrifos exposure during a critical neonatal period elicits gender-selective deficits in the development of coordination skills and locomotor activity. *Brain Res Dev Brain Res* 121(2):179-87.

Dansereau C, Perez M, Kegley SE, Tupper KA, Wang A. 2006. Poisons on the Wind. Community Air Monitoring for Chlorpyrifos in the Yakima Valley. Farm Worker Pesticide Project, Yakima, and Pesticide Action North America, San Francisco. http://www.pesticideresearch.com/site/docs/DriftCatcher/POW12-20-06YakimaSUM.pdf.

Das KP, Barone S Jr. 1999. Neuronal differentiation in PC12 cells is inhibited by chlorpyrifos and its metabolites: is acetylcholinesterase inhibition the site of action? *Toxicol Appl Pharmacol* 160(3):217-30.

Das Gupta R, Chakravorty PP, Kaviraj A. 2010. Studies on relative toxicities of six insecticides on epigeic earthworm, *Perionyx excavatus*. *Bull Environ Contam Toxicol* 85(1):83-6.

Datta S, Hansen L, McConnell L, Baker J, LeNoir J, Seiber JN. 1998. Pesticides and PCB contaminants in fish and tadpoles from the Kaweah River Basin, California. *Bull Environ Contam Toxicol* 60(6):829-36.

Davidson C, Stanley K, Simonich SM. 2012. Contaminant residues and declines of the Cascades frog (*Rana cascadae*) in the California Cascades, USA. *Environ Toxicol Chem* 31(8):1895-902.

Dayton SB, Sandler DP, Blair A, Alavanja M, Beane Freeman LE, Hoppin JA. 2010. Pesticide use and myocardial infarction incidence among farm women in the Agricultural Health Study. *J Occup Environ Med* 52(7):693-7.

De Angelis S, Tassinari R, Maranghi F, Eusepi A, Di Virgilio A, Chiarotti F, Ricceri L, Venerosi Pesciolini A, Gilardi E, Moracci G, Calamandrei G, Olivieri A, Mantovani A. 2009. Developmental exposure to chlorpyrifos induces alterations in thyroid and thyroid hormone levels without other toxicity signs in CD-1 mice. *Toxicol Sci* 108(2):311-9.

De Silva PM, Pathiratne A, van Straalen NM, van Gestel CA. 2010. Chlorpyrifos causes decreased organic matter decomposition by suppressing earthworm and termite communities in tropical soil. *Environ Pollut* 158(10):3041-7.

Dehghani R, Shayeghi M, Esalmi H, Moosavi SG, Rabani DK, Shahi DH. 2012. Determination of organophosphorous pesticides (diazinon and chlorpyrifos) in water resources in Barzok, Kashan. *Zahedan J Res Med Sci* 14(10):66-72.

Delpuech JM, Meyet J. 2003. Reduction in the sex ratio of the progeny of a parasitoid wasp (*Trichogramma brassicae*) surviving the insecticide chlorpyrifos. *Arch Environ Contam Toxicol* 45(2):203-8.

Del Prado Lu JL. 2010. Multipesticide residue assessment of agricultural soil and water in major farming areas in Benguet, Philippines. *Arch Environ Contam Toxicol* 59(2):175-81.

Deneer JW. 1994. Bioconcentration of chlorpyrifos by the three-spined stickleback under laboratory and field conditions. *Chemosphere* 29(7):1561-1575.

Deribe E, Rosseland BO, Borgstrøm R, Salbu B, Gebremariam Z, Dadebo E, Norli HR, Eklo OM. 2011. Bioaccumulation of persistent organic pollutants (POPs) in fish species from Lake Koka, Ethiopia: the influence of lipid content and trophic position. *Sci Total Environ* 410-411:136-45.

Desneux N, Rafalimanana H, Kaiser L. 2004. Dose-response relationship in lethal and behavioural effects of different insecticides on the parasitic wasp *Aphidius ervi*. Chemosphere 54(5):619-27.

Dhillon AS, Tarbutton GL, Levin JL, Plotkin GM, Lowry LK, Nalbone JT, Shepherd S. 2008. Pesticide/environmental exposures and Parkinson's disease in East Texas. *J Agromedicine* 13(1):37-48.

Dimitrov B, Gadeva P. 1997. Genotoxicity studies on the insecticide dursban in root meristem cells of *Crepis capillaris* L. *Environ Exper Bot* 37(2-3):199-209.

Donald DB, Cessna AJ, Sverko E, Glozier NE. 2007. Pesticides in surface drinking water supplies of the Northern Great Plains. *Environ Health Perspect* 115:1183-91.

Dow AgroSciences. 2013. Re Organophosphate and Carbamate Reassessment (APP201045). Submission 102675 Appendix A Chlorpyrifos. Environmental Protection Authority, Wellington. http://www.epa.govt.nz/search-databases/Pages/applications-details.aspx?appID=APP201045#.

Duirk SE, Collette TW. 2005. Organophosphate Pesticide Degradation Under Drinking Water Treatment Conditions. United States. EPA/600/R-05/103. Environmental Protection Agency, Washington. http://www.epa.gov/athens/publications/reports/Duirk600R05103OrganophosphatePesticide.pdf.

EC. 2005. Review report for the active substance chlorpyrifos. SANCO/3059/99 - rev.1.5. Health and Consumer Protection Directorate-General, European Commission. http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection.

Echeverría-Sáenz S, Mena F, Pinnock M, Ruepert C, Solano K, de la Cruz E, Campos B, Sánchez-Avila J, Lacorte S, Barata C. 2012. Environmental hazards of pesticides from pineapple crop production in the Río Jiménez watershed (Caribbean Coast, Costa Rica). *Sci Total Environ* 440:106-14.

EFSA. 2010. 2008 Annual Report on Pesticide Residues According to Article 32 of Regulation (EC) No 396/2005, European Food Safety Authority, Parma. *EFSA Journal* 8(7):1646. http://www.efsa.europa.eu/en/efsajournal/pub/1646.htm.

El-Amrani S, Pena-Abaurrea M, Sanz-Landaluze J, Ramos L, Guinea J, Cámara C. 2012. Bioconcentration of pesticides in zebrafish eleutheroembryos (*Danio rerio*). *Sci Total Environ* 425:184-90.

Elsharkawy EE, Yahia D, El-Nisr NA. 2013. Sub-chronic exposure to chlorpyrifos induces haematological, metabolic disorders, and oxidative stress in rat: attenuation by glutathione. *Environ Toxicol Pharmacol* 35(2):218-27.

El-Zaemey S, Fritschi L, Heyworth J. 2013. Occupational pesticide exposure among Yemeni women. *Environ Res* 122:45-51.

Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, Samanic C, Sandler DP, Blair A, Alavanja MC. 2005. Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. *Am J Epidemiol* 161(2):121-35.

Ertl H, Butte W. 2012. Bioaccessibilty of pesticides and polychlorinated biphenyls from house dust: in-vitro methods and human exposure. *J Expo Sci Environ Epidemiol* 22(6):574-83.

Essumang DK, Togoh GK, Chokky L. 2009. Pesticide residues in the water and fish (lagoon tilapia) samples from lagoons in Ghana. *Bull Chem Soc Ethiop* 23(1):19-27.

Estevan Martínez C, Vilanova E, Sogorb MA. 2011. Chlorpyrifos and its metabolite, chlorpyrifos-oxon, modify the genetic expression of mouse embryonic stem cells after 12 h of exposure. *Toxicol Lett* 205(S 157):P1318.

Estévez E, Cabrera Mdel C, Molina-Díaz A, Robles-Molina J, Palacios-Díaz Mdel P. 2012. Screening of emerging contaminants and priority substances (2008/105/EC) in reclaimed water for irrigation and groundwater in a volcanic aquifer (Gran Canaria, Canary Islands, Spain). *Sci Total Environ* 433:538-46.

Farag AT, El Okazy AM, El-Aswed AF. 2003. Developmental toxicity study of chlorpyrifos in rats. *Reprod Toxicol* 17(2):203-8.

Farag AT, Radwan AH, Sorour F, El Okazy A, El-Agamy E-S, El-Sebae AE-K. 2010. Chlorpyrifos induced reproductive toxicity in male mice. *Reprod Toxicol* 29(1):80-5.

Farahat FM, Fenske RA, Olson JR, Galvin K, Bonner MR, Rohlman DS, Farahat TM, Lein PJ, Anger WK. 2010. Chlorpyrifos exposures in Egyptian cotton field workers. *Neurotoxicology* 31(3):297-304.

Farahat FM, Ellison CA, Bonner MR, McGarrigle BP, Crane AL, Fenske RA, Lasarev MR, Rohlman DS, Anger WK, Lein PJ, Olson JR. 2011. Biomarkers of chlorpyrifos exposure and effect in Egyptian cotton field workers. *Environ Health Perspect* 119(6):801-6.

Fenske RA, Black KG, Elkner KP, Lee CL, Methner MM, Soto R. 1990. Potential exposure and health risks of infants following indoor residential pesticide applications. *Am J Public Health* 80(6):689-93.

Fenske RA, Lu C, Barr D, Needham L. 2002. Children's exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. *Environ Health Perspect* 110(5):549-53.

Fenske RA, Farahat FM, Galvin K, Fenske EK, Olson JR. 2012. Contributions of inhalation and dermal exposure to chlorpyrifos dose in Egyptian cotton field workers. *Int J Occup Environ Health* 18(3):198-209.

Ferrari F, Karpouzas DG, Trevisan M, Capri E. 2005. Measuring and predicting environmental concentrations of pesticides in air after application to paddy water systems. *Environ Sci Technol* 39(9):2968-75.

Fieten KB, Kromhout H, Heederik D, van Wendel de Joode B. 2009. Pesticide exposure and respiratory health of indigenous women in Costa Rica. *Am J Epidemiol* 169(12):1500-06.

Flaskos J. 2012. The developmental neurotoxicity of organophosphorus insecticides: A direct role for the oxon metabolites. *Toxicol Lett* 209(1):86-93.

Fortenberry GZ, Hu H, Turyk M, Barr DB, Meeker JD. 2012. Association between urinary 3,5,6-trichloro-2-pyridinol, a metabolite of chlorpyrifos and chlorpyrifos-methyl, and serum T4 and TSH in NHANES 1999-2002. *Sci Total Environ* 424:351-5.

Frampton GK, van den Brink PJ. 2007. Collembola and macroarthropod community responses to carbamate, organophosphate and synthetic pyrethroid insecticides: direct and indirect effects. *Environ Pollut* 147(1):14-25.

Franke C, Studinger G, Berger G, Böhling S, Bruckmann U, Cohors-Fresenborg D, Jöhncke U. 1994. The assessment of bioaccumulation. *Chemosphere* 29(7):1501-14.

Friedman-Rudovsky J. 2012. New paint wipes out infestation in a village. *The New York Times*, July 23. http://www.nytimes.com/2012/07/24/health/insecticidal-paint-shows-promise-in-curbing-disease.html?_r=0.

Furlong CE, Cole TB, Jarvik GP, Pettan-Brewer C, Geiss GK, Richter RJ, Shih DM, Tward AD, Lusis AJ, Costa LG. 2005. Role of paraoxonase (PON1) status in pesticide sensitivity: genetic and temporal determinants. *Neurotoxicology* 26(4):651-9.

Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B. 2006. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. *Pharmacogenet Genomics* 16(3):183-90.

Garbarino JR, Snyder-Conn E, Leiker TJ, Hoffman GL. 2002. Contaminants in Arctic snow collected over Northwest Alaskan sea ice. *Water Air Soil Pollut* 139(1-4):183-214.

Galloway T, Handy R. 2003. Immunotoxicity of organophosphorous pesticides. *Ecotoxicology* 12(1-4):345-63.

Galvan TL, Koch RL, Hutchison WD. 2005. Toxicity of commonly used insecticides in sweet corn and soybean to multicolored Asian lady beetle (Coleoptera: Coccinellidae). *J Econ Entomol* 98(3):780-9.

Garcia SJ, Seidler FJ, Crumpton TL, Slotkin TA. 2001. Does the developmental neurotoxicity of chlorpyrifos involve glial targets? Macromolecule synthesis, adenylyl cyclase signaling, nuclear transcription factors, and formation of reactive oxygen in C6 glioma cells. *Brain Res* 891(1-2):54–68.

Garcia SJ, Seidler FJ, Qiao D, Slotkin TA. 2002. Chlorpyrifos targets developing glia: effects on glial fibrillary acidic protein. *Brain Res Dev Brain Res* 133(2):151-61.

Garcia SJ, Seidler FJ, Slotkin TA. 2003. Developmental neurotoxicity elicited by prenatal or postnatal chlorpyrifos exposure: effects on neurospecific proteins indicate changing vulnerabilities. *Environ Health Perspect* 111(3):297-303.

García-de la Parra LM, Cervantes-Mojica LJ, González-Valdivia C, Martínez-Cordero FJ, Aguilar-Zárate G, Bastidas-Bastidas P, Betancourt-Lozano M. 2012. Distribution of pesticides and PCBs in sediments of agricultural drains in the Culiacan Valley, Sinaloa, Mexico. *Arch Environ Contam Toxicol* 63(3):323-36.

Gatto NM, Cockburn M, Bronstein J, Manthripragada AD, Ritz B. 2009. Well-water consumption and Parkinson's disease in rural California. *Environ Health Perspect* 117(12):1912-8.

Gaw SK. 2002. Pesticide Residues in Horticultural Soils in the Auckland Region. ARC Working Report No. 96. Auckland Regional Council. http://www.canterbury.ac.nz/ucresearchprofile/researcher.aspx?researcherid=2700976.

Gebara AB, Ciscato CH, Monteiro SH, Souza GS. 2011. Pesticide residues in some commodities: dietary risk for children. *Bull Environ Contam Toxicol* 86(5):506-10.

Gebremariam SY, Beutel MW, Yonge DR, Flury M, Harsh JB. 2012. Adsorption and desorption of chlorpyrifos to soils and sediments. *Rev Environ Contam Toxicol* 215:123-75.

Gels JA, Held DW, Potter DA. 2002. Hazards of insecticides to the bumble bees *Bombus impatiens* (Hymenoptera: Apidae) foraging on flowering white clover in turf. *J Econ Entomol* 95(4):722-8.

Ghisari M, Bonefeld-Jorgensen EC. 2005. Impact of environmental chemicals on the thyroid hormone function in pituitary rat GH3 cells. *Mol Cell Endocrinol* 244(1-2):31-41.

Gilliom RJ, Barbash JE, Crawford CG, Hamilton PA, Martin JD, Nakagaki N, Nowell LH, Scott JC, Stackelberg PE, Thelin GP, Wolock DM. 2006. The Quality of Our Nation's Waters—Pesticides in the Nation's Streams and Ground Water, 1992-2001. U.S. Geological Survey Circular 1291, U.S. Department of the Interior. http://pubs.usgs.gov/circ/2005/1291/.

Gore AC. 2001. Environmental toxicant effects on neuroendocrine function. *Endocrine* 14(2):235-46.

Gore AC. 2002. Organochlorine pesticides directly regulate gonadotrophin-releasing hormone gene expression and biosynthesis in the GT1-7 hypothalamic cell line. *Mol Cell Endocrinol* 192(1-2):157-70.

Gotoh M, Saito I, Huang J, Fukaya Y, Matsumoto T, Hisanaga N, Shibata E, Ichihara G, Kamijima M, Takeuchi Y. 2001. Changes in cholinesterase activity, nerve conduction velocity, and clinical signs and symptoms in termite control operators exposed to chlorpyrifos. *J Occup Health* 43(3):157-64.

Gouin T. 2003. Appendix B: Comparison of methods for estimating degradation half-lives. In: *Long-Range Transport of Organic Contaminants: The Role of Air-Surface Exchange*. MSc thesis. Trent University, Peterborough, Ontario, Canada.

Gouin T, Wania F, Ruepert C, Castillo LE. 2008. Field testing passive air samplers for current use pesticides in a tropical environment. *Environ Sci Technol* 42(17):6625-30.

Grigoryan H, Lockridge O. 2009. Nanoimages show disruption of tubulin polymerization by chlorpyrifos oxon: Implications for neurotoxicity. *Toxicol Appl Pharmacol* 240(2):143-8.

Grünefeld HT, Bonefeld-Jorgensen EC. 2004. Effect of *in vitro* estrogenic pesticides on human oestrogen receptor alpha and beta mRNA levels. *Toxicol Lett* 151(3):467-80.

Guadarrama-Naveda M, de Cabrera LC, Matos-Bastidas S. 2001. Intermediate syndrome secondary to ingestion of chlorpiriphos. *Vet Hum Toxicol* 43(1):34.

Gulson BL. 2008. Can some of the detrimental neurodevelopmental effects attributed to lead be due to pesticides? *Sci Total Environ* 396(2-3):193-5.

Gunnell D, Eddleston M, Phillips MR, Konradsen F. 2007. The global distribution of fatal self-poisoning: Systematic review. *BMC Public Health* 7:357.

Gupta SC, Mishra M, Sharma A, Deepak Balaji TG, Kumar R, Mishra RK, Chowdhuri DK. 2010. Chlorpyrifos induces apoptosis and DNA damage in *Drosophila* through generation of reactive oxygen species. *Ecotoxicol Environ Saf* 73(6):1415-23.

Hageman KJ, Simonich SL, Campbell DH, Wilson GR, Landers DH. 2006. Atmospheric deposition of current-use and historic-use pesticides in snow at national parks in the western United States. *Environ Sci Technol* 40(10):3174-3180. Supporting Information.

Hansen DJ, Goodman LR, Cripe GM, Macauley SF. 1986. Early life-stage toxicity test methods for gulf toadfish (*Opsanus beta*) and results using chlorpyrifos. *Ecotoxicol Environ Saf* 11(1):15-22.

Harman-Fetcho JA, McConnell LL, Baker JE. 1999. Agricultural pesticides in the Patuxent River, a tributary of the Chesapeake Bay. *J Environ Qual* 28(3):928-38.

Harman-Fetcho JA, McConnell LL, Rice CP, Baker JE. 2000. Wet deposition and air-water gas exchange of currently used pesticides to a subestuary of the Chesapeake Bay. *Environ Sci Technol* 34(8):1462-8.

Harnly M, McLaughlin R, Bradman A, Anderson M, Gunier R. 2005. Correlating agricultural use of organophosphates with outdoor air concentrations: a particular concern for children. *Environ Health Perspect* 113(9):1184-9.

Haviland JA, Butz DE, Porter WP. 2010. Long-term sex selective hormonal and behaviour alterations in mice exposed to low doses of chlorpyrifos *in utero*. *Reprod Toxicol* 29(1):74-9.

Hayden KM, Norton MC, Darcey D, Ostbye T, Zandi PP, Breitner JCS, Welsh-Bohmer KA, Cache County Study Investigators. 2010. Occupational exposure to pesticides increases the risk of incident AD: the Cache County study. *Neurology* 74(19):1524-30.

Hermanson MH, Isaksson E, Teixeira C, Muir DC, Compher KM, Li YF, Igarashi M, Kamiyama K. 2005. Current-use and legacy pesticide history in the Austfonna Ice Cap, Svalbard, Norway. *Environ Sci Technol* 39(21):8163-9.

Hernández AF, Parrón T, Tsatsakis AM, Requena M, Alarcón R, López-Guarnido O. 2012. Toxic effects of pesticide mixtures at a molecular level: their relevance to human health. *Toxicology* [Epub June 21].

Hodgson E, Rose RL. 2008. Metabolic interactions of agrochemicals in humans. *Pest Manag Sci* 64(6):617-21.

Hoferkamp L, Hermanson MH, Muir DG. 2010. Current use pesticides in Arctic media; 2000-2007. *Sci Total Environ* 408(15):2985-94.

Holcombe GW, Phipps GL, Tanner DK. 1982. The acute toxicity of kelthane, dursban, disulfoton, pydrin, and permethrin to fathead minnows *Pimephales promelas* and rainbow trout *Salmo gairdneri*. *Environ Pollut* 29(3):167-78.

Holland N, Furlong C, Bastaki M, Richter R, Bradman A, Huen K, Beckman K, Eskenazi B. 2006. Paraoxonase polymorphisms, haplotypes, and enzyme activity in Latino mothers and newborns. *Environ Health Perspect* 114(7):985-91.

Hopper T. 2012. Potent bed bug poison may have killed Canadian tourist, friend in Vietnam. *National Post*. Sept 19. http://news.nationalpost.com/2012/09/19/potent-bed-bug-poison-may-have-killed-canadian-tourist-friend-in-vietnam/.

Horton MK, Kahn LG, Perera F, Barr DB, Rauh V. 2012. Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? *Neurotoxicol Teratol* 34(5):534-41.

Howard AS, Bucelli R, Jett DA, Bruun D, Yang DR, Lein PJ. 2005. Chlorpyrifos exerts opposing effects on axonal and dendritic growth in primary neuronal cultures. *Toxicol Appl Pharmacol* 207(2):112-24.

HSDB. 2008. Chlorpyrifos. Number 389. Hazardous Substances Databank, US National Library of Medicine, Bethsheda. Last reviewed 1/10/2008. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

Hua F, Yunlong Y, Xiaoqiang C, Xiuguo W, Xiaoe Y, Jingquan Y. 2009. Degradation of chlorpyrifos in laboratory soil and its impact on soil microbial functional diversity. *J Environ Sci (China)* 21(3):380-86.

Huen K, Harley K, Brooks J, Hubbard A, Bradman A, Eskenazi B, Holland N. 2009. Developmental changes in PON1 enzyme activity in young children and effects of PON1 polymorphisms. *Environ Health Perspect* 117(10):1632-8.

Huen K, Bradman A, Harley K, Yousefi P, Boyd Barr D, Eskenazi B, Holland N. 2012. Organophosphate pesticide levels in blood and urine of women and newborns living in an agricultural community. *Environ Res* 117:8-16.

Huynh HPV, Nugegoda D. 2012. Effects of chlorpyrifos exposure on growth and food utilization in Australian catfish, *Tandanus tandanus*. *Bull Environ Contam Toxicol* 88(1):25-9.

ICAMA. 2012. China Pesticide Information Network, Institute for the Control of Agrochemicals, Ministry of Agriculture, P.R. China. http://www.chinapesticide.gov.cn/service/aspx/e2.aspx.

Icenogle LM, Christopher NC, Blackwelder WP, Caldwell DP, Qiao D, Seidler FJ, Slotkin TA, Levin ED. 2004. Behavioral alterations in adolescent and adult rats caused by a brief subtoxic exposure to chlorpyrifos during neurulation. *Neurotoxicol Teratol* 26(1):95-101.

Idris SB, Ambali SF, Ayo JO. 2012. Cytotoxicity of chlorpyrifos and cypermethrin: the ameliorative effects of antioxidants. *Afr J Biotechnol* 11(99):16461-7.

IUPAC. 2012. Pesticide Properties Database. International Union of Pure and Applied Chemistry. http://sitem.herts.ac.uk/aeru/iupac/154.htm.

Jamal GA. 1997. Neurological syndromes of organophosphorus compounds. *Adverse Drug React Toxicol Rev* 16(3):133-70.

Jameson RR, Seidler FJ, Qiao D, Slotkin TA. 2006. Chlorpyrifos affects phenotypic outcomes in a model of mammalian neurodevelopment: critical stages targeting differentiation in PC12 cells. *Environ Health Perspect* 114(5):667-72.

JanakiDevi V, Nagarani N, YokeshBabu M, Kumaraguru AK, Ramakritinan CM. 2013. A study of proteotoxicity and genotoxicity induced by the pesticide and fungicide on marine invertebrate (*Donax faba*). *Chemosphere* 90(3):1158-66.

Jantunen LM, Wong F, Bidleman TF, Stern G. 2007. Occurrence and levels of current-use and legacy pesticides in air: Leg 1 of ArcticNet 2007. Arctic Net. Collingwood, ON. http://www.arcticnet.

ulaval.ca/pdf/posters_2007/jantunen_et_al.pdf.

Jayawardane P, Dawson AH, Weerasinghe V, Karalliedde L, Buckley NA, Senanayake N. 2008. The spectrum of intermediate syndrome following acute organophosphate poisoning: a prospective cohort study from Sri Lanka. *PloS Medicine* 5(7)e147.

Jayawardena UA, Rajakaruna RS, Navaratne AN, Amerasinghe PH. 2010. Toxicity of agrochemicals to common hourglass tree frog (*Polypedates cruciger*) in acute and chronic exposure. *Int J Agric Biol* 12:641-8.

Jergentz S, Mugni H, Bonetto C, Schulz R. 2005. Assessment of insecticide contamination in runoff and stream water of small agricultural streams in the main soybean area of Argentina. *Chemosphere* 61(6): 817-26.

Jessup DA, Johnson CK, Estes J, Carlson-Bremer D, Jarman WM, Reese S, Dodd E, Tinker MT, Ziccardi MH. 2010. Persistent organic pollutants in the blood of free-ranging sea otters (*Enhydra lutris* ssp.) in Alaska and California. *J Wildlife Dis* 46(4):1214-33.

Jin-Clark Y, Lydy MJ, Zhu KY. 2002. Effects of atrazine and cyanazine on chlorpyrifos toxicity in *Chironomus tentans* (Diptera: Chironomidae). *Environ Toxicol Chem* 21(3):598-603.

Jirachaiyabhas V, Visuthismajarn P, Hore P, Robson MG. 2004. Organophosphate pesticide exposures of traditional and integrated pest management farmers from working air conditions: a case study in Thailand. *Int J Occup Environ Health* 10(3):289-95.

JMPR. 2013. Pesticide Residues in Food 2012. Joint FAO/WHO Meeting on Pesticide Residues. FAO Plant Production and Protection Paper 215. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Rome, Italy, 11-20 September 2012. World Health Organization, Food and Agriculture Organization of the United Nations, Rome. http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report12/JMPR_2012_Report.pdf.

Johnson S, Saikia N, Kumar A. 2006. Analysis of Pesticide Residues in Soft Drinks. Centre for Science and the Environment, and Pollution Monitoring Laboratory, New Delhi. http://cbrayton.files.wordpress.com/2006/08/labreport2006.pdf.

Joubert J, Joubert PH. 1988. Chorea and psychiatric changes in organophosphate poisoning. A report of 2 further cases. *S Afr Med J* 74(1):32-4.

Juan-Blasco M, Tena A, Vanaclocha P, Cambra M, Urbaneja A, Monzó C. 2011. Efficacy of a micro-encapsulated formulation compared with a sticky barrier for excluding ants from citrus canopies. *J Appl Entomol* 135(6):467-72.

Juraske R, Mosquerra Vivas CS, Erazo Velásquez A, García Santos G, Berdugo Moreno MB, Gomez JD, Binder CR, Hellweg S, Guerro Dallos JA. 2011. Pesticide uptake in potatoes: model and field experiments. *Environ Sci Technol* 45(2):651-7.

Kalender Y, Kaya S, Durak D, Uzun FG, Demir F. 2012. Protective effects of catechin and quercetin on antixoidant status, lipid peroxidation and testis-histoarchitecture induced by chlorpyrifos in male rats. *Environ Toxicol Pharmacol* 33(2):141-8.

Kaplan JG, Kessler J, Rosenberg N, Pack D, Schaumburg HH. 1993. Sensory neuropathy associated with Dursban (chlorpyrifos) exposure. *Neurology* 43(11):2193-6.

Karunanayake CP, Spinelli JJ, McLaughlin JR, Dosman JA, Pahwa P, McDuffie HH. 2012. Hodgkin lymphoma and pesticides exposure in men: a Canadian case-control study. *J Agromedicine* 17(1):30-9.

Kaur P, Grover IS. 1985. Cytological effects of some organophosphorous pesticides. I. Mitotic effects. *Cytologia* 50(1):187-97.

Kavitha P, Rao JV. 2008. Toxic effects of chlorpyrifos on antioxidant enzymes and target enzyme acetylcholinesterase interaction in mosquito fish, *Gambusia affinis*. *Environ Toxicol Pharmacol* 26(2):192-8.

Kegley S, Katten A, Moses M. 2003. *Secondhand Pesticides: Airborne Pesticide Drift in California.* Pesticide Action Network North America, California Rural Legal Assistance Foundation, Pesticide Education Center, San Francisco. http://www.panna.org/sites/default/files/SecondhandPesticides2003.pdf.

Kegley SE, Hill BR, Orme S, Choi AH. 2011. *PAN Pesticide Database*, Pesticide Action Network, North America, San Francisco. http://www.pesticideinfo.org.

Kenaga EE. 1980. Correlation of bioconcentration factors of chemicals in aquatic and terrestrial organisms with their physical and chemical properties. *Environ Sci Technol* 14(5):553-6.

Kerby JL, Storfer A. 2009. Combined effects of atrazine and chlorpyrifos on susceptibility of the tiger salamander to *Ambystoma tigrinum* virus. *EcoHealth* 6(1):91-8.

Kilburn KH. 1999. Evidence for chronic neurobehavioural impairment from chlorpyrifos, and organophosphate insecticide (Dursban) used indoors. Environ Epidemiol Toxicol 1:153-62. In: Abou-Donia 2003.

Kim HH, Lim YW, Yang JY, Shin DC, Ham HS, Choi BS, Lee JY. 2013. Health risk assessment of exposure to chlorpyrifos and dichlorvos in children at childcare facilities. *Sci Total Environ* 444:441-50.

Kissel JC. 2011. The mismeasure of dermal absorption. *J Expo Sci Environ Epidemiol* 21(3):302-9.

Kitada Y, Kawahata H, Suzuki A, Oomori T. 2008. Distribution of pesticides and bisphenol A in sediments collected from rivers adjacent to coral reefs. *Chemosphere* 71(11):2082-90.

Kojima H, Katsura E, Takeuchi S, Niiyama K, Kobayashi K. 2004. Screening for estrogen and androgen receptor activities in 200 pesticides by *in vitro* reporter gene assays using Chinese hamster ovary cells. *Environ Health Perspect* 112(5):524-31.

Kretowicz E. 2012. Imports make up toxic takeaways. *The Canberra Times*, Dec2. http://www.canberratimes.com.au/act-news/imports-make-up-toxic-takeaways-20121201-2aoai.html.

Kventsel I, Berkovitch M, Reiss A, Bulkowstein M, Kozer E. 2005. Scopolamine treatment for severe extra-pyramidal signs following organophosphate (chlorpyrifos) ingestion. *Clin Toxicol (Phila)* 43(7):877-9.

Kurt-Karakus PB, Teixeira C, Small J, Muir D, Bidleman TF. 2011. Current-use pesticides in inland lake waters, precipitation, and air from Ontario, Canada. *Environ Toxicol Chem* 30(7):1539-48.

Lal S, Lal R, Saxena DM. 1987. Bioconcentration and metabolism of DDT, fenitrothion and chlorpyrifos by the blue-green algae

Anabaena sp. and *Aulosira fertilissima*. *Environ Pollut* 46(3):187-96.

Landers DH, Simonich SL, Jaffe DA, Geiser LH, Campbell DH, Schwindt AR, Schreck CB, Kent ML, Hafner WD, Taylor HE, Hageman KJ, Usenko S, Ackerman LK, Schrlau JE, Rose NL, Blett TF, Erway MM. 2008. The Fate, Transport, and Ecological Impacts of Airborne Contaminants in Western National Parks (USA). EPA/600/R-07/138. U.S. Environmental Protection Agency, Office of Research and Development, NHEERL, Western Ecology Division, Corvallis, Oregon. http://www.nature.nps.gov/air/studies/air_toxics/docs/2008FinalReport/WACAP_Report_Volume_I_Main.pdf.

Landrigan PJ, Claudio L, Markowitz SB, Berkowitz GS, Brenner BL, Romero H, Wetmur JG, Matte TD, Gore AC, Godbold JH, Wolff MS. 1999. Pesticides and inner-city children: exposures, risks, and prevention. *Environ Health Perspect* 107(Suppl 3):431-7.

Lassiter TL, Brimijoin S. 2008. Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos. *Neurotoxicol Teratol* 30(2):125-30.

Latif Y, Sherazi STH, Bhanger MI. 2011. Assessment of pesticide residues in commonly used vegetables in Hyderabad, Pakistan. *Ecotoxicol Environ Saf* 74(8):2299-303.

Lavin KS, Hageman KJ, Marx SK, Dillimgham PW, Kamber BS. 2012. Using trace elements in particulate matter to identify the sources of semivolatile organic contaminants in air at an alpine site. *Environ Sci Technol* 46(1):268-76.

LeBlanc HM, Culp JM, Baird DJ, Alexander AC, Cessna AJ. 2012. Single versus combined lethal effects of three agricultural insecticides on larvae of the freshwater insect *Chironomus dilutus*. *Arch Environ Contam Toxicol* 63(3):378-90.

Lee S, McLaughlin R, Harnly M, Gunier R, Kreutzer R. 2002. Community exposures to airborne agricultural pesticides in California: ranking of inhalation risk. *Environ Health Perspect* 110(12):1175-84.

Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, Dosemeci M, Alavanja MCR. 2004. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *J Natl Cancer Inst* 96(23):1781-9.

Lee F, Lin JL. 2006. Intermediate syndrome after organophosphate intoxication in patient with end-stage renal disease. *Ren Fail* 28(2):197-200.

Lee WJ, Sandler DP, Blair A, Samanic C, Cross AJ, Alavanja MCR. 2007a. Pesticide use and colorectal cancer risk in the Agricultural Health Study. *Int J Cancer* 121(2):339-46.

Lee WJ, Alavanja MCR, Hoppin JA, Rusiecki JA, Kamel F, Blair A, Sandler DP. 2007b. Mortality among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *Environ Health Perspect* 115(4):528-34.

Lee JE, Park JH, Shin IC, Koh HC. 2012. Reactive oxygen species regulated mitochondria-mediated apoptosis in PC12 cells exposed to chlorpyrifos. *Toxicol Appl Pharmacol* 263(2):148-62.

Lehotay SJ, Harman-Fetcho JA, McConnell LL. 1998. Agricultural pesticide residues in oysters and water from two Chesapeake Bay tributaries. *Mar Pollut Bull* 37(1-2):32-44.

Lein PJ, Bonner MR, Farahat FM, Olson JR, Rohlman DS, Fenske RA, Lattal KM, Lasarev MR, Galvin K, Farahat TM, Anger WK. 2012. Experimental strategy for translational studies of organophosphorus pesticide neurotoxicity based on real-world occupational exposures to chlorpyrifos. *Neurotoxicology* 33(4):660-8.

Leong KH, Tan LL, Mustafa AM. 2007. Contamination levels of selected organochlorine and organophosphate pesticides in the Selangor River, Malaysia between 2002 and 2003. *Chemosphere* 66(6):1153-9.

Levin HS, Rodnitzky RL, Mick DL. 1976. Anxiety associated with exposure to organophosphate compounds. *Arch Gen Psychiatry* 33(2):225-8.

Levin ED, Addy N, Nakajima A, Christopher NC, Seidler FJ, Slotkin TA. 2001. Persistent behavioral consequences of neonatal chlorpyrifos exposure in rats. *Brain Res Dev Brain Res* 130(1):83-9.

Levin ED, Addy N, Baruah A, Elias A, Christopher NC, Seidler FJ, Slotkin TA. 2002. Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations. *Neurotoxicol Teratol* 24(6):733-41.

Li SQ, Liu YQ, Ni ZY, Song XO, Liu XR, Zhao L. 1993. Mutagenicity of 24 organophosphorous pesticides determined by 6 short-term tests. *Chinese J Pharmacol Toxicol* 7:73-7.

Li Q, Kobayashi M, Kawada T. 2009. Chlorpyrifos induces apoptosis in human T cells. *Toxicology* 255(1-2):53-7.

Li H, Sun B, Lydy MJ, You J. 2013. Sediment-associated pesticides in an urban stream in Guangzhou, China: implications of a shift in pesticide use patterns. *Environ Toxicol Chem* [Epub Feb 1] doi:10.1002/etc.2147.

Lieberman AD, Craven MR, Lewis HA, Nemenzo JH. 1998. Genotoxicity from domestic use of organophosphate pesticides. *J Occup Environ Med* 40(11):954-7.

Liu B, McConnell LL, Torrents A. 2001. Hydrolysis of chlorpyrifos in natural waters of the Chesapeake Bay. *Chemosphere* 44(6):1315-23.

Lizotte RE Jr, Knight SS, Cooper CM. 2010. Toxicity evaluation of a conservation effects assessment program watershed, Beasley Lake, in the Mississippi Delta, USA. *Bull Environ Contam Toxicol* 84(4):422-6.

Llácer E, Dembilio O, Jacas JA. 2010. Evaluation of the efficacy of an insecticidal paint based on chlorpyrifos and pyriproxyfen in a microencapsulated formulation against *Rhynchophorus ferrugineus* (Coleoptera: Curculionidae). *J Econ Entomol* 103(2):402-8.

Loewy RM, Monza LB, Kirs VE, Savini MC. 2011. Pesticide distribution in an agricultural environment in Argentina. *J Environ Sci Health B* 46(8):662-70.

London L, Beseler C, Bouchard MF, Bellinger DC, Colosio C, Grandjean P, Harari R, Kootbodien T, Kromhout H, Little F, Meijster T, Moretto A, Rohlman DS, Stallones L. 2012. Neurobehavioural and neurodevelopmental effects of pesticide exposures. *Neurotoxicology* 33(4):887-96.

López-Granero C, Cañadas F, Cardona D, Yu Y, Giménez E, Lozano R, Avila DS, Aschner M, Sánchez-Santed F. 2013.

Chlorpyrifos-, diisopropylphosphorofluoridate-, and parathion-induced behavioral and oxidative stress effects: are they mediated by analogous mechanisms of action? *Toxicol Sci* 131(1):206-16.

Lotti M, Moretto A. 2005. Organophosphate-induced delayed polyneuropathy. *Toxicol Rev* 24(1):37-49.

Lovasi GS, Quinn J, Rauh VA, Perera FP, Andrews HF, Garfinkel R, Hoepner L, Whyatt R, Rundle A. 2011. Chlorpyrifos exposure and urban residential environment characteristics as determinants of early childhood neurodevelopment. *Am J Public Health* 101(1):63-70.

Lu JL. 2011. Farmers' exposure to pesticides and pesticide residues in soil and crops grown in Benguet Philippines. *Phil J Crop Sci* 36(3):19-27.

Lu C, Toepel K, Irish R, Fenske RA, Barr DB, Bravo R. 2006. Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. *Environ Health Perspect* 114(2):260-3.

Lu C, Barr DB, Pearson MA, Waller LA. 2008. Dietary intake and its contribution to longitudinal organophosphorus pesticide exposure in urban/suburban children. *Environ Health Perspect* 116(4):537-42.

Lu C, Adamkiewicz G, Attfield KR, Kapp M, Spengler JD, Tao L, Xie SH. 2013. Household pesticide contamination from indoor pest control applications in urban low-income public housing dwellings: a community-based participatory research. *Environ Sci Technol* 47(4):2018-25.

Majewski MS, Foreman WT, Goolsby DA. 2000. Pesticides in the atmosphere of the Mississippi River Valley, part 1 – rain. *Sci Total Environ* 248(2-3):201-12.

Malhat F, Nasr I. 2011. Organophosphorus pesticides residues in fish samples from the River Nile tributaries in Egypt. *Bull Environ Contam Toxicol* 87(6):689-92.

Mansour SA, Mossa A-TH. 2009. Lipid peroxidation and oxidative stress in rat erythrocytes induced by chlorpyrifos and the protective effect of zinc. *Pestic Biochem Physiol* 93(1):34-9.

Manthripragada AD, Costello S, Cockburn MG, Bronstein JM, Ritz B. 2010. Paraoxonase 1, agricultural organophosphate exposure, and Parkinson disease. *Epidemiology* 21(1):87-94.

Marković M, Cupać S, Đurović R, Milinović J, Kljajić P. 2010. Assessment of heavy metal and pesticide levels in soil and plant products from agricultural area of Belgrade, Serbia. *Arch Environ Contam Toxicol* 58(2):341-51.

Marshall WK, Roberts JR. 1978. Ecotoxicology of chlorpyrifos. National Research Council of Canada, NRC Associate Committee on Scientific Criteria for Environmental Quality, Subcommittee on Pesticides and Related Compounds. Publ. No. 16079.

Martínez MA, Ballesteros S, Sánchez de la Torre C, Sanchiz A, Almarza E, García-Aguilera A. 2004. Attempted suicide by ingestion of chlorpyrifos: identification in serum and gastric content by GC-FID/GC-MS. *J Anal Toxicol* 28(7):609-15.

Mast MA, Alvarez DA, Zaugg SD. 2012. Deposition and accumulation of airborne organic contaminants in Yosemite National Park, California. *Environ Toxicol Chem* 31(3):524-33.

Mathur HB, Johnson S, Kumar A. 2003. Analysis of Pesticide Residues in Soft Drinks. Centre for Science and Environment, New Delhi. http://www.cseindia.org/content/analysis-pesticide-residues-soft-drinks-2003.

Mathur HB, Agarwal HC, Johnson S, Saikia N. 2005. Analysis of Pesticide Residues in Blood Samples from Villages of Punjab. CSE/PML/PR-21/2005. Centre for Science and Environment, and Pollution Monitoring Laboratory, New Delhi. http://www.cseindia.org/userfiles/Punjab_blood_report.pdf.

Mattingly JE, Sullivan JE, Spiller HA, Bosse GM. 2003. Intermediate syndrome after exposure to chlorpyrifos in a 16-month-old girl. *J Emerg Med* 25(4):379-81.

McConnell LL, Nelson E, Rice CP, Baker JE, Johnson WE, Harman JA, Bialek K. 1997. Chlorpyrifos in the air and surface water of Chesapeake Bay: predictions of atmospheric deposition fluxes. *Environ Sci Technol* 31(5):1390-8.

McConnell LL, LeNoir JS, Datta S, Seiber JN. 1998. Wet deposition of current-use pesticides in the Sierra Nevada mountain range, California, USA. *Environ Toxicol Chem* 17(10):1908-16.

McConnell R, Pacheco F, Wahlberg K, Klein W, Malespin O, Magnotti R, Akerblom M, Murray D. 1999. Subclinical health effects of environmental pesticide contamination in a developing country: cholinesterase depression in children. *Environ Res* 81(2):87-91.

Meeker JD, Ravi SR, Barr DB, Hauser R. 2008. Circulating estradiol in men is inversely related to urinary metabolites of nonpersistent insecticides. *Reprod Toxicol* 25(2):184-91.

Meggs WJ. 2003. Permanent paralysis at sites of dermal exposure to chlorpyrifos. *J Toxicol Clin Toxicol* 41(6):883-6.

Mehta A, Verma RS, Srivastava N. 2009. Chlorpyrifos induced alterations in the levels of hydrogen peroxide, nitrate and nitrite in rat brain and liver. *Pestic Biochem Physiol* 94(2-3):55-59.

Meire RO, Lee SC, Yao Y, Targino AC, Torres JP, Harner T. 2012. Seasonal and altitudinal variations of legacy and current-use pesticides in the Brazilian tropical and subtropical mountains. *Atmos Environ* 59:108-16.

Meyer A, Seidler FJ, Slotkin TA. 2004. Developmental effects of chlorpyrifos extend beyond neurotoxicity: critical periods for immediate and delayed-onset effects on cardiac and hepatic cell signalling. *Environ Health Perspect* 112(2):170-8.

Middlemore-Risher ML, Buccafusco JJ, Terry AV Jr. 2010. Repeated exposures to low-level chlorpyrifos results in impairments in sustained attention and increased impulsivity in rats. *Neurotoxicol Teratol* 32(4):415-24.

Miller KP, Borgeest C, Greenfeld C, Tomic D, Flaws JA. 2004. *In utero* effects of chemicals on reproductive tissues in females. *Toxicol Appl Pharmacol* 198(2):111-31.

Mills K, Kegley S. 2006. Air Monitoring for Chlorpyrifos in Lindsay, California: June-July 2004 and July-August 2005. Pesticide Action Network North America, San Francisco. http://www.pesticidereform.org/downloads/AirMonitoring-report.pdf.

Miranda J, Lundberg I, McConnell R, Delgado E, Cuadra R, Torres E, Wesseling C, Keifer M. 2002. Onset of grip- and pinch-strength impairment after acute poisonings with organophosphate insecticides. *Int J Occup Environ Health* 8(1):19-26.

Monnet-Tschudi F, Zurich MG, Schilter B, Costa LG, Honegger P. 2000. Maturation-dependent effects of chlorpyrifos and parathion and their oxygen analogs on acetylcholinesterase and neuronal

and glial markers in aggregating brain cell cultures. *Toxicol Appl Pharmacol* 165(3):175-83.

Montemurro N, Grieco F, Lacertosa G, Visconti A. 2002. Chlorpyrifos decline curves and residual levels from different commercial formulations applied to organs. *J Agric Food Chem* 50(21):5975-80.

Montes de Oca L, Moreno M, Cardona D, Campa L, Suñol C, Galofré M, Flores P, Sánchez-Santed F. 2013. Long term compulsivity on the 5-choice serial reaction time task after acute chlorpyrifos exposure. *Toxicol Lett* 216(2-3):73-85.

Montoya-Lerma J, Giraldo-Echeverri C, Armbrecht I, Farji-Brener A, Calle Z. 2012. Leaf-cutting ants revisited: towards rational management and control. *Int J Pest Manag* 58(3):225-247.

Moreno M, Cañadas F, Cardona D, Suñol C, Campa L, Sánchez-Amate MC, Flores P, Sanchez-Santed F. 2008. Long-term monoamine changes in the striatum and nucleus accumbens after acute chlorpyrifos exposure. *Toxicol Lett* 176(2):162-7.

Moretto A, Lotti M. 1998. Poisoning by organophosphorus insecticides and sensory neuropathy. *J Neurol Neurosurg Psychiatry* 64(4):463-8.

Morgan MK. Sheldon LS, Croghan CW, Jones PA, Roberston GL, Chuang JC, Wilson NK, Lyu CW. 2005. Exposures of preschool children to chlorpyrifos and its degradation product 3,5.6-trichloro-2-pyridinol in their everyday environments. *J Expo Anal Environ Epidemiol* 15(4):297-309.

Moser VC, Phillips PM, McDaniel KL, Marshall RS, Hunter DL, Padilla S. 2005. Neurobehavioural effects of chronic dietary and repeated high-level spike exposure to chlorpyrifos in rats. *Toxicol Sci* 86(2):375-86.

Mosqueira B, Chabi J, Chandre F, Akogbeto M, Hougard JM, Carnevale P, Mas-Coma S. 2010. Efficacy of an insecticide paint against malaria vectors and nuisance in West Africa – Part 2: field evaluation. *Malaria J* 9:341.

Moussaoui Y, Tuduri L, Kerchich Y, Meklati BY, Eppe G. 2012. Atmospheric concentrations of PCDD/Fs, dl-PCBs and some pesticides in northern Algeria using passive air sampling. *Chemosphere* 88(3):270-7.

Moye JK, Pritsos CA. 2010. Effects of chlorpyrifos and aldicarb on flight activity and related cholinesterase inhibition in homing pigeons, *Columba livia*: potential for migration effects. *Bull Environ Contam Toxicol* 84(6):677-681.

MPI. 2012a. Documents – Food Residues Surveillance Programme (FRSP). Ministry for Primary Industries, Wellington. http://www.foodsafety.govt.nz/policy-law/food-monitoring-programmes/food-act-1981/frsp/documents.htm.

MPI. 2012b. Documents – New Zealand Total Diet Survey (NZTDS). Ministry for Primary Industries, Wellington. http://www.foodsafety.govt.nz/policy-law/food-monitoring-programmes/total-diet-study/documents.htm.

MSU. 2013. Arthropod Pesticide Resistance Database. Michigan State University. Accessed Feb 28th, 2013. http://www.pesticideresistance.org.

Muddasir B, Dhar JK, Shafiqa A, Sabia Q, Ahmad I. 2012. Contamination of freshwater fish “Schizothorax niger” with chlorpyrifos from “Dal Lake” basins, India. *Int J Pharma Sci Res* 3(12):535-42.

Mugni H, Demetrio P, Paracampo A, Pardi M, Bulus G, Bonetto C. 2012. Toxicity persistence in runoff water and soil in experimental soybean plots following chlorpyrifos application. *Bull Environ Contam Toxicol* 89(1):208-12.

Muir DC, Teixeira C, Wania F. 2004. Empirical and modeling evidence of regional atmospheric transport of current-use pesticides. *Environ Toxicol Chem* 23(10):2421-32.

Muir DCG, Teixeira CA, Alaee M, Hermanson M. 2007. Persistent organohalogens and current use pesticides in remote lake waters, sediments, and ice caps. In: Castro-Jiménez J, Eisenreich SJ, Vices I. 2007. *Persistent Organic Pollutants (POPs) in the European Atmosphere: An Updated Overview*. Institute for Environment and Sustainability. European Commission, Directorate-General, Joint Research Centre. EUR 22876 EN. Pp88-95. http://ies.jrc.ec.europa.eu/uploads/fileadmin/Documentation/Reports/RWER/EUR_2006-2007/EUR_22876_EN.pdf.

Mukherjee I. 2003. Pesticides residues in vegetables in and around Delhi. *Environ Monit Assess* 86(3):265-71.

Mukherjee I, Arora S. 2011. Impact analysis of IPM programs in basmati rice by estimation of pesticide residues. *Bull Environ Contam Toxicol* 86:307-13.

Mulla MS, Norland RL, Westlake WE, Dell B, Amant JS. 1973. Aquatic midge larvicides, their efficacy and residues in water, soil, and fish in a warm-water lake. *Environ Entomol* 2(1):58-65.

Müller JF, Duquesne S, Ng J, Shaw GR, Krishnamohan K, Manonmanii K, Hodge M, Eaglesham GK. 2000. Pesticides in sediments from Queensland irrigation channels and drains. *Mar Pollut Bull* 41(7-12):294-301.

Mullin CA, Frazier M, Frazier JL, Ashcraft S, Simonds R, vanEngelsdorp D, Pettis JS. 2010. High levels of miticides and agrochemicals in North American apiaries: implications for honey bee health. *PLos ONE* 5(3):e9754.

Mulrooney JE, Davis MK, Wagner TL, Ingram RL. 2006. Persistence and efficacy of termiticides used in preconstruction treatments to soil in Mississippi. *J Econ Entomol* 92(2):469-75.

Muñoz D, Bonner PL, Hargreaves AJ. 2010. Effects of chlorpyrifos on transglutaminase activity in differentiating rat C6 glioma cells. *Toxicol in Vitro* 24(8):2104-7.

Muñoz-Quezada MT, Iglesias V, Lucero B, Steenland K, Barr DB, Levy K, Ryan PB, Alvarado S, Concha C. 2012. Predictors of exposure to organophosphate pesticides in schoolchildren in the Province of Talca, Chile. *Environ Int* 47:28-36.

Murphy MW, Sanderson WT, Birch ME, Liang F, Sanyang E, Canteh M, Cook TM, Murphy SC. 2012. Type and toxicity of pesticides sold for community vector control use in the Gambia. *Epidemiol Res Int* doi:10.1155/2012/387603.

Muto MA, Lobelle F Jr, Bidanset JH, Wurpel JN. 1992. Embryotoxicity and neurotoxicity in rats associated with prenatal exposure to DURSBAN. *Vet Hum Toxicol* 34(6):498-501.

Nandi S, Gupta PS, Roy SC, Selvaraju S, Ravindra JP. 2011. Chlorpyrifos and endosulfan affect buffalo oocyte maturation, fertilization, and embryo development *in vitro* directly and through cumulus cells. *Environ Toxicol* 26(1):57-67.

Naik I. 2012. Prenatal pesticide exposure in women residing in KwaZulu Natal, South Africa. 30th International Congress on Occupational Health, Cancun. March 18-23, 2012. http://icoh.

confex.com/icoh/2012/webprogram/Paper6908.html.

Navarro HA, Basta PV, Seidler FJ, Slotkin TA. 2001. Neonatal chlorpyrifos administration elicits deficits in immune function in adulthood: a neural effect? *Brain Res Dev Brain Res* 130(2):249-52.

Ndengerio-Ndossi JP, Cram G. 2005. Pesticide residues in table-ready foods in Tanzania. *Int J Environ Health Res* 15(2):143-9.

Nel L, Hatherill M, Davies J, Andronikou S, Stirling J, Reynolds L, Argent A. 2002. Organophosphate poisoning complicated by a tachyarrhythmia and acute respiratory distress syndrome in a child. *J Paediatr Child Health* 38(5):530-2.

NMFS. 2008. Endangered Species Act Section 7 Consultation. Biological Opinion. Environmental Protection Agency Registration of Pesticides Containing Chlorpyrifos, Diazinon, and Malathion. National Marine Fisheries Service, Silver Spring. http://www.nmfs.noaa.gov/pr/pdfs/pesticide_biop.pdf.

Nogueira EN, Dores EF, Pinto AA, Amorim RS, Ribeiro ML, Lourencetti C. 2012. Currently used pesticides in water matrices in Central-Western Brazil. *J Braz Chem Soc* 23(8):1476-87.

Nougadère A, Sirot V, Kadar A, Fastier A, Truchot E, Vergnet C, Hommet F, Baylé J, Gros P, LeBlanc JC. 2012. Total diet study on pesticide residues in France: levels in food as consumed and chronic dietary risk to consumers. *Environ Int* 45:135-50.

NPIC. 2009. Chlorpyrifos Technical Factsheet. National Pesticide Information Center, Oregon State University, Corvallis. http://npic.orst.edu/factsheets/chlorptech.pdf.

NRA. 2000a. The NRA Review of Chlorpyrifos September 2000 Volume 1. NRA Review Series 00.5. National Registration Authority for Agricultural and Veterinary Chemicals, Canberra. http://www.apvma.gov.au/products/review/docs/chlorpyrifos_summary.pdf.

NRA. 2000b. Section 6. Environmental Assessment. National Registration Authority for Agricultural and Veterinary Chemicals, Canberra. http://www.apvma.gov.au/products/review/docs/chlorpyrifos_env.pdf.

NZ EPA. 2012. Chlorpyrifos. Classification. New Zealand Environmental Protection Authority, Wellington. http://www.epa.govt.nz/search-databases/Pages/ccid-details.aspx?SubstanceID=2401.

Ogah CO, Coker HB. 2012. Quantification of organophosphate and carbamate pesticide residues in maize. *J Appl Pharm Sci* 2(9):093-7.

OISAT. 2004. Online Information Service for Non-Chemical Pest Management in the Tropics. PAN Germany. http://www.oisat.org.

Ojha A, Yaduvanshi SK, Pant SC, Lomash V, Srivastava N. 2011. Evaluation of DNA damage and cytotoxicity induced by three commonly used organophosphate pesticides individually and in mixture, in rat tissues. *Environ Toxicol* [Epub July 22].

Olsson O, Khodorkovsky M, Gassmann M, Friedler E, Schneider M, Dubowski Y. 2013. Fate of pesticides and their transformation products: first flush effects in a semi-arid catchment. *Clean Soil Air Water* 41(2):134-42.

Oruc EO. 2010. Oxidative stress, steroid hormone concentrations and acetylcholinesterase activity in *Oreochromis niloticus* exposed to chlorpyrifos. *Pestic Biochem Physiol* 96(3):160-6.

Oruc E. 2012. Oxidative stress responses and recovery patterns in the liver of *Oreochromis niloticus* exposed to chlorpyrifos-ethyl. *Bull Environ Contam Toxicol* 88(5):678-84.

Ostrea EM, Morales V, Ngoumgna E, Prescilla R, Tan E, Hernandez E, Ramirez GB, Cifra HL, Manlapaz ML. 2002. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. Neurotoxicology 23(3):329-39.

Ostrea EM Jr, Bielawski DM, Posecion NC. 2006. Meconium analysis to detect fetal exposure to neurotoxicants. *Arch Dis Child* 91(8):628-9.

Ostrea EM Jr, Bielawski DM, Posecion NC Jr, Corrion M, Villanueva-Uy E, Bernardo RC, Jin Y, Janisee JJ, Ager JW. 2009. Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure to environmental pesticides. *Environ Res* 109(1):116-22.

Otieno PO, Schramm KW, Pfister G, Lalah JO, Ojwach SO, Virani M. 2012. Spatial distribution and temporal trend in concentration of carbofuran, diazinon and chlorpyrifos ethyl residues in sediment and water in Lake Naivasha, Kenya. *Bull Environ Contam Toxicol* 88(4):526-32.

PAN Int. 2011. PAN International List of Highly Hazardous Pesticides (PAN List of HHP). Pesticide International. http://www.pan-germany.org/download/PAN_HHP-List_1101.pdf.

PAN UK. 2001. Chlorpyrifos pollution kills fish. *Pestic News* 53:11.

Panuwet P, Prapamontol T, Chantara S, Barr DB. 2009. Urinary pesticide metabolites in school students from northern Thailand. *Int J Hyg Environ Health* 212(3):288-97.

Pareja L, Colazzo M, Pérez-Parada A, Niell S, Carrasco-Letelier L, Besil N, Cesio MV, Heinzen H. 2011. Detection of pesticides in active and depopulated beehives in Uruguay. *Int J Environ Res Public Health* 8(10):3844-858.

Patnaik KK, Tripathy NK. 1992. Farm-grade chlorpyrifos (Durmet) is genotoxic in somatic and germ-line cells of *Drosophila*. *Mutat Res* 279(1):15-20.

Patra RW, Chapman JC, Lim RP, Gehrke PC. 2007. The effects of three organic chemicals on the upper thermal tolerances of four freshwater fishes. *Environ Toxicol Chem* 26(7):1454-9.

Paudyal BP. 2008. Organophosphorus poisoning. *J Nepal Med Assoc* 47(172):251-8.

Peck AM, Hornbuckle KC. 2005. Gas-phase concentrations of current-use pesticides in Iowa. *Environ Sci Technol* 39(9):2952-9.

Pekár S. 2012. Spiders (Araneae) in the pesticide world: an ecotoxicological review. *Pest Manag Sci* 68(11):1438-46.

Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, Bernert T, Garfinkel R, Tu YH, Diaz D, Dietrich J, Whyatt RM. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect* 111(2):201-5.

Phung DT, Connell D, Miller G, Chu C. 2012. Probabilistic assessment of chlorpyrifos exposure to rice farmers in Viet Nam. *J Expo Sci Environ Epidemiol* 22(4):417-23.

Phung DT, Connell D, Yu Q, Chu C. 2013. Health risk characterization of chlorpyrifos using epidemiological dose-

response data and probalistic techniques: a case study with rice farmers in Vietnam. *Risk Anal* [Epub March 7].

Poissant L, Beauvais C, Lafrance P, Deblois C. 2008. Pesticides in fluvial wetlands catchments under intensive agricultural activities. *Sci Total Environ* 404(1):182-95.

Prabhaker N, Morse JG, Castle SJ, Naranjo SE, Henneberry TJ, Toscano NC. 2007. Toxicity of seven foliar insecticides to four insect parasitoids attacking citrus and cotton pests. *J Econ Entomol* 100(4):1053-61.

Prakash A, Khan S, Aggarwal M, Telang AG, Malik JK. 2009. Chlorpyrifos induces apoptosis in murine thymocytes. *Toxicol Lett* 189S(V60):S83.

Prasertsup P, Ariyakanon N. 2011. Removal of chlorpyrifos by water lettuce (*Pistia stratiotes* L.) and duckweed (*Lemna minor* L.). *Int J Phytoremediation* 13(4):383-95.

Putnam RA, Nelson JO, Clark JM. 2003. The persistence and degradation of chlorothalonil and chlorpyrifos in a cranberry bog. *J Agric Food Chem* 51(1):170-6.

Qiao D, Seidler FJ, Padilla S, Slotkin TA. 2002. Developmental neurotoxicity of chlorpyrifos: what is the vulnerable period? *Environ Health Perspect* 110(11):1097-103.

Qiao D, Seidler FJ, Tate CA, Cousins MM, Slotkin TA. 2003. Fetal chlorpyrifos exposure: adverse effects on brain cell development and cholinergic biomarkers emerge postnatally and continue into adolescence and adulthood. *Environ Health Perspect* 111(4):536-44.

Quirós-Alcalá L, Bradman A, Smith K, Weerasekera G, Odetokun M, Barr DB, Nishioka M, Castorina R, Hubbard AE, Nicas M, Hammond SK, McKone TE, Eskenazi B. 2012. Organophosphorous pesticide breakdown products in house dust and children's urine. *J Expo Sci Environ Epidemiol* 22(6):559-68.

Racke KD. 1993. Environmental fate of chlorpyrifos. *Rev Environ Contam Toxicol* 131:1-150.

Racke KD, Fontaine DD, Yoder RN, Miller JR. 1994. Chlorpyrifos degradation in soil at termiticidal application rates. *Pestic Sci* 42(1):43-51.

Racke KD, Steele KP, Yoder RN, Dick WA, Avidov E. 1996. Factors affecting the hydrolytic degradation of chlorpyrifos in soil. *J Agric Food Chem* 44(6):1582-92.

Rahman MF, Mahboob M, Danadevi K, Saleha Banu B, Grover P. 2002. Assessment of genotoxic effects of chlorpyriphos and acephate by the comet assay in mice leucocytes. *Mutat Res* 516(1-2):139-47.

Raina R, Hall P, Sun L. 2010. Occurrence and relationship of organophosphorus insecticides and their degradation products in the atmosphere in Western Canada agricultural regions. *Environ Sci Technol* 44(22):8541-6.

Rajasekaran D, Subbaraghavalu G, Jayapandian P. 2009. Guillain-Barre syndrome due to organophosphate compound poison. *J Assoc Physicians India* 57:714-5.

Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, Whitehead R, Tang D, Whyatt RW. 2006. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* 118(6):e1845-59.

Rauh VA, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, Whyatt R. 2011. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ Health Perspect* 119(8):1196-201.

Rauh VA, Perera FP, Horton MK, Whyatt RM, Bansal R, Hao X, Liu J, Barr DB, Slotkin TA, Peterson BS. 2012. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci* 109(20):7871-6.

Rawlings NC, Cook SJ, Waldbillig D. 1998. Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, lindane, triallate, trifluralin, 2.4-D, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes. *J Toxicol Environ Health* A 54(1):21-36.

Reigart JR, Roberts JR. 1999. *Recognition and Management of Pesticide Poisoning*. Fifth Edition. U.S. Environmental Protection Agency, Washington. http://www.epa.gov/oppfead1/safety/healthcare/handbook/handbook.htm.

Reinecke SA, Reinecke AJ. 2007. The impact of organophosphate pesticides in orchards on earthworms in the Western Cape, South Africa. *Ecotoxicol Environ Saf* 66(2):244-51.

Riazuddin, Khan MF, Iqbal S, Abbas M. 2011. Determination of multi-residue insecticides of organochlorine, organophosphorus, and pyrethroids in wheat. *Bull Environ Contam Toxicol* 87(3):303-6.

Rice CP, Chernyak SM. 1997. Marine arctic fog: An accumulator of currently used pesticides. *Chemosphere* 35(4):867-78.

Rich JD, Gabriel SM, Schultz-Norton JR. 2012. *In vitro* effects of herbicides and insecticides on human breast cells. *ISRN Toxicol* Article ID: 232461. doi:10.5402/2012/232461.

Richards SM, Kendall RJ. 2003. Physical effects of chlorpyrifos on two stages of *Xenopus laevis*. *J Toxicol Environ Health A* 66(1):75-91.

Richendrfer H, Pelkowski SD, Colwill RM, Créton R. 2012. Developmental sub-chronic exposure to chlorpyrifos reduces anxiety-related behaviour in zebrafish larvae. *Neurotoxicol Teratol* 34(4):458-65.

Riederer AM, Lu C. 2012. Measured versus simulated dietary pesticide intakes in children. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 29(12):1922-37.

Robles-Molina J, Martín de Vidales MJ, García-Reyes JF, Cañizares P, Sáez C, Rodrigo MA, Molina-Díaz A. 2012. Conductive-diamond electrochemical oxidation of chlorpyrifos in wastewater and identification of its main degradation products by LC-TOFMS. *Chemosphere* 89(10):1169-76.

Rodríquez T, Younglove L, Lu C, Funez A, Weppner S, Barr DB, Fenske RA. 2006. Biological monitoring of pesticide exposures among applicators and their children in Nicaragua. *Int J Occup Environ Health* 12(4):312-20.

Rodríguez C, Taylor P, Devine B, Van Buynder P, Weinstein P, Cook A. 2012. Assessing health risks from pesticides in recycled water: a case study of augmentation of drinking water supplies in Perth, Western Australia. *Hum Ecol Risk Assess* 18(6):1216-36.

Rother HA. 2010. Falling through the regulatory cracks: street selling of pesticides and poisoning among urban youth in South Africa. *Int J Occup Environ Health* 16(2):202-13.

Rowsey PJ, Gordon CJ. 1999. Tumor necrosis factor is involved in chlorpyrifos-induced changes in core temperature in the female rat. *Toxicol Lett* 109(1-2):51-9.

Ruggirello RM, Hermanson MH, Isaksson E, Teixeira C, Forsström S, Muir DCG, Pohjola V, van de Wal R, Meijer HAJ. 2010. Current use and legacy pesticide deposition to ice caps on Svalbard, Norway. *J Geophys Res:Atmos* 115(D18):27.

Sabdono A, Kang S, Hur HG, Grossart HP, Simon M, Radjasa OK. 2007. Organophosphate pesticide contamination in coral tissues of Indonesian coastal waters. *Pak J Biol Sci* 10(11):1926-9.

Sabir JSM. 2010. The genotoxicity of three synthetic pesticides: chlorpyrifos, cypermethrin and their mixture chlorcyrin in *Aspergillus terreus*. *Proc III Int Conf Environ Indust Appld Microbiol (BioMicroWorld2009)*, Lisbon 2-4 December 2009. http://www.worldscientific.com/doi/abs/10.1142/9789814322119_0140.

Salazar-Arredondo E, de Jesús Solís-Heredia M, Rojas-García E, Hernández-Ochoa I, Quintanilla-Vega B. 2008. Sperm chromatin alteration and DNA damage by methyl-parathion, chlorpyrifos and diazinon and their oxon metabolites in human spermatozoa. *Reprod Toxicol* 25(4):455-60.

Salazar JG, Ribes D, Cabré M, Domingo JL, Sanchez-Santed F, Colomina MT. 2011. Amyloid ß peptide levels increase in brain of AßPP Swedish mice after exposure to chlorpyrifos. *Curr Alzheimer Res* 8(7):732-40.

Sánchez-Amate MC, Flores P, Sánchez-Santed F. 2001. Effects of chlorpyrifos in the plus-maze model of anxiety. *Behav Pharmacol* 12(4):285-92.

Sandahl JF, Baldwin DH, Jenkins JJ, Scholz NL. 2005. Comparative thresholds for acetylcholinesterase inhibition and behavioral impairment in coho salmon exposed to chlorpyrifos. *Environ Toxicol Chem* 24(1):136-45.

Sandal S, Yilmaz B. 2011. Genotoxic effects of chlorpyrifos, cypermethrin, endosulfan and 2,4-D on human peripheral lymphocytes cultured from smokers and nonsmokers. *Environ Toxicol* 26(5):433-42.

Sanghi R, Pillai MK, Jayalekshmi TR, Nair A. 2003. Organochlorine and organophosphorus pesticide residues in breast milk from Bhopal, Madhya Pradesh, India. *Hum Exp Toxicol* 22(2):73-6.

Santos MJ, Ferreira MF, Cachada A, Duarte AC, Sousa JP. 2012. Pesticide application to agricultural fields: effects on the reproduction and avoidance behaviour of *Folsomia candida* and *Eisenia andrei*. *Ecotoxicology* 21(8):2113-22.

Sapozhnikova Y, Bawardi O, Schlenk D. 2004. Pesticides and PCBs in sediments and fish from the Salton Sea, California, USA. *Chemosphere* 55(6):797-809.

Sardar D, Kole RK. 2005. Metabolism of chlorpyrifos in relation to its effect on the availability of some plant nutrientsin soil. *Chemosphere* 61(9):1273-80.

Sarnsamak P. 2012. Dangerous levels of pesticides in veggies at high-end markets. *The Nation*, July 12. http://www.nationmultimedia.com/national/Dangerous-levels-of-pesticides-in-veggies-at-high--30185981.html.

Saulsbury MD, Heyliger SO, Wang K, Johnson DJ. 2009. Chlorpyrifos induces oxidative stress in oligodendrocyte progenitor cells. *Toxicology* 259(1-2):1-9.

Schafer KS, Reeves M, Spitzer S, Kegley SE. 2004. Chemical Trespass: Pesticides in our Bodies and Corporate Accountability. Pesticide Action Network North America, San Francisco. http://www.panna.org/issues/publication/chemical-tresspass-english

Schettler T, Stein J, Reich F, Valenti M, Wallinga D. 2000. In Harm's Way: Toxic Threats To Child Development. Greater Boston Physicians for Social Responsibility, Cambridge. http://www.psr.org/chapters/boston/resources/in-harms-way-report-download.html.

Schuh RA, Lein PJ, Beckles RA, Jett DA. 2002. Noncholinesterase mechanisms of chlorpyrifos neurotoxicity: altered phosphorylation of Ca2+/cAMP response element binding protein in cultured neurons. *Toxicol Appl Pharmacol* 182(2):176–85.

Schulz R, Peall SK, Dabrowski JM, Reinecke AJ. 2001. Current-use insecticides, phosphates and suspended solids in the Lourens River, Western Cape, during the first rainfall event of the wet season. *Water SA* 27(1):65-70.

Sebe A, Satar S, Alpay R, Kozaci N, Hilal A. 2005. Organophosphate poisoning associated with fetal death: a case study. *Mt Sinai J Med* 72(5):354-6.

Serju C. 2012. Lethal pesticide banned – resort workers seek medical help after exposure to clorpyrifos. *The Gleaner*, Kingston. February 11. http://jamaica-gleaner.com/gleaner/20120211/business/business2.html.

Serrano R, López FJ, Hernández F, Peña JB. 1997. Bioconcentration of chlorpyrifos, chlorfenvinphos, and methidathion in *Mytilus galloprovincialis*. *Bull Environ Contam Toxicol* 59(6):968-75.

Serra-Bonvehí J, Orantes-Bermejo J. 2010. Acaricides and their residues in Spanish commercial beeswax. *Pest Manag Sci* 66(11):1230-5.

Sherman JD. 1996. Chlorpyrifos (Dursban)-associated birth defects: report of four cases. *Arch Environ Health* 51(1):5-8.

SIBAT. 1999a. Keeping the Balance! Alternative Pest Management Training Manual for Vegetables. Sibol ng Agham at Teknolohiya (SIBAT); Rural Reconstruction Alumni and Friends Association (RRAFA); Centre for Environment, Technology and Development, Malaysia (CETDEM); Pesticide Action Network—Indonesia; Pesticide Action Network Asia and the Pacific (PAN AP). Quezon City, Philippines.

SIBAT. 1999b. Keeping the Balance! Alternative Pest Management Training Manual for Rice. Sibol ng Agham at Teknolohiya (SIBAT); Rural Reconstruction Alumni and Friends Association (RRAFA); Centre for Environment, Technology and Development, Malaysia (CETDEM); Pesticide Action Network—Indonesia; Pesticide Action Network Asia and the Pacific (PAN AP). Quezon City, Philippines.

Silva E, Batista S, Caetano L, Cerejeira MJ, Chaves M, Jacobsen SE. 2011. Integrated approach for the quality assessment of freshwater resources in a vineyard area (South Portugal). *Environ Monit Assess* 176(1-4):331-41.

Simcox NJ, Fenske RA, Wolz SA, Lee IC, Kalman DA. 1995. Pesticides in household dust and soil: exposure pathways for children of agricultural families. *Environ Health Perspect* 103(12):1126-34.

Singh J. 2004. India finds pesticides in colas. *BBC*, Delhi. February 4. http://news.bbc.co.uk/2/hi/south_asia/3458365.stm.

Singh S, Kumar V, Thakur S, Banerjee BD, Rautela RS, Grover SS, Rawat DS, Pasha ST, Jain SK, Ichhpujani RL, Rai A. 2011. Paraoxononase-1 genetic polymorphisms and susceptibility to DNA damage in workers occupationally exposed to organophosphate pesticides. *Toxicol Appl Pharmacol* 252(2):130-7.

Sinha SN, Rao MV, Vasudev K. 2012. Distribution of pesticides in different commonly used vegetables from Hyderabad, India. *Food Res Int* 45(1):161-9.

Slotkin TA. 1999. Developmental cholinotoxicants: nicotine and chlorpyrifos. *Environ Health Perspect* 107(Suppl 1):71-80.

Slotkin TA. 2004. Guidelines for developmental neurotoxicity and their impact on organophosphate pesticides: a personal view from an academic perspective. *Neurotoxicology* 25(4):631-40.

Slotkin TA. 2011. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? *Repro Toxicol* 31(3):297-301.

Slotkin TA, Cousins MM, Tate CA, Seidler FJ. 2001. Persistent cholinergic presynaptic deficits after neonatal chlorpyrifos exposure. *Brain Res* 902(2):229-43.

Slotkin TA, Brown KK, Seidler FJ. 2005. Developmental exposure of rats to chlorpyrifos elicits sex-selective hyperlipidemia and hyperinsulinemia in adulthood. *Environ Health Perspect* 113(10):1291-4.

Slotkin TA, Levin ED, Seidler FJ. 2006. Comparative developmental neurotoxicity of organophosphate insecticides: effects on brain development are separable from systemic toxicity. *Environ Health Perspect* 114(5):746-51.

Slotkin TA, Seidler FJ, Fumagalli F. 2007. Exposure to organophosphates reduces the expression of neurotrophic factors in neonatal rat brain regions: similarities and differences in the effects of chlorpyrifos and diazinon on the fibroblast growth factor superfamily. *Environ Health Perspect* 115(6):909-16.

Slotkin TA, Seidler FJ. 2009. Oxidative and excitatory mechanisms of developmental neurotoxicity: transcriptional profiles for chlorpyrifos, diazinon, dieldrin, and divalent nickel in PC12 cells. *Environ Health Perspect* 117(4):587-96.

Sobti RC, Krishan A, Pfaffenberger CD. 1982. Cytokinetic and cytogenetic effects of some agricultural chemicals on human lymphoid cells *in vitro*: organophosphates. *Mutat Res* 102(1):89-102.

Solomon GM, Moodley J. 2007. Acute chlorpyrifos poisoning in pregnancy: a case report. *Clin Toxicol (Phila)* 45(4):416-9.

Soltaninejad K, Faryadi M, Sardari F. 2007. Acute pesticide poisoning related deaths in Tehran during the period 2003-2004. *J Forensic Leg Med* 14(6):352-354.

Song XO, Lin F, Jiang YC, Liu XR, Zhang PH, Liu YQ. 1997. Mutagenicity of 19 organophosphorus pesticides in *Saccharomyces cerevisiae* D61.M. *Chinese J Pharmacol Toxicol* 11:291-3.

Song X, Violin JD, Seidler FJ, Slotkin TA. 1998. Modeling the developmental neurotoxicity of chlorpyrifos *in vitro*: macromolecule synthesis in PC12 cells. *Toxicol Appl Pharmacol* 151(1):182-91.

Soummer A, Megarbane B, Boroli F, Arbelot C, Saleh M, Moesch C, Fournier E, Rouby JJ. 2011. Severe and prolonged neurologic toxicity following subcutaneous chlorpyrifos self-administration: a case report. *Clin Toxicol (Phila)* 49(2):124-7.

Sparling DW, Fellers GM, McConnell LL. 2001. Pesticides and amphibian population declines in California, USA. *Environ Toxicol Chem* 20(7):1591-5.

Sparling DW, Fellers G. 2007. Comparative toxicity of chlorpyrifos, diazinon and their oxon derivatives to larval *Rana boylii*. *Environ Pollut* 147(3):535-9.

Sparling DW, Fellers GM. 2009. Toxicity of two insecticides to California, USA, Anurans and its relevance to declining amphibian populations. *Environ Toxicol Chem* 28(8):1696-1703.

Srinivas Rao CH, Venkateswarlu V, Surender T, Eddleston M, Buckley NA. 2005. Pesticide poisoning in south India: opportunities for prevention and improved medical management. *Trop Med Int Health* 10(6):581-8.

Stapleton AR, Chan VT. 2009. Subtoxic chlorpyrifos treatment resulted in differential expression of genes implicated in neurological functions and development. *Arch Toxicol* 83(4):319-333.

Starks SE, Hoppin JA, Kamel F, Lynch CF, Jones MP, Alavanja MC, Sandler DP, Gerr F. 2012. Peripheral nervous system function and organophosphate pesticide use among licensed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 120(4):515-20.

Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. 1994. Chronic neurological sequelae to organophosphate poisoning. *Am J Public Health* 84(5):731-6.

Steenland K, Dick RB, Howell RJ, Chrislip DW, Hines CJ, Reid TM, Lehman E, Laber P, Krieg EF, Knott C. 2000. Neurologic function among termiticide applicators exposed to chlorpyrifos. *Environ Health Perspect* 108(4):293-300.

Sun F, Chen HS. 2008. Monitoring of pesticide chlorpyrifos residue in farmed fish: investigation of possible sources. *Chemosphere* 71(10):1866-9.

Sungur Ş, Tunur Ç. 2012. Investigation of pesticide residues in vegetables and fruits grown in various regions of Hatay, Turkey. *Food Addit Contam B Surveillance* 5(4):265-7.

Swann JM, Schultz TW, Kennedy JR. 1996. The effects of the organophosphorous insecticides Dursban and Lorsban on the ciliated epithelium of the frog palate *in vitro*. *Arch Environ Contam Toxicol* 30(2):188-94.

Tagatz ME, Gregory NR, Plaia GR. 1982. Effects of chlorpyrifos on field- and laboratory-developed estuarine benthic communities. *J Toxicol Environ Health* 10(3):411-21.

Tariq MI, Afzal S, Hussain I, Sultana N. 2007. Pesticides exposures in Pakistan: a review. *Environ Int* 33(8):1107-22.

Teijon G, Candela L, Tamoh K, Molina-Díaz A, Fernández-Alba AR. 2010. Occurrence of emerging contaminants, priority substances (2008/105/CE) and heavy metals in treated wastewater and groundwater at Depurbaix facility (Barcelona, Spain). *Sci Total Environ* 408(17):3584-95.

Terry AV Jr, Beck WD, Warner S, Vandenhuerk L, Callahan PM. 2012. Chronic impairments in spatial learning and memory in rats previously exposed to chlorpyrifos or diisopropylfluorphosphate. *Neurotoxicol Teratol* 34(1):1-8.

Thanal. 2003. A Dossier on the Pesticide Exposure of Cashew Factory Workers, Kerala, India. February 2003. Thanal

Conservation Action & Information Network, Thiruvananthapuram.

Thanh Nien News. 2012. US tourist died of brain edema, not poison: police. Sept 21st. http://www.thanhniennews.com/index/pages/20120921-us-tourist-died-of-brain-edem-a-not-poison-police.aspx.

The Gleaner. 2012. …Limit use, change lifestyle, says PCA. Feb 11th. http://jamaica-gleaner.com/gleaner/20120211/business/business3.html.

Thivakaran T, Gamage R, Gunarathne KS, Gooneratne IK. 2012. Chlorpyrifos-induced delayed myelopathy and pure motor neuropathy: a case report. *Neurologist* 18(4):226-8.

Thomas CN, Mansingh A. 2002. Bioaccumulation, elimination, and tissue distribution of chlorpyrifos by red hybrid *Tilapia* in fresh and brackish waters. *Environ Technol* 23(11):1313-23.

Thomson L. 2012. Pesticide impacts on natural enemies. Grape and Wine Research and Development Corporation, Australian Government. http://www.gwrdc.com.au/webdata/resources/factSheet/Pesticide_impacts_on_natural_enemies.pdf.

Thongsinthusak T. 1991. Memorandum. Determination of dermal absorption of chlorpyrifos in humans. Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/whs/memo/hsm91002.pdf.

Thongsinthusak T. 1999. Memorandum to Fletcher K.: Oral and dermal absorption of chlorpyrifos: a human volunteer study (Griffin et al). Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/whs/memo/hsm99026.pdf.

Thrasher JD, Madison R, Broughton A. 1993. Immunologic abnormalities in humans exposed to chlorpyrifos: preliminary observations. *Arch Environ Health* 48(2):89-93.

Thrasher JD, Heuser G, Broughton A. 2002. Immunological abnormalities in humans chronically exposed to chlorpyrifos. *Arch Environ Health* 57(3):181-7.

Tian Y, Yamauchi T. 2003. Micronucleus formation in 3-day mouse embryos associated with maternal exposure to chlorpyrifos during the early preimplantation period. *Reprod Toxicol* 17(4):401-5.

Tian Y, Ishikawa H, Yamaguchi T, Yamauchi T, Yokoyama K. 2005. Teratogenicity and developmental toxicity of chlorpyrifos. Maternal exposure during organogenesis in mice. *Repro Toxicol* 20(2):267-70.

Torres-Altoro MI, Mathur BN, Drerup JM, Thomas R, Lovinger DM, O'Callaghan JP, Bibb JA. 2011. Organophosphates dysregulate dopamine signalling, glutamatergic neurotransmission, and induce neuronal injury markers in striatum. *J Neurochem* 119(2):303-13.

Tuncel SG, Oztas NB, Erduran MS. 2008. Air and groundwater pollution in an agricultural region of the Turkish Mediterranean coast. *J Air Waste Manag Assoc* 58(9):1240-9.

Tupper K, Kegley S, Jacobs N, Marquez E, Jim S, Bjorkqvist S, Wang A, Kaastrup K. 2012. Pesticide Drift Monitoring in Minnesota June13, 2006 – August 13, 2009. Pesticide Action North America, San Francisco.

UNEP. 2012. Evaluation of non-chemical alternatives to endosulfan. POPs Review Committee. UNEP/POPS/POPRC.8/INF/14/Rev.1.

Uribe MV, Diaz SM, Monroy A, Barbosa E, Paez MI, Castro RA. 2012. Exposure to pesticides in tomato crop farmers in Merced, Colombia: effects on health and the environment. In: Soundararajan RP (Ed.). *Pesticides – Recent Trends in Pesticide Residue Assay*. InTech. http://www.intechopen.com/books/pesticides-recent-trends-in-pesticide-residue-assay.

US EPA. 1999a. Review of submittals by Dow AgroSciences on chlorpyrifos. Memorandum to Hartman M, Special Review and Reregistration Division, from Blondell J, Health Effects Division, United States Environmental Protection Agency, Washington. http://dursban-in-your-water.com/images/incidentsreview.pdf.

US EPA.1999b. HED Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No. 059101. Barcode D257953. United States Environmental Protection Agency, Washington, D.C.

US EPA. 2006. Reregistration Eligibility Decision for Chlorpyrifos. United States Environmental Protection Agency, Washington, D.C.

US EPA. 2009a. Chlorpyrifos Summary Document Registration Review: Initial Docket March 2009. Docket Number: EPA-HQ-OPP-2008-0850. Case #0100. United States Environmental Protection Agency, Washington, D.C.

US EPA. 2009b. Memorandum. Chlorpyrifos. Revised Human Health Assessment Scoping Document in Support of Registration Review. February 9. Office of Pesticide Programs, United States Environmental Protection Agency, Washington, D.C.

US EPA. 2011. Memorandum. Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review. DP No. D388070. June 30th. Office of Pesticide Programs, United States Environmental Protection Agency, Washington, D.C.

US EPA. 2013a. Chlorpyrifos: Preliminary Evaluation of the Potential Risks from Volatilization. Document ID: EPA-HQ-OPP-2008-0850-0114. United States Environmental Protection Agency, Washington.

US EPA. 2013b. *America's Children and the Environment, Third Edition*. United States Environmental Protection Agency, Washington. http://www.epa.gov/ace/publications/ACE3_2013.pdf

Usmani KA, Rose RL, Hodgson E. 2003. Inhibition and activation of the human liver microsomal and human cytochrome P450 3A4 metabolism of testosterone by deployment-related chemicals. *Drug Metab Dispos* 31(4):384-91.

Usmani KA, Cho TM, Rose RL, Hodgson E. 2006. Inhibition of the human liver microsomal and human cytochrome P450 1A2 and 3A4 metabolism of estradiol by deployment-related and other chemicals. *Drug Metab Dispos* 34(9):1606-14.

Uzun FG, Demir F, Kalender S, Bas H, Kalender Y. 2010. Protective effect of catechin and quercetin on chlorpyrifos-induced lung toxicity in male rats. *Food Chem Toxicol* 48(6):1714-20.

Uzun FG, Kalender Y. 2013. Chlorpyrifos induced hepatotoxic and hematologic changes in rats: the role of quercetin and catechin. *Food Chem Toxicol* [Epub Feb 8]. doi: 10.1016/j.fct.2013.01.056

van Wendel de Joode B, Barraza D, Ruepert C, Mora AM, Córdoba L, Öberg M, Wesseling C, Mergler D, Lindh CH. 2012. Indigenous children living nearby plantations with chlorpyrifos-treated bags have elevated 3,5,6-trichloro-2-pyridinol (TCPy) urinary concentrations. *Environ Res* 117:17-26.

Vandenberg L. 2012. State of the science in non-monotonic dose responses. Presentation at Workshop 'Low Dose Effects and Non-Monotonic Dose Responses for Endocrine Active Chemicals'. Berlin 11-13 September. Joint Research Centre Institute for Health and Consumer Protection, European Commission. http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/presentations-workshop-low-dose-effects-endocrine-active-chemicals.

van Wijngaarden RP, Brock TC, Douglas MT. 2005. Effects of chlorpyrifos in freshwater model ecosystems: the influence of experimental conditions on ecotoxicological thresholds. *Pest Manag Sci* 61(10):923-35.

Veith GD, DeFoe DL, Bergstedt BV. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. *J Fish Res Board Can* 36(9):1040-8.

Venerosi A, Calamandrei G, Ricceri L. 2006. A social recognition test for female mice reveals behavioral effects of developmental chlorpyrifos exposure. *Neurotoxicol Teratol* 28(4):466-71.

Venerosi A, Ricceri L, Scattoni ML, Calamandrei G. 2009. Prenatal chlorpyrifos exposure alters motor behaviour and ultrasonic vocalization in CD-1 mouse pups. *Environ Health* 8:12.

Venerosi A, Ricceri L, Tait S, Calamandrei G. 2012. Sex dimorphic behaviors as markers of neuroendocrine disruption by environmental chemicals: the case of chlorpyrifos. *Neurotoxicology* 33(6):1420-6.

Ventura C, Núñez M, Miret N, Lamas DM, Randi A, Venturino A, Rivera E, Cocca C. 2012. Differential mechanisms of action are involved in chlorpyrifos effects in estrogen-dependent or -independent breast cancer cells exposed to low or high concentrations of the pesticide. *Toxicol Lett* 213(2):184-93.

Verma RS, Mehta A, Srivastava N. 2009. Comparative studies on chlorpyrifos and methyl parathion induced oxidative stress in different parts of rat brain: Attenuation by antioxidant vitamins. *Pestic Biochem Physiol* 95(3):152-8.

Viswanath G, Chatterjee S, Dabral S, Nanguneri SR, Divya G, Roy P. 2010. Anti-androgenic endocrine disrupting activities of chlorpyrifos and piperophos. *J Steroid Biochem Mol Biol* 120(1):22-9.

Vogel JR, Majewski MS, Capel PD. 2008. Pesticides in the rain in four agricultural watersheds in the United States. *J Environ Qual* 37(3):1101-15.

Vogt R, Bennett D, Cassady D, Frost J, Ritz B, Hertz-Picciotto I. 2012. Cancer and non-cancer health effects from food contaminant exposures for children and adults in California: a risk assessment. *Environ Health* 11:83.

Vryzas Z, Papdakis EN, Vassiliou G, Papadopoulou-Mourkidou E. 2012. Occurrence of pesticides in transboundary aquifers of North-eastern Greece. *Sci Total Environ* 441:41-8.

Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, Cantor KP, Blair A. 2001. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes Control* 12(6):509-17.

Wang L, Liang Y, Jiang X. 2008. Analysis of eight organophosphorus pesticide residues in fresh vegetables retailed in agricultural product markets of Nanjing, China. *Bull Environ Contam Toxicol* 81(4):377-82.

Wang H-P, Liang Y-J, Zhang Q, Long D-X, Li W, Li L, Yang L, Yan X-Z, Wu Y-J. 2011. Changes in metabolic profiles of urine from rats following chronic exposure to anticholinesterase pesticides. *Pestic Biochem Physiol* 101(3):232-9.

Wang Y, Chen L, Yu R, Zhao X, Wu C, Cang T, Wang Q. 2012a. Insecticide toxic effects on *Trichogramma ostriniae* (Hymenoptera: Trichogrammatidae). *Pest Manag Sci* 68(12):1564-71.

Wang J-Z, Li H-Z, You J. 2012b. Distribution and toxicity of current use insecticides in sediment of a lake receiving waters from areas in transition to urbanization. *Environ Pollut* 161:128-33.

Wang N, Yi L, Shi L, Kong D, Cai D, Wang D, Shan Z. 2012c. Pollution level and human health risk assessment of some pesticides and polychlorinated biphenyls in Nantong of Southeast China. *J Environ Sci* 24(10):1854-60.

Wang JH, Zhu LS, Liu W, Wang J, Xie H. 2012d. Biochemical responses of earthworm (*Eisenia foetida*) to the pesticides chlorpyrifos and fenvalerate. *Toxicol Mech Methods* 22(3):236-41.

Weldon RH, Barr DB, Trujillo C, Bradman A, Holland N, Eskenazi B. 2011. A pilot study of pesticides and PCBs in the breast milk of women residing in urban and agricultural communities of California. *J Environ Monit* 13(11):3136-44.

Welling W, de Vries JW. 1992. Bioconcentration kinetics of the organophosphorus insecticide chlorpyrifos in guppies (*Poecilia reticulata*). *Ecotoxicol Environ Saf* 23(1):64-75.

Wesseling C, Aragón A, Rojas M, Blanco L, López L, Soto A, Fúnez A, Ruepert C, Miranda J, López I. 2006. Efectos del clorpirifos en la salud de trabajadores bananeros de La Lima, Honduras. Programa Salud y Trabajo en América Central (SALTRA), Instituto Regional de Estudios en Sustancias Tóxicas (IRET-UNA), Universidad Nacional, Heredia, Costa Rica

Centro de Investigaciones en Salud, Trabajo y Ambiente, Facultad de Ciencias Médicas, Universidad Nacional Autónoma de Nicaragua en León (UNAN-León), Nicaragua. http://www.saltra.una.ac.cr/images/articles/seriesaludytrabajo/seriesaludytrabajo1.pdf.

Wesseling C. Rojas M, van Wendel de Joode B, Ruepert C. 2007. Cuidado con el clorpirifos. *Enlace* 75:12-16. http://www.rap-al.org/articulos_files/Enlace%2075.pdf.

Weston DP, Ding Y, Zhang M, Lydy MJ. 2013. Identifying the cause of sediment toxicity in agricultural sediments: the role of pyrethroids and nine seldom-measured hydrophobic pesticides. *Chemosphere* 90(3):958-64.

Whitney KD, Seidler FJ, Slotkin TA. 1995. Developmental neurotoxicity of chlorpyrifos: cellular mechanisms. *Toxicol Appl Pharmacol* 134(1):53-62.

WHO. 2009a. WHO Specifications and Evaluations for Public Health Pesticides. Chlorpyrifos *O,O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate. World Health Organization, Geneva. http://www.who.int/whopes/quality/Chlorpyrifos_WHO_specs_eval_Mar_2009.pdf.

WHO. 2009b. The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification: 2009. World Health Organization, Geneva.

Whyatt RM, Barr DB. 2001. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. *Environ Health Perspect* 109(4):417-20.

Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, Hoepner LA, Diaz D, Dietrich J, Reyes A, Tang D, Kinney PL, Perera FP. 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ Health Perspect* 112(10):1125-32.

Whyatt RM, Garfinkel R, Hoepner LA, Holmes D, Borjas M, Williams MK, Reyes A, Rauh V, Perera FP, Camann DE. 2007. Within- and between-home variability in indoor-air insecticide levels during pregnancy among an inner-city cohort from New York City. *Environ Health Perspect* 115(3):383-9.

Whyatt RM, Garfinkel R, Hoepner LA, Andrews H, Holmes D, Williams MK, Reyes A, Diaz D, Perera FP, Camann DE, Barr DB. 2009. A biomarker validation study of prenatal chlorpyrifos exposure within an inner-city cohort during pregnancy. *Environ Health Perspect* 117(4):559-67.

Wickerham EL, Lozoff B, Shao J, Kaciroti N, Xia Y, Meeker JD. 2012. Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants. *Environ Int* 47:80-85.

Wickramasinghe K, Steele P, Dawson A, Dharmaratne D, Gunawardena A, Senarathna L, de Siva D, Wijayaweera K, Eddleston M, Konradsen F. 2009. Cost to government health-care services of treating acute self-poisonings in a rural district in Sri Lanka. *Bull World Health Organ* 87(3):180-5.

Widder PD, Bidwell JR. 2006. Cholinesterase activity and behavior in chlorpyrifos-exposed *Rana sphenocephala* tadpoles. *Environ Toxicol Chem* 25(9):2446-54.

Wijesinghe MR, Bandara MG, Ratnasooriya WD, Lakraj GP. 2011. Chlorpyrifos-induced toxicity in *Duttaphrynus melanostictus* (Schneider 1799) larvae. *Arch Environ Contam Toxicol* 60(4):690-6.

Wightwick A, Allinson G. 2007. Pesticide residues in Victorian waterways: a review. *Aust J Ecotoxicol* 13:91-112.

Woodburn KB, Hansen SC, Roth GA, Strauss K. 2003. The bioconcentration and metabolism of chlorpyrifos by the eastern oyster, *Carssostrea virginica*. *Environ Toxicol Chem* 22(2):276-84.

Woodruff RC, Phillips JP, Irwin D. 1983. Pesticide-induced complete and partial chromosome loss in screens with repair-defective females of *Drosophila melanogaster*. *Environ Mutagen* 5(6):835-46.

Woudneh MB, Ou Z, Sekela M, Tuominen T, Gledhill M. 2009. Pesticide multiresidues in waters of the Lower Fraser Valley, British Columbia, Canada. Part 1. Surface water. *J Environ Qual* 38(3):940-7.

Wright CG, Leidy RB, Dupree HE Jr. 1994. Chlorpyrifos in the air and soil of houses eight years after its application for termite control. *Bull Environ Contam Toxicol* 52(1):131-4.

Xing H, Li S, Wang Z, Gao X, Xu S, Wang X. 2012. Oxidative stress response and histopathological changes due to atrazine and chlorpyrifos exposure in common carp. *Pestic Biochem Physiol* 103(1):74-80.

Xu F, Chang X, Lou D, Wu Q, Zhou Z. 2012. Chlorpyrifos exposure causes alternation in dopamine metabolism in PC12 cells. *Toxicol Mech Methods* 22(4):309-14.

Xue N, Xu X, Jin Z. 2005. Screening 31 endocrine-disrupting pesticides in water and surface sediment samples from Beijing Guanting reservoir. *Chemosphere* 61(11):1594-606.

Xue N, Li F, Hou H, Li B. 2008. Occurrence of endocrine-disrupting pesticide residues in wetland sediments from Beijing, China. *Environ Toxicol Chem* 27(5):1055-62.

Yaduvanshi SK, Srivastava N, Marotta F, Jain S, Yadav H. 2012. Evaluation of micronuclei induction capacity and mutagenicity of organochlorine and organophosphate pesticides. *Drug Metab Lett* [Epub Oct 15].

Yan C, Jiao L, Zhao J, Yang H, Peng S. 2012. Repeated exposures to chlorpyrifos lead to spatial memory retrieval impairment and motor activity alteration. *Neurotoxicol Teratol* 34(4):442-9.

Yang XB, Ying GG, Peng PA, Wang L, Zhao JL, Zhang LJ, Yuan P, He HP. 2010. Influence of biochars on plant uptake and dissipation of two pesticides in an agricultural soil. *J Agric Food Chem* 58(13):7915-21.

Yin XH, Zhu GN, Li XB, Liu SY. 2009. Genotoxicity evaluation of chlorpyrifos to amphibian Chinese toad (Amphibian: Anura) by comet assay and micronucleus test. *Mutat Res/Genetic Toxicol Environ Mutagen* 680(1-2):2-6.

Yu LY, Wu XM, Li SN, Fang H, Zhan HY, Yu JQ. 2006. An exploration of the relationship between adsorption and bioavailability of pesticides in soil to earthworm. *Environ Pollut* 141(3):428-33.

Yu F, Wang Z, Ju B, Wang Y, Wang J, Bai D. 2008. Apoptotic effect of organophosphorus insecticide chlorpyrifos on mouse retina *in vivo* via oxidative stress and protection of combination of vitamins C and E. *Exp Toxicol Pathol* 59(6):415-23.

Zama D, Meraihi Z, Tebibel S, Benayssa W, Benayache F, Benayache S, Vlietinck AJ. 2007. Chlorpyrifos-induced oxidative stress and tissue damage in the liver, kidney, brain and fetus in pregnant rats: the protective role of the butanolic extract of *Paronychia argentea* L. *Ind J Pharmacol* 39(3):145-50.

Zamora C, Kratzer CR, Majewski MS, Knifong DL. 2003. Diazinon and chlorpyrifos loads in precipitation and urban and agricultural storm runoff during January and February 2001 in the San Joaquin River Basin, California. US Geological Survey, Water Resources Investigations Report 03-4091, Sacramento. http://pubs.usgs.gov/wri/wri034091/wrir034091.pdf.

Zhang X, Starner K, Spurlock F. 2012. Analysis of chlorpyrifos agricultural use in regions of frequent surface water detections in California, USA. *Bull Environ Contam Toxicol* 89(5):978-84.

Zhong G, Xie Z, Cai M, Möller A, Sturm R, Tang J, Zhang G, He J, Ebinghaus R. 2012. Distribution and air-sea exchange of current-use pesticides (CUPs) from East Asia to the high Arctic Ocean. *Environ Sci Technol* 46(1):259-67.

Zhou S, Duan C, Michelle WH, Yang F, Wang X. 2011. Individual and combined toxic effects of cypermethrin and chlorpyrifos on earthworm. *J Environ Sci* 23(4):676-80.

Ziem G, McTamney J. 1997. Profile of patients with chemical injury and sensitivity. *Environ Health Perspect* 105(Suppl 2):417-36.

Zubair M, Suhail M, Khan M, Fatima A. 2010. Teratological effects of chlorpyrifos on crown rump length and weight of developing mice. *Pak J Med Health Sci* 4(2):112-5.

Prepared by Meriel Watts, PhD

Meriel Watts is a Scientist and Technical Advisor of Pesticide Action Network Asia and the Pacific (PAN AP). She is currently co-ordinator of PAN Aotearoa New Zealand, a member of the PAN AP Steering Council, and is co-Convenor of its Task Force on Pesticides.

Pesticide Action Network Asia and the Pacific (PAN AP) is one of the five regional centres of PAN, a global network dedicated to eliminating the harm caused to humans and the environment by pesticides and promoting biodiversity-based ecological agriculture.

PAN AP's vision is a society that is truly democratic, equal, just, and culturally diverse; based on the principles of food sovereignty, gender justice and environmental sustainability. It has developed strong partnerships with peasants, agricultural workers and rural women movements in the Asia Pacific region and guided by the strong leadership of these grassroots groups, has grown into a reputable advocacy network with a firm Asian perspective.

PAN AP's mission lies in strengthening people's movements to advance and assert food sovereignty, biodiversity-based ecological agriculture, and the empowerment of rural women; protect people and the environment from highly hazardous pesticides; defend the rice heritage of Asia; and resist the threats of corporate agriculture and neo-liberal globalization.

Currently, PAN AP comprises 108 network partner organizations in the Asia Pacific region and links with about 400 other CSOs and grassroots organizations regionally and globally.

Pesticide Action Network Asia and the Pacific
P.O. Box 1170, 10850 Penang, Malaysia
Tel: (604) 657 0271 / 656 0381 Fax: (604) 658 3960
Email: panap@panap.net Homepage: www.panap.net