# Epidemiological and Clinical Studies on Acute and Chronic Organophosphate-Induced Neurotoxicity in Israel

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*Running Title*: **Studies on Organophosphates in Israel**

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## Introduction

Most reported instances of acute organophosphates (OP) poisoning in Israel have been due to agricultural use (Finkelstein *et al.*, 1988a, Finkelstein *et al.*, 1988b). For nearly four decades, OP have been the most commonly used pest-control agents in cotton and orchard cultivation in Israel (Richter *et al.*, 1992a, Richter *et al.*, 1992b), but their use has decreased over the years due to their high toxicity to mammals. Our own studies in OP exposed populations in Israel have shown these compounds lead to acetylcholine esterase (AChE) inhibition, causing cholinergic overstimulation and dysfunction in both the central nervous system (CNS) and peripheral nervous system (PNS) of affected individuals (Finkelstein *et al.*, 1988a, Finkelstein *et al.*, 1988b). In spite of this common knowledge, pesticides in Israel are still being used ubiquitously and in large quantities, given the advantages they offer in crop protection, with little consideration directed at their potential effects on human health. The findings on OP usage in Israel have been reviewed (see below) and they encompass trends in usage, as well as effects of low-level, short-term and long-term exposures on health outcomes. Symptoms and neurobehavioral tests from both occupational and community sentinel groups in Israel have been reviewed. The occupational groups studied were aerial spray pilots, ground-crews, and field workers - crop inspectors, irrigation workers and repair mechanics. The sentinel community groups studied included adult and children, residents of kibbutzim (communal agricultural settlements), moshavim (cooperative communities and farms), greenhouses and glass houses located near fields treated by aerial spraying, as well as residents in household treated by pest exterminators.

Health hazards and risks from agricultural OP exposures in Israel have been long recognized. There has been an upheaval in the employment picture, as migrant foreign workers, mainly from the Far East have been brought in to do field work formerly done by workers from the West Bank and Gaza. The hazards and risks to migrant laborers have been a regulatory no man's land. There have been multiple attempts over the last three decades to reduce OP usage. However, these attempts call to attention the unfinished agenda of control of hazards based on Legge's principle (stating "*Unless and until the employer has done everything— and everything means a good deal—the workman can do next to nothing to protect himself although he is naturally willing enough to do his share"*) in a complex and fragile political, social, and ecological setting. Israel is an ecosystem that now supports a total population of ~7 million people, 3% of which are employed in agriculture [some 50-fold or more than the Judean hills described by Josephus Flavius' in the 1st century AD, when families fed themselves from crops grown on terraced plots of land of 60 X 60 meters (Richter *et al.*, 1997)]. Yet, till the actual shortage in water supply, which has become critical during the last decade, most of Israel's agricultural landmass was used not for growing food but for cotton and orchards, both of which require large amounts of water and pesticides; cotton is grown using mechanized plowing, fertilizers, irrigation, and pesticide spray technology, and is dependent on a small numbers of field workers - itself an effective method of exposure restriction. By contrast, vegetable growth involves larger numbers of people intensively working small plots of land in family moshavim, kibbutzim, green- and glass-houses.

This chapter commences with a historical account on pesticide use in Israel. It is followed by a summary on acute and chronic OP poisonings in Israel during the last four decades, an era of different trends in use of OP pesticides. This is followed by a discussion on studies on neurotoxic and neurobehavioral effects of low-level long-term exposure to OP in Israel, as well as studies on severe cases of acute OP poisoning. The principal findings of all studies carried out in Israel between 1970 and 2009 are summarized herein, alongside with a short synopsis of ongoing studies and future directions.

**Historical Perspective on Pesticide Use in Israel**

Pesticide use in Israel has been associated with large-scale advances in agricultural productivity, and was central to vector control programs against disease-bearing mosquitoes-notably malaria in the 1940s and 1950s. In the 1960s and early 1970s, organochlorines, (OCls), notably dichlorodiphenyltrichloroethane (DDT), Lindane, and benzene hexachloride (BHC), as well as Hepatachor, Dieldrin, Endosulfan and Endrin were the most commonly used agents. By now, in Israel as in most Western countries, these agents have been banned or withdrawn, but they remain in use for selected vector control activities. The massive reduction in the use of OCls was followed with replacement with OP in the 1970s.

There has been substantial documentation of the short-term health effects from pesticide exposures in workers in kibbutzim, moshavim, and factories, and in residents exposed to pesticide drift from aerial spraying and pesticide residues in foods and fruits (Cohen *et al.*, 1979, Ratner *et al.,* 1989). In the 1980s, cotton field workers and residents complained frequently of illness episodes from exposure to spray drift, and these complaints were shown to be associated with high levels of metabolites of organophosphates in urine (Richter *et al.*, 1992a, Richter *et al.*, 1992b). In the 1990s there has been work on the possible etiologic role in Parkinson's disease (PD) of residential pesticide exposure in agricultural settings (Goldsmith *et al.,* 1990), and on the possible role of exposures to OP in increasing risks for spontaneous abortion and birth defects (Goldsmith, personal communication). During 1980-2000 there was a decline in spontaneous reports of mass outbreaks of illness in cotton field workers and residents (Richter *et al.,* 1992a, Richter *et al.,* 1992b, Richter and Safi 1997). There is evidence to indicate that reduction of risk resulted from reduced use of, and, therefore, reduced exposures to OP and other ChE inhibitors, the dominant type of pesticide applied. This trend occurred during a period when cotton cultivation was reduced, because of a severe water shortage in Israel and declining world prices of cotton. From 1980 to 1998, cotton yield per hectare increased by 21% from 1.4 to 1.7 tons. The increased yield occurred despite, or perhaps because of, reduced pesticide use. There was a massive reduction in both the total tonnage of pesticides in use and the amount of OP in use per hectare cultivated (Richter *et al.,* 1997). Furthermore, there was a shift from the use of more to less toxic agents within the OP family, notably as a result of reduced use of parathion (mean lethal dose as low as 4 mg/kg in adults). The less-toxic OP, Malathion (mean lethal dose as low as 250 mg/kg in adults) (Gosselin *et al.*, 1981), which substituted parathion has been recently banned (January, 2009). This meant that the drop in use of OP was even greater than indicated by data on tonnage used (Richter *et al.,* 1997). However, in the recent decade, the trend of OP usage has changed with increased application of OP on common crops. For example, in the Hula Valley in the northern region of Israel, OP usage has actually increased in 2006 *vs.* 2003 (Bar-Ilan and Malman 2007 ). While factors such as better cultivation and selective use of more fertile land may have been involved, the fact remains that decrease in pesticide use, at the least, did not serve as an obstacle to increased crop yield. These data support the case for action on maintaining crop yield with integrated pest management alongside reduction strategies.

**Studies on Neurotoxic Effects of Low-level Long-term Exposure to OP in Israel**

Findings on the effects of OP in selected occupational and community groups in Israel were reviewed by Richter and colleagues (Richter *et al.,* 1992a, Richter *et al.,* 1980b, Richter *et al.,* 1980a, Richter *et al.,* 1992b). The worker groups included in these studies were pilots, ground-crews, and field workers; exposed non-workers included adult children living in kibbutzim with drift exposures, and household residents in houses treated pest exterminators. In all groups, evidence of exposure-illness associations was found, even though persons with acute poisoning were not seen. Complaints of headache, dizziness fatigue and nausea, breathing problems, abdominal cramps and tingling in extremities were associated with within-normal depressions in ChE activity. Whole blood and plasma ChE activity were slightly more sensitive indicators of mixed exposure than red blood cells ChE activity. High alkyl phosphate levels and symptoms were seen in individuals with within normal limit depressions in plasma ChE activity. Complaints of weakness and tingling in hands and feet, together with minor changes in nerve conduction, suggest the possible influence of agents with a neurotoxic esterase-type activity independent from ChE activity**.** Prody and colleagues (Prody *et al.,* 1989) reported the amplification of the gene coding for ChE activity in selected moshav farmers with known heavy exposures to organophosphates; the clinical implications of this are not clear. Ilani and colleague (Ilani *et al.,* 1988) described a higher incidence of neurological symptoms, fatigue, and psychiatric disturbances in garden pest control, orchard and cotton workers with recent exposure, although no association was found with ChE activity levels.

In the 1980s, we carried out studies of neurobehavioral effects associated with low-level exposure to OP pesticides from drift in orchard workers and residents in kibbutzim of the Hula Valley (Richter *et al.,* 1984, Richter *et al.,* 1986). These studies demonstrated dose-response gradients linking everyday symptoms of illness with the measured levels of OP metabolites in residents and workers. Neurobehavioral tests in adults showed subtle short-term reversible changes in measures of mood, and mental and motor performance. Short-term memory, attention and time to reaction performance were more impaired in field workers than in other residents of the kibbutzim. Electrophysiological tests of the peripheral nervous system showed impaired nerve conduction amplitudes in sensory nerves. Transient in-season neuropsychological changes in tests of mood state and performance were associated with exposure (Richter *et al.,* 1992a, Richter *et al.,* 1992b). Evidence for intake from contaminated food sources came from the report by Ratner and associated (Ratner *et al.,* 1983) on chronic dietary poisoning from AChE inhibitors in moshav residents who ate large amounts of fresh fruits and vegetables. These individuals reported gastrointestinal complaints, insomnia and chronic fatigue that were relieved by eliminating this source of food from their diet; this relief was associated with increased ChE activity levels in their blood.

**Studies on Low-level Exposure to OP and its Short-term Neurobehavioral Effects**

The consequence of short-term exposures to OP on neurotoxic outcomes has been reviewed (Richter 1987, Richter 1993, Richter *et al.,* 1984, Richter *et al.,* 1986). Major findings from these studies attest to OP effects on clinical parameters and neurobehavioral tests, both in occupational and community sentinel groups in Israel. The occupational groups studied included aerial spray pilots, ground-crews, and field workers - crop inspectors, irrigation workers and repair mechanics. The studies addressed levels of urinary metabolites for the detection of low-level exposures, short-term illness and neurobehavioral decrements. Data from a field survey on work practices, symptoms, and ChE and alkyl phosphate levels in a group of kibbutz cotton field workers *(*n=12) and orchard workers (n=7) suggest that health risks from reduced pesticide use became submaximal in later years (Meng *et al.,* 1996). This situation contrasted with evidence of much higher exposures in previous years, when application levels, though beginning to drop from peak amounts, were substantially higher. Interviews and walk-through surveys indicated that these workers had received little formal training in hazard prevention, they worked almost daily in irrigation and crop care, they wore short pants and sleeveless shirts in field work, they did not change their clothes daily, they acknowledged odors of pesticide in their field work and they entered fields on the day of spraying. Yet our 1991 field survey indicated they were almost totally asymptomatic, and the degree of risk, as measured by erythrocyte and plasma ChE and alkyl phosphate metabolites were far below levels considered to be acutely hazardous. While these observations should not be considered an endorsement for hazardous work practices and the nonuse of protective covering, they suggest that much of the inherent protection likely came from simple reduction in the amounts of applied pesticides. By contrast, a group of moshav farmers, whose work involved intensive use and contact with pesticides in backyard greenhouses and orchards, were at greater risk, because use patterns had not been reduced over the years (Richter *et al.,* 1997). Their exposures were to Cotnion, Divipan, Monocron, Marshall, and Supracide, and their work practices were far from adequate. For this group the situation was considerably different from that of kibbutz farmers working in open fields. Kibbutz urinary metabolites of OP were more frequently detected, and at higher levels. Other data showed that headache, fatigue, nausea, and stomach aches, diarrhea, breathing difficulty and cough, running nose, muscle fatigue, and skin problems were frequent. A field survey showed that women who picked and cut flowers in glass houses were more likely to be ill than men who sprayed and were more apt to use protective clothing. Other data showed that urine metabolites varied with the frequency of reported pesticide applications, but not with the reported frequency of use of protective clothing or gloves (Meng *et al.,* 1996).

The findings on exposure and symptoms in open-fields kibbutz workers, compared with data from previous years showed the benefits of reducing risks from reduced pesticide use and substitution of more-toxic with less-toxic agents. But in the moshav, the enclosed greenhouse work conditions led to subacute and chronic illness in many men and women, which was not prevented, it appeared, even when they wore what they called protective clothing. These latter findings called for preventive measures in greenhouses based on a strategy similar to what was achieved in cotton crops, namely an integrated approach to risk prevention by reducing pesticide use, yet at the same time maintaining crop yield (Richter et al., 1998).

**Studies on Exposures of Aerial Spray Workers and their Short-Term Effects**

The work and exposure conditions of aerial spiky pilots had been described in the late 1970`s - early work hours, 4-5 h flight spraying and 20-25 takeoffs and landings per day, passes at heights of 2-3 m above ground level, several hundred U-turns following short runs no longer than several hundred meters (with possible re-exposure to spray plume), frequent close runs under telephone and power lines, and additional exposures to noise, vibration, gravitational forces, and heat (a hazard later eliminated by cockpit air-conditioning). When ultra-light volume sprays are used, the hazard from pesticide exposure may increase since smaller droplets contain more pesticide per unit mass and smaller droplets may penetrate more deeply into the respiratory system. Studies were triggered by the epidemiologic finding, observed from routine annual reports, of a steep rise in crash and incident risk per flight hours for Israeli spray pilots during the 1970s, a time of enormous expansion in cotton cultivation, pesticide application, and aerial spraying. Data from these studies showed the wide range of cockpit exposure levels to parathion; lower values with longer sampling periods appeared to result from time dilution of peak exposures from runs through aerial streams. Inhalation rates per hour, the breathing rate of spray pilots is similar to that of were usually less than 18 μg/h. Total potential dermal exposure in this group, estimated from measurements of wetted filter paper collections, ranged from 5 μg/h, to a maximum of 200 μg/h, of which 10% was estimated to be absorbed. The wearing of clean whole-body overalls significantly reduced the estimated surface area for skin absorption. Cockpit parathion concentrations were especially high when the wind direction was either parallel to the spray line or absent. Additional routes of exposures resulted from sprays, mists and vapors depositing residues in the cockpit at the landing site during wash-down, maintenance and reloading. Air sampling at the landing sites detected levels al high as 357 μg/m$^3$. As the spray season progressed, exposed pilots complained of blurred vision, headache, nausea, dizziness and thirst as mood changes as chronic fatigue. Complaints of pesticide odors were a highly specific but not sensitive indicator of exposure, although the source could have come from invert ingredients, such as mercaptans, as well as from parathion which itself is odorous. Since ever extremely high exposures could be detected ever when the ventilation shuttle was closed, it was there were other routes by which parathion could have penetrated the cockpit.

Ground-crews also suffered frequent episodes of acute poisoning and a drop in ChE activity. Walk-through surveys indicated that they were exposed to OP from contaminated dust blown and dispersed from unpaved ground strips, mist from wash-downs, direct contact with contaminated surfaced and parts of the aircraft, and volatilization of puddle of contaminant. At peripheral loading sites, where there was no wash-down of aircraft, measured parathion concentrations for aircraft loaders were always <70 μg/m$^3$. Dermal exposure measured by absorbent pads, was found to be in the range of 40-5,000 μg/h; absorption was estimated to be 10% of these levels. Total absorption calculations based on the air and dermal exposure studies, a 5-h workday, and 100% airway and 10% dermal absorption for pilots and ground-crews, led to the following conclusions concerning these two groups. Some pilots were absorbing parathion solely from breathing at levels that exceeded 350 μg, a proposed acceptable daily intake (ADI) (Maroni 1986); however, in most cases, absorption from both air and dermal routes was below this suggested threshold. Nonetheless, many pilots were reporting symptoms directly hazardous to their flying ability, which were attributable to ChE inhibition. Ratner and co-workers also reported reduced levels of ChE activity in nine residents of moshavim exposed to aerial spray drift (Ratner and Eshel 1986).

**Delayed Long-Term Effects of a Single Event of Acute OP Poisoning on Cognitive Behavior in Children**

A preliminary study of delayed long-term effects of a single acute OP poisoning on cognitive behavior in children was conducted in the Southern region of Israel. All children belonged to the Bedouin nomadic population of the Negev (Kofman *et al.*, 2006). They were 6-12 years old; all of them attended regular schools. The authors performed a neuropsychological assessment of 17 school-aged children who had been hospitalized in infancy following exposure to OP pesticides, compared with 9 children exposed to other toxins, such as kerosene and paint thinner, and with 26 age- and sex-matched non-exposed children. A comparison group of children with kerosene poisoning was chosen, because this was the most common form of childhood household poisoning in the Negev Bedouin community. The authors found it critical to use a comparison group exposed to a different type of poisoning to try to equate factors such as effects of hospitalization and trauma and the reaction of care-takers to a child following an accidental poisoning.

The study was unique in that the children were followed up for several years after a poisoning accident that occurred before the age of three. Apparently, the children seemed to have overcome the acute one-time exposure. However, although they all attended regular schools, a careful assessment of specific cognitive abilities indicated impairment in the verbal learning and motor inhibition tasks in the exposed children compared with matched control group. Four of the examined children had been reported in the hospital files to be in clouded consciousness upon admission to the emergency room with OP acute poisoning; however, their scores did not differ from the group average on any of the tests.

The subtle behavioral changes were evident in the tests which assessed the inhibitory control and motor inhibition. Statue test indicated that the children exposed to OP had more difficult restraining and controlling their motor behavior than the matched controls. This test is designed to examine the child's ability to inhibit a prepotent response to one cue and to produce this response in the presence of another cue. The outcomes of Statue test were compatible with previous evidence, relating exposure to methyl parathion to a higher incidence of parental report of behavioral problems like impulsivity and conduct disorder (Ruckart *et al.,* 2004). Impaired motor inhibition (Barkley 1997) is one of the hallmarks of attention deficit hyperactivity disorder (ADHD), and indeed, the Statue test is included in the "attention" battery of the NEPSY (Korkman *et al.*, 2001).

The deficit in motor control was more evident in the OP group in the Statue test. The fact that the deficit was evident only in the Statue test, but not in the Knock Tap test, could be related to the different types of inhibition required by each task. The Knock Tap requires inhibition of a prepotent imitation response to the experimenter's hand movement. On the other hand, the Statue test requires that the child not react to distracting stimuli. One may speculate that this test may be more anxiety-provoking as it is performed with closed eyes. In the verbal learning test, the difference between the exposed children who were poisoned before age three and controls was found in the rate of learning, but not in delayed recall and recognition. The increased gain in the recognition phase in exposed children suggests that they showed impaired retrieval only in the acquisition phase, but not after the delay, suggesting there was no effect of the early poison exposure on encoding or consolidation. The findings suggested that subtle behavioral changes may occur, even if they go undetected in school.

**Studies on Low-level Exposure to OP and its Long-term Neurobehavioral Effects**

OP pesticides have been, and are still being widely used for pest control in cotton fields and orchards in the Hula Valley. Despite their low volatility, a significant portion of applied OP remain suspended in the atmosphere, a medium for which sparse knowledge exists regarding OP degradation and fate (Harnly *et al.,* 2005). Several studies (1977-1987, supported by WHO) (Richter 1993) assessed the neurotoxic effects of long-term low-level OP exposures in workers and residents of several kibbutzim in the region. The studies uncovered abnormal effects both in the central and peripheral nervous systems. In the 1980s, we carried out studies of neurobehavioral effects associated with low-level exposure to OP pesticides from drift in orchard workers and residents in kibbutzim of the Hula Valley. These studies conclusively demonstrated dose-response gradients linking everyday symptoms of illness with the measured levels of OP metabolites in residents and workers. Neurobehavioral tests in adults showed subtle short-term reversible changes in measures of mood, and mental and motor performance. Short-term memory, attention and time to reaction performance were more impaired in field workers than in other residents of the kibbutzim. Electrophysiological tests of the peripheral nervous system showed impaired nerve conduction amplitudes in sensory nerves (Richter *et al.,* 1992a, Richter *et al.,* 1992b). Dose-response relationships have been observed between the health effects and the measured levels of OP metabolites in urine samples of children in the same kibbutzim.

**Studies on Low-level Long-term Exposure to OP and PD**

Herishanu (Herishanu *et al.,* 1989) reported an increased prevalence of PD in several kibbutzim in the Negev - the southern desert in Israel (cluster kibbutzim). Subsequent studies revealed a significant prevalence of subjects presenting extrapyramidal signs (preparkinsonism) in the same kibbutzim. On follow-up, worsening of these signs was observed in some of the older patients, some of them later being diagnosed as suffering from l-DOPA responsive Parkinson's disease (Herishanu *et al.,* 1998). An additional study was designed to evaluate possible etiologic factors for the development of preparkinsonism (Herishanu *et al.,* 1998). A group of 317 individuals over the age of 40, living in five kibbutzim was examined and interviewed. A group of 95 individuals presenting extrapyramidal signs were compared with 95 control individuals, matched for age, sex and length of residence in the kibbutz. Detectors for carbamates and organic phosphates were applied at different sites in these kibbutzim. The severity and frequency of the extrapyramidal signs were higher in the older age groups, more in the "cluster", than in other kibbutzim. A very significant association was found between field crop work exposure, particularly cotton, and preparkinsonism alongside a slightly weaker association for landscape work. The detectors picked up abundant pesticide traces (carbamates and organic phosphates) in the residential areas fairly distant from sites of aerial spray. It was concluded that the residents in these kibbutzim were passively subjected to chronic exposure to OP and carbamates, in addition to any occupational exposures.

In the 1990s an increased prevalence of PD in the Negev was observed. An additional case-control study was designed to determine which exposures were associated with PD in the urban population of this region. A group of 93 PD patients living in towns were compared to 93 age and sex matched controls. A previously validated questionnaire, including demographic data, education, data on exposures, previous diseases, family history an habits, was employed. History of work in construction sites was the strongest predictor of PD risk, followed by exposure to pesticides. In contrast, there was a negative association with smoking and history of mechanical factory employment. When the same statistical analysis was limited to association of PD with smoking, pesticides and construction work, the latter was found to be the strongest risk factor. Thus, the risk factors for PD in that urban population were work on a construction site and exposure to pesticides.

PD occurrence in Israel has been associated with rural residency and its lifestyle characteristics, such as farming, well water use and exposure to pesticidal products. A very strong association between field crop work exposure and the presence of these signs was shown alongside with an association with pesticide use (Herishanu *et al.,* 1998). It was proposed that these people present signs of preparkinsonism and that some of them may progress later to full blown Parkinson's disease (Goldsmith *et al.,* 1997). Over 15 years period (1986-2001) the annual incidence of PD among persons over 40 in these "cluster" kibbutzim increased from 27,5/10,000 to 47.1/10,000 (Herishanu *et al.,* 1998). An overall increase in prevalence of PD was also observed in the southern Israel region during the same time period. This was a period of increased immigration (starting in 1989) from the former Soviet Union. The great majority of the new immigrants settled in the towns and not in the rural communities. A study was conducted to determine whether exposures associated with PD and preparkinsonism in rural communities of the Negev, play a similar role in PD among urban Negev residents (Herishanu *et al.,* 2001).

The increase in the prevalence of PD in the urban population of southern Israel was not related to the recent immigration from former Soviet Union and it seemed be a result of a long-term (more then 25 years) exposure to environmental factors present in the region.
That study revealed an association of borderline significance between urban cases of PD and past pesticide use. In the literature there are still conflicting reports regarding the plausible connection between pesticide / herbicide exposure and the risk for PD. By using multivariate logistic regression analysis, history of word in construction was the

strongest predictor of PD risk, followed by exposure to pesticides. By using the same statistical analysis, for association of PD and smoking, exposure to pesticides and history of work in construction, the strongest risk factor was history of work in construction followed by exposure to pesticides. Again, smoking was found to be a strong protective factor for PD development, consistent with many other reports in the literature. Taken together, this case-control study on urban PD patients of the Negev found an association between PD and environmental and exposures to OP.

**Studies on Acute Exposure to OP in Israel**

We have integrated both experimental and clinical data for OP exposure cases admitted over a five year period to the intensive care units in Israeli hospitals (Finkelstein *et al.*, 1989). Data from poison centers are helpful, wherever regional or national treatment protocols can be implemented. During the period of the study 1981-1986, 38,888 consecutive consultations were requested from the Israel National Poison Control Center which serves all the population of the State of Israel. Among them, 856 cases were of exposure to organophosphate (OP) insecticides, 53 of which were included in the study. The patients' age ranged from 1 to 73 years and 31 of them were below the age of 18. All cases up to 9 years were accidental poisonings. All cases between 15 and 18 years were suicide attempts. Most mild cases in adults above the age of 18 were occupational exposures. A persistent reduction of butyryl-ChE to less than 10% was considered diagnostic. Criteria of inclusion were severe OP poisoning necessitating artificial ventilation, intensive care monitoring and treatment according to a standard protocol. The protocol was based on relatively high doses of obidoxime, relatively low doses of atropine and overriding with a pacemaker in cases of ventricular arrhythmias and prolonged Q-T interval. Seven patients (13%) died during hospitalization. 22 patients (41.5%) presented cardiac arrhythmias; eight of these 22 patients (37%) had ventricular tachycardia and/or "torsades de pointes"; four of them died; thirty-two patients (60%) had major CNS involvement. Five (9.4%) had liver dysfunction. The liver enzymes returned to normal range within 3 to 5 weeks in all patients. Five patients (9.4%) presented severe psychiatric disorder after the resolution of the acute respiratory failure. The clinical presentation resembled regression psychosis. The psychiatric syndrome was reversible in all patients within 3-5 weeks. There were 3 females and 2 males, aged, aged 16-22 years. The incidence of this psychiatric syndrome in patients above the age of 15 was 5/31 (16.1%). All the fatalities in that consecutive series were the result of intentional suicidal ingestion of concentrated OP pesticide, causing severe hypoxemic respiratory failure associated with cardiac arrhythmia. The solvent of most of the OP used in agriculture is a petroleum distillate, the aspiration of which is particularly hazardous. Finkelstein and colleagues (Finkelstein *et al.,* 1988a, Finkelstein *et al.,* 1988b) demonstrated the pattern of AChE inhibition in human brain in fatal cases of OP poisoning is regionally selective. This region-specific distribution of AChE inhibition could be correlated with some of the clinical characteristics of OP poisoning. Thus, AChE inhibition could be correlated with signs of reduced cognitive efficiency and psychomotor slowing (frontal bilateral signs), impaired reading comprehension (frontal subdominant), expressive language defects (frontal dominant), amnestic word finding difficulty (temporal dominant) and neurobehavioral changes (mesial temporal lobe) (Finkelstein *et al.,* 1988a, Finkelstein *et al.,* 1988b). This work was the basis for clinical guidelines for diagnosis and management and a widely-accepted standard protocol of treatment for severe cases of such poisoning in Israel (Finkelstein 1992).

**Studies on Acute OP and CRB Poisoning in Southern Israel**

Leibson and colleagues (Leibson and Lifshitz 2008) presented a summary of accumulated toxicological knowledge as well as clinical and laboratory experience from the main Medical Center in the Negev serving a relatively vast rural area and pediatric population in Southern Israel. OP and CRB poisoning is an important clinical problem, often life-threatening, in the pediatric population in rural areas where reaching a physician or hospital on time is difficult. During the last three decades, more than 100 infants and children have been admitted to the medical center and diagnosed as suffering from either OP or CRB poisoning. The experience gathered by the pediatric emergency department and intensive care unit staff has been described in four different reports (Leibson and Lifshitz 2008, Lifshitz *et al.,* 1994, Lifshitz *et al.,* 1999, Sofer *et al.,* 1989). Analysis of these cases provided insight into the different clinical presentations of pediatric toxicity compared to the classic descriptions of ChE inhibition toxicity that was documented in adults. Lack of history of exposure and absence of classical signs do not exclude the possibility of OP and CRB poisoning. These factors only stress the importance of a high index of clinical suspicion required in endemic areas like the Negev in southern Israel (Leibson and Lifshitz 2008).

Sofer and associates (Sofer *et al.,* 1989) described 25 infants and children aged 3 months to 7 years admitted to the pediatric intensive care unit with moderate to severe OP or CRB poisoning. The most common presentation was stupor or coma which occurred in

96% of the children; muscle weakness and dyspnea were observed in 92% of the children; bradycardia, fasciculations and gastrointestinal manifestations were the three least common presentations in those children, (Sofer *et al.*, 1989). Lifshitz and colleagues (1999) described 52 children aged 2–8 years with acute OP or CRB poisoning (16 and 36 children, respectively) who were admitted to the pediatric ICU. All the cases of acute CRB poisoning presented with stupor or coma and hypotonia; fasciculations was the least common sign (5.5%). All those with OP poisoning presented with stupor or coma and hypotonia, and bradycardia was the least commonsign (25%) (Lifshitz *et al.*, 1999). Lifshitz and colleagues (Lifshitz *et al.*, 1994) described 26 children aged 1–8 years with severe acute CRB poisoning. All were admitted with CNS depression and hypotonia and had been treated with both atropine and oximes before the toxic agent was identified as CRB – either methomyl or aldicarb. All children fully recovered within 24 hours. It was concluded that treatment with oximes is not harmful, in contrary to the common practice and belief that clinical deterioration might occur in patients with acute CRB poisoning treated with oximes. Oxime therapy did not promote the recovery of these CRB poisoned pediatric patients (Lifshitz *et al.*, 1994).

**Current OP Studies in Israel**

The atmosphere is considered an important transportation medium for pesticides, although most are semi-volatile compounds in nature (Harnly *et al.*, 2005). In addition to its importance with regard to pesticide transport, the atmosphere is also an important media for transformations of OP (Seiber *et al.*, 1993), especially in view of post-application aspects. As OP pesticides have low vapor pressure (e.g. methyl-parathion), they are susceptible to reside on airborne particles or deposited upon surfaces (Floesser-Mueller and Schwack 2001). Nevertheless, photochemical degradation of OP has been studied mainly in aqueous solutions (Bondarenko and Gan 2004). Quantification of the photochemical processes and the knowledge of their gas and condensed phases degradation products and formation rates will allow a better assessment of their atmospheric fate, and the possible impact on air quality and human health aspects with regard to this important pesticides family. Methyl parathion is an important member of the OP group, and was chosen as a model compound for a study which is now under way (Segal-Rosenheimer and Dubowski, personal communication). This study focuses on the investigation of photolysis of thin films of methyl parathion, under different atmospheric conditions (e.g., humidity, oxygen level, presence of ozone), and the identification of condensed and gas-phase products. Initial results show that reaction rates under 254 nm radiation are higher *vs.* 302 nm radiation, and produce half-lives of several hours versus several days, respectively. Half-lives between several days to a week were observed under natural conditions (Floesser-Mueller and Schwack 2001), and are comparable to the present obtained results under 302 nm radiation. It seems that humidified conditions causes buildup of products with a hydroxyl moiety, such as 4-nitrophenol and hydroquinone. We are currently revisiting the original cohorts we examined more than 20 years ago to assess long-term effects of these past and subsequent exposures to OP pesticides in some 200 residents and workers from the Hula Valley. Thus, we have generated a strong database for future follow-up, continuing the work started on the original cohort.

**Understudied Issues**

Data on the extent and distribution of pesticide contamination of groundwater supplies in Israel are not readily available, except for isolated sporadic probes showing massive contamination by pesticides in an agricultural area on the southern coastal area (Muszkat *et al.,* 1992, Muszkat *et al.,* 1989, Richter and Safi 1997). The hazards and risks of foreign workers in Israel have so far fallen far beyond the scope of traditional surveillance. Information on imports of pesticides banned or restricted in first-world countries indicates the potential for many hazards. Child labor is a neglected issue. Risks of cancer, spontaneous abortion, and birth defects have not been adequately explored, apart from the pilot studies alluded to above.

**Conclusions and Future Directions**

The scenario of ecological abuse and health risk from excessive OP pesticides use, as well as overuse of chemical fertilizers, has been seen worldwide (World Resources Institute 1994-1995). There have been case studies of crops having become "hooked" - increased pesticide use leading to increased pest resistance leading to still more use, with adverse human health effects and devastating ecosystem impact. The aforementioned description of cotton cultivation in Israel suggests that substantial reduction in pesticide use was associated with producing more, not less, cotton. What transpired with cotton cultivation represents a possible model for achieving similar results with other crops in the region. In cotton cultivation, the pesticides were used to control insects; in fruits and vegetables, the problem is to control not only insects, but also fungi, and plant viral diseases, and so the issues may be more complex. Indeed, there are some successful, sustained projects of organic agriculture in the Beit Shean area in the Jordan Valley directed at the control of fruit and vegetable crops other than cotton. But, the situation with regard to growth of fruits and vegetables remains far from ideal, with exposure risks for workers and consumers from residues, and for local and migrant workers and possibly their families from exposures during application.

Risk assessment, management, and control of the ecologic and health effects of pesticides should be based on a simple principle: risk is determined by exposure, but the best predictor of exposure is use. Therefore, reduction in use of OP pesticides should lead to reduction of exposure and risk. Sometimes, however, such reductions are a consequence not of direct policy, but of trends having to do with conversion of agricultural land to other uses. Apart from cotton, reductions in pesticide use have come from constriction of the agricultural sector. The fact that the agricultural economies of Israel and its neighbors the Palestinian Authority and Jordan are closely linked, necessitates that regional programs be based on the establishment of a single uniform standard for protection of field workers and consumers, whatever the political climate. The fact that the entire region seeks markets in the European Community serves as a potential lever for achieving such standards over a period of years. Alternatives to pesticide use and abuse have been understudied, despite rapidly growing awareness. The elements of a comprehensive program aimed at reducing risk from exposure and use include: banning use of agents outlawed elsewhere (the so-called dirty dozen); introduction of integrated pest management; effective, low-cost real-time surveillance and monitoring; delivery of information to end users; and using education, right-to-know and right-to-act in introducing such programs.

In conclusion, work on introducing safe and sustainable alternatives to pesticide use, as well as reducing excessive dependence on chemical fertilizers, is long overdue. It should be based on two questions: Can agricultural productivity be sustained and increased as pesticide use, exposure, and risk are reduced? What new organizational frameworks at the local, national, and regional levels need to be created to deliver programs aimed at reducing pesticide-associated risks?

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