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Review

Organophosphate induced chronic neurotoxicity: Health, environmental and risk exposure issues in developing nations of the world

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Organophosphate insecticides account for about half of all the insecticides used in the world and have found very wide applications in agriculture and in household vector control. Exposures of human populations to a wide variety of organophosphates have generated profound concerns about their neurotoxic consequences. Among these concerns are their potential impacts on children and exposures to the neurodegenerative diseases associated with advancing age. This paper therefore tends to make a review of the health, environmental and other risk exposure issues of organophosphates especially in Africa and other developing nations of the world where data abound to show that many agents considered toxic and banned in many parts of the industrialized world are still in use. This paper also makes recommendations on the way out of this menace.

Key words: Pesticides, organophosphates, neurotoxicity, health, environment, developing nations.

INTRODUCTION

Pesticides are chemical substances used worldwide to control pests that destroy crops and transmit diseases to humans and animals. Agriculture, horticulture, vector control, forestry and livestock production account for the greatest use of pesticides. Acute pesticide poisoning has for sometime now been an important occupational and public health problem, particularly in the developing nations of the world (WHO/ UNEP, 1990).

Organophosphates are chemical substances originally produced by the reaction of alcohols and phosphoric acid. Organophosphates contain a central phosphorus atom with a double bond to either sulphur or oxygen, R1 and R2 groups that are either ethyl or methyl in structure, and a leaving group *L, which is specific to the individual organophosphate. The general structure is shown in Figure 1. Organophosphates were developed in the early 19th century, but their effects on insects which are similar to their effects on humans were discovered in 1932. Some of them are very poisonous having been used as nerve agents during the World War II, but they usually are not persistent in the environment. Most organophosphates belong to the class of insect killers that act by disrupting the brains and nervous systems of insects. They also harm the brains and nervous systems of animals and humans by stopping or inhibiting a key enzyme in the nervous system called cholinesterase from working and this can cause a lot of health problems.

Organophosphates appear to pose the greatest risk among all the pesticides. These compounds account for more than half (by amount sold) of all insecticides used in the world. Statistics have shown that approximately over 150 million pounds of organophosphates are applied to approximately 150 million acres of agricultural crops annually, while nonagricultural uses account for about 51 million pounds per year (WHO/UNEP, 1990). These chemicals are used on many food and cash crops such as cotton, corn, wheat, fruits, nuts, vegetables, as well as in residential and commercial buildings for insect control to protect public health against diseases such as malaria, dengue fever and encephalitis. Some are also used for livestock pest control and for grain storage. This means many people may be exposed to them on a regular basis. Organophosphates also cause known effects, quick (acute) and longer term (chronic) to humans as well as to wide life. Organophosphates have

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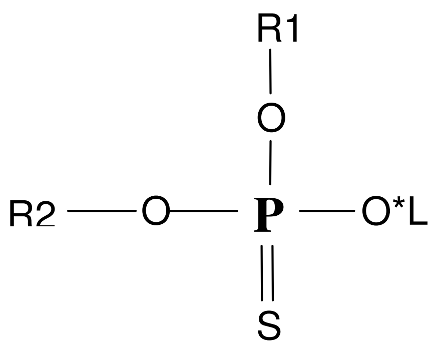

Figure 1. General structure of Organophosphate.

wide applicability for a number of reasons ranging from their affordability, broad spectrum of activity and to the fact that insects have not developed resistance to them as they have to some other pesticides.

Organophosphates insecticides are also neurotoxic. The neurotoxic effects of acute poisoning include acute cholinergic crisis (He, 1993), organophosphate-induced delayed polyneuropathy (Glynn et al., 1994) and intermediate myasthenia syndrome. Research in understanding the neurotoxic consequences of chemical exposure is critical for several reasons:

1. The economic considerations that arise from damage to the nervous system. The elderly constitute one of the fastest growing segments of the population and the costs of caring for the neurodegenerative diseases associated with this period such as Alzheimer's and Parkinson's are staggering. An understanding of the extent to which environmental chemicals contribute to neurodegenerative diseases may serve to decrease incidence of these disorders as well as associated costs.

2. The potential role of environmental chemical exposures in various developmental disabilities of childhood is also important to understand the long term health impacts with their associated economic consequences.

3. Added to the above is the issue of public trust and perception of the real and perceived risks. The psychological perception of risks of developmental anomalies arising from environmental exposures to chemicals are serious concerns for parents, just as are corresponding risks for learning disabilities or other types of neurologic dysfunctions arising from chemical exposure.

This paper therefore tends to make a review of the health, environmental and other risk exposure issues of organophosphates especially in developing nations of the world, where available data show that many agents considered toxic and long banned in the producing industrialized countries still find their ways developing countries. This paper also makes suggestions on the way out of this seeming catastrophic menace especially on children, mothers and the unsuspecting farm workers in these nations.

HUMAN EXPOSURES TO ORGANOPHOSPHATES AND POTENTIAL HEALTH EFFECTS

Because organophosphates have a wide variety of uses, the exposure routes are many: Ingestion, inhalation and dermal contacts are the most common. It can also be used as a weapon, in which case it may spread through air and is inhaled or contacted. Organophosphates affect the nervous system by reducing the ability of cholinesterase, an enzyme, to function properly in regulating a neurotransmitter called acetylcholine. Acetylcholine helps to transfer nerve impulses from a nerve cell to muscle cell or another nerve cell. If acetylcholine is not properly controlled by cholinesterase, the nerve impulses or neurons remain active longer than they should, over stimulating the nerves and muscles and causing symptoms such as weakness or paralysis of the muscles.

Recent studies show that children can be exposed to pesticides during normal oral exploration of their environments and their level of dermal contacts with floors and other surfaces. Also children living in rural agricultural areas may be exposed to higher pesticide levels than other children (Nhachi, 1988). There is toxicological evidence that repeated low level exposure to organophosphates may affect neurodevelopment in animals and humans (Song et al., 1997; Song et al., 1998; Campbell et al., 1997; Dam et al., 1998). Possible mechanisms for these effects may include inhibition of brain acetylcholinesterase, down-regulation of muscarinic receptors, decreased brain DNA synthesis and reduced brain weight in offspring (Balduini et al., 1993, Mehl et al., 1994, Eskenazi et al., 1999, Forget, 1993**)**. Researches have shown that organophosphate exposure may be related to respiratory diseases in children through dysregulation of the autonomic nervous system (Fengsheng et al., 2002). Other studies on pesticides exposure on children's health have been limited to those of birth defects and childhood cancer. Some case studies have associated parental exposure to organophosphates and organophosphates use in the home with childhood brain tumor, leukemia and lymphoma, testicular cancers and other cancers. However, there is paucity of information on whether low level chronic exposure of children to organophosphates can lead to adverse health consequences. One ecological study examined whether low level chronic exposure of children to pesticides can lead to adverse health consequences. This study of Yaqui children in Mexico found that children 4-5 years of age (n=33), living in an agricultural valley with presumably higher pesticide exposure had deficits in tests of stamina, coordination recall and ability to draw a person, compared to children (n=17), living in the foothills where there was mostly ranching (Tinoco, and Halperin, 1998). Long term health effects from prolonged exposure to pesticides including cancer mortality, reproductive effects and non-cancer health effects have been studied in many countries. However, firm conclusions on other adverse effects of chronic exposure to pesticides on human health cannot be made at present because of paucity of information (Maroni et al., 1993).

ENVIRONMENTAL EFFECTS OF ORGANOPHOSPHATES

Recent studies have shown that home environments are commonly contaminated with pesticides especially organophosphates which are the most commonly used pesticides (Eskenazi et al., 1999). Young children are therefore exposed to these pesticides because of their normal tendency to explore their environments orally, combined with their proximity to potentially contaminated floors, surfaces and air. Physiologic characteristic of children such as high intake of food, water, and air per unit body weight may also increase their exposure.

Organophosphates could cause contamination of water and injury to plants and animals that were not the original targets of the pesticide application. For example, honey bees can be killed by pesticide applications, as can insects that are being used to help control pests. Organophosphates also have the potential for contamination of water through runoff or seepage into ground water and this could have serious harmful consequences to aquatic life, plants, animals and humans.

ORGANOPHOSPHATE POISOINING IN DEVELOPING NATIONS

World estimates show that pesticides are responsible for 3 million cases of severe poisoning and 220,000 deaths each year. While most of these pesticides are produced and in developed countries, most poisonings and 99% of the deaths from them occur in third world and developing nations of the world. For example, in the USA, approximately 20,000 reported organophosphate exposures occur per year; however, it is estimated that only 1% of field worker illness from pesticide exposure is reported. According to the American Association of poison control centers, 16,392 exposures occurred in 1998 in the USA, with only 11 reported deaths.

Insecticides represent by far the greatest proportion of pesticides used in developing countries, while herbicide sales have been greater than those of others in industrialized countries. It is estimated that the use of pesticides in developing nations approximately doubles every ten years, either because pests have developed resistance to existing single pesticides which have led to development of combined pesticides or the fact that most of the pesticides considered toxic and long banned in developed countries still find their ways into developing nations. Majority of the poisoning deaths in these nations have been due to cholinesterase-inhibiting pesticides such as organophosphates. The high rate of poisoning could probably be attributed to a number of reasons including farmers' poor knowledge about pesticides and pesticide use, less protection against exposures, little formal education of agricultural workers, minimal understanding of the health risks and most importantly, inadequate safety warnings on the packages by the manufacturers.

In sub-Saharan Africa, insecticides usage accounts for approximately 25% of all pesticides used. Insecticides in use in conventional cotton production in sub-Saharan Africa include a wide range of extremely toxic active ingredients and available data shows that half of these ingredients are either not approved or have long been banned even in the producing developed countries (The lists of lists, 2001). Except for triazophos (WHO class 1b- highly hazardous) all other active ingredients in use in pesticides in sub-Saharan Africa are classified for acute toxicity by the World Health Organization (WHO) (Table 1). Carbaryl, cypermethrin and dimethoate are suspected of causing cancer in humans. Except for carbosulfan, profenofos and triazophos, all active ingredients used in pesticides for cotton cultivation in Africa are suspected endocrine disruptors which affect parts of the body's hormone systems and can lead to an increase in birth defects, sexual abnormalities and reproductive failure (Guide to active ingredient hazards, 2001) (Table 1).

In Benin, food contamination has been associated with cotton production due to the misuse of pesticides and the recycling of pesticides containers. In 1999/2000, over 70 people died following the ingestion of the cotton insecticide Endosulfan (Ton et al., 2000, Agri-Culture, 1999a, b), which had been banned or voluntarily withdrawn since the early 1980's because of their high risk to humans and the environment. This poison, however, has persisted in Africa and other developing nations (End of the road for Endosulfan, 2002). In another study involving the use of callisulfan, an organochlorine supplied by the French company Calliope, conducted in the Ndali district of Benin involving 265 victims, 75% were found to be males, accounting for 71% of deaths and 76% of acute poisonings, whereas women and girls accounted 29% of the deaths and 24% poisonings. Proportionately, the largest group affected was predominantly children, with 11 children dying as a result of pesticide exposure. Those suffering health effects were predominantly aged 21-30 (37%). Children and young people are the most vulnerable and the health effects associated with these exposures range from loss of conciousness, total

Table 1. Characteristics of the main active ingredients of pesticides used in conventional cotton production in sub-Saharan Africa in 2000/2001.

Active ingredients	Group	Who class	Possibly carcinogenic	Endocrine disruptor
Betacyfluthrine	Synthetic Pyrethroid	II	–	3
Carbaryl	Carbamate	II	3	3
Carbosulfan	Carbamate	II	?	–
Chlorpyrifos	Organophosphate	II	–	3
Cyfluthrin	Synthetic Pyrethroid	II	–	3
Cyperimethrin	Synthetic Pyrethroid	II	3	3
Deltamethrin	Synthetic Pyrethroid	II	?	3
Dimethoate	Organophosphate	II	3	3
Endosulfan	Organochlorine	II	–	3
Fenvalerate	Synthetic Pyrethroid	II	?	3
Lambdacyhalothrin	Synthetic Pyrethroid	II	–	3
Profenofos	Organophosphate	II	–	–
Triazophos	Organophosphate	1b	–	–

Source: Tovignan et al. (2001)

lethargy, sore and grating eyes, nausea, vomiting, convulsions, anxiety, drowsiness, sweating, hyper salivation, dizziness, diarrhoea, to fever (Tovignan et al., 2001).

In the Asian region, a survey of acute pesticide poisoning among agricultural workers reveal that occupational pesticide poisoning accounted for about 1.9% of the cases in Indonesia, and as many as 31.9 % in Sri lanka (He, 1998). China also recorded 52,287 cases of acute pesticide poisoning with 6,281 deaths in 27 provinces in 1993. Occupational pesticide poisoning accounted for 17.8%. In China, the number of registered pesticide formulations was about 1,600 in 1996. Insecticides accounted for about 61% of total pesticide usage, followed by fungicides and herbicides. Also more than 600 kinds of pesticide mixture preparations, mainly containing organophosphorus insecticides, have been produced and applied in China in recent years (Fengsheng et al., 2002).

In Latin America, it appears that most cases of pesticide poisoning are occupational. In Costa Rica, 67.8% were work-related. In Nicaragua, 91% of the reported cases of pesticide poisoning were occupational and 8% involved other accidents.

In all the occupational exposures, acute organophosphate poisoning accounts for 78.8% of total pesticide poisonings in China, 69.1% in Sri Lanka and 53.6% in Malaysia. Organophosphate pesticide poisoning resulting in death have also been reported from Brazil (da Silva and Lopez, 1980), Chile (Delgado and Suazo, 1981), Ethiopia (Abebe, 1991), Kenya (Kimani and Mwanthi, 1995), South Africa (Bardin et al., 1987, Hayes et al., 1978), Tunisia (Nouria et al., 1994), Turkey (Ozturk et al., 1990) and Zimbabwe (Hayes et al., 1978; Nhachi, 1988). The causal factors contributing to these acute occupational pesticide poisoning include sloppy handling during preparation and spraying of pesticides, using highly toxic pesticides or high concentration of pesticides, spraying every row, direct contact with sprayed crops, going forward into the wind during spraying, lack of personal protection and poor personal hygiene (Cheng et al., 1991).

SUMMARY AND CONCLUSION

Organophosphates are the most widely used insecticides today and the major cause of most of the incidences of pesticide poisoning and deaths world wide. Agricultural workers, women and children living in rural farmlands are at the great risk of poisoning. Available data have shown that while these pesticides are produced and used in the developed countries, the poisoning and deaths occur mostly in the third world and developing countries. Also most of the active ingredients in these pesticides that have been banned, long ago in these industrialized nations still find their ways into the markets of developing nations. This therefore calls for concerted efforts by the international community to avert what may turn out to be a catastrophic damage to an innocent generation. In view of the above, this paper tends to make the following suggestions:

1. The ban on the toxic ingredients in pesticides should be total, and there should be an international legislation to control and enforce the ban.

2. The manufacturers of these pesticides should use adequate safety labels to educate their customers about the specificity of a particular product and not the usual impression that one product can be used for a whole multitude of pest controls including seed storage. They

should also organize technical trainings in their markets to educate workers in agricultural sectors and the distribution chain aware of the hazards of the products.

3. There should be continued efforts by scientists towards developing environmentally friendly and safer compounds for both agriculture and public health use. Furthermore, there is need to define cellular and molecular mechanisms of neurotoxicity and to develop mechanistically relevant biomarkers. There should also be valid measurements of exposure to organophosphate pesticides covering long periods to be able to make good assertions about the chronic health and environmental effects. And lastly, well designed epidemiological studies need to be conducted to provide enough information to healthcare providers in occupational, environmental and public health.

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