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A Study of the Implications of Organophosphorus Agrochemical Residues Poisoning in Patients with Mental Disorders

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ABSTRACT

The aim of this study was to investigate the possible link between the mental disorder and the poisoning due to some organophosphorus agrochemicals. The study was done on a population of 40 patients and 40 healthy individuals. Open acid digestion method was used to extract organophosphate residues from blood and head hair samples. Ten patients were found to be positive for azinphos methyl at concentrations between 0.87 and 5.19 $\mu\text{g kg}^{-1}$ in hair and 6.27 to 10.98 $\mu\text{g kg}^{-1}$ in blood samples. These values fall above the FAO/WHO threshold limits and hence the possible links to the mental disorder problems.

Key words: Pollution, organophosphorus pesticides, mental disorders, high performance liquid chromatography, mass spectrometry

INTRODUCTION

Some clinical neurotoxic symptoms in humans are known to be due to the poisoning exposure from some chemical molecules used as either fumigants or agrochemicals such as carbamates and organophosphorus (Akhlaghi *et al.*, 2009; Strum *et al.*, 2010; Sanchez-Hernandez, 2010). The neurotoxic symptoms implicated on agrochemicals and fumigants are normally divided into groups such as generalized stress (Sengar *et al.*, 2008; Wesseling *et al.*, 2010) psychiatric morbidity (Xibiao *et al.*, 2009; Ghazinour *et al.*, 2009) depression (Beseler *et al.*, 2006; Stallones and Beseler, 2002) suicide (Sharma *et al.*, 2007; Malangu, 2008) and even death (Bhana and Visser, 2004; Van Wijngaarden, 2003).

Human may become exposed to the contamination of agrochemical residues mainly through contaminated water sources, diet (e.g., vegetable irrigated with contaminated water or fish and other sea foods in contaminated waters) as well as air in the case of volatile agrochemicals (Mansee *et al.*, 2004; Travisi and Nijkamp, 2008). The exposure may as well be indirect through the trophic level feeding relationship (Shayeghi *et al.*, 2007). For the sake of analysis of samples from human being, appropriate specimens need to be identified to determine residues of specific agrochemical or fumigants residues. Specimens for the analysis of OPs exposure are mainly blood, urine and saliva (Xibiao *et al.*, 2009; Kieszak *et al.*, 2002). Hair has mainly been used as a measure of long term exposure to such poisonous compounds (Tsatsakis *et al.*, 2008; Posecion *et al.*, 2006).

There have been numerous analytical techniques and tests that have been devised to study and determine the link between human agrochemicals exposure and the associated functional impact (El-Saeid *et al.*, 2011; Wesseling *et al.*, 2002). However, the analytical methods that provide an association between the agrochemical exposure to the poisoning effect on some mentally related disorders are considered more effective. Moreover, methods which provide the relationship between exposure and its effect on the cholinesterase levels have been regarded as mostly more valid (Shayeghi *et al.*, 2009; Li *et al.*, 2010; Srivastava *et al.*, 2000).

In this work, we report the analysis of two compounds belonging to the Organophosphorus Pesticides (OPs), the azinphos methyl and coumaphos in the blood and head hair samples of patients with mental disorders, namely, bipolar, postpartum psychosis, schizophrenia and some non-specific cases in the patient's population studied from Ile Ife in Nigeria.

Azinphos-methyl is a general name to a chemical S-(3,4-dihydro-4-oxobenzo (d)-(1,2,3)-triazin-3-yl)methyl-O,O-dimethyl phosphorodithioate. The Permissible Exposure Limits (PEL) set for azinphos methyl by the American Occupational Safety and Health Administration (OSHA) for general industry, skin and maritime is $0.2 \mu\text{g L}^{-1}$ (Edwards and Tchounwou, 2005). The same value has been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH) (Buratti *et al.*, 2003). The Immediately Dangerous to Life or Health concentration (IDLH) set by NIOSH is set at 10 g L^{-1} (Buratti *et al.*, 2003). Biomarkers of exposure include measurement of acetylcholinesterase activity in red blood cells and urinary excretion of the metabolites, dimethylphosphate, dimethylthiophosphate and dimethyldithiophosphate (Shayeghi *et al.*, 2009; Costa *et al.*, 2005).

The Acceptable Daily Intake (ADI) for azinphos-methyl for humans has been derived by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) to be $0.00254 \text{ mg kg}^{-1} \text{ bw per day}$ (Inigo-Nunez *et al.*, 2010; Fenske *et al.*, 2000).

The structures of the OPs analysed in this work are shown in Fig. 1a and b.

MATERIALS AND METHODS

Chemicals, reagents and materials: Pesticide standards, OPs (azinphos-methyl and coumaphos) (Fig. 1a, b) (purities >99%) were obtained from Riedel-de-Haën (Seelze-Hannover, Germany); Pesticide-quality solvents (n-hexane and toluene) and calcium chloride were purchased from Panreac (Barcelona, Spain). Sodium hydroxide pellets (98%) was from Saarchem (Krugerddorp, Republic of South Africa); Nitric Acid (AR), triton x-100 and hydrochloric were purchased from N.T. Laboratory Supplies, (Johannesburg, Republic of South Africa). A multicomponent working standard solution ($2\text{-}10 \mu\text{g mL}^{-1}$ concentration of each compound) were prepared by appropriate dilutions of the stock solutions (1000 mg L^{-1}) and stored under refrigeration (4°C).

All glassware were soaked in 5% nitric acid overnight and washed with detergents, rinsed with double distilled water and kept in the oven at 70°C (except standard flasks) for 24 h before use.

Location and general features of the study area: Ile-Ife is the locus of the research work and is situated in Osun State, South Western Nigeria. It lies approximately between latitudes $7^\circ 26'\text{N}$ - $7^\circ 33'\text{N}$ of the equator and longitude $4^\circ 30'\text{E}$ - $4^\circ 35'\text{E}$ of the prime meridian on a general elevation of about 350 m above the mean sea level. It is about 30 km to Ilesa and about 35 km south of Osogbo, the Osun State capital and 610 km south west of Abuja, the Nigerian capital.

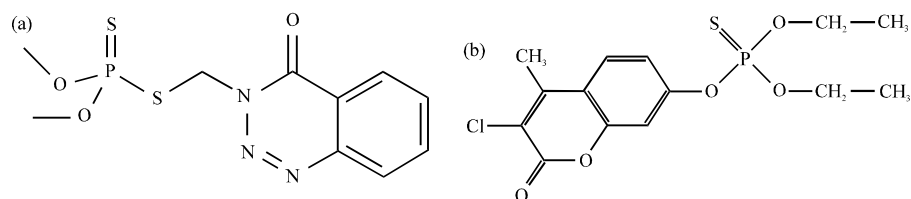


Fig. 1: Chemical structures for organophosphate compounds studied; (a) azinphos methyl and (b) coumophos

The catchments areas for patients include Osun, Ekiti, Ondo and parts of Oyo States, all located within the South Western Nigeria and there are no large industrial concentrations but mostly agrarian communities with increasing tendencies towards the use of pesticides and fertilizers.

Sample collection: The sampling was conducted from 18/06/2007 to 30/08/2007. Samples were collected from the out patients of the Department of mental health of the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria after an ethical committee review and certification. The blood samples were drawn from the cubital vein with 5 mL syringe and stored in heparinized bottle; these were later freeze-dried. The hair samples were collected at the nape of the head to prevent contamination cosmetics and facial secretions. The length of the head hair samples from all patients were about 3 mm and hair specimens were cut from the root, at the nape of the head and used for analysis. Total head hair samples were mixed to allow a homogeneous and representative sub-sampling of the head hair specimen before being analysed. After cutting, the well-mixed head hair samples were washed four times with Triton X-100 (0.5% v/v) to remove contamination due to exogenous trace elements from the hair surface. The samples were then rinsed with acetone and allowed to drain before being rinsed again three times with de-ionized water (18 M Ω) and two times rinses with acetone and then dried in an oven at 75°C, kept in clean standard envelopes ready for the extraction procedures.

Sample preparation methods

Open acid digestion of organophosphate residues from hair and blood samples: The extraction of organophosphates from blood and hair samples was carried out using open acid digestion. About 50 mg of the hair and the blood were digested separately using 10 mL of 0.1 M HNO₃ and allowed to concentrate in a hotplate to about 2 mL and then made up to 15 mL with methanol: water (75:25) and taken for HPLC analysis.

Instrumentation and apparatus: HPLC-UV-DAD and HPLC-ESI-MS Experiments: Agilent 1200 series HPLC (Wilmington, DE, USA) equipped with auto sampler, degasser and a UV-DAD detector was used as well as a C18, XDB column (4.6 mm×50 mm×1.8 μ m) were used. The detection wavelength of 254 nm was used for the compounds. The mobile phase was 75% methanol and 25% water. Injection volume was 5 μ L at flow rate of 0.3 mL min⁻¹.

The HPLC-ESI-MS system used for this work consisted of an Agilent Hewlett-Packard 1100 Series HPLC connected to Agilent 1100 Series LC/MSD Trap mass spectrometer (Wilmington, DE, USA). The quadrupole temperature of the MS was 120°C and the mass chromatograms were acquired in the Selected Ion Mode (SIM) for the negative mode. The temperature of the drying gas N₂, was 300°C and the flow rate of the nebulizing gas N₂, was 40 mL min⁻¹, being maintained at 80 psi.

RESULTS AND DISCUSSION

Evaluation of OPs in patient's samples: In this work blood and hair samples were used as specimen for the analysis of organophosphorus compounds for samples obtained from mentally ill patients. The motivation behind using these matrices is the successful use as indicators for the presence of contaminants and intoxication including in forensic and clinical practices (Tsatsakis *et al.*, 2010). For example, hair matrix was reported in the analyses of a number of drug residues (Fernandez *et al.*, 2009; Uhl and Sachs, 2004; Jurado *et al.*, 2004). Hair samples have also been used in the measurements of heavy metals (Kazi *et al.*, 2008). In other reports, hair specimens were used in the determination of chlorinated as well as the organophosphorus agrochemicals (Zhang *et al.*, 2007; Tutudaki *et al.*, 2003). In most cases human exposure to agrochemical intoxication arises from many possible avenues such as agricultural and fumigation activities. The contamination may be spread through the feeding relationship within the ecosystem (food chain) and other natural means of environmental pollution, such as water and air (Tsatsakis *et al.*, 2003). All the above reviews are in support of present research findings.

The results of the analysis of blood and hair samples from both patients and health human specimens were conducted and revealed that, in some patients residues of the OPs were detected to the levels above the recommend FAO/WHO threshold limits. The most plausible explanation for the poisoning of patients by agrochemical residues may be both the results of agrochemical misuse as well as people's careless attitude towards hygiene when dealing with foods and other consumable items such as water. The misuse of agrochemicals may be linked to a general increase in the use of chemicals in agriculture that has in turn brought about an unusual increase in the incidences of agrochemical poisoning globally and organophosphates are the most common agrochemical poisons (Aggrawal, 2006). It is therefore imperative to observe all the necessary precautions towards the agrochemicals poisoning to prevent or minimize possible exposure. To successfully implement such a strategy it is important that a basic knowledge about the adverse effects of the agrochemicals is given to the users as well to the people in areas where such molecules may find access. The contamination could have as well be a result of consuming water and/or food items in a food web chain relationship, for example the consumption of fish from contaminated waters may result into residues of organophosphorus compounds be found in a person (Tsatsakis *et al.*, 2003).

In this work, a total number of 40 samples were analyzed for the presence of OPs in hair and blood specimens. Comparing the results from the HPLC chromatograms of standards and samples it was possible to identify the presence of some OPs residues in both hair and blood samples (Fig. 2, 3). The identification was done chromatographically by analyzing the control samples (from healthy considered persons) and sample specimens from mentally ill patients by comparison of the retention times and UV-spectrum for the respective standards.

For all the forty samples analyzed from patients, 10 samples were found to be positive for Azinphos- methyl and all were negative for coumophos (the positive results were found to be consistent in both hair and blood for the same patients). The chromatographic signals for azinphos methyl obtained for the positive samples were ascertained by UV-spectra comparison and further confirmed by a mass spectrometer (LC-ESI-MS) (Fig. 3). All the control samples gave negative results for both azinphos methyl and coumophos (Fig. 4a, b).

Quantitation of azinphos methyl: Azinphos methyl from patient samples was quantified using calibration curve where a series of standards with increasing concentration were analyzed in the LC-ESI-MS and their peak areas plotted against the corresponding concentration levels. An acceptable calibration plots with r^2 value of 0.99 were obtained for both azinphos methyl and coumophos.

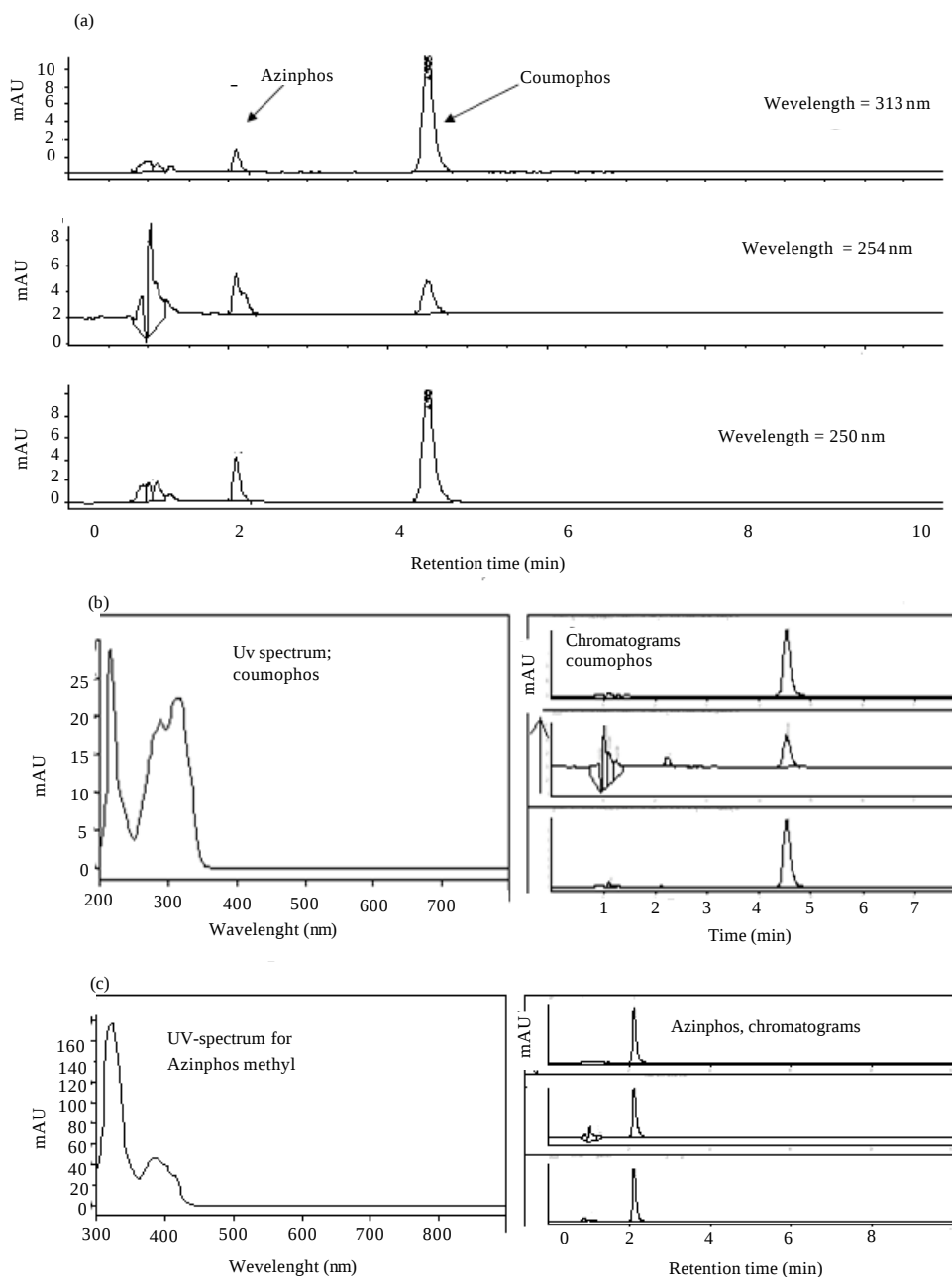


Fig. 2: HPLC Chromatograms and UV spectra for; (a) OPs standards (azinphos methyl and coumophos); (b) coumophos standard and (c) azinphos methyl standard

The level of azinphos found in patient hair samples ranged from 0.87 to 5.19 $\mu\text{g kg}^{-1}$ while in blood samples the range was from 6.27 to 10.98 $\mu\text{g kg}^{-1}$ (Fig. 5).

In other previous works, there have been reports on agrochemical residue determination in head hair samples. For example, Tsatsakis *et al.* (2008) reported the presence of diazinon at low levels (2.8 pg mg^{-1}) in head hair samples using GCMS for analysis. They did not detect other organophosphorus pesticide residues in their work.

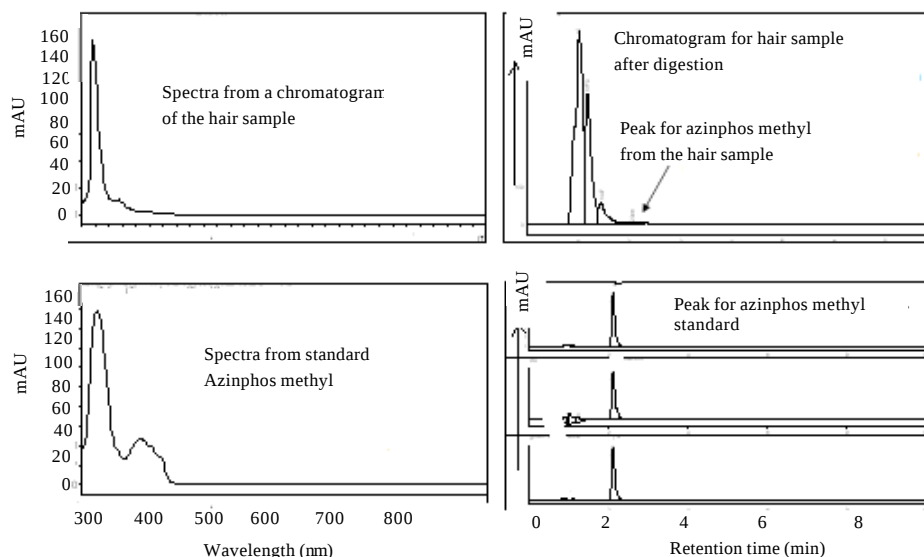


Fig. 3: Chromatograms and UV spectra for hair samples obtained from a patient

Trend of azinphos methyl residues in the sample specimens analyzed: In general more concentrations were detected in the blood than in hair samples. This indicates that the partition coefficient for this compound was higher in the blood than in the head hair. The same samples were then subjected to LC-MS for further confirmation. The results from the LC-MS showed the presence of ions and fragments that correspond to the azinphos methyl (Fig. 4a, b). Other ions (fragments) observed include the ones for the one with mass ($m/z = 299$) as well as the one due to loss of a methyl group ($m/z = 302$). The fragment with $m/z = 299$ may have arisen due to the fact that this compound undergoes oxidation, reduction as well as hydrolysis. There is possibility of oxidation product of thiono sulfur, in which one of the sulfur might have changed to oxygen (O) which was then followed by reduction and then hydrolysis that gave the mass $m/z = 299$. The standard azinphos methyl gave a sodiated molecular ion ($m/z = 340$) (Fig. 4a) and the same ions were also observed from the hair sample from patient H11 (Fig. 4b).

More other ions were also observed in the sample including the ion due to potassium ($m/z = 356$) as well as the protonated molecular ion ($m/z = 318$). This confirmed that azinphos methyl residues were present in the sample. Coumophos was not detected from any of the samples. All the control samples gave negative results. From the quantification results, it was evident that, the concentration of azinphos methyl found in some patients, exceeds the ADI threshold limit set by WHO/FAO and other international health regulating bodies. This may give an indication of the possible link to the illness.

Limitations of this study: Despite the successful performance of the method developed in this work, still there are drawbacks that are obvious and may need to be addressed in the ongoing work. Firstly, the work did not involve any of the metabolites associated with the organophosphorus compounds analyzed but instead it assumed that the parent molecules, at least in part remain intact for a certain length period of time. This may be only valid if it doesn't take too long as it is known that organophosphorus compounds are rapidly metabolized to non-specific dialkylphosphate

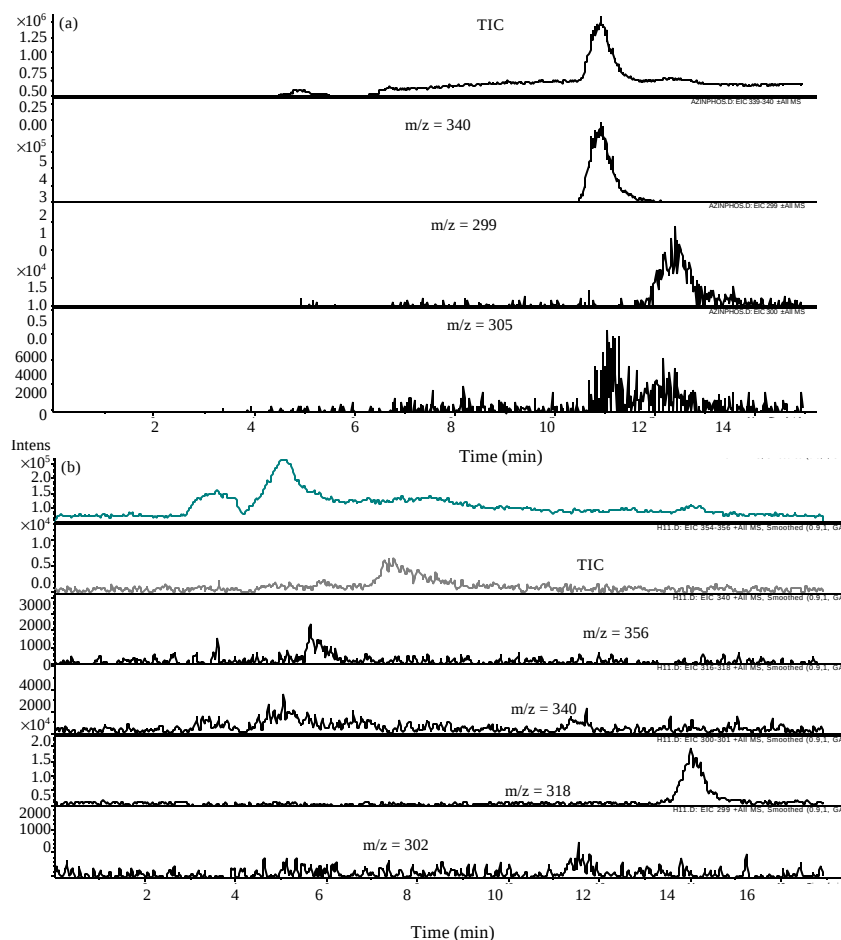


Fig. 4: LC-ESI-MS chromatograms for; (a) azinphos methyl standard and (b) azinphos methyl from hair sample H11 (NB: TIC = Total ion chromatogram)

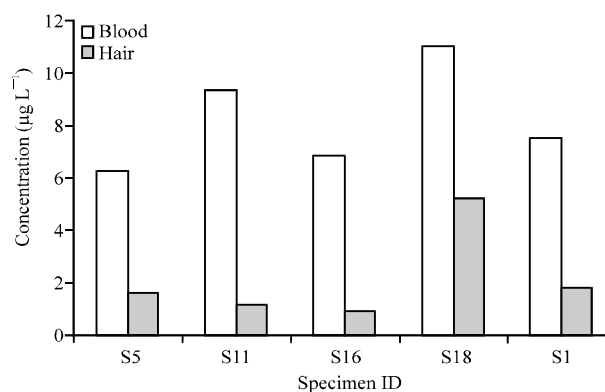


Fig. 5: Concentration of Azinphos-methyl in patient samples

metabolites (Tsatsakis *et al.*, 2010). Another limitation is from the fact that only 40 individuals from a highly populated area in Nigeria (the most populated country in Africa), participated in the

study and this may not necessarily be representative enough of the people in area. A much larger sample size from the area would have provided a more precise probability of the outcome from the population such that even a stronger basis for generalization of these findings would have been more meaningful. This may be part of the work that will be taking place at the moment. Thirdly, this work does not include the analysis of water or other food items which would have given an evidential correlation of the contamination and the link to mental disability.

CONCLUSION

The present study gives an indication that anthropogenic activities may result into contamination of environment and hence poison the sources of water and food which may lead to serious neuro-health concerns. The results have shown the possibility of pesticide poisoning in patients with mental disorders, though they may not be very conclusive as more other tests need to be performed, such as the measurement of acetylcholinesterase activity in the blood and the presence of respective OPs metabolites in urine. The measurements of such parameters will be the next move.

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