UNIVERSITY OF ILORIN

THE ONE HUNDRED AND NINETY-TWO (192nd) INAUGURAL LECTURE

PREVENTING PESTICIDES FROM POISONING AWAY OUR HEALTH AND FUTURE- THE OXIDATIVE APPROACH

By

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My Lords, Spiritual and Temporal,
Members of my nuclear and extended family,
Esteemed Invited Guests, Friends and Relatives,
Distinguished Students of the Faculty of Veterinary Medicine,
Great Students of the University of Ilorin (Greatest Unilorites),
Gentlemen of the Print and Electronic Media,
Distinguished Ladies and Gentlemen.

Preamble

I give glory to the Almighty Allah, the Greatest, the Giver and Taker of life, for making it possible to stand before you today to present this unique inaugural lecture, the one hundred and ninety-second in the series. Mr. Vice-Chancellor, sir, this inaugural lecture is unique because it is the first from the Department of Veterinary Pharmacology and Toxicology and indeed the first from the Faculty of Veterinary Medicine. I give glory to the Almighty Allah for making today a reality. As an

academic tradition, an inaugural lecture of this nature provides one with the opportunity to showcase one's contribution to knowledge in a manner that can be easily understood by researchers in fields unrelated to that of the lecturer and even understood by the public, as it is a forum for the town and the gown to meet. The inaugural lecture is also a forum to chart a way forward in terms of the future research direction in one's area of specialization.

Mr. Vice-Chancellor, sir, as a child growing up, my interest had been to be a farmer, as I watched with admiration how my father brought farm produce home while also engaging in the rearing of his goats and local chickens in our compound. My dad really loved animals. It was not surprising that I signified my interest to study agriculture at the University of Ilorin in my first attempt at UME after my secondary school education but was not granted the opportunity. Not deterred, I was determined to pursue my dream after my A- level but a guest that lodged in the hotel near my family compound, who is a Veterinary Doctor, introduced me to Veterinary Medicine, a discipline I was hearing its name or even knowing about for the first time. Introducing the course to my dad was easy knowing fully well that he loved animals. As a matter of fact, he encouraged me to go for the course and the rest is now history. For what I have become today, I must pay a glowing tribute to my father, whose love for education knew no bounds. Apart from being my first teacher, my father showed genuine interest in my education as he provided enough resources to ensure I excel in my chosen field, despite the obvious financial limitations. I thank the Almighty Allah that he was alive to witness my elevation to the exalted position of Professor, and when he left this world some three years ago, I am sure he died a fulfilled man. Mr. Vice-Chancellor sir, permit me to dedicate this lecture to the memory of this amiable man, a disciplinarian, teacher, mentor, friend, confidant, adviser and spiritual guide, my father, **Alhaji Ambali Hidhir Agbogunlori Atunluse**, without whose support I would not have been here today to present this lecture. May the Almighty Allah continue to grant him Aljannah Firdaus (Amin). I

must not forget to thank my darling and dutiful mother, **Hajia Asmau Ambali,** who gave a helping hand to make sure that my aspiration was not aborted. 'Mama, as you were fondly called, I thank you for all the care and support.

My Journey to the World of Toxicology

Mr. Vice-Chancellor sir, I can only describe myself as a lucky "chap" because the Almighty Allah in His infinite mercy granted my request to be a **Toxicologist**, a request I made to Him in 400 level during my undergraduate days at the great Ahmadu Bello University, Zaria. The journey started when the Late **Prof. Josiah Nwankwo Nwude**, a foremost toxicologist and first Professor of Veterinary Toxicology in West and Central Africa entered our lecture room to teach Toxicology. After a week of interaction with this foremost toxicology teacher cum researcher, I concluded that this is a man to emulate and model myself after. Therefore, when it was time to pick a supervisor for my undergraduate project at 600 Level, I did not hesitate to approach Prof. Nwude for the first time in his office that I wanted him to supervise my work. He was pleasantly surprised as he told me that was the first time in his 21-year career as an academic that an undergraduate student would make that kind of request and he asked me if I had clearly thought it out. Of course, the implication of his question was well understood as I answered positively and affirmatively. I remembered many of my colleagues then, some of whom are in this hall today told me that I had committed an "academic suicide" going by the no-nonsense disposition of my chosen supervisor. Mr. Vice-Chancellor sir, I am happy to report that I was one of the earliest in my class to complete and submit my project to the Department. This was the beginning of my journey to the world of Toxicology. My interest in Toxicology was not by accident, but a product of deep interest, thought and guidance from the Most High (SWA). After my youth service, the professor expressed his interest in having me back in the Department whenever there was the opportunity, and he did just that when the opportunity presented itself. Unfortunately, after

four years of my appointment, precisely on the 22nd of March 2000, I lost my mentor, Prof. Josiah Nwankwo Nwude to the cold hands of death, but not before he gave me a solid research and teaching foundation laced with discipline and academic integrity. As a show of appreciation for the contribution of this disciplinarian and foremost toxicologist to my career, Mr. Vice Chancellor, sir, please permit me to also dedicate this lecture to his memory.

Venturing into Pesticide Toxicology

Mr. Vice-Chancellor, sir, Prof. Nwude's plan for me was to be a mycotoxicologist, working on mushrooms and their toxic potentials. That was my research focus for my M.Sc. degree. However, in the course of planning for my Ph.D., an event happened that completely changed my focus. Somebody, who was into pest control, reported a fertility problem he suspected to have suffered in the aftermath of accidental exposure to a pesticide. As a baby toxicologist then, he came with the belief that "I can do something" after several visits to the hospitals did not yield much success. In my search through literature, I came across an emerging term "oxidative stress" as being one of the proposed mechanisms of pesticides poisoning. Of course, I suggested vitamin C to him, and he moved on. That encounter motivated me to research further into pesticides poisoning and oxidative stress and using antioxidants to mitigate its toxicity. That marks the beginning of my journey into the pesticide world.

Although, oxidative stress was suspected to be involved in pesticide poisoning, *in vivo* use of antioxidants to mitigate the poisoning has not been evaluated. I capitalized on this knowledge gap, and the product of my research is what is going to be presented today.

Mr. Vice-Chancellor sir, with all sense of modesty I'm happy to inform this distinguished audience that I pioneered research in this area of pesticide toxicology in this part of the world. Achieving this was not an easy task, as I ran into many "bumps" because of lack of expertise coupled with the lack of

requisite equipment, especially in the area of neurotoxicology. My supervisors and other mentors however encouraged me, as I crossed the hurdles one after the other. The encouragement was fueled by the positive impression and comments of experts that served as reviewers of the manuscripts I submitted to top journals across the globe. These efforts were crowned as top indexing bodies and libraries across the globe cited and archived my publications, while many top researchers in the field requested for the electronic and even hard copies of my publications. To God be the glory, *Alhamdulilahi robili alamina.*

Mr. Vice-Chancellor, sir, we are currently in the era I refer to as "pesticides storm" as more people across the globe embrace the use of pesticides without minding the consequence on the health and wellbeing of the human and animal population. Therefore, the topic of this lecture was carefully chosen in order to highlight how repeated exposure to pesticides is **poisoning *away* our health and future**, and how my research using oxidative approach can help stem the tide of these pesticide-induced adverse health consequences. I have used animal models to mimic human poisoning encounters. However, in order to "legitimise" my findings in human subjects, I have decided to juxtapose my results with the data obtained from clinical and epidemiological studies in humans.

Introduction

Mr. Vice-Chancellor, sir, the story of man is that of a hungry creature in search of food.[1] In this process, man competes with various elements including pests to obtain an adequate supply of food for his sustenance. Pest, over time, has proven to be a major competitor of man, reducing the quantity and quality of food available for his wellbeing. This is further compounded by its ability to cause and enhance the spread of diseases to plants, animals and man. Man, being a selfish and domineering creature, has therefore identified and/or developed agents known as pesticides, to combat the menace posed by this creature called pest. The use of pesticides by man to combat the menace of pests

dates to ancient times. One of the earliest documented pesticides used by man to control mites and other insects was sulfur, which was used by the ancient Sumerians around 2500 BC.[2]

Pesticide has been defined by FAO (1986)[3] as any substance or mixture of substance intended for preventing, destroying or controlling any pest, including vectors of human and animal diseases, unwanted plants or animals causing harm during, or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuff or substances administered for the control of insects, arachnids, or other pests in or on their bodies.

Pesticides usage have been on the increase, especially following the development of more potent synthetic ones after the second world war. This becomes pertinent in the present-day world, as one of the dilemmas currently facing human civilization is how to eradicate hunger in a more sustainable way through improving agricultural production, and reduction of wastages. Even more crucial is the upsurge in human global population, which the United Nations estimated will exceed 10 billion by the year 2100.[4] This population crisis is likely to be felt more in Nigeria with a current population of about 190 million, accounting for more than one-quarter of the population of sub-Saharan Africa or one in every 6 black persons in the world.[5] Therefore, food crisis is one of the most important challenges being faced by the present generation and may even be worse in generations to come. Pesticides usage is very key to achieving food sufficiency. This is because it is estimated that approximately 40% of the yearly crop production is damaged globally prior to harvest as a result of pest infestation during post-harvest.[6] Apart from improving human and animal nutrition, pesticides also lower the cost of food, reduced farm labour requirements, and its attendant injury, control vector and vector-borne diseases, and improve public health and quality of living.[7]As pleasant as these advantages of pesticides use are, it is noteworthy that they do impair the health of man and animals.

Mr. Vice-Chancellor, sir, let me use this opportunity to pay a glowing tribute to a woman environmentalist, Rachel Carson, whose book "Silent Springs" made the world realize the catastrophic effect of pesticides on health and the environment. The book changed the perception of many to our toxic world "and was considered as the effective beginning of toxic discourse".[8] Her book served as a catalyst for the formation of the environmental movement in the 1960s and 1970s, culminating in the banning of Dichloro-diphenyl-trichloroethane (DDT), an effective but notoriously persistent chemical pesticide widely used at that time. Perhaps, without her beautiful work, I would not have stood before you today to speak on the devastating effect of pesticides on health and my little contribution to the mitigation of its effect.

Prevalence of Pesticide Poisoning

Exposure to pesticides is one of the most important occupational risks especially among farmers globally. The WHO and the UN Environmental Program estimated that 3 million workers in agriculture in the developing world experience pesticide poisoning annually with about 18,000 death.[9] Most of the deaths associated with acute pesticide poisoning occur in developing countries which paradoxically utilize only about ¼th of the world production.[10] According to one study, as many as 25 million workers in developing countries may suffer mild poisoning yearly.[11] It has been estimated that there are 250,000 deaths annually from pesticide self-poisoning worldwide accounting for about 30% of the suicides globally.[12] Although actual records of deaths are difficult to come by in Nigeria since most poisoning incidences occur in rural areas where there are no competent clinics or physicians. However, cases of poisoning or death from pesticides are mostly obtained from newspapers and eyewitnesses account.

Mr. Vice-Chancellor, sir, some of the reasons advanced for widespread exposure and attendant morbidity and mortality due to

pesticide poisoning in developing countries such as Nigeria include lack of or less strictly enforced pesticide usage regulations and porous country borders, which have turned these countries into dumping grounds for banned or restricted hazardous chemical pesticides. In Nigeria, the laws governing the use of chemicals are integrated wholly in the ECOWAS Regulations on Pesticides which cover all activities involving experiments on, as well as authorization, marketing, use and control of pesticides in the West African subregion; and the National Environmental (Hazardous Chemicals and Pesticides) Regulations, 2013, which deals with import, export, storage, usage, and marketing of hazardous chemicals and pesticides including other agrochemicals. These laws have not been strictly enforced as there has been a lack of political will to address head-on the menace caused by pesticide abuse and misuse[7]. In addition, the instructions that accompany many of these pesticides are often written in foreign languages or come with poor labeling, which always make interpretation difficult, and lack of technical knowledge on handling and application. Indeed, in Nigeria, pesticides are displayed openly in local markets in both rural and urban areas under inappropriate conditions that are inimical to the maintenance of its efficacy or that may modify their biochemical composition to a more hazardous one (Figure 1).



Figure 1: Open display of pesticides in a local market in Nigeria

This is further compounded by the fact that most arable and livestock farmers, who are the end-users of these pesticides, are illiterate and ignorant of the sequelae associated with pesticide exposure, especially the long-term effect. Furthermore, many farmers who use pesticides do not strictly adhere to the decay period before turning pesticide-preserved foodstuff or animal products contaminated with pesticides into the market.[7] Therefore, residues of pesticides can be found in a great variety of everyday foods and beverages, including for instance cooked meals, water, wine, fruit juices, refreshments, and animal feeds.[13]Contrary to claims in some quarters, it should be noted that washing and peeling cannot completely remove the residues. In many instances, the concentrations may not, however, exceed the legislatively determined safe levels.[14] However, these "safe limits" may underestimate the real health risk as in the case of simultaneous exposure to two or more hazardous chemical substances, which occurs in real-life conditions and may have synergistic or even potentiating effects.[13] This results in the presence of pesticide residues in the tissue or organs of unintended targets, which further endangers public health. Pesticides have been detected in the breast milk of mothers in Nigeria,[15] thereby posing threat to the health of the neonates.

Mr. Vice-Chancellor, sir, based on their rate of use and misuse, it is a fact that exposure to pesticides will continue to be a problem in developing countries for a very long time to come. While farmers and other pesticide users are aware of the association between pesticides exposure and acute toxicity, they are, however, unaware of the health complications arising from repeated exposure to their low-level. Therefore, when a person is exposed to a pesticide over a long period of time, it is difficult to relate the source of the illness to the pesticide when the individual eventually becomes sick. In such an instance, the chances of misdiagnosis by clinicians are high.

Organophosphate Insecticides

Mr. Vice-Chancellor, sir, I have devoted a large part of my research life studying the toxicity of organophosphate (OP) insecticide. OP insecticides were first recognized in 1854 but their toxicity was not established until 1938 when a group of German chemists produced tetraethyl pyrophosphate as a by-product of nerve poison or chemical warfare agent during the World War II and were later developed into less potent chemicals.[16] In view of its widespread use and contact, poisoning by OP compounds has become a major public health concern as it relates to health, morbidity, and mortality. Owing to increasing concern of adverse public health impacts, the residential uses of OP pesticides have been largely phased out and commercial applications of OPs are being restricted in the USA and many European countries. Despite the decline in their use, OPs remain among the most widely used group of insecticides worldwide, particularly in developing countries because of their lower cost, relative to the newer insecticides.[17] OPs also remain among the most detected anthropogenic contaminants in the global environment, including human tissues.[18]

Exposure to OP insecticides may either be from occupational or non-occupational (environmental) sources.[19] However, farmers and their families may also be exposed to OP poisoning via the para-occupational means- that is by living close to where pesticides are used or when agricultural workers bring home contaminated articles and thus expose their family members.[20] Unintentional accidental or suicidal poisoning may occur in occupational or non-occupational exposure. Homicidal poisoning would include suicide poisoning as well as intentional poisoning of one individual by another.[21] Chemical warfare with OPs is a form of terrorism with homicidal intent targeted to affect a large population[22] as observed during the first gulf war in the 1990s.

Mr. Vice-Chancellor, sir, permit me to dwell more on the suicidal poisoning with OP insecticides, which is currently

trending in the country. It is estimated that more than 168,000 persons die from OP pesticide self-poisoning every year across the globe.[23] Culturally, suicide is a taboo in African culture. However, the recent upsurge in suicidal intents among our teenagers is alarming, and this may have come about as a result of social media influence and/or erosion of our norms and values. As an environmental toxicologist, I have tried to look beyond these reasons, as I perceive the influence of environmental contaminants, including pesticides in the upsurge. This will become clearer as this lecture proceeds.

Organophosphate insecticides are the major culprit in suicidal poisoning in Nigeria. The most popular source of poisoning before now is the locally made variety called "Otapiapia", whose main ingredient is dichlorvos or 2,2-dichlorovinyl dimethyl phosphate (DDVP), which is readily available for purchase on the street. It has now come in a more refined packaging called Snipper®, which is a leading agent used for suicidal and homicidal intent in the country at present. There have been increasing incidences of snipper suicide poisoning in Nigeria, with many ending in fatalities. Many individuals and governmental and non-governmental organisations have shown grave concerns about this unfortunate trend.

The primary mechanism of acute OP poisoning is the inhibition of acetylcholinesterase (AChE), resulting in the accumulation of acetylcholine (ACh) at cholinergic synapses, with over-stimulation of muscarinic and nicotinic receptors and an ensuing "cholinergic syndrome". Another form of acute syndrome exhibited by a few OP insecticides is known as OP-induced delayed polyneuropathy (OPIDP), which is a neurodegenerative disorder characterized by a delayed onset of prolonged ataxia and upper neuron spasticity.[24] The syndrome, which arises 24-96 hours after an encounter with OP insecticide, can last for up to 18 days.[24] The pathogenesis of this condition involves phosphorylation and subsequent ageing of the nervous system enzyme, neuropathy target esterase (NTE), an enzyme whose specific function is not known for certain.

Another syndrome associated with acute OP poisoning is the intermediate syndrome, which arises between the period of the early cholinergic syndrome and late-onset peripheral neuropathy. It is considered as a major contributing factor of OP-related morbidity and mortality because of its frequent occurrence and probable consequent of respiratory failure.[25,26] Several mechanisms involved in the pathogenesis of intermediate syndrome include delayed inhibition of AChE, myocyte necrosis, downregulation of postsynaptic ACh receptors, inhibition of ACh release of postsynaptic ganglions, and induction of oxidative stress.[27]

The other form of the syndrome associated with chronic exposure to OPs is organophosphate-induced chronic neurotoxicity (OPICN), which persists for years after exposure to a single large dose or small subclinical doses of OP. It is a nervous system disorder that is characterized by neuronal degeneration and subsequent neurological, neurobehavioural and neuropsychological consequences.[28]

Chlorpyrifos

Mr. Vice-Chancellor, sir, the particular OP compound that I have conducted most of my research on is chlorpyrifos (CPF; O-O-diethyl, 0, 3, 4, 6-trichloro-2-pyridyl phosphorothioate), a chlorinated OP insecticide used in both agricultural and domestic pest control.[29] It was first marketed in the USA in 1965, and its use has increased rapidly, in part due to the banning of chlordane for termite control by US Environmental Protection Agency in 1988.[29] Chlorpyrifos (CPF) is one of the most widely used OP insecticides globally, accounting for about 50% of the global OP usage.[30] and one of the most common residues in food.[31] Under certain conditions, CPF residues on food can be very persistent. It is this pervasiveness combined with its toxicity that led US EPA to restrict the domestic and residential uses of CPF in 2001.[32] Despite this restriction, CPF remains one of the most widely used insecticides.

Oxidative Stress

Mr. Vice-Chancellor sir, I have tried to approach the mitigation of pesticide toxicity using the **oxidative approach.** However, there is a need to provide an overview of this oxidative approach for us to properly contextualize this lecture.

Under normal conditions, the oxidants generated during the body's metabolic processes are detoxified by the innate intracellular antioxidants abundant in the body. This ensures the maintenance of the body's redox status. However, in a pathological or altered physiologic state either arising from endogenous or exogenous sources, the redox status is altered. In this instance, the innate antioxidant molecules are not able to cope with the detoxification of the oxidants produced in the body, resulting in oxidative stress. Hence, oxidative stress is an imbalance between oxidants and antioxidants, in favour of the oxidants potentially leading to cell damage.[33] This disruption of the equilibrium between pro-oxidant and antioxidant systems results in damage to cellular macromolecules such as carbohydrates, lipids, proteins and nucleic acid. The formation and retention of these reactive oxygen species (ROS) in the tissues lead to the initiation and progression of many diseases such as diabetes mellitus, cardiovascular diseases, atherosclerosis, hepatic injury, and neurologic conditions, among others.

The Antioxidant Defense System

In order to combat the menace posed by oxidative injury, biological systems have evolved endogenous defense mechanisms through substances called antioxidants. An antioxidant is a substance that delays, prevents, or removes oxidative damage to a target molecule.[34] In the course of evolution, higher organisms have developed a remarkably efficient antioxidant defense system. The antioxidant system prevents oxidative damage by scavenging ROS and other reactive intermediates; decreasing the conversion of less reactive ROS to more reactive ROS; facilitating the repair of damage caused by ROS; and providing a favourable environment for the activity of other antioxidants.[35] When an antioxidant destroys a free radical, this antioxidant itself becomes

oxidized. Therefore, the antioxidant resources must be constantly restored in the body.

The antioxidant defense systems have been categorized into two; the primary and the secondary antioxidant defense systems. The primary antioxidant system has been further divided into two, the non-enzymatic antioxidants (antioxidant compound or free radical "sweeper" and (ii) the antioxidant enzyme system. The non-enzymatic antioxidants include ascorbic acid (vitamin C), vitamin E, β-carotene, uric acid, bilirubin, ceruloplasmin, and glutathione, among others.[36] The three primary classes of antioxidant enzymes include catalase, superoxide dismutase, and glutathione peroxidase. Other primary antioxidant enzymes include glutathione reductase, thiol disulfide oxide reductases and peroxidoxins.[37] The primary enzymes are involved in the direct elimination of toxic oxygen species. The secondary antioxidant enzymes such as glucose -6. phosphate dehydrogenase and cytosolic glutathione sulfur-transferase (GST) help in the detoxification of ROS by decreasing peroxide levels or maintaining a steady supply of metabolic intermediates like glutathione and NADPH necessary for optimum function of the primary antioxidant enzymes.[38] The antioxidant enzymes are primarily intracellular. Therefore, the extracellular pro-oxidants either produced extracellularly or from the environment must be inactivated by circulating antioxidants such as vitamins C and E and ceruloplasmins.[39] The antioxidants require micronutrients such as selenium, zinc, iron, copper, and manganese as cofactors for optimum catalytic activity and effective antioxidant activity.[40]

In the course of our research on mitigating pesticide toxicity in the laboratory, we have tried an array of antioxidant molecules with resounding success. The antioxidant molecules include vitamins C and E, melatonin, zinc, acetyl-L-carnitine, taurine, and even the plant phenolics.

Health Consequences of Pesticides (Organophosphate) Exposure

Mr. Vice-Chancellor sir, pesticides including OP insecticides are deliberately released into the environment to kill pests. This they do by inhibiting the activity of certain enzymes or altering ion's permeability in the pest. These processes are also shared by unintended targets such as humans and other higher animals. Therefore, when released to the environment, the toxicity produced by pesticides is not limited to the pests, but other higher animals including man are affected. Evidence continues to accumulate that pesticide exposure is associated with impaired health in man. I have earlier highlighted the symptoms and mechanisms of acute OP poisoning, which are associated primarily with cholinergic toxicity. The health consequences associated with chronic pesticide poisoning include:

1. Neurotoxicity

Organophosphate insecticide poisoning most often affects the nervous system. The neurotoxicity associated with chronic OP pesticide poisoning is predominantly associated with oxidative stress. Since the brain is highly susceptible to oxidative injury, it is no gainsaying that a myriad of neurotoxic syndromes is produced. These include:

a. Psychomotor and Cognitive Dysfunctions

Studies in humans have shown that pesticide exposure causes a deficit in psychomotor function apparently due to impairment in sensory input, motor output, or associative delay. Studies of individuals with a history of pesticide poisoning – farmworkers[41], farmers[42] or individuals identified from hospital or pesticide registries[43] – have found deficits in cognitive and psychomotor function and motor dysfunction long after the immediate episode is resolved. In some cases, these effects were observed $\geq$ 10 years after poisoning[44], indicating that residual damage may have been permanent.

In a laboratory study, **Ambali *et al.*** (2010e)[45] recorded sensorimotor and cognitive deficit (learning and memory deficit) in rats, weeks after exposure to a single large dose of CPF. Studies in our laboratory have also shown that long-term exposure to low

dose CPF caused a cognitive decline.[46-48] Similar results have been obtained in humans as cognitive deficits have been reported in sheep dippers[49] nursery workers[50] and other workers[51] exposed to OPs.

The use of pesticide mixture by our farmers to combat the menace of pesticide resistance by pests with its attendant consequence has made my laboratory to conduct studies to mimic this emerging environmental reality. A study by Idris and **Ambali *et al.*** (2014)[52] revealed cognitive decline following repeated exposure of rats to CPF and CYP mixture in rats. Another reality in the environment is that of multiple chemicals interacting with each other and the environment, in a way that will affect our health. One of the ubiquitous heavy metal contaminants interacting with pesticides and other environmental contaminants is lead. In this light, **Ambali *et al*.** (2011j)[53] recorded a decline in cognitive performance following subchronic co-exposure of rats to CPF and lead. A similar result was obtained by Akande and **Ambali *et al.*** (2014a)[54] following chronic co-exposure of rats to CPF and lead.

Mr. Vice-Chancellor, sir, this cognitive decline induced by pesticides poses a lot of challenges to learning and memory acquisition in school children. A study by Guillette *et al*. (1998)[55] found children exposed to OP pesticides had long-term memory deficit, among other neurotoxic signs. Similarly, Hertz-Picciotto (2014)[56] reported that exposure to OPs increases the risk of reduced IQs, memory and attention deficits and autism for prenatal children. To support these assertions, a study in our laboratory revealed that prenatal and lactational exposure of rats to a mixture of CPF and cypermethrin results in cognitive decline at adulthood.[57]

A downward trend in IQ scores has been noted across the countries of the world. A study by Bouchard *et al*. (2011)[58] found a deficit in IQ score in 7-year-old children prenatally exposed to OP pesticides, as well as reducing their working memory, processing speed, verbal comprehension, and perceptual reasoning. It has been reported that elevated levels of OP

metabolites in a woman's urine during the third trimester of pregnancy resulted in reduced cognitive development in her child at 12 months of age, particularly perceptual reasoning.[59] A summary of numerous studies in the USA has shown that OPs were responsible for lowering of IQ level by 17 million points in children, not much less than the 23 million points lost to lead poisoning, and considerably more than that caused by Attention deficits and hyperactive disorders (ADHD), autism and a number of other childhood conditions.[60]

Mr. Vice-Chancellor sir, the question begging for answer is **for how long are we going to be poisoning *away* our future if we allow this trend to continue?**

b. Sensory and Motor Dysfunction

Studies from our laboratory have demonstrated sensorimotor deficits following chronic exposure to OPs. Studies by **Ambali *et al.*** (2010e)[45] and **Ambali** and Aliyu (2012)[47] shown deficits in motor and neuromuscular coordination 8 weeks after acute exposure to CPF. Similarly, **Ambali *et al.*** (2012 a[46] &b[47]) demonstrated impairment of motor and neuromuscular coordination following 17 and 4 weeks of repeated exposure to CPF, respectively. **Ambali** and Ayo (2012)[61] recorded impairment of sensorimotor performance characterized by deficits in the efficiency of locomotion, motor strength, righting reflex and excitability scores following chronic CPF exposure in rats. Shittu and **Ambali** *et al.* (2019)[62] also demonstrated impaired sensorimotor reflex following prenatal and perinatal exposure to CPF. **Ambali** and Ayo (2011)[63] demonstrated a deficit in sensorimotor reflex– postural reflex, limb placing, and vibrissae touch- in rats chronically exposed to CPF.

In humans, occupational exposure to OP pesticides on the nerve and neuromuscular condition showed reduced sensory conduction velocity and motor conduction velocity in farmers between cultivation season in Sri Lanka.[64] Chronic neurological effects associated with pesticide exposure include slowing of nerve conduction velocity, slowing of reaction time, slowing of

motor-visual speed tests, impaired vibrotactile sensitivity, abnormal postural sway, decreased amplitude in visual evoked potentials and decreased motor strength.[65] Apart from oxidative injury to the muscle, and interference with neuronal transmission, **Ambali** and Ayo (2012)[61] attributed the reduction in motor strength partly to depletion of glycogen in the muscle by repeated OP insecticides exposure.

Mr. Vice-Chancellor, sir, the implication of these findings on the health and productivity of the exposed individuals cannot be overemphasized, as it interferes with motor skill, information processing and general productivity. The implication of motor skill development on the overall development of a child cannot be underestimated.

c. Attention and Impulsivity

Epidemiological evidence indicates that OP exposure induces changes in attention and impulsive behaviour in adults.[66,67] Attention and impulse control are critical aspects of executive function that play a fundamental role in information processing and are also impaired in numerous psychiatric disorders. This has also been demonstrated in animal models of repeated, low or moderate exposure to OP.[68,69] In psychology, impulsivity or impulsiveness is a tendency to act on a whim, displaying behaviours characterized by little or no forethought, reflection or consideration of the consequences.[70] Impulsive actions are typically poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation that often results in undesirable consequences,[71] which imperil long-term goals and strategies for success.[72]

Mr. Vice-Chancellor, sir, perhaps, low-level pesticide exposure, among other causes may have been partly responsible for the lackluster executive performance that has resulted in low quality of governance which has pervaded our political and administrative landscape in the modern world, especially in developing countries like Nigeria. In summary, pesticides, by interfering with executive performance is **"poisoning *away* our**

future" as good executive functioning is critical to the positive development of any nation, including its present and future generations.

d. Anxiety and Depression

Anxiety and depression are common mental health conditions affecting millions of people around the world.[73]. In an experimental animal study, Chen *et al.* (2011)[74] demonstrated anxiety-like behaviour in rats exposed repeatedly to CPF. **Ambali** (2009)[75] also demonstrated anxiety-like behaviour during the open-field evaluation of rats repeatedly exposed to CPF. In a study conducted in our laboratory, Akande and **Ambali** ***et al.*** (2016a)[76] reported depression-like behaviours in rats following chronic exposure to a combination of CPF and lead using the Porsolt forced swimming test. Shittu (2018)[57] also recorded depression-like behaviour in rats prenatally and perinatally exposed to CPF. Disruption of neurotransmitters, including serotonin, that are involved in mood regulation may have been partly responsible for the depression and other psychiatric symptoms associated with OP insecticides.[77]

Epidemiological studies suggest that occupational exposure to OPs induce changes in the emotional state of the individuals, based on correlations between occupational exposure and depression, anxiety, and suicide[78,79] with the highest incidence in farmers and agricultural workers. The reason for the elevated risk of mood disorder in the farming population is unclear but OP insecticide is associated with an elevated risk of neuropsychiatric disorder.[80] The association appears strongest in individuals who report previous instances of acute poisoning.[81] Besseler *et al* (2006)[82] established an association between depression and pesticide exposure in female spouses of licensed pesticide applicators. Mr. Vice-Chancellor sir, **Perhaps, we should begin to look at environmental exposure to a multitude of chemical agents, including pesticides for the increasing prevalence of suicidal intents among our teenagers.**

e. Cytotoxicity

Many *in vitro* and *in vivo* studies have shown that OP insecticides induce neuronal damage and death, even at levels that do not ablate AChE activity. An *in vitro* study has shown that CPF oxon – a metabolite of CPF caused neuronal injury in the CA_I and CA_3 regions of the hippocampus in a concentration-dependent manner.[83] *In vivo* repeated OP exposure studies have also resulted in cytotoxicity and cell death. **Ambali** and Ayo (2011)[63] demonstrated cortical neuronal degeneration following chronic CPF exposure in rats (Figure 2). Similarly, Idoga and **Ambali *et al.*** (2018)[48] reported widespread neuronal degeneration following subchronic CPF exposure in rats. In the same vein, Akande and **Ambali** *et al.* (2014a)[54] showed cortical neuronal degeneration following chronic co-exposure of male rats to CPF and lead. Mr. Vice-Chancellor sir, the implication of neuronal degeneration on the optimal performance in the day-to-day activities of individuals and even as a precursor for many of the neurogenerative diseases associated with pesticides exposure cannot be underscored. **Pesticides is certainly poisoning *away* our health**.

f. Neuroinflammation

Neuroinflammation and immune responses are important mechanisms of neurotoxicity evoked by OP. Neuroinflammation is an immune-mediated, glial cell-propagated response organized within the nervous system in response to brain injury or systemic inflammation.[84] Neuroinflammation is critical for neuroprotection and neuro-repair following an injury to the brain,[85] however, when it is done in a dysregulated manner, it can compromise the neural circuit or even cause neuronal cell death, which contributes to the initiation, progression and/or exacerbation of neurologic diseases.[86] It has been shown that acute or even repeated low-level exposure to OP pesticides or even nerve agents can also increase neuroinflammation.[87]. Repeated administration of CPF at levels that do not inhibit RBC cholinesterase activity induces glial fibrillary acid protein (GFAP) expression in the mouse hippocampus.[87] GFAP expression is commonly associated with

gliosis, an inflammatory response of the brain to neuronal injury that usually results in hypertrophy or proliferation of glial cells, including astrocytes and microglia. Indeed, **Ambali** and Ayo (2011)[63] observed gliosis following chronic repeated CPF exposure in rats (Figure 2). This may be the sequelae of brain inflammatory injury induced by the OP insecticide either directly, through oxidative stress and/or induction of inflammatory cytokines.

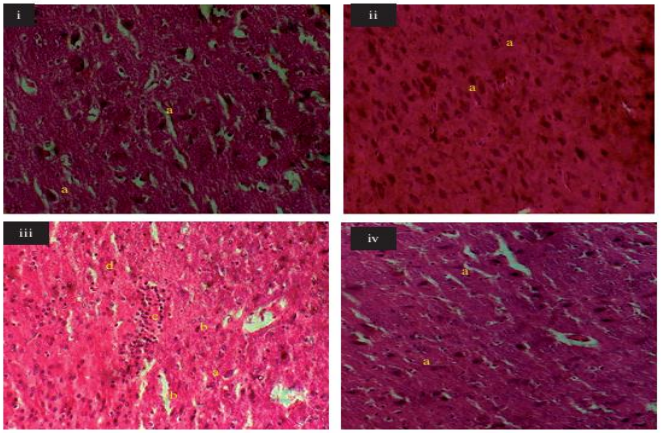


Figure 2. (i–iv): Section of the brain of rats exposed to soya oil (i), vitamin C (ii) chlorpyrifos only iii) and vitamin C and chlorpyrifos (iv) showing apparently normal neurons (a), degenerated neurons (b), glial cells infiltrations (gliosis) (c) and degenerated glial cells (d). H&E400.

g. Neurodegenerative diseases

Mr. Vice-Chancellor, sir, the prevalence, and incidence of neurodegenerative diseases that destroy the motor neurons are on the increase. These diseases are incurable and debilitating, causing progressive degeneration and/or death of nerve cells. This results in problems with movement (ataxias) or mental functioning. Neurodegenerative diseases affect millions of people worldwide. They include Alzheimer's disease, Parkinson's disease (PD), Prion disease, motor neuron diseases, Huntington's disease,

spinocerebellar ataxia, spinal muscular dystrophy, and amyotrophic lateral sclerosis, among others. Pesticides are among the environmental factors implicated in the pathogenesis of many of the neurodegenerative diseases. For example, there has been a reported increase in the risk of PD following OP poisoning.[88,89]

h. Developmental Neurotoxicity

Mr. Vice-Chancellor sir, one of the areas of public health concern to the environmental and clinical toxicologists is the devastation caused to foetuses and neonates as a result of exposure to pesticides in the womb, during breastfeeding or early childhood. Due to its pervasive application in domestic and agricultural settings, the likelihood of pregnant and lactating mothers having contact with pesticides is high, thereby posing risk to the health of the developing foetuses and the neonates. One of the organs commonly affected in the developing foetus is the nervous system, as the organ is still developing during the perinatal period. During development, the neurologic effect of OP exposure, even at low levels, may be detrimental, because neurotransmitters, including ACh, play essential roles in the cellular and architectural development of the brain.[90] Women involved in agricultural activities have been shown to have an increased risk of having children with defects in the nervous system, and oral cleft multiple anomalies.[91] Paradoxically, developmental neurotoxicity to foetuses and neonates is not limited to maternal exposure to pesticides. It has been reported that fathers who were involved in agriculture had an increased risk of having offspring with a defect in the nervous or musculoskeletal system.[92]

Developmental neurotoxicity studies have been confirmed by epidemiological data showing that prenatal exposure to OP pesticides may be associated with an increased risk of pervasive developmental disorders, delays in cognitive development and attentional deficits.[93,94] According to Watts (2013),[95] prenatal exposure to pesticides is now implicated in what has been termed 'a silent pandemic' of developmental toxicity. There is a burgeoning body of evidence that prenatal and early childhood exposure to pesticides that are toxic to the nervous system, especially OPs, is causing serious developmental, learning and behavioural disabilities in children, many of which may last throughout life. These include reduced IQ, learning disabilities, poor memory, poor communication, reduced motor

ability, reduced response speed, poor visual performance, and behavioural problems including emotional problems, autism, and attention deficit hyperactivity disorder. The result is reduced learning and increased social alienation, with profound consequences for the society, including significantly reducing intellectual capacity and increasing behavioural disorders such as aggression and other social effects that cascade from these.

Postnatal OP exposure has been associated with behavioural problems, poorer short-term memory and motor skills, and longer reaction time in children.[96,97] Postnatally, children are at a greater risk from OP toxicity than the adults because the brain is rapidly developing, the dose of pesticides per body weight is likely to be larger in children and children have a reduced capacity for detoxifying xenobiotics.[98]

One of the neurodevelopmental disorders associated with prenatal or perinatal pesticide exposure is Autism Spectrum Disorder (ASD), which is characterized by impaired social interaction, restricted communication, and repetitive stereotypic behaviours and sometimes mental retardation.[99] It is generally believed that ASD arises from alterations to specific brain structures during critical windows of vulnerability in foetal development. It may be caused by genetic or environmental factors or a combination of the two.[100] Pesticides are now regarded as one of the leading causes of autism with both OPs and organochlorines listed in the top ten causes.[101] Shittu (2018)[57] and Shittu and **Ambali *et al*.** (2019)[62] demonstrated sensorimotor and cognitive deficits, respectively in rats exposed prenatally and via lactation to mixture CPF and cypermethrin. Shittu (2018)[57] also showed that prenatal and perinatal exposure to CPF cause depression in a rat model.

Mr. Vice-Chancellor, sir, from the laboratory, clinical and epidemiological studies, it is obvious that prenatal and perinatal, and even childhood pesticide exposure may be playing a role in multiple behavioural problems the society is currently plagued with among children and the adolescents. Exposure to pesticides is certainly **poisoning *away* our health and future**.

2. Haemotoxicity

Pesticides have been shown to have haemotoxic properties resulting in aplastic anaemia, agranulocytosis, neutropenia, and thrombopenia.[102]A study on Nigerian farmworkers occupationally exposed to OP pesticides indicates deficits in haematological and immunological indices.[103]A depressed haemoglobin value has been recorded in cocoa farmers in South-Western Nigeria following pesticide application.[104]

In a laboratory animal study, **Ambali *et al.*** (2010b)[105] demonstrated haematological alterations characterized by low packed cell volume (PCV), low haemoglobin and red blood cells (RBC) count, absolute and differential leucocyte counts, 8 weeks post-exposure to a single large dose of CPF. The study revealed that anemia and other haematological alterations can still occur long after restitution of acute clinical syndrome. Similarly, studies have shown haematological changes following subacute, subchronic and chronic CPF exposure in rats.[106-108]. Tizhe and **Ambali *et al*.** (2019)[109] revealed that chronic exposure of glyphosate (a non-cholinesterase inhibiting OP herbicide) caused changes suggestive of anaemia and lymphocytic leukopenia in rats.

In an experimental animal study to evaluate the effect of pesticide combination on haematology, Uchendu and **Ambali *et al.*** (2018b)[110] recorded haematological alterations following chronic exposure to a mixture of CPF and deltamethrin. In relation to multiple chemical exposures, a study by **Ambali *et al*.** (2011f)[111] revealed macrocytic hypochromic anemia, anisocytosis, leucopenia and thrombocytopenia following subchronic exposure of rats to CPF and Lead. Akande and **Ambali *et al.*** (2014b)[112] also demonstrated microcytic hypochromic anemia, lymphopenic leukopenia, and thrombocytopenia following chronic exposure to CPF and lead.

To evaluate the effect of repeated exposure to OP pesticides on the integrity of the RBC membranes, **Ambali *et al*.** (2010d)[113] and (2011k)[114] recorded increased erythrocyte fragility following

subacute and chronic CPF exposure, respectively in rats. Tizhe and **Ambali *et al*.** (2019)[109] demonstrated that chronic exposure to glyphosate caused increased erythrocyte fragility in rats. Similarly, Akande and **Ambali *et al.*** (2014b)[112] also demonstrated increased erythrocyte fragility following chronic exposure to CPF and lead. The increased erythrocyte fragility caused by pesticide exposure is due to the vulnerability of its membrane to oxidative injury.

Mr. Vice-Chancellor, sir, from the foregoing, it is obvious from the records of laboratory and epidemiological studies that repeated low dose CPF exposure causes anaemia. This is especially important to our physicians and other healthcare providers to take the occupation of their patients into cognizance in determining the aetiopathogenesis of anemic diseases. The implication of lymphophenic leukopenia observed in most of our studies is a demonstration of immunodeficiency following repeated exposure to OP, which makes the exposed individuals vulnerable to diseases that can otherwise be easily combatted by the body's innate immune system. Thrombocytes are involved in blood coagulation. Therefore, the thrombocytopenia recorded following pesticide exposure is indicative of the interference with blood coagulation, which have serious implications for the health and wellbeing of the affected individuals.

3. Biochemical Alterations by Pesticides

Studies in both humans and animals have shown that exposure to OP insecticides causes alterations in biochemical parameters such as electrolytes, proteins, urea, creatinine, and hepatic enzymes. In a study involving an animal model, **Ambali *et al.*** (2010b)[105] demonstrated alterations in the concentrations of glucose, total proteins, albumin, globulin, and serum electrolytes 8 weeks after acute OP exposure. Subacute exposure of rats to CPF resulted in alterations in the levels of total proteins, albumin, globulin, urea, creatinine concentrations.[115] **Ambali *et al*.** (2011e, 2018)[116,117] also demonstrated alteration in serum biochemical parameters following subchronic and chronic CPF

exposure, respectively. Similar results were obtained following chronic exposure of rats to a mixture of CPF and deltamethrin.[118] **Ambali *et al.*** (2011a),[119] and Akande and **Ambali *et al.*** (2014c)[120] demonstrated alterations in serum biochemical parameters following subchronic and chronic exposure, respectively to a mixture of CPF and lead.

From all these studies, the lower concentrations of total proteins and albumin following pesticide exposure is a pointer to hepatic injury since the liver is responsible for the biosynthesis of proteins. The low globulin concentration recorded in these studies demonstrates the ability of OP pesticides to compromise the immune status. Similarly, the increased level of urea and creatinine indicated the ability of the pesticide or pesticide mixture to cause renal lesions since the urea produced by the body is supposed to be eliminated by the kidneys. Increased creatinine concentration following CPF exposure demonstrates renal parenchyma injury. Indeed Ambali (2009)[75] showed degeneration of the glomeruli and renal tubules following chronic exposure to CPF.

Alsarar *et al*. (2009)[121] demonstrated increased concentrations of urea and creatinine, indicating renal toxicity in a cohort of pesticide sprayers employed in Riyadh municipality. Indeed, a relationship has been established between lower AChE activity and chronic renal failure among Sri Lanka farmers.[64] Aroonvilairat *et al.* (2015)[122] recorded decreased levels of total protein and albumin in Thai orchid farmers.

Mr. Vice-Chancellor, sir, from the results of these studies, it is inferred that exposure to pesticides has variable impacts on multiple organs, including the liver, kidney and immune organs. This should be noted by our healthcare providers in terms of diagnosis, therapy, and prophylaxis.

4. Hepatotoxicity (Liver Injury)

The liver is a metabolically complex organ that plays eminent roles in many functions essential for the body's sustenance including metabolism and detoxification of foreign substances. This makes the liver vulnerable to injury as it's the organ that has maximum contact with xenobiotics and their metabolic by-products.[117]Various studies conducted in our laboratory using the animal model have indicated hepatotoxicity following CPF exposure. **Ambali *et al*.** (2010b)[105] demonstrated increased activity of hepatic enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), 8 weeks after acute exposure of rats to CPF. This demonstrates that disruption of the functionality of the liver persists long after the resolution of acute poisoning. Similarly, Uchendu and **Ambali *et al.*** (2011a)[115] recorded increased serum ALT, AST and ALP activities following subacute CPF exposure in rats. **Ambali *et al.*** (2018)[117] recorded increased activities of ALT, AST, ALT and γ-glutamyl transferase (GGT), and hepatocellular degeneration (Figure 3) following low dose chronic CPF exposure in rats. In a study involving pesticide mixture, Uchendu and **Ambali *et al.*** (2017)[118] demonstrated increase activities of ALT, AST, ALP and lactate dehydrogenase (LDH) following chronic exposure of rats to a mixture of CPF and deltamethrin. In the same vein, in studies involving CPF and lead exposure, **Ambali *et al.*** (2011a)[119] and Akande and **Ambali *et al*.** (2014b)[112] showed increased activities of hepatic enzymes – ALT, AST, ALP, GGT, and LDH in rats subchronically and chronically exposed, respectively to mixtures of CPF and lead. In all these studies, oxidative injury to the hepatocytes has been implicated in the hepatoxicity evoked by exposure to pesticides.
Epidemiological studies involving individuals occupationally exposed to pesticides revealed impairment of liver functions as shown by the increased level of enzymes biomarkers of hepatic dysfunction.[121,123]

Mr. Vice-Chancellor, sir, from the foregoing, it is obvious that pesticides cause toxic hepatocellular injury. Therefore, it is

pertinent to alert our healthcare providers to consider pesticide poisoning as a differential in hepatic-related diseases, especially when dealing with individuals with the potential to be occupationally exposed or have been exposed to pesticides.

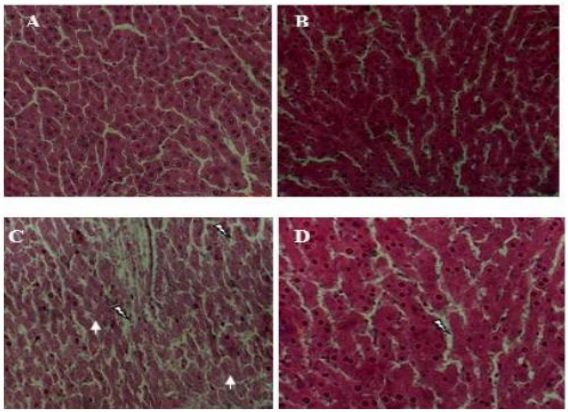


Figure 3. Histological changes in the liver of rats chronically exposed to Soya oil (A), vitamin C only (B), chlorpyrifos only (C), vitamin C+chlorpyrifos (D). Diffuse hepatocellular degeneration (arrow) and dilated sinusoids (lightning bolt). H&E x 400

5. Reproductive Toxicity

a. Effect on Male Reproduction

Mr. Vice-Chancellor, sir, many environmentalists believe that the human species is approaching a fertility crisis based on evidence of disturbing trends in male reproductive health.[55] Scientists studying the impact of man-made chemicals on human health claim human males will be infertile by the middle of the next century if the present industrial trends are maintained[124]. The culprits are chemicals, including pesticides, which mimic hormones, particularly the female sex hormone, oestrogen. Humans are not the only unique target affected by those agents, as many birds and animals in the wild have displayed this problem.

Mr. Vice-Chancellor, sir, the world was astonished when four Danish scientists led by Carlsen published a research study that suggested that the sperm counts of men have declined by about 50% since 1940 worldwide.[125]The researchers analysed the result of sperm counts between 1938 and 1991. Since then, several other studies have confirmed the decline.[126,127]

Mr. Vice-Chancellor, sir, of more pertinent and greater concern is the changes in the normal trend of sperm quality as both the volume of the semen produced, as well as the vigor of sperm have declined.[128] The study by Carlsen *et al*. (1992)[125] also revealed that semen volume declined by about 20% and that the proportion of men with a sperm count below 20 million per ml tripled between 1938 and 1991. Van Waeleghem (1996)[127] also noticed a time-related decrease in the normal morphology and progressive and total motility of the sperm. The trends in the fertility crisis are further buttressed by the fact that one in six couples has troubles conceiving, with males equally responsible for the fertility crisis.

It is widely believed that environmental causes including pesticides especially those that cause endocrine changes in fetal/prepubertal life prior to birth or during childhood or during breastfeeding are involved in the decline of semen quality.[129] Substances acting like natural hormones result in permanent impairment of the reproductive system. In particular, the hormone disruption at a sensitive time of the development may block the development of Sertoli cells, the cells within the testes that "nurse" sperm cells as they develop.[124] The number of Sertoli cells determines the amount of sperm, which a man can produce.

Anti-androgenic effects of pesticides have been demonstrated in many laboratory and clinical studies. In a study involving 322 male partners in couples presenting to a USA infertility clinic, their urinary levels of metabolite 3,5,6-Trichloro-2-pyridinol (TCP), the metabolite of CPF, were associated with a dose-dependent decrease in oestradiol,[130] which plays important role in germ cell survival. Yucra *et al*. (2006)[131] demonstrated a significant reduction in serum luteinizing hormone (LH) and

testosterone concentrations in male agricultural workers. It has also been shown that OP disrupts the hypothalamic-pituitary endocrine axis, with follicle stimulating hormone (FSH) and LH mostly affected,[132]in addition to decreasing testosterone levels.[133] In a study of farmers in Malaysia, Hossain *et al*. (2010)[134] reported a higher risk for abnormal sperm parameters for men exposed to OP pesticides when compared to those unexposed. OP exposure was also found to be significantly associated with decreased semen volume.[131,135]

In an animal study conducted in our laboratory, Shittu and **Ambali** *et al*. (2013)[136] recorded a decrease in sperm count, FSH, LH and testosterone concentrations, with the decrease in pituitary and testicular AChE activities following chronic CPF exposure in rats. A study by Shittu and **Ambali** *et al.* (2012)[137] showed increased lipoperoxidation and decreased antioxidant enzymes' (SOD and CAT) activities in pituitary glands and testes of rats following chronic exposure to CPF. Male rats exposed to prenatally and via lactation to CPF and cypermethrin resulted in decreased sperm count, motility, live/dead ratio; increased sperm morphological abnormalities, decreased FSH, LH and testosterone concentrations.[57] From the results of our laboratory studies, it believed that oxidative injury to the hypothalamus, pituitary glands, and the testes may be responsible for the endocrine disruption and altered semen parameters following OP exposure.

Mr. Vice-Chancellor, sir, going by the troubling data from the laboratory, clinical and epidemiological studies, it is obvious that the world will soon witness fertility crises if we do not act. I feel it is time to take a stand against this looming danger inimical to human existence. Silence will not be golden in this situation.

b. Female Reproduction

Mr. Vice-Chancellor, sir, about 21% of farmworkers are women[138] who may be directed to or inadvertently enter recently treated farms, sometimes while pregnant.[139] Similarly, women in farmworker households who do not work in the fields may still be exposed to pesticide residues brought home by farmworker household, especially in poor quality housing.[140]

Farr *et al.* (2004)[141] established an association between pesticide exposure and menstrual cycle characteristic. They observed that women who worked with pesticides that are endocrine disruptors had a 60-100% increased odds of experiencing long cycles, missed periods and intermenstrual bleeding compared with women who have never worked with pesticides. These would have effect on women's fecundability and risk of hormonal-related diseases. Time to pregnancy in greenhouse workers has been established to increase in an epidemiological study.[142]

In an experimental animal study, **Ambali *et al*.** (2010i)[143] recorded a dose-dependent increase in percentage pre-implantation loss in mice exposed to CPF. This indicates that the OP insecticides could decrease conception rate or cause early loss of the conceptus before implantation. In another study, **Ambali** *et al.* (2009a)[139] observed a dose-dependent increase in post-implantation loss (apparently due to foetal resorption) culminating in decreased litter size. The result of these two studies shows the ability of CPF to interfere with pregnancy by preventing implantation of the conceptus or causing loss of the fetuses after implantation, thereby resulting in an individual not being able to carry the pregnancy through.

Several studies have reported the risk of spontaneous abortion[144] and stillbirths[145]among women exposed to pesticides by virtue of their occupation and/or working in the agricultural sector. **Ambali** *et al.* (2009a)[139] also revealed that gestational exposure to CPF caused prolonged gestational length, decreased litter size, weight, and survivability of the foetuses. A study involving gestational exposure to a mixture of CPF and

cypermethrin recorded shorter gestation length and in the resultant offspring (F1 generation), relative reduction in mating index, sex ratio, with relatively more females than males, in addition to reduced pregnancy index in nulliparous female rats after mating with the exposed F1 offspring.[57] These alterations may not be unconnected to the disruption of hormonal activities, as pesticides have been shown to interfere with the hypothalamo-pituitary–ovarian axis.

Mr. Vice-Chancellor sir, the issue of sex ratio, which is the ratio of males to females in a population has been marred by inconsistencies and controversies. The ratio of male to female offspring may be a simple and non-invasive way to monitor the reproductive health of a population.[146] Except in societies where selective abortion skews the sex ratio, approximately 104-107 boys are born for every 100 girls. However, Astolfi and Zonta[147] noted a trend towards a declining proportion of male births in many industrialised countries, a development partly attributed to chemical contaminants, including pesticides. In their study, Garry *et al*. (2002)[148] reported a decrease in the sex ratio of children born to pesticide applicators. In an experimental animal study, Ramon–Yusuf and **Ambali** ***et al.*** (2017)[149] reported that prenatal exposure to a mixture of dimethoate (an OP insecticide) and cypermethrin caused a decrease in sex ratio. A similar study conducted in our laboratory by Shittu (2018)[57] following gestational exposure to CPF and cypermethrin showed more female births than males.

Mr. Vice-Chancellor sir, going by the result of laboratory and epidemiological studies, the effect of chemical pesticides on birth sex ratio is in favour of more females than males. This trend is worrisome as human activities continue to change the natural demography in favour of women, as a lesser number of male births occurs. This dangerous trend if not checked may result in a lesser population of men globally, which is a real threat to human existence.

6. Organophosphate Pesticides and Thyroid Dysfunction

Mr. Vice-Chancellor, sir, one of the hormones disrupted by pesticides is thyroid hormones (T_4, T_3, TSH). Apart from playing a critical role in brain development, thyroid hormones are involved in metabolism, reproduction, and development of the reproductive tracts. Epidemiological studies carried out on agricultural workers indicated that exposure to OP insecticides alters thyroid function, with hypothyroid effects mainly observed in the most highly exposed workers.[150] Requena and Alarcron (2019)[151] established an association between pesticide exposure and the risk of thyroid diseases.

In a laboratory animal study, **Ambali** (2009)[76] recorded no significant change in the concentrations of TSH and T_3 but a relative decrease in that of T_4 following chronic CPF exposure. However, Shittu and **Ambali** ***et al.*** (2014)[152] recorded a decrease in the concentrations of T_3 and T_4 and an increase in the TSH level following subchronic CPF exposure in rats, in addition to increased thyroid lipoperoxidation. **Ambali** *et al.* (2011d)[153] recorded a decrease in the concentrations of T_3 and T_4 and an increase in that of TSH concentrations following subchronic co-exposure to CPF and lead. In a developmental study conducted in our laboratory, Shittu (2018)[57] demonstrated decreased concentrations of T_3 and T_4 and an increase in that of TSH following prenatal and perinatal exposure of rats to a mixture of CPF and cypermethrin. An epidemiological study found an association between exposure to OP and thyroid dysfunction in pregnant women in Shandong, China.[154] The implication of prenatal thyroid dysfunction is severe considering the role of thyroid hormone in child neurodevelopment. Perhaps the anti-thyroid effect of the pesticide mixture has certainly played a role in the sensorimotor and cognitive deficit in animals exposed prenatally and via lactation to a mixture CPF and cypermethrin, as recorded by Shittu (2018)[57] in our laboratory.

7. Pesticides and Diabetes Mellitus

Mr. Vice-Chancellor, sir, there has been an alarming increase in the global burden of diabetes in the last decade. Diabetes is an important public health problem. According to the International Diabetes Federation (IDF) Diabetes Atlas (2013),[155] it is estimated that there were 382 million people (or 8.3% of the adult world population) living with diabetes of which 80% live in low and middle-income countries; this number is estimated to reach 592 million by 2035. Although lifestyle and genetics have been implicated in the aetiopathogenesis of the disease, there has been a growing body of evidence over the role of environmental pollutants, including pesticides. Several studies have demonstrated an association between OP pesticide exposure and hyperglycemia, hence risk for diabetes mellitus.[156,157] In a meta-analysis of 21 studies involving more than 66,000 people, investigators found that being exposed to any type of pesticide was associated with a 61% risk of type II diabetes, with some pesticides appearing riskier than others.[158] Several human and animal studies have also suggested an association between pesticide exposure and the development of insulin resistance and diabetes.[159]

In an animal study in our laboratory, **Ambali** (2009)[75] recorded hyperglycemia, following chronic repeated CPF exposure. The study attributed the hyperglycemia to the oxidative injury to the islet cells as demonstrated by degenerative changes. Similarly, **Ambali** *et al.* (2011h)[160] also recorded hyperglycemia, increased hepatic glycogen, and pancreatic lipoperoxidation following subchronic exposure to CPF and lead. Furthermore, Uchendu & **Ambali** *et al.* (2017)[118] recorded hyperglycemia following chronic exposure to a mixture of CPF and deltamethrin mixture in rats. Tizhe and **Ambali** *et al.* (2018)[161] recorded hyperglycemia and severe degeneration of the islet of Langerhans following chronic glyphosate administration in rats.

Mr. Vice-Chancellor, sir, the results from laboratory and epidemiological studies converge to implicate pesticides in the increasing prevalence of diabetes mellitus in our risky world.

Indeed, with the suggestion that the use of pesticides has increased 50-fold over the past 50 years,[162] it will not be unreasonably out of place to speculate that pesticides may be a cog in the wheel contributing in some way to the huge explosion in the incidence and prevalence of diabetes. In this case, **pesticides will likely be poisoning *away* our health and wellbeing** for a very long time to come, if measures are not put in place to curb their influence. Therefore, there is the need for our healthcare professionals to include chemical pollutants, including pesticides in the arsenals of aetiological causes of diabetes mellitus, especially among individuals that may be occupationally exposed to them. Awareness of this important causal agent will also go a long way in expanding our prophylactic strategies in the control and management of this debilitating disease.

8. Pesticides and Dyslipidaemia

Dyslipidaemia is a state that arises as a result of abnormalities in the plasma lipids, in terms of quantity and quality[163] and is associated with a high burden in terms of morbidity, mortality, and medical cost. There is a direct relationship between plasma lipid levels and cardiovascular risk; indeed, it is the second most prevalent cardiovascular risk factor.[164] Dyslipidaemia also contributes to the development of atherosclerosis, the chronic inflammatory disorder in arteries which causes major clinical signs such as acute myocardial infarction and stroke.[165] WHO (2002)[166] estimated that dyslipidemia accounts for 18% of ischaemic heart disease, 56% of stroke, and more than 4 million deaths per year globally.

Mr. Vice-Chancellor, sir, studies have shown that OP pesticide exposure is associated with elevated cardio-metabolic risk such as increased triglycerides (TG),[167,168] low concentrations of high-density lipoprotein (HDL),[168] and hyperglycemia.[156] Similarly, Berg *et al.* (2019)[169] have shown that occupational exposure to pesticides may be playing a role in the development of coronary heart diseases and cerebrovascular accidents.

In an animal experimental study, **Ambali** *et al*. (2011b)[170] observed an increase in the levels of total cholesterol, LDL-c and atherogenic index and reduced concentrations of TG, HDL-c and very low-density lipoprotein-cholesterol (VLDL-c) following chronic exposure of rats to CPF. In a similar study, Uchendu and **Ambali** *et al*. (2013)[171] also reported high levels of TG, Tc, LDL-c, VLDL-c and atherogenic index and low levels of HDL-c following subchronic exposure of rats to CPF. In a pesticide mixture study, Uchendu and **Ambali** *et al.* (2018a)[172] recorded dyslipidaemia following chronic exposure of rats to a mixture of CPF and deltamethrin. Furthermore, Akande and **Ambali** *et al.* (2016b)[173] demonstrated elevated levels of Tc, LDL-c, VLDL-c, and TG, while eliciting a reduction in HDL-c levels following co-exposure to CPF and lead Although hypercholesterolaemia is universally accepted as a major risk factor atherosclerosis, however, oxidative modification of LDL may be a crucially more important step in the development of atherosclerotic plaque.[174] The low HDL-c following OP exposure indicates an increased tendency for atherosclerosis and increased risk for coronary artery disease.[175] HDL plays an important role in cholesterol efflux from tissues and carries it back to the liver for removal as bile acids.[176]

Mr. Vice-Chancellor sir, from the results of the laboratory, clinical and epidemiological studies, it is obvious that exposure to pesticides results in alteration of both the quantity and quality of lipids in the blood, which predisposes affected individuals to the risk of cardiovascular and metabolic diseases. There is no gainsaying that pesticide is truly **poisoning *away* our health**. Therefore, it is pertinent for our healthcare providers to take into cognizance the occupational or accidental exposure to pesticides, among other factors in the diagnosis, therapy, and prophylaxis of cardiovascular and metabolic diseases.

9. Pesticides and Cancer

Mr. Vice-Chancellor sir, cancer is a major cause of morbidity and mortality globally[177] According to WHO (2018),[178]

cancer is the second leading cause of death globally as it is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths have been attributed to cancer, with approximately 70% of the deaths occurring in low- and middle-income countries. In Nigeria, some 100,000 new cases of cancer occur every year, with a high case fatality ratio.[179] The increased cancer risk has been associated with several OP insecticides in epidemiologic studies.[180,181] In prospective agricultural health study cohorts, different OP compounds have been linked with different types of cancer. For example, OPs such as CPF have been associated with lung cancer.[182] An increase in the incidence of aggressive prostate cancer among male pesticide applicators have been reported.[183] In a prospective agricultural cohort study involving female spouse of pesticide application. Lerro *et al*. (2015)[184] observed that exposure to OP compounds increased the risk of having several hormonal-related cancers including breast, thyroid, and ovary. An association has been established between maternal exposure to pesticides and childhood leukemia.[185]. Although our laboratory has not been involved in animal modeling of OP-induced cancer, Cabello *et al*. (2001)[186] were able to demonstrate mammary carcinomas following OP exposure to female rats.

Mr. Vice-Chancellor, sir, despite this abundance piece of evidence relating pesticide exposure to cancer, the awareness about pesticides as a risk factor for tumour development is low. Our healthcare providers, however, need to be aware that in the course of advocacy on the reduction of cancer burden in our society, exposure to pesticides should be listed as one of the risk factors in the pathogenesis of cancer.

Oxidative Stress as a therapeutic and prophylactic target in pesticide poisoning– The use of antioxidants

Mr. Vice-Chancellor, sir, the records obtained from numerous laboratory, clinical and epidemiological studies strongly suggest oxidative stress involvement in the pathophysiology of pesticide-related illnesses.[61,63,117,187]. Surajudeen *et al*. (2014b)[188] demonstrated oxidative stress in both farmers and pesticide applicators occupationally exposed to OP in Nigeria, with the latter showing more severity. Our laboratory is one of the very few that pioneered the *in vivo* administration of antioxidants to prevent pesticides from **poisoning away our health and future**. In the course of our studies, we have explored the use of an array of antioxidants that have shown promise in ameliorating pesticide-induced toxicities.

Mitigation of Pesticide-Induced Neurotoxicity

Mr. Vice-Chancellor, sir, in the course of our studies, we have tried an array of antioxidants for the mitigation of pesticide-induced neurotoxicity**. Ambali** *et al.* (2010e)[45] for the first time showed that vitamin C mitigated sensorimotor arid cognitive decline observed weeks after single large dose exposure of rats to CPF. **Ambali** and Aliyu (2012)[189] obtained similar results with vitamin E. Similarly, **Ambali** *et al.* (2012 a & c)[46,190] attenuated the sensory and motor dysfunctions and cognitive deficits induced by chronic CPF exposure using vitamins C and E, respectively. Furthermore, **Ambali** and Ayo (2011, 2012)[61,63] have also used vitamin C to mitigate deficits in sensory and motor reflex, postural reflex, and nerve conduction induced by chronic CPF exposure in rats. **Ambali** (2009)[75] mitigated the anxiety-like syndrome evoked by chronic CPF exposure in rats using vitamin C. In a study conducted in our laboratory, Lasisi (2012)[191] also demonstrated the ameliorative effect of acetyl-l-carnitine on sensorimotor and cognitive decline induced by subacute CPF administration. We have also used extracts from plants rich in polyphenolic compounds such as *Phyllanthus niruri*[47] and *Moringa oleifera*[48] to mitigate sensorimotor and cognitive deficits evoked by repeated

CPF exposure in rats. In pesticide mixture studies, Idris and **Ambali** *et al*. (2014, 2017a and b)[52,192,193] used melatonin to attenuate the cognitive, brain biochemical and sensorimotor changes, respectively evoked by repeated exposure to cypermethrin and CPF. In the same vein, Akande and **Ambali** *et al.* (2014a)[54] also used taurine to mitigate the cognitive deficit induced by chronic CPF and lead exposure in rats. Similarly, Akande and **Ambali** *et al.* (2016)[76] also reported the antidepressant effect of taurine by mitigating the depression-like symptom induced by chronic CPF and lead exposure.

On neurodevelopmental toxicity, a study conducted in our laboratory by Shittu (2018)[57] and Shittu and **Ambali** *et al*. (2019)[62] showed that melatonin mitigated the sensorimotor, behavioural and cognitive deficits induced by prenatal and perinatal exposure to a mixture of CPF and cypermethrin in rats.

On alteration of neuronal cytoarchitecture, a study by **Ambali** and Ayo (2011)[63] showed that vitamin C attenuated alterations of neuronal and glial cells cytoarchitecture evoked by chronic CPF exposure in rats. Similar results have been obtained by vitamin E and a combination of vitamins C and E.[75] Idoga and **Ambali** *et al.* (2018)[48] also demonstrated that extract of *Moringa oleifera* ameliorated the neuronal degeneration evoked by subchronic CPF exposure in rats.

Mr. Vice Chancellor, sir, from the foregoing, it is suggested that when used appropriately before exposure to pesticides, antioxidants will mitigate the various forms of neurotoxicity, including those associated with cognitive, sensorimotor, behavioural, psychomotor, neuropsychiatric, and neurodevelopmental changes, and may help mitigate incidences of neurodegenerative diseases evoked by exposure to pesticides. The use of appropriate safety/protective devices, when complemented with prophylactic use of antioxidants will mitigate toxicity associated with long-term pesticide exposure, thereby preventing pesticides from **poisoning *away* our health and our future.**

Mitigation of Pesticides-Induced Haemotoxicity

Mr. Vice-Chancellor, sir, **Ambali** *et al.* (2007)[194] was able to mitigate hematological changes induced by subchronic CPF exposure in rats with vitamin C. In a similar study, **Ambali** *et al.* (2011g)[107] protected rats from erythrocyte lipoperoxidation, anemia, leukopenia, and thrombocytopenia with vitamin C. In another study, **Ambali** *et al.* (2010b)[105] showed that vitamin C attenuated short-term hematological alterations 8 weeks after acute CPF exposure in rats. Studies in our laboratory have shown the vitamin E[195] and vitamins C and E[196] mitigated the haematological alterations evoked by subchronic CPF exposure. **Ambali** *et al.* (2010g)[197] used Zinc to mitigate the haematological alterations induced by CPF exposure in Wistar rats. Tizhe and Ambali *et al.* (2013) [198] and Tizhe and **Ambali** *et al.* (2019) [109] used zinc to mitigate the haematological alterations evoked by subchronic and chronic glyphosate exposure, respectively in rats. Other antioxidant molecules used to mitigate adverse haematological changes induced by pesticides and/or pesticide mixture include acetyl-L-carnitine[108] and α-lipoic acid.[110] **Ambali** *et al.* (2011f)[111] and Akande and **Ambali** *et al.* (2014b)[112] used vitamin C and taurine, respectively to mitigate haemotoxicity induced by subchronic and chronic co-exposure to CPF and lead,

Studies in our laboratory have shown that OPs caused the erythrocyte membrane to become more fragile, thereby increasing its vulnerability to damage or decreasing its lifespan. We were the first to mitigate increased erythrocyte fragility following OP exposure. **Ambali** *et al.* (2010c)[199] mitigated increased erythrocyte fragility evoked by insecticide exposure in rats using vitamin E. Other antioxidants molecules explored to mitigate insecticide-evoked erythrocyte fragility were vitamin C,[114] and combinations of vitamins C and E.[200] zinc,[197] acetyl-L-carnitine,[201], α-lipoic acid,[202] and *Phyllantus niruri.*[113]Akande and **Ambali** *et al.* (2014b)[112] also showed that taurine ameliorated the increased erythrocyte fragility induced by chronic CPF and lead exposure in rats.

Amelioration of Pesticides-Induced Alterations of Biochemical Parameters

Mr. Vice-Chancellor, sir, studies conducted by my group and that of other researchers have demonstrated that exposure to pesticides alters certain biochemical parameters such as proteins, electrolytes, urea, creatinine and some other enzymes that are indicative of perturbation in the body systems. **Ambali** ***et al.*** (2007, 2010a, 2011b)[194-196] showed that vitamins C, E, and combination of vitamins C and E, respectively ameliorated the alterations in serum total proteins, albumin, electrolytes, urea and creatinine following subchronic CPF exposure in mice. In a study that evaluated the biochemical alterations observed 8 weeks after exposure to a single large dose of CPF, **Ambali** ***et al.*** (2010b),[105] reported that vitamin C protected rats against adverse alterations in total proteins, albumin, globulin, and electrolytes (Na^+, K^+, Cl^-). **Ambali** *et al.* (2011e)[116] and 2018[117] demonstrated that zinc and vitamin C, respectively mitigated the biochemical alterations recorded following subchronic and chronic CPF exposure in rats. Similarly, acetyl-L-carnitine was shown to alleviate biochemical alterations following subacute CPF exposure in rats.[115] In a chronic toxicity study involving pesticide mixture, Uchendu and **Ambali** *et al.* (2017)[118] showed that α-lipoic acid alleviated the alterations in serum biochemical profiles altered by CPF and deltamethrin. Tizhe and **Ambali** *et al.* (2013b)[203] recorded amelioration of the alterations in the levels of serum proteins, albumins, globulin, urea, creatinine and electrolytes (Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, PO_4^{2+}) induced by subchronic glyphosate exposure in rats. **Ambali** ***et al.*** (2011a)[121] and Akande and **Ambali** ***et al.*** (2014c)[120] mitigated the biochemical changes induced by subchronic and chronic exposure to CPF and lead, using vitamin C and taurine, respectively.

Mr. Vice-Chancellor, sir, from these studies, antioxidants have been shown to mitigate hepatic and renal impairments following OP pesticide exposure. Studies from our laboratory have also shown that antioxidants restored the AChE activity inhibited by OP pesticides.[61,63, 114, 190] The restoration of AChE activity by the antioxidant molecules is one of the bases of their therapeutic and prophylactic efficacy.

Amelioration of Pesticides-Induced Hepatotoxicity

The liver is a very complex and important organ within the body. Because of its role in the detoxification of xenobiotics, including pesticides the liver is one of the main targets of toxic injury. We have used arrays of antioxidants to attenuate toxic hepatic injury elicited by OP exposure in rats. **Ambali** *et al*. (2007, 2010a, 2011i)[193-195] have used vitamins C, E, and combination of vitamins C and E, respectively to mitigate alterations in the activities of hepatic enzymes biomarkers evoked by subchronic CPF exposure in rats. Similarly, **Ambali** *et al.* (2011e)[116] also demonstrated that vitamin C mitigated the elevations in the activities of the enzymatic biomarkers of hepatic injury (ALT, AST, ALP and GGT) induced by chronic CPF exposure in rats. Similarly, **Ambali** *et al.* (2018)[117] also showed that vitamin C protected the liver from oxidative injury (as demonstrated by increased lipoperoxidation and reduced antioxidant enzymes' activities) and degenerative changes in the hepatocytes following chronic CPF exposure in rats. Similarly, **Ambali** *et al.* (2010b)[105] showed that vitamin C mitigates hepatic injury recorded 8 weeks after acute single large exposure to CPF in rats. Uchendu and **Ambali** *et al* (2011a)[115] and **Ambali** *et al.* (2011e)[116] also demonstrated the protective effect of acetyl-L-carnitine and zinc, respectively on hepatic injury, as shown by normalization of hepatic enzymes' activities following subchronic CPF exposure in rats. Tizhe and **Ambali** *et al.* (2013b)[203] ameliorated the alterations in hepatic enzymes' activities with zinc following subchronic glyphosate exposure in rats. Uchendu and **Ambali** *et al.* (2017)[118] used α-lipoic acid to mitigate the rise in hepatic enzymes' (ALT, AST, ALP and LDH) activities and level of hepatic tumor necrosis factor, (a potent indicator of inflammatory injury) following chronic exposure of rats to the mixture of CPF and deltamethrin. **Ambali** *et al.* (2011a)[119] and Akande and **Ambali** *et al*. (2014c)[120] demonstrated the ameliorative effect of vitamin C and taurine on increased hepatic enzyme activities

elicited by subchronic and chronic exposure, respectively to a mixture of CPF and lead.

Mr. Vice-Chancellor, sir, from the results of these studies, it is obvious that antioxidants protected hepatic cells from injury following exposure to pesticides. This further demonstrates that oxidative stress plays a central role in the pathophysiology of hepatocellular injury engendered by pesticide exposure. Therefore, it is suggested that individuals that are exposed to pesticides by virtue of their occupation or accidental exposure will benefit from hepatoprotective properties of the antioxidants, thereby preventing pesticides from "**poisoning *away* their health".**

Alleviation of Reproductive Toxicity

According to Genesis 9 verse 7 "As for you, be fruitful and increase in number; multiply on the earth and increase upon it." Similarly, according to a Hadeeth narrated by Abu Dawood, Prophet Muhammad (SAW) said" ……. **"Marry those who are loving and fertile, for I will be proud of your great numbers before the other nations."** Mr. Vice-Chancellor, sir, these beautiful divine commandments are now being threatened by the activity of man himself in a self-destructive manner. It is widely believed that pesticides, among other chemical contaminants, are contributing to the global fertility crisis currently being witnessed, not only by man but also other creatures, including wildlife within the ecosystem. My research group is at the forefront of identifying agents that can halt the effect of pesticides from **poisoning *away* our future** through mitigation of the fertility crisis evoked by them. Shittu and **Ambali** *et al.* (2012 a & b)[137,204] showed that oxidative changes induced by CPF in the pituitary gland and testes were mitigated by vitamins C and E, respectively. In a similar study, Umosen and **Ambali** *et al.* (2012)[205] also revealed that melatonin mitigated oxidative injury to the pituitary gland and testes induced by co-exposure to a mixture of CPF and cypermethrin. These studies gave us an insight into how pesticides can be prevented from causing reproductive toxicity in males.

Since the pituitary gland and the testes are the main endocrine organs involved in endocrine disruption (which is partly responsible for the fertility crisis), preventing oxidative injury to these organs is key to alleviating the reproductive toxicity induced by the pesticide exposure. Building on the success of attenuating the oxidative injury, we proceeded to evaluate the effect of antioxidants on the reproductive toxicity induced by exposure to pesticides. Shittu & **Ambali** *et al.* (2013)[136] showed that vitamin C mitigated the azoospermia and alterations in the concentrations of LH, FSH, and testosterone, and testicular injury induced by chronic CPF exposure in male rats. In the same vein, Shittu and **Ambali** *et al.* (2014)[152] demonstrated the ameliorative effect of methanolic extract of *Hibiscus sabdarifa* on impaired sex hormones (LH, FSH and testosterone) concentrations induced by subchronic CPF exposure in male rats A study from our laboratory, has shown that reductions of sex hormones concentration, sperm counts, and motility evoked by subacute CPF exposure were alleviated by melatonin.[206]

In a developmental reproductive toxicity study conducted in our laboratory, Shittu (2018)[57] reported that melatonin ameliorated the abnormal semen parameters and low concentrations of FSH, LH and testosterone in male rats exposed prenatally and via lactation to a mixture of CPF and cypermethrin.

Mr. Vice-Chancellor, sir, from the various studies conducted in our laboratory, it is obvious that antioxidants mitigate endocrine disruption, which is the major factor in determining the fertility potential of the spermatozoa and protect vital reproductive organs from toxic injury. Since antioxidants have been shown from these studies to prevent pesticides from **poisoning *away* our future**, it is therefore suggested that individuals who are likely to be exposed to pesticides by virtues of their occupation would benefit from antioxidant prophylaxis in order to mitigate the adverse reproductive consequence.

Mitigating thyrotoxicosis induced by pesticides

Mr. Vice-Chancellor, sir, thyroid hormones are one of the hormones disrupted by endocrine-disrupting chemicals pesticides, including OP insecticide. Ambali (2009)[75] was able to mitigate the alterations in the concentration of thyroid hormones with vitamins C, E and combinations of Vitamins C and E evoked by chronic CPF exposure in rats. Shittu and **Ambali** *et al*. (2014)[152] reported that the extract of *Hibiscus sabdarifa* alleviated the decreased level of T_3, T_4 and TSH levels caused by subchronic CPF exposure in rats. The plant extract was also able to mitigate thyroid lipoperoxidation caused by pesticides. In a developmental toxicity study, Shittu (2018)[57] showed that melatonin mitigated alterations in thyroid hormones' concentrations in male rats exposed prenatally and via lactation to a mixture of CPF and cypermethrin. In a study involving CPF and lead, **Ambali** *et al.* (2011d)[153] reported that vitamin C alleviated the alteration in thyroid hormone concentration and thyroid lipoperoxidation following subchronic exposure to CPF and lead. From the result thus far, antioxidants have demonstrated thyroid protective effect following pesticide exposure, which may have been partly responsible for the mitigation of reproductive and neurotoxicity evoked by pesticides.

Amelioration of Pesticides-evoked Diabetes Mellitus

The contribution of chemicals, especially pesticides to the global burden of diabetes cannot be overemphasized. Therefore, efforts at preventing the pesticides from **poisoning *away* our health and well-being** is a welcome development. In the light of this, Ambali (2009)[75] mitigated the hyperglycemia and degeneration of the islet of Langerhans evoked by chronic CPF exposure in rats with vitamins C, E, and combinations of C and E. In a study involving pesticide mixture, Uchendu and **Ambali** *et al.* (2017)[118] reported that the hyperglycemia induced by chronic exposure of rats to mixture of CPF and deltamethrin was mitigated by α-lipoic acid. In a related study, **Ambali** *et al*. (2011h)[160] mitigated with vitamin C, the hyperglycemia, increased hepatic glycogen and pancreatic lipoperoxidation evoked by subchronic

exposure to a mixture of CPF and lead. In a chronic toxicity study involving glyphosate, Tizhe and **Ambali** ***et al.*** (2018)[161] reported that zinc mitigated the apparent hyperglycemia and hyperinsulinemia, coupled with islet cells degeneration following chronic glyphosate exposure. These studies have shown that antioxidants, when used before exposure to pesticides may assist in reducing the incidence of diabetes in high-risk individuals.

Amelioration of Pesticide-Induced Dyslipidaemia

Dyslipidemia has no doubt contributed to the incidence of obesity, diabetes mellitus and cardiovascular diseases such as atherosclerosis, hypertension, and stroke. Experimental laboratory, clinical and epidemiological studies have revealed the role of pesticides in increasing the incidence and prevalence of dyslipidemia. To reduce the impact of pesticides on dyslipidemia, our laboratory has conducted some studies utilizing various antioxidants. Ambali (2009)[75] has shown that vitamins C and E mitigated the dyslipidaemia evoked by chronic CPF exposure. In the same vein, **Ambali** ***et al.*** (2011b)[170] reported that the elevated levels of Tc, LDL-c and atherogenic index and the decreased levels of TG, HDL-c, and VLDL-c following chronic CPF exposure were mitigated by vitamin C. A study by Uchendu **Ambali** ***et al.*** (2013)[171] showed that acetyl-L-carnitine attenuated dyslipidemia following subacute CPF exposure in rats. Similarly, Uchendu and **Ambali** *et al.* (2018a)[173] reported that α-lipoic acid mitigated dyslipidemia induced by chronic exposure to CPF and deltamethrin. Akande and **Ambali** *et al.* (2016)[85] reported that taurine ameliorated dyslipidemia following chronic exposure to CPF and lead.

Mr. Vice-Chancellor, sir, from the result of these studies, it is obvious that antioxidants mitigate the dyslipidaemia evoked by pesticide exposure. By doing this, antioxidants are preventing pesticides from **poisoning *away* our health** by reducing the incidence of cardiovascular diseases and obesity that accompany dyslipidaemia.

Future Research Direction

Mr. Vice-Chancellor, sir, there is so much prospect in antioxidant research that has not been tapped. My research future will focus on the pharmacokinetics of some of the antioxidants in order to improve on their absorption and hence therapeutic/prophylactic efficacies. I want to work on improving the strategies in the therapeutic management of acute OP insecticides intoxication in order to reduce fatalities associated with accidental/homicidal/suicidal poisoning. Similarly, I hope to work with other stakeholders like physicians, neuropsychiatrists, behavioural scientists, child psychologists, extension workers, and neuroscientists in a multidisciplinary fashion to evaluate the impact of pesticides on the health and well-being of various segments of agrarian communities, and even in urban settings, and how antioxidants can mitigate the devastations caused by them

Conclusions

From the results of our studies, it is concluded that:

1. Pesticides cause adverse health consequences to human beings and animals in terms of morbidity and mortality, as they contribute to the incidence and prevalence of many diseases that have negative consequences on the quality of living of humans, especially in those whose occupation involves handling of pesticides. More disturbing is the role pesticides play in the health of our neonates and children, which negatively affect their health and future well-being. **Pesticides are truly poisoning *away* our future.**
2. Oxidative stress plays an important role in the molecular mechanism of pesticide poisoning.
3. Antioxidants mitigate pesticide poisoning, with the potential to reduce the severity of the adverse health consequences in individuals that are occupationally exposed to pesticides and even following accidental or deliberate poisoning incidences. **Therefore, antioxidants have demonstrated that**

they can prevent pesticides from poisoning *away* our health and future.

Recommendations

Mr. Vice-Chancellor, sir, from the alarming results obtained from the highlighted experimental, clinical and epidemiological studies, it is obvious that these economic poisons called pesticides have been damaging the health of the human and animal populace in an unprecedented manner, contributing to prevalence and incidence of some diseases; of particular note is the poisoning of the unborn children through their mothers, and childhood poisoning. Looking critically at the health consequences of prenatal, neonatal and childhood exposure to pesticides, **I say with all sense of responsibility that "we have been poisoning *away* the future of our children,** which in other words means we are "**poisoning *away* our future"**. As men and women of conscience, this should be a source of concern to all of us. Therefore, all hands must be on deck to check the devastation caused by pesticides so that we and our unborn children can stay healthy even while continuing to use pesticides safely.

In the light of this, I, therefore, make the following recommendations:

1. There should be Increase in the level of awareness and advocacy on the dangers associated with indiscriminate use and disposition of pesticides. Governmental and non-governmental organisations should be mobilized on this task. The general populace should be enlightened on the danger of indoor use of pesticides, especially where children and pregnant mothers reside. Women, especially pregnant mothers, and children who participate in farming activities should be well protected from getting exposed to pesticides. Proper and regular maintenance of spraying equipment to avoid splashing of pesticides should be practised.
2. Measures aimed at encouraging safe usage of pesticides by farmers, pesticide applicators, and other individuals whose occupations are related to pesticides should be put in place.

Policies aimed at reducing the use of pesticides in agriculture should be put in place. Farmers should be encouraged to use an integrated approach in controlling pests and where necessary develop alternative cropping systems less dependent on pesticides, revert to traditional hand hoeing, hand weeding, use of pest-resistant seeds and organic farming systems devoid of agrochemical application.

4. There is a need to strengthen the regulatory framework and processes for the continuous re-evaluation of all registered pesticides in line with currently available information, especially on all aspects of safety to people and the environment. Many pesticides are placed on the market with insufficient testing other than the traditional acute and chronic toxicity studies. Many of the tests related to specific end-points are absent from regulatory directives. National Agency for Food Drug and Control (NAFDAC) and National Environmental Standards and Regulations Enforcement Agency (NESREA) should take the lead in this aspect by working with research experts in our higher institutions of learning. I recommend that the 5-year validity permit granted by NAFDAC for specific brands of pesticides that can be used in the country should be downgraded to three years as new information concerning safety level of the chemicals comes out frequently. There is a need to also tighten the procedures for registration of new pesticides, with safety considerations put at the front burner. Pesticides that are poorly labeled or labeled with foreign languages not intelligible to the populace should be banned from being imported into the country.

5. There is a need for the development of the national strategic framework that will ensure the enforcement and constant revision of legislation and regulatory control on pesticide manufacture, importation, sales, usage, and residues. Indeed, taking into consideration the role of residues from pesticides and other chemical contaminants, to the prevalence and incidence of many diseases, I am advocating that a **National Agency for the Monitoring and Control of Residues from Hazardous Chemicals** be established. This is to be excised from NAFDAC

whose role in combatting the menace of fake drugs and pharmacovigilance is already overwhelming.

6. Strengthening of research facilities existing in higher institutions of learning in order to develop local safety limits such as acceptable daily intake of pesticides, as data being branded were those from Western countries where climate, diet, culture, economic and social status differ from what is obtainable in our environment. In addition, these institutions can be encouraged to develop cheap but effective substitutes to pesticides that accurately target pest, more environmentally friendly and that does not leach into the soil.

7. It is a well-known fact that newer pesticide formulations in the market are relatively safer, less hazardous and more environmentally friendly compared to the traditional ones being patronized by farmers, but they are very expensive. Therefore, the government must continuously subsidise the cost of procuring these newer pesticide formulations to encourage their use by farmers. In doing that, the government may consider raising tax payable for the imported traditional and more hazardous pesticides to discourage their use.

8. There should be provision of more storage facilities by the government at all levels, in order to ensure that chemicals and methods used for storage of agricultural produce are in line with the global best practice.

9. The government should as a matter of urgency address economic inequalities that have made peasant farmers poorer. The lack of adherence to specified decay period of pesticides used for storage of agricultural produce by arable farmers and non-adherence to withdrawal periods before turning by-products from recently treated animals such as milk, eggs, and meat into the market borders more on economic pressure than even awareness of the hazards.

10. Enlightenment of our healthcare providers and other personnel in the health management team on the need to consider pesticide poisoning as a differential in the diagnosis of some diseases, especially in those individuals that are exposed to

pesticides by virtue of their occupation. This will help streamline the management and prognostic options available.

11. Border control: The country's borders must be strengthened to control the importation of dangerous and hazardous pesticides, some of which have been banned in the developed countries of the world.

12. The government should ban the open sales of pesticides and ensures those that are involved in their sales and procurement are knowledgeable enough to understand the health and environmental implications of unwholesome pesticide handling and application.

13. Since oxidative stress is central to pesticide poisoning, it is strongly advocated that antioxidants be incorporated into its therapeutic and prophylactic management strategies in man and animals. Indeed, it is recommended that individuals who are likely to be involved with pesticides application take a prophylactic dose of antioxidants to mitigate the expected health outcomes following accidental exposure.

Mr. Vice-Chancellor, sir, invited guests, ladies and gentlemen, **this is the story thus far, but the story continues.**

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