Environmental chemical risk factors of breast cancer in Nigeria IV: Pesticides

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Abstract
Pesticides are widely used to protect pests in agricultural production and in homes. Women, like men, are heavily involved in Nigerian agriculture. Since pesticides are essentially poison meant to kill or ward off unwanted living organisms, it is not surprising that they could produce adverse health impacts in people. The pesticides identified as potential breast cancer risk factors discussed in this study are DDT, Lindane, Formaldehyde, Naphthalene/Mothballs, 2,2-Dichlorovinyl dimethyl phosphate/Aluminium phosphate, Calcium carbide and Diphenylamine. DDT continues to be used against vectors of malaria parasites. Lindane is used by agricultural workers, sprayed in homes by pesticide applicators, used for treating head lice or scabies as shampoos and lotions, and transferred to household members by clothing of workers who are occupationally exposed to Lindane.
Formaldehyde is largely released into the air by cosmetics/nail polish, detergents, household furniture, from control of fish parasites and preservation of frozen fish and poultry. The main source of naphthalene is from mothballs sometimes used when storing clothing against moths like Tineola bisselliella. Mothballs are also used as a recreational drug – “Bagging” (sniffing mothballs fumes) particularly among adolescent girls. Dichlorovinyl dimethyl phosphate/Aluminium phosphate are used to protect beans from weevils. Calcium carbide is used as a ripening agent, and Diphenylamine is used as a coating agent on fruit and vegetables to preserve moisture. These chemicals are among the pesticides banned/restricted under the auspices of UNEP but continued to be used in Nigeria because they are cheap. Recommendations are proffered on how to rid pesticides from food.

Keyword: Breast cancer; Organochlorine pesticides, Formaldehyde, Nigeria

Introduction
This is the 4th of four Publications in this group of serialized systematic review articles (case studies) on Environmental Chemical Risk Factors of breast cancer in Nigeria. Part 1 is a “Broad Overview” on the subject; Part II is on “Adolescent Hormonal Contraceptives Use”; and Part III is on “Lead: Metal” The “Broad Overview” contains: (1) what informed the study on environmental chemical risk factors of breast cancer, (2) the broad and specific objectives of the study. (3) Breast cancer is a hormone dependent malignancy; the relationship between endocrine disrupting chemicals (EDCs) and breast cancer was discussed. (4) What constitute the “environment” within the context of “environmental chemical risk factors” was defined. (5) Method of study: study identification and selection, biological evidence of carcinogenesis, and data extraction and synthesis, was described. (6) The result of the search generated the list of notable environmental chemical risk factors of breast cancer highly relevant to Nigeria. The chemicals were listed on a Table and grouped as listed in...
Committee’s Evidence Review by National Academy of Sciences. The serialized articles in this special themed edition were selected “case studies” on some of the chemicals on the list.

Search engine for Pesticides
A review of published studies and documents was conducted in Medline, Scopus, PubMed, Google Scholar, Global health, Science Direct, EMBASE, and African Journals Online for published studies and documents in English from 2000-2020 that reported studies on Breast Cancer and Pesticides. Some earlier dates of articles were chosen if found highly relevant to the study. Searches included “Breast cancer:” “Mammary tumors” in combination with ‘DDT;’ ‘Lindane;’ ‘Formaldehyde;’ ‘Naphthalene’ ‘Mothballs’. We also searched for studies on Pesticides use/exposures in Nigeria particularly chemicals used by farmers to preserve food products.

Outline of Presentation
- General Discourse on Pesticides
- Some relevant studies done on organochlorine pesticides
- The DDT Issue
- Lindane
- Formaldehyde
- Naphthalene and Mothballs
- Mitigating pesticide risks
- The Special Scenarios of pesticide use in Nigeria
- Conclusion and Recommendations

1.0 General Discourse on Pesticides
Nearly 50% of the world labor force is employed in agriculture. Over the last 50 years, agriculture has deeply changed with a massive utilization of pesticides and fertilizers. Pesticides are widely used in agricultural production to control pests, diseases, weeds and other plant pathogens in an effort to enhance crop protection and production reduce or eliminate yield losses, maintain high product quality and food preservation.

In a developing country, like Nigeria, agricultural work is one of the predominant job. The experience of many countries has shown that prevention of health risk caused by pesticides is technically feasible and economically rewarding for the individuals and the whole community. A proper risk assessment and management of pesticide use is an essential component of this preventative.

This discourse on pesticides is being given some prominence because the subject is very relevant to Nigeria and other countries in the sub-Saharan region. A better understanding of the patterns of exposure, the underlying variability within the human population, and the links between the animal toxicology and human health effects will improve the evaluation of the risks to human health posed by pesticides. Improving epidemiology studies and integrating this information with toxicology data will allow the human health risks of pesticide exposure to be more accurately judged by public health policy makers.

1.1 Definition and Exposure
Pesticides are defined as “substances used to prevent, destroy, repel or mitigate any pest ranging from insects, animals and weeds to microorganisms.” Pesticides are commonly referred to by their functional class for the organisms that they are designed to control (e.g., herbicides, insecticides, rodenticides, bactericides, larvicides, fungicides). Products are widely used in agriculture, public health, domestic and urban areas. In Europe, pesticides used outside of agriculture are called biocides. Pesticides are also sometimes described in terms of their modes of actions. For example, fumigants are pesticides applied as gases to “sterilize” soil, while systemic work their way through a plant’s tissue after being taken up at the root. Pesticides may also be grouped by their chemical class [e.g.,
organophosphates, carbamates, organochlorines]. Pesticides are a ubiquitous component of our environment. Occupational exposure to pesticides often occurs in the case of agricultural workers in open fields and greenhouses, workers in the pesticides industry, and exterminators of house pests. Occupational exposure to pesticides in agriculture concerns product distributors, mixers and loaders, applicators, bystanders, and rural workers re-entering the fields shortly after treatment. Pesticides are widely used in agricultural and other settings, resulting in continuing human exposure. Use of these chemicals entails exposure to the population from a variety of sources, including residues in food and water, applications to public spaces, home, garden, and lawn use and for some, occupational exposures. Individuals may be exposed to pesticides through both direct and indirect routes. Direct exposure occurs to individuals who personally apply pesticides in agricultural, occupational, or residential settings and is likely to result in the highest levels of exposure, whereas indirect exposures occur through drinking water, air, dust, and food and represent routes of long-term, generally low-level exposure. Household members acquire pesticides from ‘take home’ sources if any member of the family is occupationally exposed to the chemicals. The clothing and skin of such workers are coated with pesticides; hence the home environment is contaminated with pesticide fumes.

1.2 Some adverse health effects of pesticides

Since pesticides are essentially poisons meant to kill or ward off unwanted living organisms, it is not surprising that they could produce adverse health impacts in people. Although pesticides are developed through very strict regulation processes to function with reasonable certainty and minimal impact on human health and the environment, serious concerns have been raised about health risks resulting from occupational exposure and from residues in food and drinking water. Most affected are the people who directly apply the pesticides (such as farmers and applicators), followed by members of their household (family and domestic staff), and ultimately, the general public who consume food products with high residues of pesticides. Children are most vulnerable, partly due to biological factors as well as enhanced exposure factors. While acute effects such as respiratory allergy—wheezing, or urticarial are quickly observed and could be swiftly contained and remedied, chronic effects are difficult to recognize. Chronic effects of pesticide poisoning are mainly neurological, reproductive, developmental, carcinogenic, and immunological. Harmful effects are assessed based on persistence, bioaccumulative toxicity, endocrine disrupting potentials, mammalian acute and chronic toxicity, and carcinogenicity. Hundreds of thousands of people could therefore have suffered irreparable damages before these insidious effects are noticed.

Pesticides are unique chemicals as they are intrinsically toxic for several biological targets, are deliberately spread into the environment, and their toxicity has a limited species selectivity. Pesticides toxicity depends on the compound family and is generally greater for the older compounds. Regarding the adverse effects on the environment (water, soil and air contamination from leaching, runoff, and spray drift, as well as the detrimental effects on wildlife, fish, plants, and other non-target organisms), many of these effects depend on the toxicity of the pesticide, the measures taken during its application, the dosage applied, the adsorption on soil colloids, the weather conditions prevailing after application, and how long the pesticide persists in the environment. Therefore, the risk assessment of the impact of pesticides either on human health or on the environment is not an easy and particularly accurate process because of differences in the periods and levels of exposure, the types of pesticides used (regarding toxicity and persistence), and the environmental characteristics of the areas where pesticides are usually applied. Assessing and managing the occupational health risks posed by the use of pesticides in agriculture is a complex but essential task for occupational health specialists and toxicologists. Other problems and issues associated with the use of pesticides include disruption of ecological balance and collapse of biodiversity; unsustainable chemical reliance; pesticide resistance and economic issues.
1.3. Organophosphate pesticides

Neurotoxic organophosphate compounds the Nazis produced in huge quantities for chemical warfare during World War II were luckily never used. After the war ended, American scientists used the same chemistry to develop a long line of pesticides that target the nervous system of insects. Organophosphates (also known as phosphate esters or OPes) have been widely used in various products as pesticides, flame retardants, plasticizers, and performance additives to engine oil. Today, organophosphates make up about 50% of the killing agents in chemical pesticides. Parathion, one of the first organophosphate pesticides (OPPs) commercialized, is many times more potent than malathion, an insecticide used in combating the Mediterranean fruit fly (Medfly) and West Nile virus-transmitting mosquitoes. Human and animal exposure to them can be through ingestion of foods containing them, or via absorption through the skin or lungs.

Despite many studies linking organophosphate exposure to effects on brain development, behaviours and fertility, they are still among the more common pesticides in use today. Organophosphates (OPs) are among the most widely used insecticides in the world, and many do not appear on restricted lists. They are among the most acutely toxic of all pesticides to vertebrate animals and humans as well as insect pests. OPs act as ‘cholinesterase inhibitors’: they deactivate an enzyme called cholinesterase which is essential for healthy nerve function. OPs are used in both professional and amateur products. They are common in veterinary medicines such as sheep dips as well as agricultural products. A few of the many ways that organophosphate can affect the human body include interfering with the way testosterone communicates with cells, lowering testosterone and altering thyroid hormone levels. There is a link between thyroid hormone and breast cancer.

The human and animal toxicity of OPPs make them a societal health and environmental concern; the EPA banned most residential uses of organophosphates in 2001, but their agricultural use as pesticides on fruits and vegetables, is still permitted, as is their use in mosquito abatement in public spaces such as parks. For instance, the most commonly used OPP in the U.S., malathion, sees wide application in agriculture, residential landscaping, and pest control programs (including mosquito control in public recreational areas). Examples of OPP are parathion, malathion, dichlorvos, chlorpyrifos, Organophosphates degrade faster than the organochlorides. They are regularly detected as residues in food items such as fruit and vegetables, and may occur above the safety level known as the Acute Reference Dose (ARD), a measure of the highest dose which can be safely consumed at one sitting. In 1993 the US National Research Council expressed concern over potential medium or long-term damage to brain function from children’s exposure to very low levels of organophosphate and other neurotoxic pesticides found on a routine level in foodstuffs. This was instrumental in the US setting its Food Quality Protection Act of 1996, requiring much stricter residue levels for organophosphate and carbamate pesticides to be set to protect children. The International Agency for Research on Cancer (IARC), found that some organophosphates may increase cancer risk. Tetrachlorvinphos and parathion were classified as “possibly carcinogenic,” whereas malathion and diazinon were classified as probably carcinogenic to humans.

1.4. Organochlorine Pesticides

The two main groups of organochlorine insecticides are the DDT-type compounds and the chlorinated alicyclics. Their mechanism of action differs slightly. Chlorinated cyclodienes includes aldrin, dieldrin, endrin, heptachlor, chlordane and endosulfan. Other examples of hydrochlorine pesticides are dicrofoll, mirex, kepone, and pentachlorophenol. Rachel Carson brought the issue of DDT pesticide toxicity to public awareness with her 1962 book Silent Spring. While many countries have phased out the use of some types of organochlorides such as the US ban on DDT, persistent DDT, PCBs, and other organochloride, residues continue to be found in humans and mammals across the
planet many years after production and use have been limited. In Arctic areas, particularly high levels are found in marine mammals. These chemicals concentrate in mammals, and are even found in human breast milk. In some species of marine mammals, particularly those that produce milk with a high fat content, males typically have far higher levels, as females reduce their concentration by transfer to their offspring through lactation.\(^\text{13}\)

Organochlorine Pesticides (OCPs) are a group of chemicals that was widely used in the past, but had many problems including broad spectrum toxicity that affected both target pests and nontarget species along with a very long persistence in the environment. Persistence defines the ability of a chemical to remain unchanged for long periods in the environment, during which time it is able to be transmitted through long distance via air, water and living creatures. Such chemicals could then be found copiously in areas where they were never used or produced. Furthermore, they store easily in fatty tissue and build up in food chains.\(^\text{8}\) Organochlorines as a class are lipophilic and resistant to degradation. They were banned from use in the 1970s and 1980s because of toxicities. OCPs are known to bioaccumulate in organisms and this process can involve bioconcentration and biomagnification. Bioaccumulation means that OCPs enter the tissues of organisms; another term for this is that they are assimilated. They may be found in higher concentrations in some tissues, such as breast, liver or kidney than in others like muscle because of their lipophilic nature; this is bioconcentration. Note that most of the OCPs were higher in the mussels than they were in the sediment that contained the mussels. Organochlorine pesticides can also biomagnify in that the concentrations of the compounds increase at higher trophic levels. For instance, concentrations of DDT, DDE, or other OCPs may be in the parts per billion in water. Animals such as zooplankton assimilate these OCPs. Zooplankton are eaten by insects which are consumed by small fish that are ingested by bigger fish, etc. and, at each step, the concentrations of OCPs increase through biomagnifications. Because the concentrations of OCPs are very low initially, no negative effects may be seen until the highest trophic levels are reached. At that point concentrations may be 10 million times those in water. This process of biomagnification was very important in the population declines seen in many fish-eating raptors in the 1980s and 1990s.\(^\text{8,14-16}\)

Organochlorine pesticides, such as dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), dieldrin, and \(\alpha\)- and \(\beta\)-hexachlorocyclohexane (\(\alpha\)- and \(\beta\)-HCH), were removed from the market several years ago because of their long persistence in nature with resulting accumulation in the human food chain, including high levels in body fat and mother’s milk. Lindane (gamma-hexachlorocyclohexane) has also been banned for agricultural use in recent years, but medical uses for the topical treatment of lice and scabies continue. Despite bans on use, organochlorine pesticides and their breakdown products have persisted in the environment, including the food chain, resulting in widespread human exposure, albeit a declining exposure. Exposure to organochlorine pesticides should be avoided in pregnancy wherever possible.\(^\text{8,16}\)

Over 160 chemicals, including a number of organochlorine and related pesticides have induced carcinogenesis in the breast glands of animals. Some 350 chemicals have been detected in human body tissues and secretions including breast milk.\(^\text{17}\) Studies of indoor air quality in American homes found five to 10 times higher concentrations of pesticides than was found in outdoor air.\(^\text{16}\) Carpets absorb outdoor pesticides, which may be brought inside on footwear and clothing or drift in through open windows or doors. Pesticides that would normally be degraded in a matter of days by the action of sunlight and bacteria may persist for years in carpets.\(^\text{18}\) The relationship of two organochlorine pesticides, DDT and Lindane, as regards breast cancer shall be featured in greater details below because of their special relevance to Nigeria and sub-Saharan Africa.
1.5. Mitigating pesticide risks
The Pesticide Action Network (PAN) UK has documented a compilation of listings of those pesticides which have been identified as particularly harmful, or on which bans of restrictions have been placed, by various Governments and intergovernmental organizations. PAN UK is a member of PAN International, a global network of over 600 organizations in over 90 countries, working to eliminate the hazards of pesticides. Some pesticides have been identified as posing a long-term, global environmental hazard, and are banned or severely restricted by international conventions (the Stockholm Persistent Organic Pollutants (POPs), the convention on Long-range Transboundary Air Pollution (LRTAP) and OSPAR (Oslo/Paris Convention (for the Protection of the Marine Environment of the North-East Atlantic)).

Final decisions about which pesticides can be used are primarily taken at country level or by a regional authority such as the European Union. The classifications included in The List of Lists. PAN UK are of real value for assisting authorities in developing countries to take practical actions to mitigate pesticide risks and to prioritise specific problematic pesticides for review in their regulatory procedures. Increasingly, private standard schemes in the food and fibre sectors are making use of official hazard classifications of EU and US regulatory decisions to prohibit, restrict or phase out specific hazardous pesticides in their supply.

1.6. World Health Organization (WHO) classifications of pesticides
The WHO classification measures mammalian acute toxicity, that is, the risk to health of single or multiple exposures over a relatively short period of time. Acute toxicity is measured through LD 50 tests on mammals (see box for explanation). Tests are carried out only on individual active ingredients, not on the final pesticide products: the toxicity of the product may vary, depending on the formulation. Some countries have their own system of hazard classification for products, e.g., the US EPA.

The FAO recommends in its Pesticide Code of Conduct that WHO Ia and Ib pesticides should not be used in developing countries, and if possible, class II should also be avoided. In recent years, several private voluntary standards in the food retail sector, including Fair Trade and Rainforest Alliance, have decided to prohibit or phase out the use of WHO Class 1 pesticides. Some supermarket companies have also included WHO acute toxicity rank as one of their criteria for prohibiting or restricting the use of particular hazardous pesticides by growers in their supply chain.

**WHO Classifications**

<table>
<thead>
<tr>
<th>Class</th>
<th>LD 50 for the rat (mg/kg body weight)</th>
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<tbody>
<tr>
<td></td>
<td>Solids (Oral)</td>
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<tr>
<td>Ia Extremely hazardous</td>
<td>5 or less</td>
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<tr>
<td>Ib Highly hazardous</td>
<td>5-50</td>
</tr>
<tr>
<td>II Moderately hazardous</td>
<td>50-500</td>
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<tr>
<td>III Slightly hazardous</td>
<td>500-2000</td>
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<td>U</td>
<td>Over 2000</td>
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<tr>
<td>O</td>
<td>Active ingredients believed to be obsolete or discontinued for use as pesticides</td>
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The terms ‘solid’ and ‘liquids’ refer to the physical state of the active ingredient. The LD 50 value is a statistical estimate of the number of mg of toxicant per kg of body weight required to kill 50% of a large population of test animals.

1.7. IARC Monographs evaluating DDT, lindane, and 2,4-D
The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has evaluated the carcinogenicity of the insecticides gamma-
hexachlorocyclohexane (lindane) and dichlorodiphenyltrichloroethane (DDT) and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). After thoroughly reviewing the latest available scientific literature, a Working Group of 26 experts from 13 countries convened by the IARC Monographs Programme classified the insecticide lindane as carcinogenic to humans (Group 1). There was sufficient evidence in humans for the carcinogenicity of lindane for non-Hodgkin lymphoma (NHL). The insecticide DDT was classified as probably carcinogenic to humans (Group 2A), based on sufficient evidence that DDT causes cancer in experimental animals and limited evidence of its carcinogenicity in humans. Epidemiological studies found positive associations between exposure to DDT and NHL, testicular cancer, and liver cancer. There was also strong experimental evidence that DDT can suppress the immune system and disrupt sex hormones. However, overall, there was no association between breast cancer and DDT levels measured in samples of blood or fat.

The herbicide 2,4-D was classified as possibly carcinogenic to humans (Group 2B), based on inadequate evidence in humans and limited evidence in experimental animals. There is strong evidence that 2,4-D induces oxidative stress, a mechanism that can operate in humans, and moderate evidence that 2,4-D causes immunosuppression, based on in vivo and in vitro studies. However, epidemiological studies did not find strong or consistent increases in risk of NHL or other cancers in relation to 2,4-D exposure.

Lindane has been used extensively for insect control, including in agriculture and for treatment of human lice and scabies. High exposures have occurred among agricultural workers and pesticide applicators; however, the use of lindane is now banned or restricted in most countries. Large epidemiological studies of agricultural exposures in the USA and Canada showed a 60% increased risk of NHL in those exposed to lindane.

DDT was introduced for the control of insect-borne diseases during the Second World War and was later applied widely to eradicate malaria and in agriculture. Although most uses of DDT were banned from the 1970s, DDT and its breakdown products are highly persistent and can be found in the environment and in animal and human tissues throughout the world. Exposure to DDT still occurs, mainly through diet. The remaining and essential use of DDT is for disease vector control, mainly for malaria. This use is strictly restricted under the Stockholm Convention.

Since its introduction in 1945, 2,4-D has been widely used to control weeds in agriculture, forestry, and urban and residential settings. Occupational exposures to 2,4-D can occur during manufacturing and application, and the general population can be exposed through food, water, dust, or residential application, and during spraying.

What does the classification mean in terms of risk?
The classification indicates the strength of the evidence that a substance or agent causes cancer. The Monographs Programme seeks to identify cancer hazards, meaning the potential for the exposure to cause cancer. However, it does not indicate the level of risk associated with exposure. The cancer risk associated with substances or agents assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the strength of the effect of the agent.

What is the difference between “risk” and “hazard?”
The IARC Monographs Programme evaluates cancer hazards but not the risks associated with exposure. An agent is considered a cancer hazard if it is capable of causing cancer under some circumstances. Risk measures the probability that cancer will occur, taking into account the level of exposure to the agent. The distinction between hazard and risk is important, and the Monographs
2.0. Some relevant studies done on organochlorine pesticides

2.1. Organochlorine pesticides in serum and adipose tissue

Organochlorines as a class are lipophilic and resistant to degradation. They were banned from use in the 1970s and 1980s because of toxicities. Nevertheless, organochlorines are still ubiquitous in the environment and can be measured in biospecimens from virtually all US and UK adults and children where relevant studies have been conducted.

Traditional epidemiologic observational studies in adulthood of the association between organochlorines and breast cancer have been inconsistent, however some cohort studies have found association with one organochlorine, for example dieldrin, but not others. Even in studies of large populations who were logically at very high risk of exposure during adulthood, such as farmer’s wives in the Agricultural Health Study, no clear relationship between overall pesticides exposure and breast cancer were established. Associations with earlier menarche have been positive in several but not all studies.

Twenty-one studies published from 2000 to June 2006 reported on 14 organochlorine pesticides other than DDT and DDE, although 5 of the compounds were included in just 1 study during this time period. Each has been linked to higher risk in at least 1 study. In a blood testing study carried out in the United Kingdom in 2003—all the 154 volunteers, 105 of whom were female were found to have high level of 12 organochlorine pesticides in their blood.

Ibarluzea JM et al conducted a study in Spain aimed to determine whether the combined effects of environmental estrogens measured as the total effective xenoestrogen burden (TEXB-alpha) are a risk factor for breast cancer over and above the risk potentially linked to specific pesticides. They measured the levels of 16 organochlorine pesticides as well as TEXB in adipose tissue of 198 women at the time of breast cancer diagnosis. These were compared with findings in 260 age and hospital matched control women without breast cancer. They found an increased risk for breast cancer in the leaner women, especially in the leaner postmenopausal subgroup, related to the TEXB-alpha. The pesticides Aldrin and lindane are also individually associated with risk.

Most published data on organochlorines and breast cancer evaluated the exposure to chemicals individually ignoring the potential effects exerted by the mixtures of chemicals. Boada Luis et al in a population-based study evaluated the profile of mixtures of organochlorines detected in 103 healthy women and 121 women diagnosed with breast cancer in the Canary Islands (Spain). They found that the most prevalent mixture among healthy women was the combination of lindane and endrin which was not detected in any affected women. Breast cancer patients presented more frequently a combination of aldrin, dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD), and this mixture was not found in any healthy woman. After adjusting for covariables, the risk of breast cancer was moderately associated with DDD. The researchers concluded that the study indicates that healthy women show a very different profile of organochlorine pesticide mixtures than breast cancer patients, suggesting that organochlorine pesticide mixtures could play a relevant role in breast cancer risk.

As regards further studies on the association between other organochlorine pesticides other than DDT and DDE, each has been linked to higher risk in at least one study. Hoyer et al reported a dose-related increased risk of ER-tumors, but not ER + tumors. Charlier et al reported a 4-fold to 9-fold higher incidence associated with hexachlorobenzene, Demers et al found associations between
tumors size and lymph-node involvement for beta-HCH, Oxychlordane, and trans-nonachlor. There was a dose-related increased risk of death with higher dieldrin exposure.

Lydia Louis et al\textsuperscript{17} in 2017 evaluated the association between the use of specific organochlorines (OCs) and cancer among the female spouses of pesticide applicators in the Agricultural Health Study. There was increased risk of glioma among lindane users. Multiple myeloma was associated with chlordane. There were also positive associations between pancreatic cancer and lindane, and ER-PR-breast cancer and dieldrin. No other association with breast cancer were found. The overall conclusion of the researchers was that they were limited by the small number of exposed cancer cases. They recommended that future research should attempt to expand on these findings by assessing environmental sources of OC exposures, to fully evaluate the role of OCs exposures on cancer risk in women.

2.2. Pesticides assessed by geographic location, job history, and self-report
A critical limitation of the biological markers of organochlorine exposure is that they may not accurately measure or rank exposure during the years when a tumor was initiated or during critical exposure periods in the life cycle when susceptible developing breast tissue was at risk.\textsuperscript{38,39} To date, blood and adipose techniques are not useful in assessing exposure to nonpersistent current-use pesticides. The challenge in studies of these compounds is that exposure is usually episodic, so many measurements over a long time would be needed to accurately rank subjects on exposure, and this cannot be done retrospectively because the new pesticides are nonpersistent and no permanent marker of their effect has been identified. In order to circumvent those limitations, it is essential to explore other exposure assessment tools for many pesticides (and other compounds) that are hormonally active or shown to be mammary gland carcinogens. Residential location and job histories have been the primary alternatives. Residential location has the advantage that people spend much of their time at home; occupational studies have the advantage of assessing higher exposures than general populations. Using Geographic Information Systems (GIS) for exposure and historical records to reconstruct residential exposure, a dose-related, but statistically unstable increase in risk for women who lived near cranberry bogs in which persistent pesticides were applied. Residential or occupational exposure, based on date, location, and other characteristics of pesticide application, some studies found association between breast cancer and exposure\textsuperscript{40,41,42}

3.0 The DDT Issue
One of the most widely known Organochlorine pesticides is DDT, an insecticide which was widely used during World War II. Because of its low toxicity to humans, DDT powder was widely applied by the US Army to the skin of soldiers to kill parasitic skin insects. Because of their low water solubilities and environmental persistence, DDT and other organochlorine pesticides also found widespread use as poisons for subterranean nests of termites. About 100,000 tons per year were produced in the late 1950s in the United States alone. DDT (dichloro-diphenyl-trichloroethane) was developed as the first of the modern synthetic insecticides in the 1940s. It was initially used with great effect to combat malaria, typhus, and the other insect-borne human diseases among both military and civilian populations. It was also effective for insect control in crop and livestock production, institutions, homes, and gardens. DDT is known to be very persistent in the environment, will accumulate in fatty tissues, and can travel long distances in the upper atmosphere. Under the auspices of the United Nations Environment Programme, countries joined together and negotiated a treaty to enact global bans or restrictions on persistent organic pollutants (POPs), a group that includes DDT. This treaty is known as the Stockholm Convention on POPs. The Convention includes a limited exemption for the use of DDT to control mosquitoes that transmit the microbe that causes malaria—a disease that still kills millions of people worldwide. In September 2006, the World Health Organization (WHO) declared its support for the indoor use of DDT in African countries where
malaria remains a major health problem, citing that benefits of the pesticide outweigh the health and environmental risks. The WHO position is consistent with the Stockholm Convention on POPs, which bans DDT for all uses except for malaria control. DDT is one of 12 pesticides recommended by the WHO for indoor residual spray programs. It is up to individual countries to decide whether or not to use DDT. Environmental Protection Agency (EPA) works with other agencies and countries to advise them on how DDT programs are developed and monitored, with the goal that DDT be used only within the context of programs referred to as Integrated Vector Management (IVM). IVM is a decision-making process for use of resources to yield the best possible results in vector control, and that it be kept out of agricultural sectors.43

3.1 DDT Exposure Sources
DDT and DDE are most likely to be found in:44

— Contaminated foods, such as root crops and leafy vegetables, fatty meats, fish, and poultry, especially in countries that still allow the use of DDT to control pests.
— Contaminated air, dust and water near waste sites and landfills that contain high levels of these chemicals
— Breast milk from mothers who have been exposed45

3.2 DDT and Breast Cancer Risk
DDT has been shown, like many other synthetic organochlorine chemicals, to act as an endocrine disruptor in numerous studies.46,47,48 Recent work by the Centers for Disease Control (CDC) on the leukemia cluster investigation in Churchill County, Nevada found the chemical DDE in relatively high concentrations in urine sample.49 DDE is produced by natural degradation of the pesticide DDT. The pesticide has been out of use in the United States for more than three decades, but it persists in the environment especially in the soil. Some studies in humans linked DDT levels in the body with breast cancer while other studies have not made this link.50,51,52 Other studies in humans have suggested that exposure may be linked to lymphoma, leukemia, and pancreatic cancer. However, no definitive association with exposure to DDT or DDE and illness with these cancers have been made.50

Several case control studies found a metabolite of DDT-DDE and PCB residues in women with breast cancer. These studies found an elevated risk of breast cancer among women with higher levels of DDE.53-56 Brody et al29 assessed twenty-five reports from case-control studies and nested case-control studies published in 2000 to June 2006 on the association between serum or adipose levels of DDT/DEE and breast cancer. Most studies did not support an association. Charlere et al34 reported higher risk in European whites with detectable DDT in serum, and Romieu et al57 found evidence of a dose-response association with DDE in serum in Mexico City. Studies of disease progression have the advantage that biological measures taken near diagnosis are more plausibly indicative of exposure during a time relevant to the outcome studied. Three studies investigated DDT and DDE levels and breast cancer aggressiveness,58 recurrence,59 or survival.60 Dermers et al36 found a dose-related increased risk for DDE and large tumors with lymph node involvement in a hospital-based case control study.

The cause of most breast cancer is unknown, but a study by Cohn et al61 found that women exposed in the womb to the now banned pesticide DDT have a quadrupled risk of developing the disease. The legacy of the insecticide is so ubiquitous that most people still carry traces of it in their bodies and continues more than four decades after it was banned in the United States. Nearly everyone in the 1950s and 1960s was exposed to the now banned pesticide DDT, which was widely sprayed on crops and vegetation to kill an array of insects. It was banned in the United States in 1972, a decade after Rachel Carson sparked outrage by documenting its effects in her classic book Silly Spring.82 DDT is an endocrine disruptor, a predictor of breast cancer, and a marker of high risk. At a time when no
direct evidence links in utero DDT exposure to human breast cancer, within the context that in utero exposure to another xenoestrogen, diethylstilbestrol, predicts an increased breast cancer risk, Cohn et al.\textsuperscript{61} working with the hypothesis that in utero exposure to DDT is associated with an increased risk of breast cancer, designed a case-control study. In the new study by the state and federally funded Public Health Institute, based in Berkeley, California, DDT levels were measured in the mothers of 118 daughters who were diagnosed with breast cancer by age 52 as at 2002 and compared with levels in mothers of 354 daughters without breast cancer. After accounting for known risk factors, including family history and age, the women with the highest DDT exposures had daughters who were 3.7 times more likely to have been diagnosed with breast cancer than the women with lower exposures. The strongest relationship was seen in women who were born in 1945. The study supports the concept that the timing of exposure (i.e., early development window) may be critical to the contribution of EDCs to carcinogenesis.\textsuperscript{38} In addition, daughters exposed to the higher levels of DDT were more likely to be diagnosed with aggressive tumors and advanced stages of the disease. Women who were exposed to the pesticide during the 1950s and 1960s are just now reaching the age of heightened breast cancer risk. In their study, the researchers cite several limitations of the study, including a small number of participants with breast cancer. They also say that they cannot rule out that other environmental exposures, not measured in the study, could have affected the results.

This study by Cohn et al.\textsuperscript{61} was a case-control study nested in a prospective 54-years follow-up of 9300 daughters in the Child Health and Development Studies pregnancy cohort (n=118 breast cancer cases, diagnosed by age 52y and 354 controls matched on birth year). Participants were Kaiser Foundation Health Plan members who received obstetric care in Alameda County, California, from 1959-1967, and their adult daughters participated in the study. The main outcome measure was Daughters’ breast cancer diagnosed by age 52 years as of 2012. Daughters are now reaching the age of heightened breast cancer risk. The findings of the research are based on a research project involving three generations of women. Tracked since the 1960s, the nearly 15,000 mothers, daughters, and grand-daughters have been called a “national treasure” because they’re helping scientists determine if toxic exposures of pregnant women are linked to diseases in their children decades later. Studying what happens before birth may hold the key to understanding who gets breast cancer.

### 3.3 The African/Nigerian DDT Exposure Scenarios

It is noteworthy that the use of DDT continues in sub-Saharan Africa where malaria which is spread by mosquitoes is endemic. DDT is sprayed in homes to combat mosquitoes; hence people are highly exposed inside their homes. DDT remains relevant to living populations for numerous reasons. First, most women born while DDT was extensively used worldwide are still alive today and are hence at risk for breast cancer. Second, DDT remains in active use for control of malaria in Africa and Asia in accordance with World Health Organization recommendations despite intense debate.\textsuperscript{63,64} Third, because of its persistent presence in the environment, people worldwide continue to be exposed to DDTs that are already present.\textsuperscript{65} Hence the findings of the study are relevant to breast cancer, even in countries in which DDT is not currently used. In addition, DDT remains a global environmental contaminant due to its environmental persistence and semivolatility.\textsuperscript{66} In those countries that continue to use DDT to control malaria, human exposure remains high.\textsuperscript{67} Thus, the findings of this study are relevant to current populations in which high in utero exposure is certainly occurring, such as in South Africa.\textsuperscript{68} The impact of DDT use on unborn generations has been recently raised as an ethical consideration.\textsuperscript{69} This discovery on causal relationship of DDT to breast cancer is relevant to this debate.
4.0 Lindane
Lindane, also known as gamma-hexachlorocyclohexane (γ-HCH), gammaxene, gammallin and sometimes incorrectly called benzene hexachloride (BHC), is an organochlorine chemical and an isomer of hexachlorocyclohexane that has been used both as an agricultural insecticide and as a pharmaceutical treatment for lice and scabies. Lindane is used in agriculture as a spray for foliage, to treat soil and seed grains, and in baits for rodent pests. Lindane can kill a broad range of insects including worms that eat leaves, insects that live in the soil, and human and animal parasites such as fleas, ticks and lice. It was also used in treatments for scabies and mange. Besides its agricultural uses, lindane was used in forestry for wood and timber protection, and as a household insecticide. Lindane has been used in small amounts (1%) in shampoos and lotions to control head lice and scabies for humans, and as an insecticide in dog dips and shampoos. Lindane was classified as a Restricted Use Pesticide by the U.S. Environmental Protection Agency (EPA) in 1985. Since then, insecticides containing lindane can be applied only by certified applicators, who are required to use protective equipment.

Use of lindane was restricted by the EPA due to concerns over its potential to cause cancer and birth defects in animals. The EPA has set the maximum level of lindane that is allowed in public drinking water supplies. This maximum contaminant level (MCL) for lindane has been set at no more than 0.2 micrograms of lindane in one liter of water (one microgram is one-millionth of a gram, one liter is approximately a quart). The EPA also sets tolerances which are the maximum levels of lindane allowed in different foods for humans, and for animal feed. The U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) monitor the levels of lindane in domestic and imported foods. Foods that exceed the tolerances can be seized and destroyed by local or federal officials. Lindane was removed from UK stores and from use in agriculture in July 2002, not because of 100% evidence of harm but because of suspicion of harm. Still used on cocoa crops in the south it enters the UK via the chocolate the people eat.

4.1 Lindane and Breast Carcinogenesis
Lindane is an endocrine disruptor in experimental animals. Lindane is also an immune suppressor. The immune system plays an important role in the body’s defense against cancer. Lindane has been linked with breast cancer and is a hormone disruptor. It was used extensively on the sugar beet crops in Lincolnshire. Lincolnshire has one of the highest rates of breast cancer in the UK. Levels of Lindane have also been found in dairy products in the UK. Occupational related studies have found three-fold elevated breast cancer risk among women ever employed in fruit and vegetable farming. And a seven-fold elevated breast cancer risk among women ever employed in other vegetable farming. In a blood testing study carried out the UK in 2003—all the 154 volunteers tested—105 of whom were female were found to have levels of 45 PCBs, 12 organochlorine pesticide and 21 PBDEs in their blood. In a pilot study in India, Siddiqui et al. found significantly higher levels of lindane in blood samples from 25 cases of cancer of the breast compared with 25 controls with benign disease. The limitations of this study included the small sample size, the recruitment of cases from a single hospital, and the lack of controls for confounders.

Women have been rarely exposed in chemical industrial processes, therefore the systematic follow-up of the entire crew of a chemical production site of chlorinated pesticides such as Lindane in Hamburg, Germany provided some useful profile. This factory started production of chlorinated pesticides before the World War II and continued a bigger scale after 1950. Since 1952 documented 398 employed women formed a cohort followed up for survival until 2007. The male cohort of the same plant comprised more than 1800 workers. After closure of the plant in 1984 circumstances provided the opportunity to study the 398 women ever employed. The significantly increased
mortality of 19 women from breast cancer indicated a specific and highly probable modification of cancer risk for workers after this occupational and environmental exposure, because housings of employees were close to the plant and exposure was proven by analyses of whippings of the house dust.

4.2 Who might have been exposed to lindane in the past? 
People most likely to have been exposed to this chemical in the past and currently in Nigeria.

- Workers involved in the manufacture of lindane
- Pesticide applicators who treated buildings with lindane-containing products
- Farmers and agricultural workers who treated soil and seed with lindane, or worked with treated soil and seed
- Forestry and timber production workers who treated wood with lindane
- People who handled or laundered lindane-contaminated clothing
- Pet groomers, veterinary workers or pet owners who used lindane-containing products to treat animals for fleas, ticks, or mange
- Homeowners who treated their house or yard with lindane
- Children and adults who were treated for head lice or scabies with lindane-containing shampoos and lotions
- Infants can be exposed to very small amounts of lindane through the breast milk of mothers who were exposed to lindane previously
- Household members of workers occupationally exposed to lindane are secondarily exposed through “take home” transfer from lindane workers.

5.0 Formaldehyde

Formaldehyde is one of the organic solvents. Formaldehyde is an industrial chemical that can exist in liquid form (formol) or solid form (paraformaldehyde). Formaldehyde (systematic name methanol) is a naturally occurring organic compound with the formula CH₂O(H-CHO). It is the simplest of the aldehydes (R-CHO). The common name of this substance comes from its similarity and relation to formic acid. Formalin is a generic term which describes a solution of 37% formaldehyde gas dissolved in water. It is used to manufacture various consumer products.

5.1 Uses and sources of formaldehyde

According to IARC information, formaldehyde is produced worldwide on a large scale, used mainly in the production of resins that are used as adhesives and binders for wood products, pulp, paper, as well as in the production of plastics and coatings, in textile finishing and in the manufacture of industrial chemicals. It is used as a disinfectant and preservative (formalin) in many applications. Common sources of exposure include vehicle emissions, particle boards, and similar building materials, carpets, paints and varnishes, foods and cooking, tobacco smoke, and the use of formaldehyde as a disinfectant. Levels of formaldehyde in outdoor air are generally low but higher levels can be found in the indoor air of homes. Occupational exposure occurs in a wide variety of occupations and industries—for example, it is estimated that more than one million workers are exposed to some degree across the European Union, according to the IARC. Short-term exposures to high levels have been reported for embalmers, pathologists, and paper workers; and lower levels have usually been encountered during the manufacture of man-made vitreous fibers, abrasives, and rubber and in formaldehyde-production industries. Formaldehyde is also used as a denaturing agent in RNA gel electrophoresis, preventing RNA from forming secondary structures. A solution of 4% formaldehyde fixes pathology tissue specimens at about one mm per hour at room temperature. In photography, formaldehyde is used in low concentrations for process C-41 (color negative film) stabilizer in the final wash step, as well as in the process E-6 pre-bleach step, to make it unnecessary.
in the final wash. Formaldehyde preserves or fixes tissue or cells. The process involves cross-linking of primary amino groups. The European Union has banned the use of formaldehyde due to its carcinogenic properties as a biocide (including embalming) under the Biocidal Products Directive (98/8/EC).\textsuperscript{77,78} Formaldehyde is also approved for use in the manufacture of animal feeds in the US. It is an antimicrobial agent used to maintain complete animal feeds or feed ingredients Salmonella negative for up to 21 days.\textsuperscript{79} An aqueous solution of formaldehyde can be useful as a disinfectant as it kills most bacteria and fungi (including their spores). Formaldehyde releasers are used as biocides in personal care products such as cosmetics. Although present at levels not normally considered harmful, they are known to cause allergic contact dermatitis in certain sensitised individuals.\textsuperscript{80} Formaldehyde is used in drug testing. Formaldehyde and an 18 M (concentrated) sulfuric acid makes a solution of formaldehyde reagent—which can identify alkaloids and other compounds. Aquarists use formaldehyde as a treatment for the parasites Ichthyophthirius multifiliis and Cryptocaryon irritans.\textsuperscript{81}

It is present in various consumer products such as furniture, cleaning products, paints, textiles, pesticides, medications, and personal care products. More precisely formaldehyde can be found in antiseptics, cosmetics, nail polish, dishwasher detergent, fabrics and fabric softeners, carpet cleaners, wallpaper, glues and adhesives, coatings, and plastics. Formaldehyde is also released into the air by the use of certain building materials such as: binders, resins, and composite wood products. These materials are used to make carpets, furniture, cabinets, insulation, and paneling. Finally, formaldehyde is released when there is combustion. It can then be present in the air during fires, by car exhaust and cigarette smoke. Formaldehyde can react with other chemicals in the atmosphere and create carbon monoxide which contributes to smog formation.\textsuperscript{75,76}

5.2 Toxicity and Carcinogenicity of formaldehyde

Although the short-term health effects of formaldehyde exposure are well known, less is known about its potential long-term health effects. In 1980, laboratory studies showed that exposure to formaldehyde could cause nasal cancer in rats. This finding raised the question of whether formaldehyde exposure could also cause cancer in humans. In 1987, the U.S. Environmental Protection Agency (EPA) classified formaldehyde as a probable human carcinogen under conditions of unusually high or prolonged exposure.\textsuperscript{82} Since that time, some studies of humans have suggested that formaldehyde exposure is associated with certain types of cancer. The International Agency for Research on Cancer (IARC) classifies formaldehyde as a human carcinogen.\textsuperscript{83} In 2011, the National Toxicology Program, an interagency program of the Department of Health and Human Services, named formaldehyde as a known human carcinogen in its 12th Report on Carcinogens.\textsuperscript{84} Cancers that have been identified with formaldehyde are hematopoietic and lymphatic cancers, myeloid leukemia, brain tumors, nasopharyngeal cancer and lung cancer.\textsuperscript{80}

5.3 International bans on formaldehyde

Several web articles claim that formaldehyde has been banned from manufacture or import into the European Union (EU) under REACH (Registration, Evaluation, Authorization, and restriction of Chemical substances) legislation. That is a misconception, as Formaldehyde is not listed in the Annex I of Regulation (EC) No 689/2008 (export and import of dangerous chemicals regulation), nor on a priority list for risk assessment. However, formaldehyde is banned from use in certain applications (preservatives for liquid-cooling and processing systems, slimicides, metalworking-fluid preservatives, and antifouling products) under the Biocidal Products Directive.\textsuperscript{85,86} In the EU, the maximum allowed concentration of formaldehyde in finished products is 0.2%, and any product that exceeds 0.05% has to include a warning that the product contains formaldehyde.\textsuperscript{80}

In the United States, Congress passed a bill July 7, 2010 regarding the use of formaldehyde in hardwood plywood, particle board, and medium density fiberboard. The bill limited the allowable
amount of formaldehyde emissions from these wood products to .09 ppm, and required companies to meet this standard by January 2013. The final Environmental Protection Agency rule specified maximum emissions of "0.05 ppm formaldehyde for hardwood plywood, 0.09 ppm formaldehyde for particleboard, 0.11 ppm formaldehyde for medium-density fiberboard, and 0.13 ppm formaldehyde for thin medium-density fiberboard." Formaldehyde was declared a toxic substance by the 1999 Canadian Environmental Protection Act.

5.4 How can people limit formaldehyde exposure in their homes?

The EPA recommends the use of “exterior-grade” pressed-wood products to limit formaldehyde exposure in the home. These products emit less formaldehyde because they contain phenol resins, not urea resins. (Pressed-wood products include plywood, paneling, particleboard, and fiberboard and are not the same as pressure-treated wood products, which contain chemical preservatives and are intended for outdoor use.) Before purchasing pressed-wood products, including building materials, cabinetry, and furniture, buyers should ask about the formaldehyde content of these products. Formaldehyde levels in homes can also be reduced by ensuring adequate ventilation, moderate temperatures, and reduced humidity levels through the use of air conditioners and dehumidifiers.

Exposure to formaldehyde is most commonly found in these workplaces.

- Funeral home employees
- Anatomy and mortuary science laboratory workers
- Pathology/cytology laboratory workers
- Cosmetologist, beauticians, and nail salon technicians

Working with formaldehyde may increase your chances of having fertility problems or a miscarriage. Formaldehyde may enter breast milk at exposure levels that are found in some workplaces, such as anatomy and mortuary science.

5.5 Use of Formalin to Control Fish Parasites:

Formalin is a generic term which describes a solution of 37% formaldehyde gas dissolved in water. Solutions of formalin for use on fish should contain 10 to 15% formaldehyde (methanol), which inhibits formation of paraformaldehyde, a highly toxic compound. Two commercial products have been approved for use in aquaculture by the Food and Drug Administration (FDA). These are Formalin-F sold by Natchez Animal Supply, Natchez, Miss. and Paracide-F, sold by Argent Chemical Laboratories, Redmond, Wash. Both of these products have been approved by FDA for use on food fish (trout, salmon, catfish, largemouth bass and bluegill) as a parasiticide. There is no legal withdrawal time (time after the chemical was used before fish can be slaughtered for food) for either of these products.

5.6 Denaturation of fish proteins during frozen storage: role of formaldehyde

Proteins of fish muscle undergo chemical and physical changes during frozen storage which may result in, under certain conditions (i.e. long periods of storage, poor freezing practices, temperature fluctuations, etc), loss of quality, reflected mainly by an unacceptable texture as well as an undesirable flavour, odour and colour. In frozen gadoid fish species, most of these changes are caused by the production of formaldehyde in the muscle. Formaldehyde is produced, along with dimethylamine, by the enzymatic reduction of trimethylamine oxide (TMAO). Many aspects of formaldehyde production by TMAO demethylase (TMAOase) have been studied throughout the last decade.
5.7 Contaminant in food

Scandals have broken in both the 2005 Indonesia food scare and 2007 Vietnam food scare regarding the addition of formaldehyde to foods to extend shelf life. In 2011, after a four-year absence, Indonesian authorities found foods with formaldehyde being sold in markets in a number of regions across the country. In August 2011, at least at two Carrefour supermarkets, the Central Jakarta Livestock and Fishery Sub-Department found a sweet glutinous rice drink (cendol) contained 10 parts per million of formaldehyde. In 2014, the owner of two noodle factories in Bogor, Indonesia, was arrested for using formaldehyde in noodles. 50 kg of formaldehyde was confiscated. Foods known to be contaminated included noodles, salted fish, and tofu. Chicken and beer were also rumored to be contaminated. In some places, such as China, manufacturers still use formaldehyde illegally as a preservative in foods, which exposes people to formaldehyde ingestion. In humans, the ingestion of formaldehyde has been shown to cause vomiting, abdominal pain, dizziness, and in extreme cases can cause death. Testing for formaldehyde is by blood and/or urine by gas chromatography-mass spectrometry. Other methods include infrared detection, gas detector tubes, etc., of which high-performance liquid chromatography is the most sensitive. In the early 1900s, it was frequently added by US milk plants to milk bottles as a method of pasteurization due to the lack of knowledge and concern regarding formaldehyde’s toxicity. In 2011 in Nakhon Ratchasima, Thailand, truckloads of rotten chicken were treated with formaldehyde for sale in which “a large network,” including 11 slaughterhouses run by a criminal gang, were implicated. In 2012, 1 billion rupiah (almost US$100,000) of fish imported from Pakistan to Batam, Indonesia, were found laced with formaldehyde. Formalin contamination of foods has been reported in Bangladesh, with stores and supermarkets selling fruits, fishes, and vegetables that have been treated with formalin to keep them fresh. However, in 2015, a Formalin Control Bill was passed in the Parliament of Bangladesh with a provision of life-term imprisonment as the maximum punishment and in addition 2,000,000 BDT as fine but not less than 500,000 BDT for importing, production or hoarding of formalin without license.

5.8 Possible exposure scenario to formalin in Nigeria

Formalin is used to prevent parasites in fish. A possible source of general public exposure to formaldehyde in Nigeria is from frozen fish, turkey, and chicken. Nigeria is a heavy importer of these products, and the smell of formaldehyde is highly pervasive in imported frozen fish. Nigerians are also heavy consumers of noodles. Since these foods have been found to be illegally contaminated in China, Thailand, Indonesia, Pakistan, and Bangladesh, NAFDAC should look into these products and act appropriately. Nail salon technicians, female funeral home employees anatomy and mortuary science laboratory workers, pathology/cytology laboratory workers may need to reconsider their occupations because their workplace is permanently effusing the odor of formaldehyde.

6.0 Naphthalene and Mothballs as pesticides

Naphthalene belongs to a class of air pollutants called polycyclic aromatic hydrocarbons (PAH). The primary use for naphthalene is in the production of phthalic anhydride. However, o-xylene is replacing naphthalene as the preferred raw material for phthalic anhydride production. Other uses of naphthalene include carbamate insecticides, surface active agents and resins, as a dye intermediate, as a synthetic tanning agent, as a moth repellent, and in miscellaneous organic chemicals.

Mothballs (known as camphor) are small balls of chemical pesticide and deodorant, sometimes used when storing clothing and other articles susceptible to damage from mold or moth larvae (especially clothes’ moths like Tineola bisselliella). Older mothballs consisted primarily of naphthalene, but due to naphthalene’s flammability, many modern formulations use 1,4-dichlorobenzene, variously labeled as para-dichlorobenzene, p-dichlorobenzene, pDCB or PDB. Both naphthalene and 1,4-
dichlorobenzene undergo sublimation, evaporating from a solid state directly into a gas toxic to moths and moth larvae. Both formulations have the strong, pungent, sickly-sweet odour associated with mothballs.

6.1 Sources and potential exposure
— Individuals may be exposed to naphthalene through the use of mothballs.
— Workers may be occupationally exposed to naphthalene during its manufacture and use, especially in coal tar production, wood preserving, tanning, or ink and dye production.
— Naphthalene is released to the air from the burning of coal and oil and from the use of mothballs. Coal tar production, wood preserving, and other industries release small amounts.
— It is present in automotive exhaust. Typical air concentrations of naphthalene in cities are about 0.18 parts per billion (ppb).
— Naphthalene has also been detected in tobacco smoke.

6.2 Carcinogenic and Endocrine disrupting potentials of naphthalene
The IARC and EPA have classified Naphthalene as Group 2B and C respectively, possibly carcinogenic to humans.$^{104,108}$ Naphthalene or its breakdown products can be measured in fat, urine, and feces. Studies on the carcinogenic effect of naphthalene gave inconclusive results. In an uncontrolled study in which subjects were exposed to complex mixtures containing other demonstrated carcinogens, workers occupationally exposed to vapors of naphthalene and coal tar developed laryngeal carcinomas or neoplasms of the pylorus and cecum.$^{102,103}$ An increased number of alveolar/bronchiolar adenomas and carcinomas were reported in female mice exposed by inhalation; while di-, tri-, and tetramethyl naphthalene contaminants of coal tar were found to be carcinogenic when applied to the skin of mice, but naphthalene alone was not.$^{102,103}$ No carcinogenic responses were reported in rats exposed to naphthalene in their diet and by injection.$^{104,105}$

Researchers from the Columbia Center for Children’s Environmental health (CCCEH) at the Mailman School of Public Health, Columbia University Medical Center, have established a link between prenatal exposure to PAH and increased risk for childhood obesity, IQ deficits, and chromosomal aberrations (CAs).$^{109}$ Children exposed to high levels of the common air pollutant naphthalene are at increased risk for chromosomal aberrations (CAs), including chromosomal translocations, a potentially more harmful and long-lasting subtype, previously associated with cancer. Previous studies have suggested that chromosomal breaks can double an adult’s lifetime risk for cancer.$^{110}$ To clarify the long-term consequences of naphthalene exposure, the CCEH investigators followed some of the children to provide more evidence of the vulnerability of the young child to carcinogenic air pollutants.

Mechanisms by which naphthalene and para-dichlorobenzene (pDCB) which are widely used as moth repellents and air fresheners, cause cancer in rodents and act as potential human carcinogens remain unclear. David Kokel et al,$^{111}$ found that naphthalene and pDCB inhibit apoptosis in C. elegansa nematode or roundworm, suggesting a cellular mechanism by which these chemicals may promote the survival and proliferation of latent tumor cells. In addition, the researchers found that a naphthalene metabolite directly inactivates caspases by oxidizing the active site cysteine residue; this suggests a molecular mechanism by which these chemicals suppress apoptosis.

The European Union banned the supply of naphthalene in 2008 as part of the EU’s REACH (Registration, Evaluation and Authorization of Chemicals) directive, which regulates chemical use in member countries.$^{112}$
6.3 Exposure scenarios of mothballs/naphthalene in Nigeria
Nigerians are heavy users of mothballs which are available in various forms (small round balls, flakes and larger egg shaped or blocks). They are commonly sold by street and market place vendors, sometimes in unmarked cling film-wrapped packs. “Original” or ‘genuine’ mothballs containing naphthalene are tested if they sink in tap water but float in a saturated salt solution. Brightly colored mothballs are now available and sold in big department stores; and these are particularly dangerous because they could be mistaken for sweets.

Mothballs are used as insect repellents against cockroaches (put around or in bowls containing edibles to repel ants); air fresheners for toilet-bowl urinals, diaper-pail deodorizers, and fungicides. Naphthalene is poorly soluble in water, is not expected to cause harm and is considered a purification tool when used internally. However, ingestion of camphor water often caused hemolytic anaemia in people with glucose-6-phosphate dehydrogenase deficiency and extended use can cause liver and kidney damage.113

More disturbing is the use of mothballs as a recreational drug. “Bagging” (sniffing mothball fumes) daily for 5-10 minutes a day is now being used by young people for self-intoxication. The incidence of this type of recreational activity particularly among adolescent girls is now on the increase and, since such addicts usually deny self-intoxication, it is probably underestimated. In Europe, mothballs containing naphthalene have been banned following reports of their ingestion.114 Pulverized camphor ball (naphthalene) is also a notable ingredient in the homemade skin bleaching concoctions used in various countries across sub-Saharan Africa.115,116

7.0 Mitigating pesticide risks
The Pesticide Action Network (PAN) UK has documented a compilation of listings of those pesticides which have been identified as particularly harmful, or on which bans of restrictions have been placed, by various Governments and intergovernmental organizations.117 PAN UK is a member of PAN International, a global network of over 600 organizations in over 90 countries, working to eliminate the hazards of pesticides. Some pesticides have been identified as posing a long-term, global environmental hazard, and are banned or severely restricted by international conventions (the Stockholm Persistent Organic Pollutants (POPs), the convention on Long-range Transboundary Air Pollution (LRTAP) and OSPAR (Oslo/Paris Convention (for the Protection of the Marine Environment of the North-East Atlantic))

Final decisions about which pesticides can be used are primarily taken at country level or by a regional authority such as the European Union. The classifications included in The List of Lists. PAN UK117 are of real value for assisting authorities in developing countries to take practical actions to mitigate pesticide risks and to prioritize specific problematic pesticides for review in their regulatory procedures. Increasingly, private standard schemes in the food and fibre sectors are making use of official hazard classifications of EU and US regulatory decisions to prohibit, restrict or phase out specific hazardous pesticides in their supply.

8.0 The Special Scenarios of pesticide use in Nigeria
8.1 The scope
The World Bank Group/African Region Gender Policy Brief described the scope and gender practice in the agricultural practice in Nigeria.118 In Nigeria the agricultural sector employs more than 60 percent of the labor force and many small holder farmers and food producers are women. Women constitute a large share of the agricultural labor force in Nigeria. Women are heavily involved in the production of both staple (food) crops and cash crops, the agricultural value chain, and livestock production. A general Household Survey-Panel (GHS-Panel) was conducted in 2010/11 by the
Nigeria National Bureau of Statistics (NBS) in collaboration with the World Bank Living Standard Measurement Study (LSMS) team, to capture a comprehensive picture of agriculture across the nation of Nigeria. It is representative at the national, zonal and rural/urban levels and includes all six geopolitical zones in Nigeria. An agricultural household is defined as a household where at least one member is involved in crop cultivation and/or livestock activity. Cash crops include groundnut, cotton, cocoa, rubber, cotton and oil palm. Agriculture is the main economic activity in every zone of Nigeria, except for the South South and South West, and although men are more likely than women to participate in agriculture, the difference is minimal. Across the nation, 57 percent of all households are involved in agriculture, the figure does not vary much between male- and female-headed households, of which 60 percent and 48 percent participate, respectively. As expected, the number of households participating in agriculture is higher in rural areas (78 percent) and lower in urban areas (25 percent).

8.2 The importance of pesticides in Nigeria
In 2014, a state government in northern Nigeria declared a state of emergency after the moth *Tuta absoluta* destroyed swaths of tomato fields, threatening supplies of the country’s leading staple food. Such was the degree of devastation that Nigerian farmers described the outbreak as “tomato Ebola” after the deadly disease that devastated West Africa in 2014. *Tuta absoluta*, which originated in South America and spread to Europe and Africa, quickly developed resistance to pesticides. More than 200 tomato farmers in the region suffered losses of more than one billion naira ($5·02m) from the disease as more than 90% of 17,000 hectares (42,000 acres) of tomato fields outside the northern city of Kano were affected by the moth. The tomato shortage caused by the outbreak led to an astronomically increase in prices. Without pesticides, unimaginable loss of products could occur while on the other hand, the health hazards these pesticides could pose to people and the severe adverse impacts on the ecosystem and economy remain troubling.

8.3 Identified Problems with Pesticides Use in Nigeria
Pertinent environmental health issues related to the use of (synthetic) chemical pesticides, in agriculture and general household in Nigeria have been well characterized by Ojo Joshua. In Nigeria, many people engage in backyard vegetable farms, poultry, and fishponds. Furthermore, farming is a ready occupation for school dropouts, unemployed graduates, and pensioners. Pesticides are used in many homes to control soldier ants, mosquitoes, cockroaches, termites, rats amongst others. Hence, there is a high prevalence of pesticide use by unskilled farmers.

The low level of information, knowledge, and awareness among Nigerians on the dangers associated with the use of pesticides is alarming. In a 2011 survey at the Dawanau International grain market, Kano State, responsible for a large percentage of cowpea consumed in Nigeria, over 80% of the traders interviewed averred that government’s ban on the use of gammalin (lindane) to preserve beans against weevils is unjustified. Based on perceived effectiveness, lower costs, and non-persuasion about associated adverse effects, many of the merchants indicated they would continue to use the “time-tested” product. Pesticide applicators in Nigeria get unnecessarily high exposure to pesticides due to a combination of factors which include ignorance, unaffordable cost of protective gadgets and unfavorable climatic conditions. Working in the tropical sun in a hot humid climate where ambient temperatures get as high as 40°C makes it difficult for applicators to wear protective clothing including gloves, respirators, and boots. even when they could afford them. Leakage of chemicals is common from backpack sprayers. These applicators transport the dangerous chemicals on their body clothing and shoes to their families, especially children who traditionally welcome their fathers by warm embraces and body contact. Carpets and rugs also absorb the toxic fumes of the lindane where it persists.
In 2001, under the auspices of the United Nations Environment Programme, nine highly persistent pesticides (viz Aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex, toxaphene, and hexachlorobenzene) were officially proscribed for use in agriculture. Regrettably, several of these are still openly sold in Nigeria. Some are smuggled in or donated by “caring” donor countries from stockpiles.\textsuperscript{123} The deadliest pesticides in terms of toxicity and persistence are used in Nigeria. WHO documented that small-scale farmers in developing countries use large amounts of pesticides belonging to classes Ia, 1b and II because they are cheaper than the less hazardous newer ones.\textsuperscript{124} Some farmers pour pesticides (particularly old stock of Gammalin-Lindane) into rivers to kill fish, which is then sold for human consumption. Many have become poisoned as a result of such practices. Some farmers spray Gammalin 20 on drying cocoa beans to prevent development of moulds and maggots.\textsuperscript{125}

In Nigeria, farmers face great risks of exposure due to the use of toxic chemicals that are banned or restricted in other countries. Some of the factors identified include poor pesticide education leading to extensive misuse, poorly maintained or totally inappropriate spraying equipment, inadequate storage; issues with correct, effective, and safe applications of pesticides; and the use of the cheaper but deadliest types of pesticides. Other factors include poor legislation and lack of enforcement of available legislation; lack of adequate information, knowledge, and awareness of the inherent dangers of pesticides; lack of training on correct handling of pesticides at home; absence of monitoring for pesticides residues on locally consumed products, compared to products meant for export; and inadequacies in medical recognition and responses to pesticide poisoning.

There is pervasive misuse and abuse of pesticides even among government-trained, or agency-trained and assisted small-scale farmers. There is excess use prescribed pesticides due to the general expectation that it would effect more rapid killing of crop pests. Different classes of pesticides (fungicides and insecticides) are mixed together to reduce the workload of spraying each differently. There is use of wrong formulations and doses, and wrong timing of application. Counterfeiting, faking, and recycling of old stocks abound. Empty plastic containers are sold at reduced prices for refilling with adulterated agrochemicals or for marketers of dried foodstuffs to use as measuring jars to consumers.

Oguntoye\textsuperscript{126} alerted the public on the dangers posed by the use of dangerous pesticides to preserve foods in his article “The dangers of some common foods in Nigeria. He noted that calcium carbide used as a ripening agent for banana and plantains and mangoes contain lead, arsenic and phosphorus. Most Nigerian farmers use a chemical called “Sniper” as pest control. ‘Sniper’ is DDVP, 2,2-Dichlorovinyl dimethyl phosphate compound, an organophosphate which is classified by IARC as “possibly carcinogenic.”\textsuperscript{12} Aluminium phosphate (ALP) is used to control weevils in beans. Weevils in beans can destroy the entire year’s harvest of the farmer in a few days if not controlled. Aluminium phosphate is a metaloestrogen, a potent breast cancer risk factor.\textsuperscript{127} Aluminium phosphate liberates lethal phosphine gas when it comes in contact either with atmospheric moisture or with hydrochloric acid in the stomach. The National Agency for food and Drug Administration and Control (NAFDAC) recently released an alert warning against the use of Aluminium phosphate as pesticides on food products.\textsuperscript{128}

\textbf{8.4 Other hazardous chemical agents in food apart from pesticides}\textsuperscript{126,129}  
There are 3 types of hazardous chemical agents: Pesticides, Ripening Agents and Coating Agents. Ripening agents are mostly used on banana, plantains and mangoes. It contains calcium carbide. Calcium carbide reacts with moisture to form acetylene which mimics natural ripener, ethylene. Industrial calcium carbide contains heavy metals like lead and arsenic which are dangerous to humans. Coating agents like Wax and Diphenylamine (DPA) are used on apples and berries in exotics.
and vegetables to preserve the moisture and consistency of fruits so that they look fresh for longer. The white powder on grapes is due to a chemical agent which prevents grapes from getting soggy. Wax is a petroleum product, while DPA reacts with nitrogen to form Nitrosamine which is a suspected carcinogen.\textsuperscript{126,129} The most hazardous chemical agents consumed in food are pesticides. Systemic pesticides are put at the bottom of the tree nearer to the roots, so they are absorbed by the plant, and they remain in the leaves, stem, fruit and flowers for about 10-15 weeks. These pesticides protect the plant from pests that penetrate the skin to suck out the juice inside. Contact pesticides remain on the fruits and vegetables when they are purchased at the market or grocery store.

8.5 How to get rid of pesticides from food\textsuperscript{126,129}
Fruits and vegetables are among the healthiest foods on the planet but when eaten without washing leads to consumption of residual chemicals on them. Heavily treated fruits and vegetables are apples, mangoes, banana, cauliflower, tomatoes, grapes, and papaya. Less treated fruits and vegetables are onions, watermelon, carrots, sweet potatoes, snake gourd, potatoes, beetroot and radish. This may lead to food poisoning, diarrhea, hormone disrupting issues, skin and hair problems and long-term deadly diseases of the brain, kidney, lung, and cancer.

Arnab et al\textsuperscript{129} prescribed some simple and practical ways to mitigate pesticide consumption in foodstuff. This includes buying organic foods which are safer in spite of being treated with pesticides. The soaring prices of “Organic Foods” makes them impractical options for many people. The best and the most practical solution that has proven to remove almost 98% of pesticides residue from fruits and vegetables include soaking of fruits and vegetables in large amount of water, adding baking soda, and leaving for 15-20 minutes, before thorough washing in running water. Baking Soda (Sodium Bicarbonate) is known for its alkalizing nature which reduces the effect of pesticides to as much as 98%. Others measures include peeling off the first layers of food items like cabbage or onion; and keeping the lid open while cooking vegetables. Grains like beans particularly ones without weevils which have been heavily treated with pesticides are first parboiled, and the water drained off, rinsed before final cooking for consumption. Use EWG’s Shopper’s Guide to Pesticides in Produce, can help consumers find the fruits and vegetables that have the fewest pesticide residues.\textsuperscript{130}

9. Conclusion and Recommendations
Pesticides are widely used in agricultural production to control pests, diseases, weeds and other plant pathogens in an effort to enhance crop protection and production, reduce or eliminate yield losses, maintain high product quality and food preservation. Since pesticides are essentially poison meant to kill or ward off unwanted living organisms, it is not surprising that they could produce adverse health impacts in people. Women, like men, are heavily involved in Nigerian agriculture including producing staple (food) crops and cash crops, and participating all along the agricultural value chain, and livestock production. Many women engage in backyard vegetable farms, poultry, and fishponds. Furthermore, farming is a ready occupation for school drop outs, unemployed graduates and pensioners. Pesticides are used in many homes to control soldier ants, mosquitoes, cockroaches, termites, rats among others. Hence, there is a high prevalence of pesticide use by unskilled farmers. In addition to the direct exposure of women involved in Nigerian Agricultural sector, women are further exposed through a variety of sources, including residues in food and water, applications to public spaces, home, garden, and lawn use. Women and other household members acquire pesticides from ‘take home’ sources if any member of the family is occupationally exposed to the chemicals. The clothing and skin of such workers are coated with pesticides; hence the home environment is contaminated with pesticides fumes. The experience of many countries has shown that prevention of health risk caused by pesticides is technically feasible and economically rewarding for the individuals and the whole community.
Several responsible bodies and organizations are taking the initiative to ensure safe use of pesticides in Nigeria. Government agencies such as National Environmental Standards and Regulations Enforcement Agency (NESREA), National Agency for Foods and Drugs Control (NAFDAC), the Cocoa Research Institute of Nigeria (CRIN), and the Nigerian Stored Products Research Institute (NSPRI) are at the forefront of translating research findings to regulations and communicating these to the nation through various workshops. There are also private organizations such as the Pest Control Association of Nigeria (PECAN) and the West African Agricultural and Productivity Programme (WAAPP-Nigeria) working to ensure safe use of pesticides in Nigeria. However, most of these bodies address, largely, organized groups of stakeholders such as farmers' groups, and pesticide marketers, while neglecting the majority of Nigerians who do subsistent farming and use pesticides at home for pest control. There is therefore the need for mass education of the general public to effectively address the issues involved in pesticide use, misuse, and abuse in the country.

A better understanding of the patterns of exposure, the underlying variability within the human population, and the links between the animal toxicology and human health effects will improve the evaluation of the risks to human health posed by pesticides. Improving epidemiology studies and integrating this information with toxicology data will allow the human health risks of pesticide exposure to be more accurately judged by public health policy makers.

**List of Acronyms**

2,4-d – 2,4-dichlorophenoxyacetic acid  
ALP – Aluminium phosphate  
Beta-HCH – beta-Hexachlorocyclohexane  
BHC - benzene hexachloride  
CA – Chromosomal aberrations  
CCCEH – Columbia Center for Children’s Environmental health  
CDC – Centers for Disease Control  
DCB – dichlorobenzene  
DDD – dichlorodiphenyl/dichloroethane  
DDE – dichlorophenyldichloroethylene  
DDT – Dichloro-diphenyl-trichloroethane  
DDVP – Dichlorovinyl dimethyl phosphate  
DPA – Diphenylamine  
EPA – Environmental Protection Agency  
ER – tumors – Estrogen Receptor  
EU – European Union  
EWG – Environmental Working Group  
FAO – Food and Agriculture Organization  
FDA – Food and Drug Administration  
GHS – Panel-general Household Survey-Panel  
HCH – Hexachlorocyclohexane  
IARC - International Agency for Research on Cancer  
IVM – Integrated Vector Management  
LRTAP – Long-range Trans-boundary Air Pollution  
LRTAP – Transboundary Air Pollution  
LSMS – Living Standard Measurement Study  
MCL – Maximum contaminant level  
NAFDAC – National Agency for Food and Drug Administration and Control  
NHL – non-Hodgkin lymphoma
OCs – Organochlorines
OSPAR – Oslo/Paris Convention
OSPAR – Oslo/Paris Convention (for the Protection of Marine Environment of the North-East Atlantic)
PAH – Polycyclic aromatic hydrocarbons
PAN – Pesticides Action Network
PBDEs – Polybrominated diphenyl ethers
PCB – para-dichlorobenzene
PCBs – Polychlorinated Biphenyls
PDB – ParaDichloroBenzene
PDCB – para-dichlorobenzene
POP – Persistent Organic Pollutants
PR – Progesterone Receptor
R-CHO – Aldehyde group
REACH – registration, Evaluation, Authorization, and restriction of Chemical substances
RNA – Ribonucleic acid
TEXB – Total effective xenoestrogen burden
TMAO – Trimethylamine oxide
UNEP – United Nations Environment Programme
US – United States
USDA – United States Department of Agriculture
WHO – World Health Organization

References


46. German Chemical Society Advisory Committee on Existing Chemicals (2001). Biological Impact of Synthetic and Natural Endocrine Active Substances—Effects on Human Health.


71. PAN UK. Ban Lindane site- http://www.panuk.org/banlindane/


90. Ruth Francis-Floyd. Use of Formalin to Control Fish Parasites. IFAS# VM-77. http://www.biofilter.com/VM77.htm


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