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Exposure Assessment Policy Recommendation for Neurodevelopmental Testing in Communities
Exposed to DDT Through Indoor Residual Spraying

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Abstract

Exposure Assessment Policy Recommendation for Neurodevelopmental Testing in Communities Exposed to DDT Through Indoor Residual Spraying

By Allison Kniola

Dichlorodiphenyltrichloroethane (DDT) is an insecticide that has been used primarily for vector control. Years of known environmental destruction and identified adverse human health effects lead to a global ban of the use of DDT, with an exception being made for countries struggling to control vector borne diseases. With the introduction of malaria control initiatives, DDT use increased as it became the primary insecticide for indoor residual spraying (IRS). IRS and other forms of community spraying have now existed for decades. DDT has been found to persist in the environment for years, putting both current and future communities at risk of DDT exposure and its potential adverse effects. DDT exposure results in fertility loss, increased risk of diabetes, and increased risk of cancers. DDT exposure has also been determined to lead to neurological deficits including Parkinson's disease, impaired cognitive functioning, and an increase in neuropsychological symptoms. In utero exposure to DDT leads to impaired neurodevelopment of children; studies show low general cognitive index scores and decreased verbal, quantitative, and memory skills for prenatal exposure. Limited studies have been conducted among populations who have long-term, high dose exposure to DDT through IRS. In order to achieve the Sustainable Development Goals (SDGs) and work towards health equity for all, an exposure assessment must be conducted in communities exposed to DDT through IRS in order to determine the true health status of individuals in these communities. The exposure assessment will allow us to address any potential neurological disorders as well as promote alternative and sustainable vector control solutions.

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CHAPTER 1: INTRODUCTION

Overview and Global Status of DDT

Dichlorodiphenyltrichloroethane (DDT) is an insecticide in the organochlorine class that has been used primarily for vector control of malaria and leishmaniasis in low- and middle-income countries (LMICs) (van den Berg, 2009). After major environmental destruction and identified adverse human health effects due to DDT exposure, the United States banned the use of DDT in 1972 and further international use was restricted with the Stockholm Convention (Stockholm Convention, 2008; van den Berg, 2009). The Stockholm Convention, though, in agreement with the World Health Organization (WHO), permitted use of DDT for the purpose of vector control, including indoor residual spraying (IRS) (Stockholm Convention, 2008; World Health Organization, 2011). DDT use in Africa actually increased after the Stockholm Convention and although multiple programs and vector control methods have been employed in malaria endemic areas, malaria persists in more than one hundred countries with almost half of the world's population at risk (Centers for Disease Control, 2017). In 2017, the World Health Organization (WHO) employed a new global vector control strategy which focuses on phasing out DDT and utilizing local and sustainable vector control options (World Health Organization, 2017b).

A number of studies confirm adverse health effects of DDT exposure. Most studies have focused on North American and European populations, that have been exposed to lower levels of DDT than those in malaria-endemic areas who have long-term exposure to DDT through indoor residual spraying (IRS). The studied populations still reflect multiple health concerns including diabetes, fertility loss, increased risk for cancer, and neurological deficits (Garabrant, Held, Langholz, Peters, & Mack, 1992; van den Berg, 2009). Neurological deficits have been

confirmed among children who were exposed in utero as well as among those who had long-term occupational exposure to DDT. Prenatal exposure to DDT can result in low general cognitive index scores and decreased verbal, quantitative, and memory skills (Ribas-Fitó et al., 2006; Torres-Sánchez et al., 2013). In utero exposure to DDT is accepted to be negatively associated with the neurodevelopment of children (Eskenazi et al., 2006). Farmers and agricultural workers with long-term occupational exposure to DDT have been found to have impaired cognitive functioning, an increase in neuropsychological symptoms, and an increased risk for Parkinson's disease (Elbaz et al., 2009; Misra, Nag, & Murti, 1984; van Wendel de Joode et al., 2001).

There is very limited data regarding the neurological effects of DDT exposure through IRS. The few studies that do exist confirm a negative association between DDT and neurodevelopment, showing lower psychomotor development scores and lower mental development scores among children (Eskenazi et al., 2006).

Problem Statement

DDT exposure has been proven to produce harmful human health effects, including neurodevelopmental disorders. The populations with the longest and highest level of exposure from IRS have never been tested to understand the current burden of neurological disease. The WHO advocated for DDT use for vector control despite the documented consequences that could result and in contradiction to their stated mission to “achieve the highest possible level of health for all humans” (World Health Organization, 2020). Although they finally have chosen to phase out the use of DDT, this insecticide is proven to persist in the environment, being found in dust, indoor air, and outdoor soil twenty-one years after IRS with DDT (Booij et al., 2016). Therefore, future generations are still at risk of DDT exposure. In keeping with their mission statement, the

WHO must utilize the new vector control strategy to incorporate an exposure assessment to test for neurodevelopmental disorders. By researching and understanding the neurological impact of DDT, the WHO will be able to provide guidelines to member countries affected populations for appropriate treatment and care.

Purpose

The purpose of this thesis is to outline the current evidence surrounding the neurological deficits resulting from DDT exposure and provide an exposure assessment that can be used in IRS areas. It is suggested that the WHO take responsibility for the exposure assessment and incorporate this testing into their current global vector control strategy.

CHAPTER 2: LITERATURE REVIEW

Overview of Major Insecticides

Insecticides are classified as “chemicals that are used to control insects” (United States Environmental Protection Agency, 2018). They are categorized into groups based on their chemical structure and mode of action, the way in which the insecticide causes physiological disruption at its target site (Michael E. Scharf, 2011; United States Environmental Protection Agency, 2018). Insecticides are used in agriculture to prevent the destruction of crops as well as in industrial applications and household use to control the presence of insects (United States Environmental Protection Agency, 2018). Insecticides also play a major role in vector control interventions. Diseases transmitted by vectors, which include mosquitoes, flies, and ticks, “account for 17% of the estimated global burden of communicable diseases” (World Health

Organization, 2019d). Major classes of insecticides include organophosphates, pyrethroids, and neonicotinoids, organochlorines.

Organophosphates

Organophosphates are produced through the process of esterification between phosphoric acid and alcohol (Adeyinka & Pierre, 2019). The use of organophosphates rose in the 1960s due to restrictions placed upon organochlorines and are used in agriculture, homes, gardens, and veterinary practices (W. Michael Caudle, 2015; United States Environmental Protection Agency, 2013). Beyond their use as an insecticide, organophosphates were also used as neurotoxins during World War II (Adeyinka & Pierre, 2019). Organophosphates cause acetylcholinesterase (AChE) inhibition (United States Environmental Protection Agency, 2018). Acetylcholine is an important neurotransmitter responsible for muscle movement (William Michael Caudle, 2015). Organophosphates “[assert] [their] effects through irreversible inactivation of the enzyme acetylcholinesterase, which is essential for nerve function in humans, insects and many other animals” (Jayaraj, Megha, & Sreedev, 2016). When acetylcholine remains in the synaptic cleft and continues to interact with and activate acetylcholine receptors, the resulting neurological symptoms, including salivation, lacrimation, urination, diarrhea, gastrointestinal motility, and emesis, can lead to death (William Michael Caudle, 2015). Although organophosphates do not accumulate and persist in the environment to the same extent as organochlorines, the manufacture and use of organophosphates has been restricted or discontinued due to toxicity with the exception of thirty-six organophosphate insecticides still registered for use in the United States (W. Michael Caudle, 2015; United States Environmental Protection Agency, 2013). Organophosphate exposure can occur through inhalation, ingestion, or dermal contact (Robb &

Baker, 2019). Agricultural laborers who work with crops that use organophosphates (apples, peaches, lettuce, potatoes) are at an increased risk of exposure (Robb & Baker, 2019).

Pyrethroids

Pyrethrum's insecticidal properties were first discovered around 1800 in Asia (Agency for Toxic Substances & Disease Registry, 2003). "Pyrethrum is a naturally occurring mixture of chemicals found in certain chrysanthemum flowers" (Agency for Toxic Substances & Disease Registry, 2003). The active insecticidal properties within the pyrethrum extract are called pyrethrins and they are often used in household insecticide products to control insects on pests and livestock (Agency for Toxic Substances & Disease Registry, 2003; United States Environmental Protection Agency, 2019). Pyrethroids are adapted from the botanical insecticide pyrethrin with the modification to increase their stability in sunlight, lasting longer in the environment, as well as the modification of increased toxicity to insects and mammals (Agency for Toxic Substances & Disease Registry, 2003; United States Environmental Protection Agency, 2019). Pyrethroids target the sodium channel; sodium channels are kept open in the neuronal membranes, which affects both the peripheral and central nervous system and leads to paralysis of the organism (Jayaraj et al., 2016; United States Environmental Protection Agency, 2018). Exposure to high levels of pyrethroid compounds in the air, food, or water has been shown to cause negative side effects including headache, low energy, muscle twitching, convulsions and loss of consciousness (Goel & Aggarwal, 2007). Exposure to pyrethroids can occur through eating foods that have been contaminated, breathing in air that contains the insecticide or through dermal contact, especially right after the insecticide has been sprayed (Agency for Toxic Substances & Disease Registry, 2003). Another major route of exposure is through insecticide-treated nets (ITNs), a primary tool used in the current effort for malaria

control (Spitzen, Koelewijn, Mukabana, & Takken, 2017). The mosquito nets are dipped in the pyrethroid insecticide and hung over a sleeping area to create a protective barrier from mosquitoes and other insects (Centers for Disease Control, 2019a). Individuals then sleep under these infused nets every night for years, if not a lifetime. Pyrethroids have a fast biodegradation capacity, typically lasting one to two days before being degraded (Agency for Toxic Substances & Disease Registry, 2003; Jayaraj et al., 2016). The Environmental Protection Agency is currently evaluating an ecological and human health risk assessment for each pyrethroid currently undergoing registration review with an interim decision for each pyrethroid anticipated to be released in 2020 (United States Environmental Protection Agency, 2019).

Neonicotinoids

Neonicotinoids are insecticides chemically similar to nicotine and are currently the most commonly used insecticides for pest management, representing more than 25% of the global pesticide market (Friedli, Williams, Bruckner, Neumann, & Straub, 2019; Yamamuro et al., 2019). Neonicotinoids protect plants, crops, livestock, and pets from insects and are used in more than 120 countries (Han, Tian, & Shen, 2018; Jeschke, Nauen, Schindler, & Elbert, 2011). These insecticides “act on the central nervous system causing irreversible blockage of the postsynaptic nicotineric acetylcholine receptors” which leads to paralysis and death of the organism (Friedli et al., 2019; United States Environmental Protection Agency, 2018). Neonicotinoids were considered to be highly effective and much less harmful to mammals than other pesticides, but there is increasing concern surrounding human health due to the “systemic accumulation of neonicotinoids in food” (Han et al., 2018). Rodent studies have shown that neonicotinoid use “resulted in measurable health effects on multiple organ systems...most notable on the neurological system and on developing pups in utero” (Craddock, Huang, Turner, Quirós-Alcalá,

& Payne-Sturges, 2019). Bees have also become an unintended target of neonicotinoid use. Due to the environmental pollution from these insecticides, bee poisonings were identified throughout Europe with further research showing that neonicotinoid exposure interferes with honey bee metamorphosis, affecting their development stability (Friedli et al., 2019; Han et al., 2018). A study in Japan determined that the use of neonicotinoids in rice agriculture had major effects on aquatic life due to water contaminated with neonicotinoids from the effluent of rice paddies (Yamamuro et al., 2019). Aquatic insects and crustaceans suffered decreased survival, growth, and reproduction; these invertebrates serve as food for fish, so their decrease led to the reduction in fish yields (Yamamuro et al., 2019). A study conducted in the Netherlands found that the declining bird population, at 3.5% annually, was associated with high neonicotinoid concentrations as it reduced the availability of insect prey (Hallmann, Foppen, van Turnhout, de Kroon, & Jongejans, 2014). It is apparent that the use of neonicotinoids has the potential to drastically alter the ecosystem.

Organochlorine Utilization and Persistence

Use of organochlorines, a group of chlorinated compounds began in the 1940s in agriculture and control of malaria and typhus (W. Michael Caudle, 2015; Jayaraj et al., 2016). Organochlorines share certain physicochemical characteristics including persistence, bioaccumulation, and toxicity (Jayaraj et al., 2016). Persistence varies across the compounds but is defined as “half-life greater than two months in water or six months in soil sediment” (Jayaraj et al., 2016). Organochlorines as a group are all resistant to degradation and therefore persistent in the environment (Coats, 1990). Organochlorines also have bioaccumulation potential, both in the environment and in human tissue, and therefore can still be detected in these settings, despite

discontinued use for many years (W. Michael Caudle, 2015; Jayaraj et al., 2016). Toxicity of organochlorines is due to the stimulation of the central nervous system (Jayaraj et al., 2016). These compounds have varied modes of action. Some organochlorines “affect the function of the sodium and calcium channels and transporters as well as interfering with γ -aminobutyric acid (GABA) neurotransmission by blocking specific GABA receptors” (W. Michael Caudle, 2015). GABA is a neurotransmitter that sends chemical messages to the brain and nervous system and regulates communication between brain cells (Konkel, 2015). GABA’s role “is to inhibit or reduce the activity of the...nerve cells” (Konkel, 2015). When GABA receptors on the nerve cells are blocked, they are unable to receive the chemical message to inhibit or reduce nerve impulses (Konkel, 2015). Organochlorine insecticide compounds result in hyperexcitation or overexcitation of the neurons that then “manifest as tremors and seizures and ultimately death of the insect” (William Michael Caudle, 2015). Organochlorine exposure can occur through diet as these chemical compounds accumulate in “fatty food such as meat, fish, poultry, and dairy products” (Jayaraj et al., 2016). Direct exposure, including inhalation, or indirect exposure to organochlorines can also occur, especially in agricultural laborers and their families as they absorb a measurable amount of pesticides when working or passing through an area where the pesticides have been applied (Jayaraj et al., 2016).

DDT History and Status

Dichlorodiphenyltrichloroethane, commonly known as DDT, is an organochlorine compound developed as the first major modern synthetic insecticide in 1939 (United States Environmental Protection Agency, 2017). DDT acts on the peripheral nervous system with sodium channels as the primary target of action (Zhorov & Dong, 2017). DDT “[prevents] the

deactivation...of [the sodium gate] after activation and membrane depolarization” resulting in sodium ion leakage through the nerve membrane (Coats, 1990). DDT causes nerve cells to repeatedly generate an impulse, which results in repetitive body tremors in exposed animals (National Pesticide Information Center, 2000).

Widespread use began in the 1940s during World War II, primarily by the military, as an effort to combat vector-borne diseases including malaria and typhus (National Pesticide Information Center, 2000; United States Environmental Protection Agency, 2017). Major aerial spraying of DDT was enacted in towns and cities with endemic malaria in Europe and the South Pacific, but U.S. soldiers were also provided with DDT powder which they were encouraged to sprinkle on their clothes and sleeping bags (Ganzel, 2003). Use of DDT proved successful in eradicating malaria in Italy and the United States and controlled a typhus epidemic in Italy and Germany (Majori, 2012; National Pesticide Information Center, 2000). Due to the noted effectiveness in vector control during the war, DDT then began being used globally for agricultural purposes on a variety of food crops including beans, cotton, and peanuts (National Pesticide Information Center, 2000). DDT use steadily increased and in 1959 80 million pounds of DDT were applied in the United States (Environmental Protection Agency, 1972). Usage steadily decreased domestically over the years after DDT production reached its peak in the United States in 1963 at 188 million pounds due to insect resistance, development of alternative pesticides, and concern over negative environmental effects (Environmental Protection Agency, 2016; National Pesticide Information Center, 2000).

DDT use was banned in the United States in 1972 after years of growing concern around the insecticide’s negative environmental and human health effects (Centers for Disease Control, 2009). Rachel Carson published the acclaimed *Silent Spring* in 1962, documenting the adverse

environmental effects that she attributed to the cavalier use of pesticides, most specifically, DDT (Yang, Ward, & Kahr, 2017). During her years of extensive research, she utilized personal connections with government scientists and investigated hundreds of incidents of landowners reporting ecological damage and human illness (Yang et al., 2017). She attributed the decline in bird and wildlife populations to the use of DDT, as they feed on the dead or dying insects, and attributed the accumulation of chemicals within fat tissues to cause medical problems later in life, including, with help from the NIH, discovering evidence to support the pesticide-cancer connection (Carson, 1962; Yang et al., 2017). *Silent Spring* sparked an environmental revolution; the public and government officials took her concerns seriously and soon policies began to change (American Chemical Society, 2012). Pesticide regulation had been the responsibility of the United States Department of Agriculture, but Carson and supporters viewed this as a conflict of interest since the department's primary concern was agriculture policy and not the effect of policy on wildlife or the environment (Yang et al., 2017). The Environmental Protection Agency (EPA) was created in 1970; and in 1972, the EPA issued a ban on the use of DDT, based on adverse environmental effects and potential human health risks (United States Environmental Protection Agency, 2017).

The production and use of DDT were further restricted internationally through the Stockholm Convention on Persistent Organic Pollutants (van den Berg, 2009). The purpose of the convention was to create a global treaty to protect both human health and the environment from persistent organic pollutants (POPs) as it was realized that exposure to POPs results in serious health effects including cancer, birth defects, and dysfunctional immune systems (Stockholm Convention, 2008). As of May 2007, 147 countries signed as parties to the Convention (World Health Organization, 2011). The United States signed the Stockholm

Convention in 2001 but has yet to ratify (U.S. Department of State, 2019). Due to a lack of effective and efficient alternatives, the Convention made an exemption for the production and use of DDT in indoor application for vector disease control (World Health Organization, 2011). In 2005, an estimated 5,000 metric tons of DDT was used for disease vector control, with India as the largest consumer (van den Berg, 2009). Over the years India has reduced consumption, but use increased in African countries from 2001-2009 due to indoor residual spraying (IRS) as a result of the President's Malaria Initiative (van den Berg, 2009). Vector control is one the primary components of the malaria control program and indoor residual spraying plays an essential role in reducing or interrupting malaria transmission (Centers for Disease Control, 2018b; van den Berg, 2009; Wangdi et al., 2018). Twelve insecticides are recommended for IRS use, including DDT. The World Health Organization supported and promoted the use and effectiveness of DDT in indoor residual spraying for malaria control (World Health Organization, 2011).

Malaria and Vector Control

Malaria is a parasitic disease that spreads from human to human through the mosquito, or the "vector" (Centers for Disease Control, 2018a). The lifecycle of malaria involves cyclical infection of humans and female Anopheles mosquitoes (Centers for Disease Control, 2018a). The malaria infected female Anopheles mosquito inoculates the human host during a blood meal (Centers for Disease Control, 2018a). The parasites grow and multiply first in the liver cells of the human host and then in the red blood cells (Centers for Disease Control, 2018a). The blood stage parasites cause the clinical symptoms of malaria (Centers for Disease Control, 2018a). Blood stage parasites (gametocytes) are ingested by the female Anopheles mosquito from the

human during the blood meal, then grow and multiply in the mosquito (Centers for Disease Control, 2018a). Another form of the parasite, a sporozoite, migrates to the mosquito's salivary glands and during the next human blood meal, the mosquito injects the sporozoites, beginning a new cycle (Centers for Disease Control, 2018a). Unlike the human host, the mosquito is not infected by the malaria parasite (Centers for Disease Control, 2018a). Life cycle is represented in Figure 1.

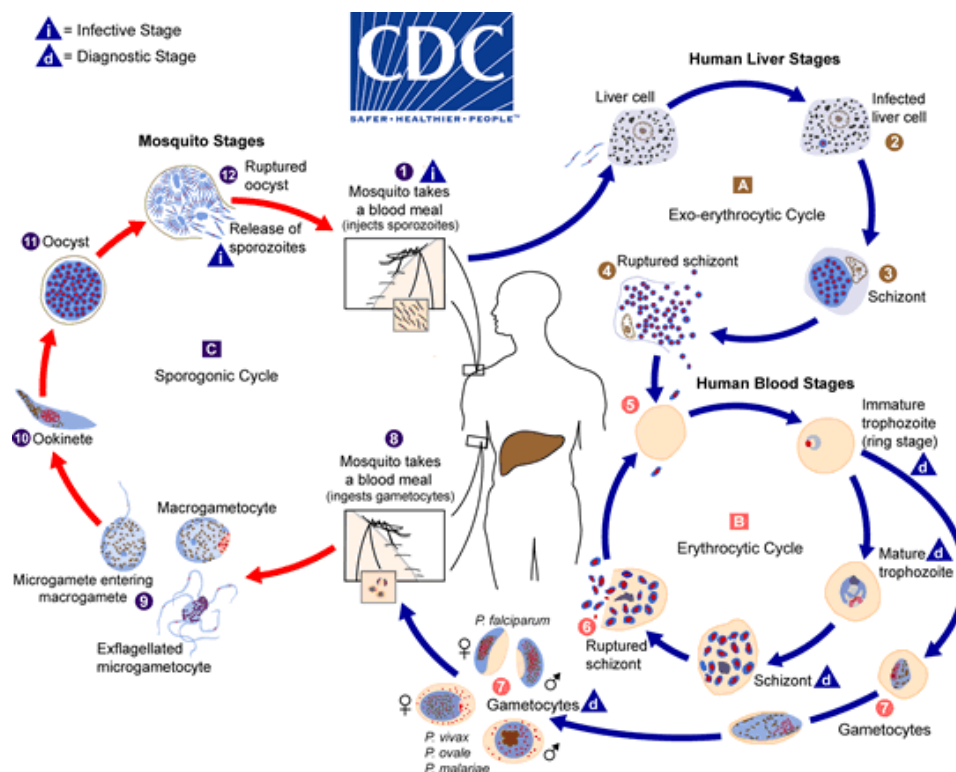


Figure 1: Malaria parasite life cycle, Centers for Disease Control, 2018

Malaria transmission occurs in 92 countries worldwide, with 219 million cases in 2017, an 18% decrease in incidence since 2010 (World Health Organization, 2018). Death rates due to malaria have decreased by almost 30% over the past decade; 435,000 malaria deaths occurred in 2017 (Figure 2) (World Health Organization, 2018). The burden of disease due to malaria is the largest in the African Region, where 93% of malaria-related deaths occur (World Health

Organization, 2018). Children under five are also at high risk with 61% of malaria-related deaths occurring in children under five (World Health Organization, 2018).

Trends in malaria case incidence rate (cases per 1000 population at risk), globally and by WHO region, 2010-2017

The WHO European Region has reported zero indigenous cases since 2015. Source: WHO estimates

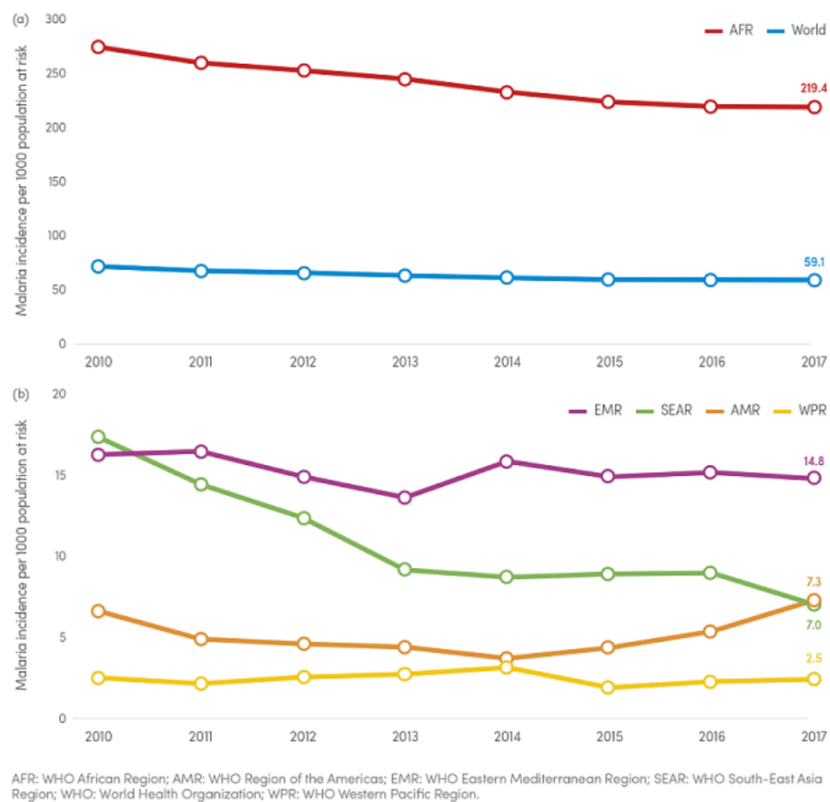


Figure 2: Malaria case incidence rate, World Health Organization, 2018

The Centers for Disease Control estimates that seven million lives were saved globally since 2001 and malaria deaths in Africa have been cut by more than half (Centers for Disease Control, 2019b). The scaling up of treatment and prevention efforts has been a result of the interventions by the President’s Malaria Initiative (PMI) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. PMI launched in 2005 to reduce malaria-related mortality by half, focusing within fifteen high-burden countries in sub-Saharan Africa (President’s Malaria Initiative, 2019). The Global Fund is an organization that developed in 2002 and finances AIDS,

TB, and malaria prevention, treatment, and care programs (The Global Fund to Fight AIDS, 2019). Scale-up interventions include insecticide-treated mosquito nets (ITNs), indoor residual spraying (IRS), accurate diagnosis and prompt treatment with artemisinin-based combination therapies (ACTs), and intermittent preventive treatment of pregnant women (IPTp) (President's Malaria Initiative, 2019; Wangdi et al., 2018). IRS consists of spraying insecticide on the interior walls of a home to kill mosquitoes (President's Malaria Initiative, 2019). Five pre-qualified insecticides are approved for IRS use by the World Health Organization (WHO), with DDT only recently being phased out (President's Malaria Initiative, 2019). The goal is to produce community protection by ensuring at least 80% of houses receive proper IRS (President's Malaria Initiative, 2019). The reduction in malaria incidence is primarily attributed to the introduction and now widespread use of IRS (President's Malaria Initiative, 2019). Although IRS reduces the burden of malaria, it also puts inhabitants at risk of exposure to these insecticides. Exposure can occur through inhalation, dermal contact, and/or ingestion of contaminated food and/or water (Aneck-Hahn, Schulenburg, Bornman, Farias, & de Jager, 2007). Although studies in North America have shown the detrimental effects of DDT, little research has been done to understand the effects from the use of IRS in malaria endemic areas (van den Berg, 2009). One study conducted in South Africa found that DDT values were "statistically significantly higher in men living in sprayed homes than in men from nonsprayed houses" (Aneck-Hahn et al., 2007). From these results, the study concludes that indoor residual spraying contributes to increased exposure to DDT (Aneck-Hahn et al., 2007).

Alternative vector control options exist, but IRS is one of the two core prevention measures supported by the WHO (World Health Organization, 2019a). The second core prevention method is insecticide-treated nets (ITNs), including long-lasting insecticide-treated

nets (LLINs) (World Health Organization, 2019a). ITNs prevent malaria transmission by both stopping people from being bitten by mosquitoes and killing the mosquitoes that come in contact with the net (Vlasits, 2016). WHO advises that malaria control programs should prioritize the delivery of either ITNs or IRS at a high coverage level rather than implementing both at lower standards (World Health Organization, 2019a). The WHO states that ITNs reduce the rate of the prevalence of *P. falciparum* and state with moderate certainty that ITNs reduce all-cause child mortality in comparison to the use of untreated nets (World Health Organization, 2019b).

Research also suggests that malaria infection rates are lower among individuals who use nets versus those who do not use nets in areas with pyrethroid resistant mosquitoes (World Health Organization, 2019c). This shows that nets can still provide personal protection despite insecticide resistance. The WHO recommends malaria endemic countries to achieve and maintain universal coverage of ITNs, but that is not without financial, operational, technical, and political challenges (Lengeler, 2004; World Health Organization, 2019b). A large gap remains not only with access to ITNs but also with use of ITNs in households (Ahorlu et al., 2019). Other supplementary interventions include larval source management (LSM), space spraying, housing improvements, and personal protection measures such as topical repellents, insecticide-treated clothing, and airborne repellents (World Health Organization, 2019b). These interventions are effective, but only as supplementary measures. One of these interventions alone would not be as effective as a core intervention methods (World Health Organization, 2019b).

Another major emerging challenge in vector control is insecticidal resistance. Among the various types of pests, insects are exhibiting resistance to pesticides at alarming rates; more than 500 species of insects or arthropods worldwide are resistant to insecticides (Buhler, 2019). Insecticide resistance can occur due to several factors, with two main factors being genetics and

intensive application of insecticides (Buhler, 2019). Although it is possible for resistance to develop to a single insecticide, the problem is exacerbated by two other forms of resistance: cross-resistance and multiple resistance (Buhler, 2019). Cross-resistance is seen when insects are resistant to one insecticide and then exhibit resistance to other insecticides with the same mode of action (Buhler, 2019). Multiple resistance occurs when insects are resistant to two or more insecticide classes with different modes of action (Buhler, 2019). The WHO reports that resistance to the four commonly used insecticides classes (pyrethroids, organochlorines, carbamates, and organophosphates) is widespread in malaria vectors across the Africa, Americas, South-East Asia, Eastern Mediterranean, and Western Pacific regions (World Health Organization, 2019c). The WHO's *Global report on insecticide resistance in malaria vectors: 2010-2016* stated that since 2010, sixty-eight countries report resistance to at least one class of insecticides and fifty-seven of those countries report resistance to two or more insecticide classes (World Health Organization, 2019c). Due to the increase in resistance, combined with the effects of global climate change, mosquito borne diseases are on the rise, which can become detrimental to human health and reverse the progress made in reducing malaria transmission (Liu, 2015; Tanser, Sharp, & le Sueur, 2003)

Neurological Effects of DDT Exposure

Studies surrounding the health effects of DDT have focused on North America and Europe with subjects exposed to lower levels of DDT than those in malaria-endemic areas who experience IRS (van den Berg, 2009). Although inconsistencies exist between some studies, general adverse health effects are recognized to be associated with DDT exposure in this population. Health effects include neurological deficits and an increased risk for certain types of

cancers including pancreatic cancer and leukemia as well as diabetes, and fertility loss (Garabrant et al., 1992; van den Berg, 2009). In utero and early childhood exposure to DDT also drastically increases the risk of developing breast cancer as an adult (Chang, El-Zaemey, Heyworth, & Tang, 2018; Cohn et al., 2015). Given this information, it is likely countries will soon, if not already, see an increase in breast cancer and other diseases in the population due to DDT's environmental persistence and generational impact.

Prenatal Exposure

DDT inhibits “neuronal repolarization” in insects and the effects of DDT poisoning in humans arise by the same mechanism (Longnecker, Rogan, & Lucier, 1997). Mammals share the neuronal features of insects that are effected by insecticides, so the neurotoxic effects of DDT and other insecticides are not exclusive to insects (William Michael Caudle, 2015). Due to the lipid solubility of pesticides, they can pass through the placenta and result in effects in early development (Vester & Caudle, 2016). Organochlorines bioaccumulate and persist in human bodies and the environment and are able to cross the placenta and excrete in breastmilk (Vester & Caudle, 2016). Small alterations to brain development during early life may result in neurodegenerative changes or neurodegenerative susceptibility as the brain develops (Vester & Caudle, 2016). It was observed in mice that neonatal exposure to pesticides, including DDT, can potentiate adult susceptibility and accelerate dysfunction, including behavioral abnormalities and learning and memory impairment (Alipour, Hoseinpour, & Vatanparast, 2019). When considering the observations of decreasing cognitive skills and neurobehavioral functioning from DDT exposure, combined with the plethora of other confirmed adverse health effects of DDT, these findings raise ethical concerns for countries still using DDT and call for definitive research

on the risk versus benefit debate of continued DDT use for vector control (Cohn et al., 2015; Ribas-Fitó et al., 2006).

Research to determine the neurodevelopmental effects of DDT exposure in utero has been conducted among multiple cohorts in different countries. For example, DDT has been banned in Spain since 1978 but was found to still be present in cord serum (Ribas-Fitó et al., 2006). In 2005, Sunyer et al. reported they discovered higher concentrations of DDE (a metabolite of DDT) in newborns in Menorca, Spain compared to those in Ribera d'Ebre (Sunyer et al., 2005). Ribera d'Ebre is a rural village in the vicinity of an electrochemical factory whereas Menorca is an island in the Mediterranean sea with no local pollution sources, suggesting exposure was dietary (Ribas-Fitó et al., 2006). Researchers in this group followed up with the children in the two birth cohorts, born between 1997-1999, to analyze and examine the association between cord serum levels of DDE and DDT with neurodevelopment at age four years (Ribas-Fitó et al., 2006). Neuropsychological testing included assessment of intellectual abilities, attention, and social competence through use of the Spanish version of the McCarthy Scales of Children's Abilities (MCSA) (Ribas-Fitó et al., 2006). The cohort study concluded that prenatal exposure to low concentrations of DDT and DDE is associated with a decrease in "verbal, memory, quantitative, and perceptual-performance skills" among four-year-old children (Ribas-Fitó et al., 2006). A dose-response relation between DDT and the verbal and memory areas was also observed; children with DDT cord serum levels above 0.20 ng/ml had much lower scores on the verbal and memory scales compared to children with concentrations below 0.05 ng/ml (Ribas-Fitó et al., 2006). Associations were also typically stronger among the girls, which could indicate a mechanism of action of DDT neurotoxicity that may apply specifically to females (Ribas-Fitó et al., 2006).

Similar

neurodevelopmental tests were done among a cohort in Morelos, Mexico to examine the prenatal effect of DDE exposure. Mothers who enrolled had blood samples drawn each trimester (Torres-Sánchez et al., 2013). Children of mothers with DDE serum levels in at least one trimester were followed and

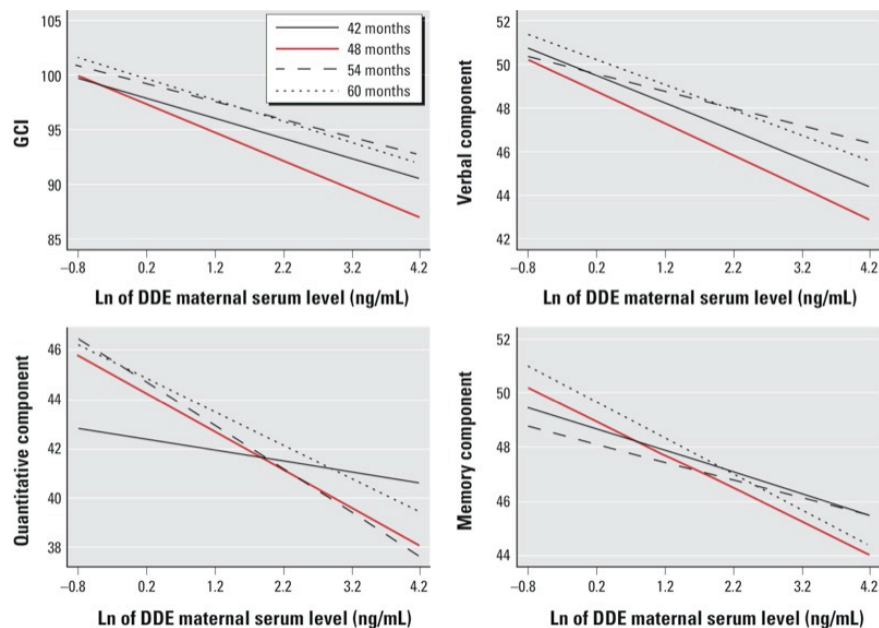


Figure 3: Maternal serum DDE and MSCA scores, Torres-Sánchez et al., 2013

examined at multiple intervals (Torres-Sánchez et al., 2013). Results show that maternal serum DDE during the third trimester is negatively associated with general cognitive index (GCI), quantitative, verbal, and memory skills for children ages 3.5-5 years using the McCarthy scale (Figure 3) (Torres-Sánchez et al., 2013). Maternal serum DDE levels during the third trimester had more negative associations than associations with maternal serum DDE levels during the first trimester, suggesting that developmental functions can be affected differently depending on exposure during developmental stages (Torres-Sánchez et al., 2013).

Occupational/Long-term Exposure

Professionals who deal with pesticides, such as farmers and agricultural workers, are at increased risk of experiencing negative health effects from pesticides. A study conducted in Costa Rica examined the nervous system effects of long-term occupational exposure to DDT. Recruitment consisted of retired men who had been involved in DDT use/application for at least

two years between 1955 and 1996 (the exposed group) and retired guards and drivers with a similar socioeconomic status who were employed during the same timeframe (the control group) (van Wendel de Joode et al., 2001). Researchers discovered that the DDT exposed group had an overall poorer performance in all neurobehavioral tests, with verbal attention and visuomotor speed and sequencing differing the most (van Wendel de Joode et al., 2001). When the two groups were stratified, results indicated the high exposure group experienced more apparent deficits than the medium exposure group in all tests except one, finger tapping (van Wendel de Joode et al., 2001). The exposed group also had significantly more neuropsychological and psychiatric symptoms than the control group (van Wendel de Joode et al., 2001). The dose effect relationship regarding years of DDT application was significant for cognitive, motor, and sensory domains tests (van Wendel de Joode et al., 2001). The results from this study conclude that “chronic occupational exposure to DDT is associated with a permanent decline in neurobehavioral functioning and an increase of neuropsychological and psychiatric symptoms” with the amount of decline directly associated with years of DDT application (van Wendel de Joode et al., 2001).

Workers who were/are involved with the spraying of DDT are also at risk for impaired cognitive functioning. A matched case-control study in India examined the cognitive status of DDT sprayers who have been engaged with DDT spraying for at least one year (Misra et al., 1984). Almost 30% of subjects reported psychological symptoms, including irritability, anxiety, depression, and forgetfulness; 10% reported worsening psychological symptoms following spraying (Misra et al., 1984). One quarter of subjects reported “soft” neurological signs such as tremulousness and hyperreflexia (Misra et al., 1984). Sprayers also had significantly higher Bender Visuomotor Gestalt Test (BGT) scores, which indicates impaired visuomotor functioning

(Misra et al., 1984). BGT scores were also correlated with DDT levels (Misra et al., 1984). Of those with abnormal BGT scores, over half showed electroencephalographic changes during monitoring (Misra et al., 1984).

Parkinson's Disease

A study conducted among agricultural workers in France examined the relationship between professional pesticide exposure and Parkinson's disease. Participants for this case-control study were recruited from the Mutualité Sociale Agricole (MSA), the health insurance for workers in agriculture and related occupations (Elbaz et al., 2009). Parkinsonism defined in the study is greater than or equal to two cardinal signs, including rest tremor, bradykinesia, rigidity, and impaired postural reflexes, identified by a movement disorder neurologist (Elbaz et al., 2009). To determine pesticide exposure, occupational history and declaration of personal pesticide spraying were obtained via self-questionnaires (Elbaz et al., 2009). Pesticide history information was also obtained through participant interviews conducted by MSA occupational health physicians (Elbaz et al., 2009). Participants recounted past professional information including farms where they worked, land size, crops information, which pesticides were used and detailed information about each pesticide such as frequency, duration, and spraying method (Elbaz et al., 2009). Analysis of the results showed "an association between Parkinson's Disease and professional pesticide use with a dose-effect relation" (Elbaz et al., 2009). Cumulative lifetime hours of exposure was used for the dose-effect analysis (Elbaz et al., 2009). Men showed the strongest association between insecticides and Parkinson's disease, with the most robust association found for organochlorines (Elbaz et al., 2009). Results from this study support an

association between pesticide exposure and Parkinson's disease and show particular pesticides, organochlorine insecticide, may play a particular role in disease acquisition.

A similar study conducted at Duke University in North Carolina examined a set of Parkinson's disease cases and their unaffected relatives as controls to determine the association between direct pesticide application, well-water consumption, and farming residences/occupations with Parkinson's disease (Hancock et al., 2008). Family members were utilized in this study to help negate any confounding genetic and environmental factors. Participants provided a blood sample, a detailed medical history questionnaire, a three-generation family history report, an environmental risk factor questionnaire, and underwent a standard cognitive status test (Hancock et al., 2008). A Parkinson's case was defined here as individuals demonstrating "at least two cardinal signs of [Parkinson's disease], an asymmetry of symptom onset, and no atypical signs during examination" (Hancock et al., 2008). To determine direct pesticide application, individuals were asked if they have ever applied a pesticide and if yes, further information was gathered that included listing names of the specific pesticides used, the number of days used per year, if currently being used, years of application, and whether or not protective gear was used (Hancock et al., 2008). Those reporting "yes" were recorded as "ever exposed" (Hancock et al., 2008). The sum of both frequency and duration was recorded as well as cumulative exposure, "calculated as the multiplicative result of frequency and duration" (Hancock et al., 2008). Participants with Parkinson's disease were 1.61 times as likely to report ever being exposed (e.g. direct pesticide application) compared to their unaffected relatives (Hancock et al., 2008)." Frequency, duration, and cumulative exposure were [also] associated with [Parkinson's disease] in a dose-dependent manner (Hancock et al., 2008). The use of protective gear did not affect the association between direct pesticide application and Parkinson's

disease (Hancock et al., 2008). Analysis of the chemical classes used reported by the participants was also conducted. Individuals who reported “ever applying insecticides were significantly more likely to develop [Parkinson’s disease]”; insecticides were the strongest association of all pesticide types (Hancock et al., 2008). Furthermore, organochlorines and organophosphorus chemical classes of pesticides were also found to be significantly associated with Parkinson’s disease (Hancock et al., 2008). In this sample, DDT was one of the top two reported organochlorine chemicals used (Hancock et al., 2008). Researchers in this study discovered that those without a family history of Parkinson’s disease had significant associations between pesticides and Parkinson’s disease while the association was absent in those with a positive family history (Hancock et al., 2008). A family-based case-control study helps eliminate confounding genetic influences (Hancock et al., 2008). This conclusion warrants further research between genetic susceptibility and pesticide exposure. Findings from this study support the argument that pesticides, most notably organochlorines and organophosphorus compounds, are risk factors for the development of Parkinson’s disease (Hancock et al., 2008).

Neurological Effects of Indoor Residual Spraying

Indoor residual spraying (IRS) using DDT was the primary method for mosquito control in malaria endemic areas (Channa, Rollin, Nost, Odland, & Sandanger, 2012). Although IRS is an essential component to malaria control, the residue of DDT can persist in the environment for years, exposing residents in IRS areas to DDT and its metabolites through multiple pathways including contaminated indoor air, floor dust, outdoor soil, food, and water (Van Dyk, Bouwman, Barnhoorn, & Bornman, 2010). DDT was found in indoor air, dust, and outdoor soil in Oman twenty-one years after the use of DDT with IRS (Booij et al., 2016). Concentrations of

DDT and its metabolites can also be found in the blood plasma of residents in malaria endemic IRS areas (Channa et al., 2012). In a group of mothers, whose serum concentration levels were measured when they presented to the hospital for delivery, those living in a home that was sprayed with DDT for malaria control, had 5-7 times higher DDT concentrations than mothers who had never lived in a home that had been sprayed (Gaspar et al., 2017). The children from this group of mothers also had their DDT levels examined at 12 months and 24 months (Verner et al., 2018). Results from this cohort showed that during the first two years of life, the children had higher DDT levels than their mothers at delivery (Verner et al., 2018). The study suggests that these high levels are also influenced by breastfeeding (Verner et al., 2018). Some studies also hypothesize that IRS is responsible for levels of DDT in individuals who have no history in residing in IRS areas (Channa et al., 2012). There is limited existing data that examines the adverse health effects of DDT for individuals living in IRS homes or areas, but there are a few studies that aim to determine the consequences of DDT exposure through IRS. South African men living in malaria endemic areas where DDT was sprayed annually were found to have impaired seminal parameters associated with DDT concentrations (Aneck-Hahn et al., 2007). This shows great concern regarding the reproductive health of current and future generations (Aneck-Hahn et al., 2007).

There is also insufficient data regarding the neurological effects of exposure to DDT through indoor residual spraying. In a recent systematic review of “Chronic adverse effects of long-term exposure of children to dichlorodiphenyltrichloroethane (DDT) through indoor residual spraying,” only three studies were discovered that examine neurodevelopmental outcomes (Osunkentan & Evans, 2015). Eskenazi et al. examined the effects of in utero exposure to DDT and DDE on the neurodevelopment of Mexican American infants. Mexico restricted the

use of DDT in 1995 but did not ban it entirely until 2000, so a large majority of the women included in the study were exposed in the 1990s to DDT through IRS for malaria control prior to immigration (Eskenazi et al., 2006). At the time of the study, Mexican agricultural workers were also likely exposed through occupational work prior to immigration to the United States, but the authors mention it is possible occupational exposure could still occur in the United States from the persistence of DDT in the soil (Eskenazi et al., 2006). Utilizing the Center for the Health Assessment of Mothers and Children of Salinas, pregnant women were enrolled and blood samples collected to measure DDT and DDE exposure (Eskenazi et al., 2006). Interviews with the women revealed that 83% of the women were from agricultural households and almost half, 42%, worked in agriculture during pregnancy, which was found in analysis to be associated with DDT and/or DDE levels (Eskenazi et al., 2006). Using the Bayley Scales of Infant Development (BSID), the psychomotor development and mental development of the infants of enrolled pregnant mothers were examined at six, twelve, and twenty-four months (Figure 4) (Eskenazi et al., 2006). With each ten-fold increase of DDT levels, there was a two-point decrease in psychomotor development scores at six and twelve months (Eskenazi et al., 2006). Two-point to three-point decreases in mental development scores at twelve and twenty-four months were associated with a ten-fold increase in DDT serum levels (Eskenazi et al., 2006). Researchers

conclude that in utero exposure to DDT is negatively associated with the neurodevelopment of children (Eskenazi et al., 2006). DDT exposure is associated with lower psychomotor development scores at six and twelve months and associated with lower mental development

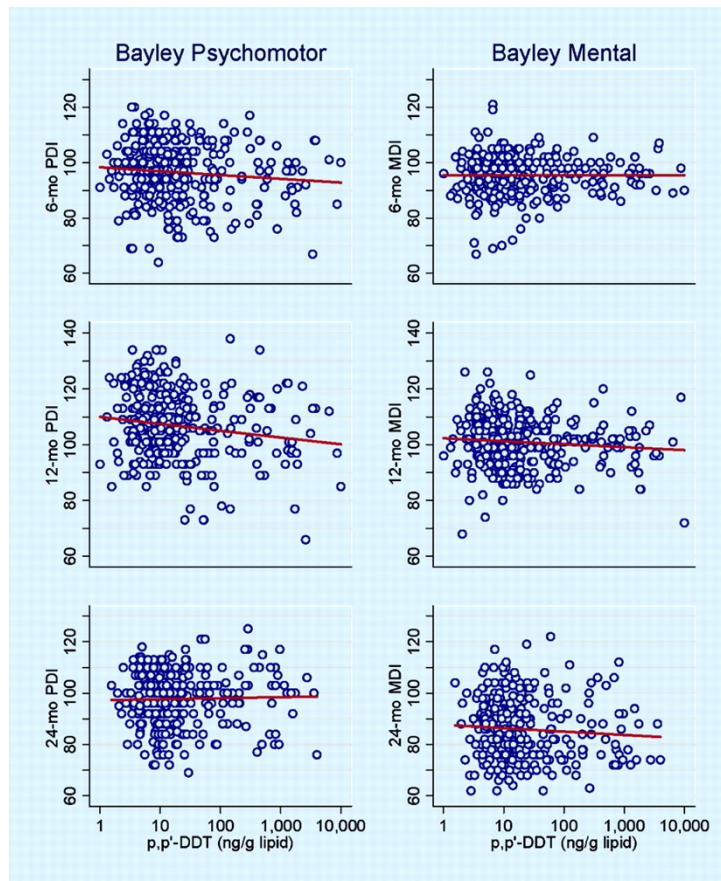


Figure 4: Association of *p,p'*-DDT levels with Bayley scores, Eskenazi et al., 2006

scores at twelve and twenty-four months (Eskenazi et al., 2006). Although adverse neurological effects are seen in this study, there was no stratification surrounding occupational exposure, which limits the correlation between IRS and adverse neurological effects.

Further research was done in Mexico with a different birth cohort, where participating mothers were not occupationally exposed to DDT, but they did live in a malaria endemic area of Mexico (Torres-Sanchez et al., 2007).

Questionnaires and blood samples were collected from each mother during a home visit that occurred each trimester (Torres-Sanchez et al., 2007). Postnatal visits to evaluate the children were conducted at one, three, six, and twelve months of age (Torres-Sanchez et al., 2007). Researchers determined that higher DDE levels during the first trimester are significantly associated with reduced psychomotor development in the child's first year of life; there was a reduction of two points for every ten-fold increase in DDE level (Torres-Sanchez et al., 2007). No association was found between maternal DDE levels in the second or third trimester and

neurodevelopment (Torres-Sanchez et al., 2007). A follow-up to this study was conducted among the children when they had reached ages twelve to thirty months to evaluate the persistence of DDT/DDE exposure (Torres-Sanchez et al., 2009). Evaluations of the children occurred as described above and then occurred every six months after the child reached twelve months of age (Torres-Sanchez et al., 2009). After analysis, results concluded that there is no persistency of the association between DDE levels and neurodevelopment beyond twelve months of age (Torres-Sanchez et al., 2009). Authors discuss that these results do not imply that there are no harmful effects, as effects may manifest at older ages or may be negatively associated with other brain functions not examined in this study (Torres-Sanchez et al., 2009).

The neurological effects of DDT exposure are evident in multiple studies across different populations. Unfortunately, the populations with the longest exposure due to indoor residual spraying for malaria control, which has been occurring for the past seven decades, have not been appropriately studied to determine the true effect of DDT (Osunkentan & Evans, 2015). Exposure prevention and proper diagnosis and treatment of neurological diseases cannot be adequately carried out without understanding what is occurring in these populations. Although the WHO has recently phased out the use of DDT with IRS, research has shown us that this chemical persists for many years in the environment, which in turn can have adverse health effects for adults, children, and those not yet born. The WHO may wish to consider creating long-term, coordinated studies to document outcomes to determine and treat the neurological effects of DDT exposure from indoor residual spraying.

CHAPTER 3: EXPOSURE ASSESSMENT

The World Health Organization (WHO) advocated for use of DDT for indoor residual spraying in countries that continue to be malaria endemic, despite its known adverse health effects (United States Environmental Protection Agency, 2017). Since DDT previously played a significant role in global malaria control, the advantage of its use (decrease in vector borne diseases) outweighed the potential disadvantages (e.g. adverse health effects). For years, DDT has been used with IRS without an understanding of the health status of the exposed communities. Research in DDT exposed areas, including India and many African countries, generally focuses on communicable diseases or infectious diseases but there is little to no research examining genetic or neurological diseases. The reasoning behind a lack of research on this topic is not explicitly stated. Communicable and infectious diseases remain a major global public health threat in these regions and are therefore at the forefront of research and the focus of the health burden. These diseases are also often regarded as preferable to donors as the influence of their investment can be easily determined as there are more immediate results, e.g. decrease in disease incidence. In contrast, the neurological effects of pesticides may not occur for years after exposure, so cohort studies need to follow subjects exposed to DDT for many years which can be prohibitively expensive and results are not immediate. (Johnson, de Roode, & Fenton, 2015)

In 2017 the WHO announced a new plan surrounding global vector control and their approach to tackling vector-borne diseases (World Health Organization, 2017b). The WHO plans to phase out the use of DDT and replace it with “locally adapted sustainable vector control” (World Health Organization, 2017b). The new comprehensive vector control plan advocates

using a combination of effective proven vector control methods (including insecticide treated bed nets and community-wide spraying inside houses and on surfaces) with promising new approaches which include new insecticides with different modes of action, vector traps and targets, and spatial repellents (World Health Organization, 2017b). The combination of old and new methods is not only anticipated to reduce the burden of vector borne diseases but to also help achieve multiple Sustainable Development Goals including Goals 1, 3, 6, 11, 13, 17 (World Health Organization, 2017a). Although activities are promising, literature shows that DDT can persist in the environment for years (Van Dyk et al., 2010). Many communities have been exposed to DDT for decades and the future generations are at risk of being exposed as well. The true effect of DDT can only be determined through additional research. The WHO can augment the global vector control response to include a current health status report for the communities subjected to DDT exposure through IRS and establish policies that allow for treatment as countries roll out updated response methods.

Methodology

The following sections describe a proposed exposure assessment to test the connection between DDT levels and neurodevelopment. The United States Environmental Protection Agency (EPA) uses the International Programme on Chemical Safety's (IPCS) definition of an exposure assessment: "the processing of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed" (International Programme on Chemical Safety, 2004). The exposure assessment was developed with help from existing exposure assessments published in literature. The literature was reviewed to determine appropriate information that should be incorporated into the exposure

assessment, including geographic study area and/or study population, collecting the chemical sample, and anticipated analysis. The EPA's "Guidelines for Exposure Assessment" was also used as a resource in order to create appropriate study procedures. The exposure assessment will determine the levels of DDT that still persist, and analysis will determine the association between DDT and neurodevelopment.

Study Area

South Africa formerly had success with using DDT for malaria control, and in 2000 a malaria epidemic due to pyrethroid resistance prompted the South African government to call for allowed use of DDT in vector disease control as it had previously played such an instrumental role (Wells & Leonard, 2006). After negotiations, a treaty was signed in support of DDT for malaria control in 2006 and South Africa re-introduced DDT with IRS in anticipation of eventual

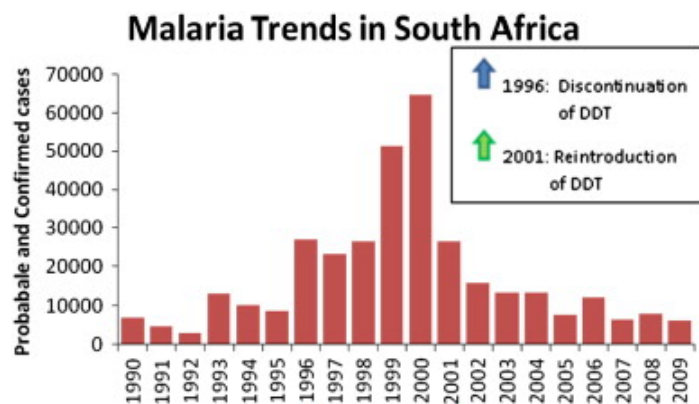


Figure 5: Malaria Trends in South Africa, Aneck-Hahn et al., 2007

country-wide malaria elimination (Brand South Africa, 2006). DDT was sprayed in three South African provinces considered to be at risk, which accounted for about 10% of the population: Limpopo Province, Mpumalanga Province, and KwaZulu Natal (Aneck-

Hahn et al., 2007). Considering that collaboration with the government will be required to determine areas that have been sprayed and amount sprayed, South Africa is an appropriate country to conduct an exposure assessment since it is one of a limited number of countries that has already allowed for in-country research examining health effects of DDT. Government and

community partnerships will aid in identifying provinces and districts within the provinces that are appropriate to approach for assessment based on spraying and population data.

Study Population and Sampling Procedure

A nearby clinic or hospital will be partnered with and used as the assessment base for recruitment and sample collection. Pregnant women (≥ 18 years of age) who present to the clinic/hospital for pre-natal care will be approached to participate in the assessment. Based on population size and female participation in previous studies, the sample size is expected to be 300 women. Women who agree will go through the informed consent process with a trained local health worker to reduce any language barrier complications. They will then complete a short questionnaire with the health worker that asks for demographic, socio-economic, diet, and lifestyle information, including smoking status, alcohol consumption, and time spent indoors versus outdoors. Since the majority of DDT spraying is done indoors, stratification of the route of exposure may provide more concrete evidence about the harmful effects of IRS using DDT. Breastfeeding information will also be gathered after birth during one of the child's follow-up assessments. Cord blood will be collected to evaluate DDT levels at time of delivery as will further infant information including gender, gestational age, and birth weight. Children of these mothers will have blood drawn every six months for the first two years of life and then once a year through age six. These collections will determine if children were exposed in utero or exposed after birth.

Neurodevelopmental Testing

Children will undergo neurodevelopmental testing at six months and twelve months followed by once a year thereafter with the last assessment at age six. The Bayley Scales of Infant Development (BSID) will be used to measure mental and motor development of infants from one month to 42 months of age (Laberge, 2020). The infant will undergo a series of developmental play tasks that take about one hour to administer (Laberge, 2020). The BSID provides three different scales to help identify children at risk for developmental delay: mental scale, motor scale, and behavior rating scale (Laberge, 2020). The mental scale evaluates multiple abilities including sensory acuity, memory learning and problem solving, beginning of verbal communication, and habituation (Laberge, 2020). The motor scale assesses the degree of body control, large muscle coordination, finer skills of hands and fingers, and stereognosis (Laberge, 2020). The behavior scale measures attention, arousal, orientation, and emotional regulation (Laberge, 2020). For children aged four and older, the McCarthy Scales of Children's Abilities (MSCA) can be used. Administration requires 45-50 minutes for children aged 2.5-5 and 60-75 minutes for older children (Sands & D'Amato, 2017). The MSCA uses six domains to measure cognitive ability: verbal, perceptual-performance, quantitative, general cognitive, memory, and motor (Sands & D'Amato, 2017). The verbal scale includes pictorial memory, word knowledge, verbal memory and verbal fluency (Sands & D'Amato, 2017). The perceptual performance scale includes block-building, puzzle-solving, tapping sequence, and conceptual grouping (Sands & D'Amato, 2017). The quantitative scale includes number questions, numerical memory, and counting and sorting (Sands & D'Amato, 2017). The general cognitive scale includes the subtests that compose the verbal, perceptual-performance, and quantitative scales (Sands & D'Amato, 2017). The memory scale includes pictorial memory, tapping

sequence, verbal memory, and numerical memory (Sands & D'Amato, 2017). The motor scale includes leg coordination, arm coordination, imitative action, and draw-a-design (Sands & D'Amato, 2017). Both the BSID and MSCA have been previously used in studies examining neurodevelopment and DDT exposure and are therefore appropriate to use for this assessment (Eskenazi et al., 2006; Ribas-Fitó et al., 2006; Torres-Sánchez et al., 2013).

Exposure Measurement and Analysis

Each blood sample collected from mothers, cord blood, and children will be analyzed using gas chromatography mass spectrometry to measure DDT (*p,p'*-DDT) and DDT metabolite (*o,p'*-DDT and *p,p'*-DDE) levels. Total lipid concentrations will be estimated based on total cholesterol and triglyceride levels and measured using standard enzymatic methods. Regression analysis will be used to examine if any covariates should be considered in this analysis. The covariates examined will be those mentioned in literature to be associated with child neurodevelopment or those that might have affected the child's assessment results, including mother age, smoking status, alcohol use, breastfeeding duration, socioeconomic status, gestational age, and birthweight. Once covariates are determined and the final model is selected, further analysis will examine the association between DDT/DDE levels and child BSID or MSCA scores. Further stratification can be conducted during analysis by separating BSID/MSCA scores into their separate scale scores. This separation will allow the researchers to examine if DDT affects specific areas of development such as motor, memory, or cognition.

CHAPTER 4: CONCLUSION

Public Health Implications

The adverse neurological effects of DDT exposure from indoor residual spraying (IRS) are a public health issue that should be addressed (Eskenazi et al., 2006; Torres-Sanchez et al., 2007). Implications of exposure were proven decades ago, but research was limited to certain communities (mainly the Americas) and limited data are available to provide the specific factors that connect IRS with DDT and neurodevelopment. Even though the Environmental Protection Agency banned DDT in 1972, the World Health Organization (WHO) advocated for DDT use with IRS due to its effectiveness in mosquito control, a primary focus of the WHO at the time. This practice was continued despite the health risks posed and the amount of residual DDT found within the environment years after initial application. (Environmental Protection Agency, 1972; United States Environmental Protection Agency, 2017).

After decades of use, many of these areas have not only been exposed to DDT and its negative effects, but malaria is still an endemic issue that has yet to be resolved. The objective of the WHO is “attainment by all peoples of the highest possible level of health” (World Health Organization, 2020). For this objective to be achieved fully, the WHO may wish to balance the continued need for vector control with a deeper understanding of the additional health burden resulting from use of DDT. There is insignificant testing in communities that have used and/or continue to use insecticides for vector control. By researching the negative effects of the insecticides in these communities, public health practitioners will have a better understanding of

the burden of disease as well as evidence to research and propose alternative vector control strategies. Achieving the highest possible level of health in these communities will not be possible without evidence of the current health status of said communities.

Limitations

The neurodevelopmental effects of DDT are evident from the findings discussed in the literature review section; however, these findings are generally limited to countries in the Americas and Europe. Further, very limited data exists demonstrating the neurological effects of IRS with DDT. The information that does exist has been used here to support the assumption that the same adverse health effects exist within similar populations that have never been tested.

The BSID and MSCA are tests that were normed in the United States. These scales are valid neurodevelopmental tests in the Americas as well as valid in cross-cultural contexts including Europe (Hoskens, Klingels, & Smits-Engelsman, 2018). The scales are generally used in other international research efforts, but validity is limited. Pendergast, et al. examined the validity of the BSID across seven international research sites, which included South Africa, and concluded that these scales are a promising tool for research purposes in low and middle-income countries (Pendergast et al., 2018).

Conducting an exposure assessment will involve significant time, effort, and coordination. An organization will have to take on the research responsibility and then share the findings with the WHO. With finite resources, competing priorities, and limited malaria prevention options, the WHO may be unable to implement a practice of incorporating treatment guidelines based on the results of the exposure assessment into their new vector control policies.

In addition, South Africa and other countries that have used DDT may not have appropriate capacity to manage and/or treat neurodevelopmental disorders. If testing is conducted and disease burden is understood, it may be challenging for countries to appropriately treat the affected individuals due to their own limited resources. In this case, exposure assessment would be for the sole purpose of protecting future generations from the harmful effects of DDT and similar vector control chemicals by advocating for novel approaches to malaria prevention. Concrete evidence on the neurodevelopmental effects of IRS with DDT may be able to push countries toward limited use of insecticides for vector control and instead focus on local, sustainable solutions that do not have harmful human health effects.

Future Directions

Although DDT has recently been removed as a WHO prequalified chemical, organochlorines as a class are still recommended for IRS. Exposure assessment research in communities exposed to DDT through IRS can provide a deeper understanding of the levels of DDT that persist along with the burden of disease in these communities. It is expected that with these findings, governments will have more information to provide appropriate care and treatment for their citizens. With an understanding of the adverse health effects of DDT, the results of the exposure assessment can also result in governments identifying alternative forms of vector control that include limited use of insecticides. This effort will require consistent collaboration between the World Health Organization and their international partners to ensure this important issue receives the resources and focus to facilitate innovative and improved vector control methods.

Conclusion

This thesis provides significant evidence of the harmful neurodevelopmental effects of DDT exposure and provides a strategy to conduct an exposure assessment to understand the current status of communities that were subjected to DDT exposure through IRS. As DDT is known to persist in the environment for years, if an exposure assessment is not conducted, individuals in these communities may continue to suffer from adverse health effects due to exposure. Unaddressed neurodevelopmental disorders may also result in other negative consequences such as stigma, poor academic performance or potential inability to attend school, substance abuse, reduced life expectancy, or incapability to contribute to the workforce which then influences the country's economy (Barkley, 2019; Williams, 2015). To achieve the highest possible level of health, public health professionals must advocate for the elimination of harmful insecticide use and find alternative novel and sustainable vector control solutions that allow communities to live to their fullest potential.

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