Dichloro-diphenyl-trichloroethane (DDT): An unforgettable and powerful pesticide

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Abstract

Dichloro-diphenyl-trichloroethane (DDT) is one of the mostly widely used pesticides in human history because of its effectiveness, long shelf life and affordability. DDT's usage dates back decades and it has probably saved innumerable lives. However, it also has a propensity to spread easily through the biosphere and can persist for long time periods in flora, fauna and in the environment. DDT's environmental legacy has had deleterious effects; some of them, egregious when used irresponsibly. It inhibits plant growth, reduces bird populations, is toxic to other animals, and contributes to human diseases. The environmental fallout due to its injudicious use has raised public concern with emerging and continuing consequences such as being banned for agricultural use. However, DDT still plays a significant role in malaria control in malaria infested tropical and sub-tropical countries. DDT's impact on the environment and on public health could be mitigated by formulating policies that limit its spillage into the environment, by formulating it into safer products that minimize environmental impact, by researching DDT alternatives and by using non-pesticidal interventions including genetic engineering, for vector control. Scientists should also research therapeutic approaches that can limit or reverse the toxic physiological effects of DDT. Equally important, various programs and strategies should be developed to raise the awareness of the dangers of inappropriate DDT use, to advocate for proper use under safe regulations thereby reducing its potential negative impact, and to find safer alternatives. By increasing awareness and developing more environmentally friendly formulations or alternatives that are as effective as DDT, we can either phase out this pesticide or continue to use it in significantly safer ways.

Keywords

Pesticide, DDT, Toxicity, Malaria, Environmental safety, Malaria vaccine, Malaria transmission

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Introduction

DDT: A Powerful Pesticide

Dichloro-diphenyl-trichloroethane (DDT) is an organic compound (Figure 1) that was widely used as a pesticide decades ago. DDT is not produced in nature; instead, it is a man-made chemical that is colorless, tasteless, and almost odorless (1). DDT is synthesized by reacting chloral and chlorobenzene along with an acidic catalyst such as sulfuric acid. DDT can degrade into dichloro-diphenyl-dichloroethylene (DDE) and dichloro-diphenyl-dichloroethane (DDD), both of which have similar pesticidal properties as DDT.

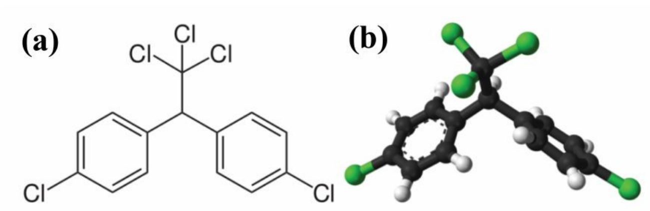

Figure 1. (a) Chemical structure and (b) ball-and-stick model of DDT (https://en.wikipedia.org/wiki/DDT).

DDT was chemically produced in 1874 by the Austrian chemist Othmar Zeidlerbut. A Swiss scientist, Paul H. Müller reported its pesticidal properties in 1939. DDT has primarily been used either as a pesticide or for malaria control. Following the discovery of its pesticidal properties, DDT was first applied to control malaria and typhus during World War II. DDT was soon widely applied as a powerful pesticide worldwide on many crops, plants, and even food to protect them from insects, because it was inexpensive, chemically stable, and highly toxic to insects. Large scale production commenced in 1943, and it was widely used for insect and vector control. In 1948, the Nobel Prize was awarded to Paul H. Müller for his contribution in discovering DDT's pesticidal properties. In 1955, the World Health Organization (WHO) established the first program to eliminate malaria mainly using DDT. DDT became one of the most widely used pesticides worldwide during the period from 1940 through 1970 (2). In the US, DDT started to have wide agricultural (applied to cotton, peanut, and soybean crops) and commercial use after 1945, and about 80 million pounds of DDT was used in 1959 alone. Worldwide, approximately 400,000 tons of DTT were applied each year during the 1960s. There is no doubt that DDT may have saved countless lives (3).

With its increasing use, more attention was generated toward DDT's toxic effects to animals. In 1962, Rachel Carson from the U.S. published a book titled "Silent Spring" (4) and raised awareness of the dual roles (i.e., the good and the bad) of pesticides like DDT and the need for better pesticide controls. Governments and various international organizations have since established restrictions on the use of DTT, and many countries have banned it. The Stockholm Convention treaty, established in 2001 with the help and support from the United Nations Environment Program, called for a global ban of persistent organic pollutants including DDT. This treaty though allows the use of DDT to control malaria, a mosquito-transmitted disease that still kills millions of humans worldwide. Meanwhile, the WHO is also supportive for DDT indoor use in places (especially those countries in Africa) where malaria is still a major health concern. Therefore, DDT is currently used in certain tropical and subtropical areas.

Harmful effects of DDT on the environment, animal, and human health

DDT is chemically stable, and its persistence, which contributed to its early popularity, is the basis for public concerns over its dangers to the environment including to plants, animals, and humans. DDT and its degraded products can persist from months to decades in the environment and in animal/human tissues. DDT has multiple possible travel routes to spread throughout the biosphere (Figure 2). DDT is insoluble in water, a necessary material for plants and animals, and can persist in water. DDT can travel through the water cycle (snow, rain, hail), and can also travel far away with ease in rivers and seas, and be passed on to animals and humans when they drink such contaminated water. When contaminated water evaporates, DDT can travel all over the world. It is also rich in contaminated soil and can be taken up by plants. DDT may persist within plants and animals (including humans) and may be passed on to other plants or animals within their food chains. People and animals travel from one place to another, and food, plants, etc. are transported worldwide. This travel and transportation may also spread DDT from one place to another. As a result, the historically broad use of DDT and its ongoing small scale uses in some countries have left deleterious marks of DDT on the environment including plants, animals, and humans (Table 1), with DDT being found even in remote regions like the Arctic (5-7).

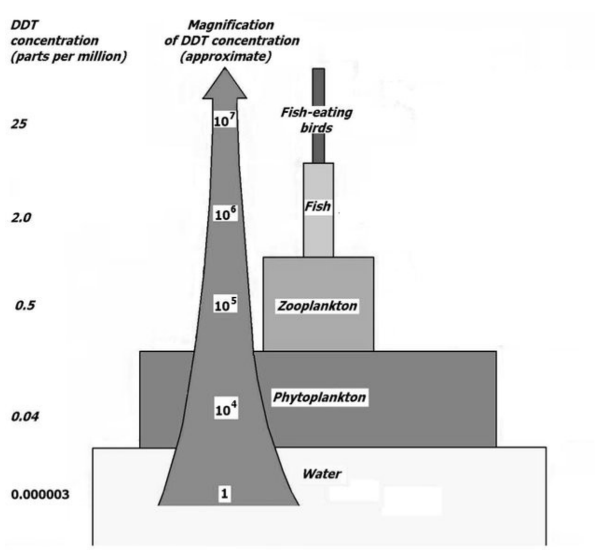

Figure 2: Pathways of DDT exposures to plants, animals, and humans. DDT is sprayed onto crops, plants, water, etc., and may enter the water cycle. Animals eat plants and drink water and are also part of the food chain, and humans eat vegetables and meats and drink water. Image taken from Lushchaka VI et.al., EXCLI Journal 2018;17:1101-1136 – ISSN 1611-2,
DOI: http://dx.doi.org/10.17179/excli2018-1710

	Phenomenon	Mechanism
Plant	DDT exposures inhibit the growth of plants.	DDT is taken up into the cytoplasm and interferes with cellular metabolism which leads to inhibition of plant growth.
Animal	DDT results in eggshell-thinning phenomenon and decline of bird population.	DDT decreases calcium in eggs and thins eggshells, which are unable to support the weight of incubating birds making it difficult for birds to be fully hatched.
	DDT exposures may lead to tumor formation, pathological complications, and even death in rats.	DDT may result in oxidative stress that could damage cells, proteins, DNA, and contribute to aging, cancer, diabetes, and neurodegenerative diseases.
Human	DDT may play a significant role in cancer, neuropsychological dysfunction, reproductive complications, etc.	DDT is considered a carcinogen, and may contribute to adverse effects in humans likely due to various reasons including those observed in rats as mentioned above.

Table 1: Examples of adverse impact and related mechanisms of DDT exposure on the environment.

DDT is a plant growth inhibitor. Its effect on a variety of species was studied, including peanut, mustard plant, rice, barley, mung bean, pigeon pea, and cotton. The amount of DDT taken up by the seeds depended on the size of the seed (8). The experiments indicated that the lipids of the plant solubilized and distributed DDT within the cytoplasm, and interfered with metabolism within the cell therefore inhibiting the growth of plants. DDT exposure resulted in more inhibition of the growth of peanuts and mustard plants compared to the other species studied (8).

DDT exposure also results in a significant impact on animals. For instance, the use of pesticides like DDT is believed to be linked to colony collapse disorder (9-11), where worker bees abandon their honeybee hives. In her book, Rachel Carson described the mass loss of honey bees due to DDT being used for gypsy moth control (4). DDT exposure can also decrease the amount of calcium in eggs, making it hard for birds to be fully hatched. This eggshell-thinning phenomenon (12,13) was observed in fish-eating birds, and the decline in this bird population was linked to DDT (14). To initiate the eggshell-thinning phenomenon, only 100 ppm of DDT is believed to be sufficient. The toxicity of DDT was also linked to marine mammals. Elevated levels of DDT found in beluga whales were believed to contribute to the documented immunosuppression, reproductive impairment and lesions (15). Moreover, scientists have conducted experiments with DDT to see what happens if an animal is exposed to DDT. Feeding rats with 350 ppm (parts per million) DDT results in tumors, pathological complications in the liver, and subsequent death (16). Histological alterations of kidney tissues have revealed that DDT exposure may lead to oxidative stress which could damage cells, proteins, DNA, and could contribute to aging, cancer, diabetes, and neurodegenerative diseases. Compared to controls without DDT exposure, the proliferation of cells in rats that were treated with DDT was significantly higher within the first few days. It was hypothesized that DDT exposure might enable certain cells like precancerous cells to grow faster. It has been proven that, by activating the constitutive androstane receptor, DDT produces microsomal enzymes and inhibits the gap junctional intercellular communication (16). Moreover, DDT prevents sodium ion channels from closing, inhibits potassium gates from opening, and targets a specific neuronal adenosine triphosphatase (ATPase) (17). Experiments have demonstrated the ability of DDT in limiting the transport of calcium ions, without which the body's neurotransmitter release rate decreases causing an impairment in transmitting signals across the chemical synapse. It has also been shown that DDT may impact the reproductive system through influencing the estrogenic or androgenic systems.

Exposure to DDT may also lead to adverse effects in humans. DDT is currently categorized as a carcinogen, a chemical that can induce cancer, by the International Agency for Research on Cancer. DDT exposure may have contributed to autism, cancer, reproductive complications and obesity in exposed populations (18-29). For instance, it has been recently reported that the development of autism, a complex neurodevelopmental disorder (30) that is prevalent in children and has dramatically increased in recent years (31), was associated with DDT exposure (32-36). Children exposed to persistent organic pollutants including DDT during prenatal or postnatal periods were found to be more likely to present signature traits of autism and also to exhibit higher body burden of such chemicals or their metabolites (32). Unfortunately, comprehensive evidence linking DDT exposure to autism or other diseases in humans is lacking or does not exist, there is limited evidence to accurately predict its risk to humans, and further research is warranted.

Discussion

How can the impact of DDT be reduced?

Clearly, DDT exposure is an environmental problem. Some solutions to reduce DDT toxicity toward animals and to limit its toxic effects to the environment, to develop and use safer alternatives, or otherwise to decrease or even eliminate the use of this chemical, as summarized in Table 2.

Strategies
• Decrease or even eliminate the use of DDT
• Use chemicals for malaria control that are less harmful (compared to DDT) to the environment
• Develop non-pesticidal interventions such as environmental management and personal protection for vector control
• Potentially apply biotechnology-based alternatives like genetically engineered mosquitoes to reduce wild-type female mosquito populations
• Encourage healthy choices of food with less fat intake
• Research therapeutic medicines that can neutralize or reduce the toxic effects of DDT exposure

Table 2: Approaches to reduce the use and effects of DDT.

One approach is to develop new chemicals for malaria control that may have less harmful impact on the environment compared to DDT. By identifying such chemicals, we can reduce the use of DDT and its effects on the environment.

Non-pesticidal interventions should be pursued through the development of environmentally-based strategies (environmental management and personal protection) as alternative methods to the use of DDT in vector control. The major strategies may include the modification of environments, interrupting the mosquito life-cycle, and applying physical approaches such as traps to eliminate adult mosquitoes at a large scale. For instance, many countries including the US have successfully applied the environmental modification approach on a large scale to render the environment (land, water, vegetation) unfavorable as a vector habitat. Note that there are biotechnology-based alternatives as well. For instance, mosquitoes have been genetically engineered and commercialized to reduce the population of female mosquitoes which spread vector-borne diseases among humans (37). Oxitec engineered mosquitoes have been field tested in multiple countries including Brazil, Panama, Malaysia, and the USA to control mosquito populations. Manipulation of genes using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) can be used to delete selected genes in mosquitoes so as to make them resistant to the plasmodium parasite. CRISPR can also be used to modify the mosquito sex-determining gene making the male gene dominant. As an new alternative to pesticides like DDT, these genetically engineered mosquitoes could be a unique way to control all kinds of insect populations, regardless of resistance. However, such new technologies are not without concerns - residents are concerned about being bitten by such genetically engineered mosquitoes and it is uncertain if such engineered mosquitoes may disrupt the ecosystem.

For most people in the world, the major exposure route to DDT is *via* food. Although it seems that we cannot completely avoid consuming food that contains traces of DDT, there are choices that can help reduce potential exposure. DDT and its degradation products are lipid-soluble and mostly accumulate in fatty tissues. They are more likely to be found in fat-containing foods like meat, fish, milk, cheese, and oil, than in fruits, vegetables, and grains. Therefore, diets containing more soy products, curcumin, and cruciferous vegetables, and that are lower in fat could be beneficial in reducing the intake of DDT (38). By consuming fewer animal fats, we can reduce the exposure to DDT in the diet. Commercial fish like bluefish, Atlantic salmon, and wild striped bass may have higher levels of DDT and other pesticides, hence trimming the fat while preparing the fish for cooking may reduce exposure.

It is also possible that we may be able to develop therapeutic strategies or vaccines to mitigate the toxic effects of DDT exposure. For instance, it may be possible to treat DDT exposed animals or patients with drugs that can restore the proper closing of sodium ion channels or opening of the potassium gates thereby reversing the effects of DDT exposure and returning the animals or patients to their normal state. Based on the finding that DDT resistant mosquitos were more efficient in metabolizing DDT compared to susceptible ones due to the L119F mutation (39), scientists may develop future medicines that can break down DDT efficiently inside humans into harmless metabolites thereby reducing its unwanted health effects. WHO approved the world's first malaria vaccine, Mosquirix® , among children in sub-Saharan Africa and in other regions with moderate to high *Plasmodium Falciparum* malaria transmission.

Gaps in current knowledge and understanding of DDT

There is no doubt that great success in managing Malaria, a life-threatening mosquito-borne infectious disease that has threatened human lives for thousands of years, has been achieved by vector control. Meanwhile, malaria still poses a threat to almost half of the world's human population. In 2018, there were more than 228 million malaria cases and more than 400,000 associated deaths worldwide (40). There are also risks that malaria outbreaks or a resurgence in malaria-free countries may occur. One of the major tools for malaria control is indoor residual spraying (IRS) of pesticides. DDT is the most effective pesticide for IRS due to its long duration of activity, while its persistence is also the major reason for environmental and health concern. IRS of DDT has been a key component of malaria control in Africa. The benefit of DDT use includes the reduction of malaria cases and associated deaths, and reduction in economic losses from malaria; IRS of DDT can quickly reduce malaria transmission by up to 90%. The risk of DDT use may include inadvertent environmental and health effects and associated costs. The benefit will likely outweigh the risk if DDT is properly and responsibly used for malaria control, especially in countries and areas in Africa with high malaria incidence rates. The majority (>90%) of malaria cases occur in Africa, although malaria is also endemic in Asia, Latin America and Europe (40). In 2006, WHO recommended IRS of DDT as a primary tool for malaria control (41), although it subsequently retreated from this position in a 2019 report (42). Overall, careful assessment of benefit and risk should be carried out for each circumstance, other measurements for vector control should be considered based on scientific evidence, and systems for long-term monitoring of potential adverse DDT effects should be established. Therefore, it is important that the use of DDT for malaria control and the need for environmental and human health protection should be balanced. DDT causes environmental and health concerns, while its role in controlling malaria in certain countries or areas cannot yet be replaced by any non-pesticidal methods. DDT use in such countries or areas should not be prohibited until safer, effective, and feasible strategies become available.

DDT was very successful in the first several decades when it was first introduced and saved millions of lives, but unfortunately, it ultimately was shelved. Most people might consider that its loss of support was due to its environmental toxicity, however, a major contributing factor may have been the development of resistance to DDT, which is inimical to its pesticidal activity. Any effort to renew DDT's use or to return DDT to prominence will have to consider new formulations that have reduced or little resistance. Meanwhile, there is little doubt that DDT's wide use resulted in unwanted impact to the environment and human beings (43). However, it is reasonable to hypothesize that reducing the amounts of DDT to be used by developing DDT formulations that have higher pesticidal activitiy may reduce such environmental and human impact. For instance, stabilizing amorphous DDT using polymers may increase its pesticidal efficacy thereby minimizing the DDT dosage required for vector control (44). Also, a polymorphic crystal form of DDT was found to be more active against fruit flies as a solid-state aerosol formulation (45). However, little is known how these new formulations may reduce the potential development of resistance, and this warrants further research in this field.

One major challenge related to DDT use is the development of insect resistance (46), which was largely fueled by widely, unrestricted agricultural use decades ago. The underlying resistance mechanisms are now being identified and studied. Recent genetic, molecular, and structural studies have shown that a single amino acid change L119F played an important role in DDT resistance. This single amino acid change in the glutathione-s-transferase epsilon 2 (GSTe2) gene resulted in high DDT resistance in *Anopheles funestus*, the major African malaria vector (39). Fortunately, researchers have shown that there are ways to manage resistance development. For instance, the rapid killing of insects (Figure 3) was achieved by manipulating an old contact pesticide (i.e., difluoro congener) and fast killing could slow resistance development (47). Similarly, it is possible to engineer the solid-state chemistry of other contact pesticides derivatives of DDT to achieve the rapid killing of malaria-carrying insects and to reduce insect resistance development.

In addition to its pesticidal properties, DDT is also able to repel mosquitoes, and showed a significant reduction of mosquitoes around DDT sprayed spaces by creating an atmosphere that is inimical to mosquitoes that transmit disease (48-50). Such mosquito-repellent properties have been argued as an alternative way to use DDT for malaria control since this may enable DDT to stay effective for disease control even if vector resistance develops.

It is noteworthy mentioning that there were contrarian views on whether the scientific information about DDT was misused to influence public policy. As an example, Roberts et. al. suggested that the United Nations (UN) agencies were deliberately and incorrectly interpreting malaria control data to demonize DDT (51). A recent critical review paper seemed to offer a convincing argument that DDT product manufacturers deliberately misinterpreted toxicology studies so as to oppose DDT environmental regulations (52).

Raising awareness of proper DDT use and its potential dangers?

Not everyone knows what DDT is, what the regulations of DDT uses are, and the harmful side effects it may cause. In order to ultimately reduce the impact of DDT on animals and human beings, it is necessary to widely disseminate information on the proper methods to use DDT, the availability of safer alternatives or measures, and the problems that the improper use of DDT can cause.

To raise awareness, a variety of strategies can be developed. We can establish programs to advocate for research and development in new, safer DDT formulations and alternatives, to educate the public about the potential toxic impact of DDT exposure on the environment including on plants, animals, and humans, to increase public knowledge about this chemical and encourage smart choices of food with less fat. For people living in countries where DDT is currently in use, they should know the proper procedure to apply DDT indoors, and the available alternatives including environmentally-based strategies for vector control.

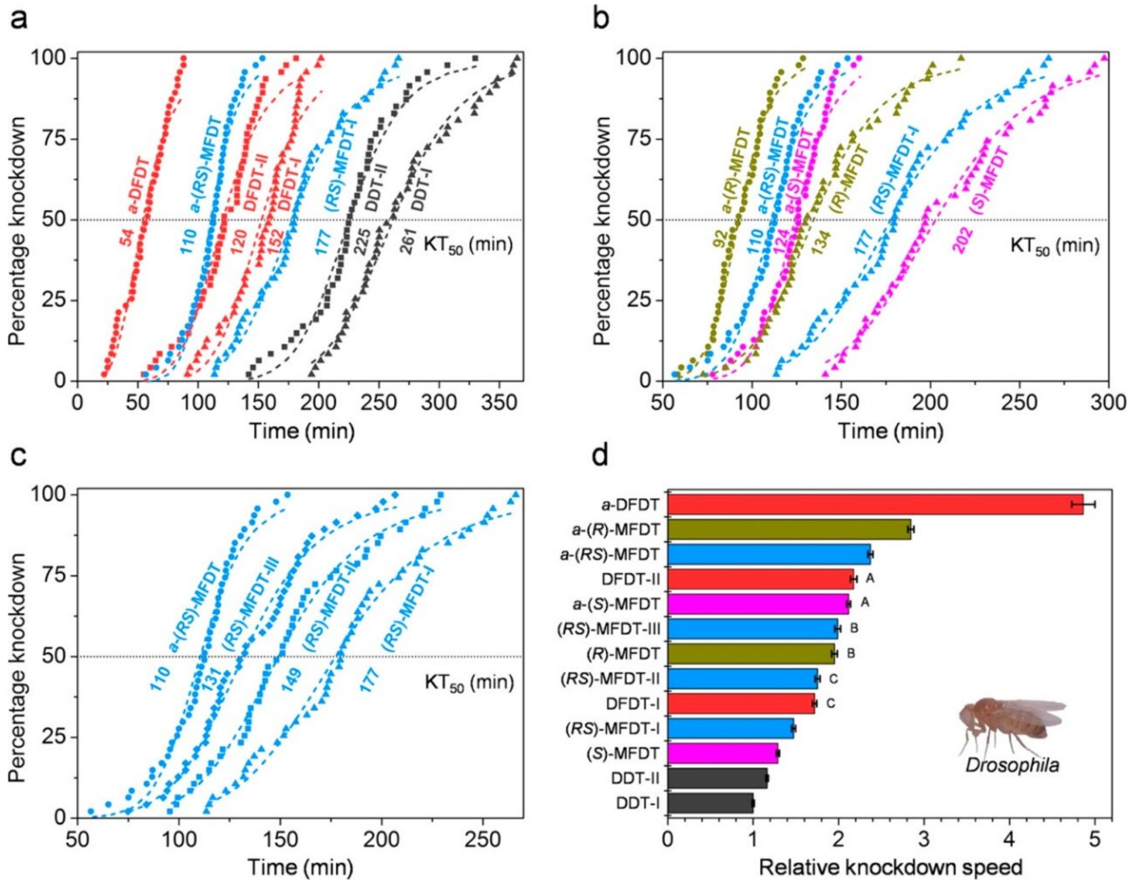

Figure 3: Lethalities of solid-state forms of three contact pesticides of (1,1,1-trichloro-2,2-bis(4-fluorophenyl)ethane or DFDT, (1,1,1-trichloro-2,2-(4-chlorophenyl)-(4-fluorophenyl)-ethane or MFDT, and DDT for Drosophila melanogaster. (a–c) Each symbol corresponds to one female. Dashed lines indicate logistic regression of knockdown-time curves. The median knockdown time for each curve is denoted by its intersection with the horizontal KT50 (median knockdown time) marker. (d) Comparison of the knockdown speeds (1/KT50) relative to DDT I. Error bars represent 95% confidence intervals (CI). Values with the same letter have overlapping 95% CIs, and differences are considered insignificant. Inset: Photo of a typical female fly. Reprinted (adapted) with permission from reference 47. Copyright 2019 American Chemical Society.

We should also raise the awareness of environmentally-based strategies and programs that may introduce other chemicals that may kill pests but cause less harm to the environment, so that people will have choices when considering pesticides. We can publicize all of these DDT-related programs and related information on many social media apps such as Twitter, Facebook, Instagram, Snapchat, etc. Through these programs, we should not only let people worldwide know more about DDT proper use and safer formulations or alternatives, but also the dangers of DDT to the environment and ways, as described above, to reduce potential exposure to DDT and other pesticides.

Conclusion

The use of DDT for malaria control has saved millions of lives, and it is still important in countries and in areas where malaria is a primary health challenge. DDT has proven itself to be the most powerful pesticide that played a critical role in malaria management in the past decades, while at the same time, its persistence has left unforgettable marks on the environment. DDT is toxic and can cause harm to humans, animals, and plants. DDT can persist for long periods of time in water, soil, animals and plants. The publication of the book, Silent Spring, was the beginning of the debates - some controversial - of the benefits and risks of DDT use. As the risk of outbreaks or resurgence of infectious diseases like malaria still exist, the use of pesticides like DDT may not be entirely avoidable. Safer DDT formulations and environment-friendly alternatives should be developed, innovative therapeutics such as vaccines, and ways to control the vector such as by genetic engineering, may be explored, and the public should be educated in proper ways to use DDT so as to reduce its environmental impact.

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