DDT as anti-malaria tool: the bull in the China shop or the elephant in the room?

Chapter 12

DDT as Anti-Malaria Tool: The Bull in the China Shop or the Elephant in the Room?

Mauro Prato, Manuela Polimeni and Giuliana Giribaldi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53241

1. Introduction

Malaria is a parasitic disease confined mostly to the tropical areas, caused by *Plasmodium* parasites and transmitted by *Anopheles* mosquitoes. In 2010, nearly 655.000 human deaths, mainly of children ≤5 years of age, were registered among more than 200 million cases worldwide of clinical malaria; the vast majority of cases occurred in the African Region (81%) and South-East Asia (13%), and 91% of them were due to *P. falciparum*, the most virulent among *Plasmodia* strains (WHO, 2011a).

In order to achieve malaria eradication, an ambitious objective which has been prosecuted since 2007 by the Bill and Melinda Gates Foundation, the World Health Organization (WHO) and the Roll Back Malaria association, several strategies are currently adopted, and a major role is played by vector control (Roberts & Enserink, 2007; Greenwood, 2008; Khadjavi et al., 2010; Prato et al., 2012). Dichlorodiphenyltrichloroethane (DDT), one of the insecticides recommended by the WHO for indoor residual spraying or treated bednets approaches against *Anopheles* mosquitoes, is currently used by approximately fourteen countries, and several others are planning to reintroduce it as a main anti-vector tool; however, it strongly polarizes the opinion of scientists, who line up on the field as opponents, centrists or supporters, highlighting DDT health benefits or putative risks depending on their alignment (Bouwman et al., 2011). In this context, the present chapter will review the current knowledge on DDT use, and will suggest some possible future directions to be taken for malaria vector control.

The chapter will open on a short illustration of the *Plasmodium* life cycle, which occurs either in mosquito vector (sexual reproduction) or in human host (asexual replication). Since anti-vector control measures are directed to mosquito killing, *Plasmodium* sexual cycle will be prioritized. Therefore, the insecticides currently allowed for malaria vector control, including organochlorines (OCs), organophosphates (OPs), carbamates (Cs), and pyrethroids (PYs), will be briefly described. After such a brief introduction, a special attention will be paid to DDT. Formulation, cost-effectiveness, mechanisms of action, resistance and environmental issues will be discussed. The big debate among pro-DDT, DDT-centrist, or anti-DDT scientists will be examined. In this context, the state-of-the-art of knowledge on DDT toxicity will be analyzed, and few tips on possible alternatives to DDT will be given.

Taken altogether, these notions should help the reader to arise his own opinion on such a hot topic, in order to feed the ongoing debate. In areas endemic for malaria, is DDT dangerous as the bull in a China shop? Or perhaps is it worth using DDT, since its advantages related to malaria prevention are self-evident as the elephant in the room? Any answers aimed at finding the most practicable way to fight malaria through vector control are urgently required.

2. Materials and methods

All data were obtained from literature searches, by using the search engines Scopus and Pubmed. Because of the complexity of the subject, only the most relevant studies were selected, and reviews were prioritized. Old literature was accessed electronically, or hard copies were obtained from libraries. Information on human exposure and health effects was based on reviews published over the past ten years and supplemented with recent studies on exposure due to indoor spraying and treated bednets.

3. *Plasmodium* life cycle

Malaria parasites have evolved a complicated life cycle alternating between human and *Anopheles* mosquito hosts, as represented in Figure 1. Five *Plasmodium* strains (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*) can affect humans in more than 90 countries, inhabited by 40% of the global population. In some of these areas, over 70% of residents are continuously infected by the most deadly form of the parasite, *P. falciparum*. Surviving children develop various levels of natural immunity; however, it does not protect them from repeated infections and illness throughout life.

3.1. *Plasmodium* life cycle in *Anopheles* mosquitoes

Plasmodium is transmitted to humans by female mosquitoes of *Anopheles* species. There are approximately 484 recognised species, and over 100 can transmit human malaria; however, only 30–40 commonly transmit *Plasmodium* parasites in endemic areas. *Anopheles gambiae* is one of the best known malaria vectors that lives in areas near human habitation (Rogier &

http://dx.doi.org/10.5772/53241

Hommel, 2011). The intensity of malaria parasite transmission varies geographically according to vector species of *Anopheles* mosquitoes. Risk is measured in terms of exposure to infective mosquitoes, with the heaviest annual transmission intensity ranging from 200 to >1000 infective bites per person. Interruption of transmission is technically difficult in many parts of the world because of limitations in approaches and tools for malaria control. In addition to ecological and behavioral parameters affecting vectorial capacity, *Anopheles* species also vary in their innate ability to support malaria parasite development. Environmental conditions such as temperature in mosquito microhabitats serve to regulate both the probability and timing of sporogonic development (Rogier & Hommel, 2011).

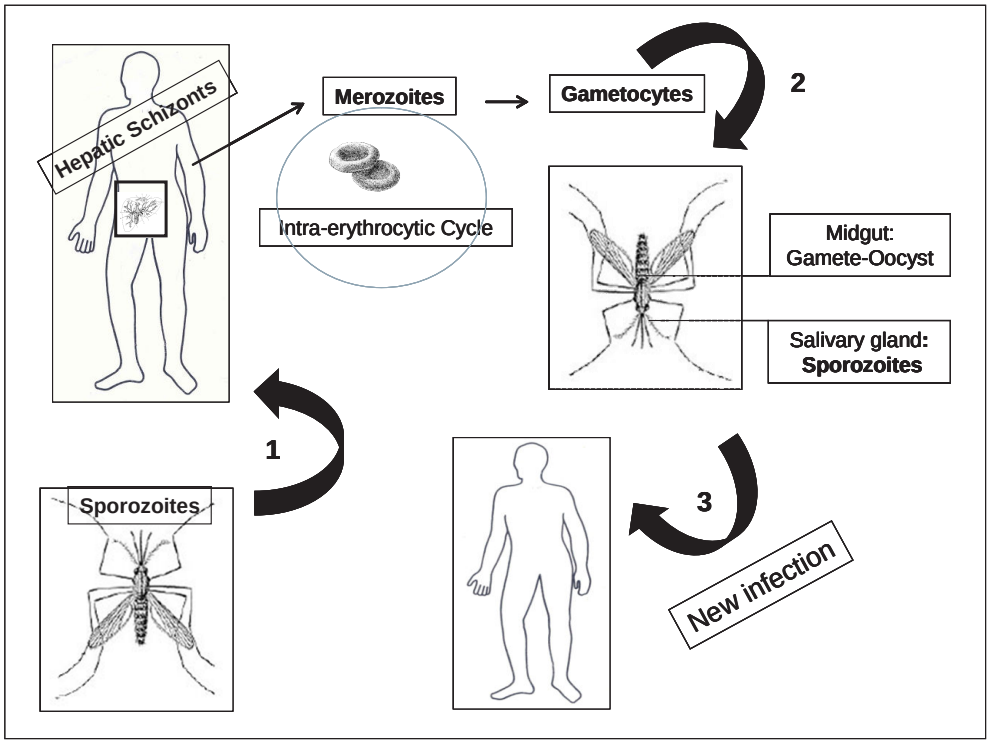

Figure 1. *Plasmodium* parasite life cycle.

In the mosquito, three phases of life of the parasite involve developmental transitions between gametocyte and ookinete stages, between ookinetes and mature oocysts, and between oocysts and sporozoites. When a female Anopheles sucks the blood of a malaria patient, the gametocytes also enter along with blood. They reach the stomach, and gamete formation takes place (Aly et al., 2009). Two types of gametes are formed: the microgametocytes (male) originate active microgametes, and the megagametocyte (female) undergoes some reorganization forming megagametes. Fertilization of the female gamete by the male gamete occurs

rapidly after gametogenesis. The fertilization event produces a zygote that remains inactive for some time and then elongates into a worm-like ookinete. The ookinete is one of the most important stages of *Plasmodium* development in the mosquito. It is morphologically and biochemically distinct from the earlier sexual stages (gametocytes and zygote), and from the later stages (oocyst and sporozoites). Development to ookinete allows the parasite to escape from the tightly packed blood bolus, to cross the sturdy peritrophic matrix, to be protected from the digestive environment of the midgut lumen, and to invade the gut epithelium. The success of each of these activities may depend on the degree of the biochemical and physical barriers in the mosquito (such as density of blood bolus, thickness of peritrophic matrix, proteolytic activities in the gut lumen etc.) and the ability of the ookinete to overcome these barriers. Ookinete motility, resistance to the digestive enzymes, and recognition/invasion of the midgut epithelium may play crucial roles in the transformation to oocyst. At the end of the process oocysts produce sporozoites, which can navigate successfully to the salivary glands, where they will be ready for further infection of human beings, and continuation of their life cycle (Beier, 1998).

3.2. *Plasmodium* life cycle in humans

The transmission of the parasite to humans starts when the mosquito injects a small amount of saliva containing 5-200 sporozoites (resident in the salivary gland of the vector) into the skin of the human vector (Menard, 2005). Once in the bloodstream, sporozoites reach the liver and infect the hepatocytes (Trieu et al., 2006). In the liver district, sporozoites grow and change into a new structure of parasite called schizont, a large round cell. The schizont divides through an asexual reproduction (schizogony) resulting in the formation of a thousand small cells called merozoites. After a developmental period in liver, during which patients do not show any clinical symptoms of disease, merozoites are released from liver schizonts into the blood, entering host erythrocytes and starting the intraerythrocytic stage of parasite development (Banting et al., 1995).

This occurs inside a parasitophorous vacuole, the membrane of which separates the cytosol of the erythrocyte from the plasma membrane of the parasite. In the erythrocyte young 'ring' forms of the parasite grow to become trophozoites. lntraerythrocytic development is completed by the formation of new plasma membranes after multiple nuclear divisions (schizogony). Infectious merozoites are then released from the erythrocyte and a new cycle restart (Cowman & Crabb, 2006). One erythrocytic cycle is completed in 48 hours. The toxins are liberated into the blood along with merozoites. The toxins are then deposits in the liver, spleen and under the skin. The accumulated toxins cause malaria fever that lasts for 6 to 10 hours and then it comes again after every 48 hours with the liberation of new generated merozoites. During the erythrocytic stage, some merozoites increase in size to form two types of gametocytes, the macrogametocytes (female) and microgametocytes (male). This process is called gametocytogenesis. The specific causes underlying this sexual differentiation are largely unknown. These gametocytes take roughly 8–10 days to reach full maturity. The gametocytes develop only in the appropriate species of mosquito. If this does not happen, they degenerate and die (Rogier & Hommel, 2011).

http://dx.doi.org/10.5772/53241

4. Vector control as a key strategical approach for malaria eradication

The historical successful elimination of malaria in various parts of the world has been achieved mainly by vector control (Harrison, 1978). Since early nineteenth century (Breman, 2001), vector control has remained the most generally effective measure to prevent malaria transmission and therefore is one of the four basic technical elements of the Global Malaria Control Strategy. The principal objective of vector control is the reduction of malaria morbidity and mortality by reducing the levels of transmission. Vector control methods vary considerably in their applicability, cost and sustainability of their results.

4.1. Classification of insecticides used for vector control

The most prominent classes of insecticides act by poisoning the nervous system of insects, which is very similar to that of mammals. They are often subclassified by chemical type as organochlorines (OCs), organophosphates (OPs), carbamates (Cs) and pyrethroids (PYs) (Prato et al., 2012).

OCs belong to a larger class of compounds called chlorinated hydrocarbons, containing chlorine and including DDT. They have various chemical structures, and are cheap and effective against target species. OCs can alter and disrupt the movement of ions (calcium, chloride, sodium and potassium) into and out of nerve cells, but they may also affect the nervous system in other ways depending on their structure. OCs are very stable, slow to degrade in the environment and soluble in fats: unfortunately, due to persistence and fat solubility, OCs can bioaccumulate in the fat of large animals and humans by passing up the food chain.

OPs were developed in the 1940s as highly toxic biological warfare agents (nerve gases). On the other hand, Cs feature the carbamate ester functional group. OPs and Cs are very different at a chemical level; however, they have a similar mechanism of action. OPs and Cs block a specific enzyme, the acetylcholinesterase, which is able to remove an important neurotransmitter, the acetylcholine, from the area around the nerve cells stopping their communication. Hence, these insecticides are called acetylcholinesterase inhibitors. Structural differences between the various OPs and Cs affect the efficiency and degree of acetylcholinesterase blockage, highly efficient and permanent for nerve gases, temporary for commonly used pesticides. Many different OPs have been developed in order to replace DDT and find compounds that would be less toxic to mammals. Unfortunately, OP Parathion acute toxicity is greater than DDT, and this characteristic causes a significant number of human deaths.

Finally, synthetic PYs, developed in the 1980s, represent one of the newer classes of insecticides. Although their chemical structure is quite different from that of other insecticides, the target of action is also the nervous system. PYs affect the movement of sodium ions (Na^+) into and out of nerve cells that become hypersensitive to neurotransmitters.

4.2. Indoor Residual Spraying (IRS) and Insecticide-Treated Nets (ITNs)

Indoor residual spraying (IRS) with insecticides continues to be the mainstay for malaria control and represents the process of spraying stable formulations of insecticides on the inside walls of certain types of dwellings, those with walls made from porous materials such as mud or wood but not plaster as in city dwellings. Mosquitoes are killed or repelled by the spray, preventing the transmission of the disease. The main purpose of IRS is to reduce malaria transmission by reducing the survival of malaria vectors, life span of female mosquitoes, thereby reducing density of mosquitoes (WHO, 2006b). Several pesticides have historically been used for IRS, the first and most well-known being DDT.

Space spraying, or fogging, relies on the production of a large number of small insecticidal droplets, that resemble smoke or fog by rapidly heating the liquid chemical, intended to be distributed through a volume of air over a given period of time. When these droplets impact on a target insect, they deliver a lethal dose of insecticide. It is primarily reserved for application during emergency situations to rapidly reduce the population of flying insects in a specific area resulting in decrease of transmission (CDC, 2009). It is effective as a contact poison with no residual effect, thus it must be repeated at intervals of 5-7 days in order to be fully effective. The application must coincide with the peak activity of adult mosquitoes, because resting mosquitoes are often found in areas that are out of reach to the applied insecticides. The best moment to kill adult mosquitoes by fogging is at dusk, when they are most active in forming swarms. The most commonly used products are natural pyrethrum extract, synthetic PYs, and Malathion.

Mosquito nets treated with insecticides—known as insecticide treated nets (ITNs) or bednets—were developed in the 1980s for malaria prevention. Properly used, a mosquito net effectively offers protection against mosquitoes and other insects, and thus against the diseases they may carry. Two categories of ITNs are available: conventionally treated nets and long-lasting ITNs (LLINs). ITNs are estimated to be twice as effective as untreated nets, and offer greater than 70% protection compared with no net. These nets are impregnated with PYs, which will double the protection over a non-treated net by killing and repelling mosquitoes, and are proved to be a cost-effective prevention method against malaria (D'Alessandro et al., 1995). Washing and the associated regular retreatment of the nets determine a rapid loss of efficacy of ITNs, thus limiting the operational effectiveness of an ITN program (Lines, 1996).

Biological activity of LLINs, a relatively new technology, generally retains the efficacy for at least 3 years (WHO, 2005), and can reduce human–mosquito contact, which results in lower sporozoite and parasite rates. Different types of long-lasting insecticide impregnated materials are under field trials in different countries. Treatments of screens, curtains, canvas tents, plastic sheet, tarpaulin, etc., with insecticides may provide a cheap and practical solution for malaria vector control. Particularly, the residual insecticides in insecticide-treated wall lining (ITWL) are durable and can maintain control of insects significantly longer than IRS by providing an effective alternative or additional vector control tool (Munga et al., 2009).

http://dx.doi.org/10.5772/53241

5. Dichlorodiphenyltrichloroethane (DDT)

DDT is an OC insecticide; it is white, crystalline solid, tasteless, and almost odorless (PAN, 2012). It is a highly hydrophobic molecule, nearly insoluble in water but with good solubility in most organic solvents, such as fats and oils. DDT is not present naturally, but is produced by the reaction of chloral (CCl_3CHO) with chlorobenzene (C_6H_5Cl) in the presence of sulfuric acid, which acts as a catalyst. DDT was originally synthesised in 1874, but its action as an insecticide was not discovered until 1939. It was the first widely used synthetic pesticide, employed extensively by allied forces during the Second World War for the protection of military personnel from malaria and typhus, released commercially only in 1945. The Swiss chemist Paul Hermann Müller was awarded the Nobel Prize in Physiology or Medicine in 1948 for his discovery of the high efficiency of DDT as a contact poison against several arthropods.

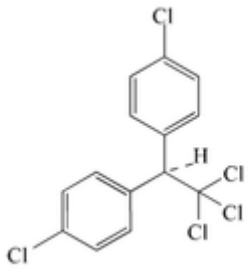

Figure 2. DDT

5.1. Production and use

While the post-war period also saw the introduction of most of the other major families of insecticides still in use today, DDT remained the most extensively used insecticide throughout the world until the mid 1960s. By this time, it had been credited with a number of significant public health successes, including the eradication of malaria from the United States and Europe (Attaran & Maharaj, 2000). DDT is currently being produced in three countries: India, China, and the Democratic People's Republic of Korea (North Korea). By far the largest amounts are produced in India for the purpose of disease vector control. In China, the average annual production during the period 2000–2004 was 4,500 metric tons of DDT, but 80–90% was used in the production of Dicofol, an acaricide, and around 4% was used as additive in antifouling paints. The remainder was meant for malaria control and was exported (PAN, 2012).

5.2. Cost-effectiveness

Both the effectiveness and costs of DDT are dependent on local settings and deserve careful consideration in relation to alternative products or methods (Walker, 2000). DDT has been known as the only insecticide that can be used as a single application in areas where the malaria transmission season is > 6 months. However, information is lacking on the potential variability in residual action of DDT (e.g., due to sprayable surface, climatic conditions, social factors). Direct costs of IRS are the procurement and transport of insecticide, training of staff, operations, awareness-raising of communities, safety measures, monitoring of efficacy and insecticide resistance, monitoring of adverse effects on health and the environment, and storage and disposal. Apart from the direct costs, it is essential that the unintended costs of DDT to human health and the environment are included in the cost assessment. In addition, contamination of food crops with DDT could negatively affect food export. A comprehensive cost assessment of DDT versus its alternatives should include the potential costs of atmospheric transport and chronic health effects.

5.3. Mechanism of action

The basic mechanism of action for most pesticides is an alteration in the transfer of a signal along a nerve fiber and across the synapse from one nerve to another or from a nerve to a muscle fiber. The transfer of a signal along a nerve occurs by changes in the electrical potential across the nerve cell membrane which is created by the movement of ions in and out of the cell. At the terminal end of a nerve, the signal is transferred across the synapse to the next nerve cell by the release of neurotransmitters. Different classes of pesticides inhibit this process in different ways, but the end result is an alteration in normal nerve signal propagation. OCs pesticides act primarily by altering the movement of ions across the nerve cell membranes, thus changing the ability of the nerve to fire.

The WHO has designated DDT as a Class II pesticide, based on its LD_{50} of 250 mg/kg (WHO, 1996). The mechanism by which DDT causes neurotoxicity is well studied. In insects DTT opens sodium ion channels in neurons, causing them to burn spontaneously. By causing repetitive firing of nerve cells, the cells eventually are unable to fire in response to a signal. DDT produces tremors and incoordination at low doses, convulsions at higher doses caused by the repetitive discharge (over-firing) of the nerves. Effects of chronic exposures to DDT are difficult to identify because they are general nervous systems alterations that can occur through many causes (apathy, headache, emotional lability, depression, confusion and irritability).

5.4. Resistance issues

As the number and size of programs that use DDT for indoor spraying increase, insecticide resistance is a matter of growing concern. Insects with certain mutations in their sodium channel gene are resistant to DDT and other similar insecticides. DDT resistance is also conferred by up-regulation of genes expressing cytochrome P450 in some insect species (Denholm et al., 2002).

http://dx.doi.org/10.5772/53241

Many insect species have developed resistance to DDT. The first cases of resistant flies were known to scientists as early as 1947, although this was not widely reported at the time (Metcalf, 1989). Since the introduction of DDT for mosquito control, DDT resistance at various levels has been reported from > 50 species of anopheline mosquitoes, including many vectors of malaria (Hemingway & Ranson, 2000). Unless due attention is paid to the role of insecticide resistance in the breakdown of the malaria eradication campaign of the 1960s, resistance may once again undermine malaria control.

In the past, the use of DDT in agriculture was considered a major cause of DDT resistance in malaria vectors, as many vectors breed in agricultural environments. By 1984 a world survey showed that 233 species, mostly insects, were resistant to DDT (Metcalf, 1989). Today, with cross resistance to several insecticides, it is difficult to obtain accurate figures on the situation regarding the number of pest species resistant to DDT. At present, DDT resistance is thought to be triggered further by the use of synthetic PYs (Diabate et al., 2002). This is due to a mechanism of cross-resistance between PYs and DDT, the so-called sodium channel mutation affecting neuronal signal transmission, which is governed by the *kdr* (knock-down resistance) gene (Martinez-Torres et al., 1998). The *kdr* gene is being reported from an increasing number of countries; thus, even in countries without a history of DDT use, resistance to DDT is emerging in populations of malaria vectors (WHO, 2006a). Contemporary data from sentinel sites in Africa indicate that the occurrence of resistance to DDT is widespread, especially in West and Central Africa. In Asia, the resistance to DDT is particularly widespread in India.

5.5. Environmental issues

Part of the success of DDT can be attributed to its persistence in the environment, thus reducing the need for frequent application. DDT is one of nine persistent organic pollutants (POPs) which bioaccumulate and are transported by air and water currents from warmer climates to temperate zones, where they have never been used. DDT has low to very low rates of metabolism and disposition, depending on ambient temperatures: the process of degradation is dramatically slowed down in cooler climates. It is degraded slowly into its main metabolic products, 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE) and dichlorodiphenyldichloroethane (DDD), which have similar physicochemical properties but differ in biological activity.

DDT is emitted through volatilization and runoff. It is more volatile in warmer than in colder parts of the world, which through long-range atmospheric transport results in a net deposition and thus gradual accumulation at high latitudes and altitudes (Harrad, 2001). Loss through runoff is low because DDT is extremely hydrophobic and has a strong affinity for organic matter in soils and aquatic sediment but is virtually insoluble in water. However, when applied to aquatic ecosystems, DTT is quickly absorbed by organisms and by soil or it evaporates, leaving little amount of DDT dissolved in the water itself (Agency for Toxic Substances and Disease Registry, 2002). Half-lives of DDT have been reported in the range of 3–7 months in tropical soils (Varca & Magallona 1994; Wan-

diga, 2001) and up to 15 years in temperate soils (Ritter et al., 1995). The half-life of each of its metabolic products is similar or longer.

The global risk of adverse effects to human health and the environment has led the international community to mandate the UN Environment Programme (UNEP) to convene an intergovernmental negotiating committee (INC) for a POPs Convention to phase out production and use (UNEP, 1997a; UNEP, 1997b). As a result of these environmental concerns, the use of DDT was increasingly restricted or banned in most developed countries after 1970.

DDT and its metabolic products present in the global environment have originated mostly from its previous large-scale use in agriculture and domestic hygiene. Because DDT is currently allowed only for indoor spraying for disease vector control, its use is much smaller than in the past. Nevertheless, DDT sprayed indoors may end up in the environment (e.g., when mud blocks of abandoned houses are dissolved in the rain). Even today, DDT remains so widespread in the environment that it is likely that exposure to it is unavoidable. While exposure in the industrialised world has fallen dramatically, exposure remains high in some developing countries where DDT continues to be used in vector control.

DDT is very fat-soluble and could therefore be found in fatty foods such as meat and diary products. Even in countries across North America and Northern Europe, where its use has been banned for over a decade DDT residues are still often found in food. This is because of environmental persistence, illegal use, or importation of contaminated food from regions where DDT is still used.

6. The big debate on DDT as anti-malaria tool

In 1955, the WHO commenced a program to eradicate malaria worldwide, relying largely on DDT. The program was initially very successful, eliminating the disease in Taiwan, much of the Caribbean, the Balkans, parts of northern Africa, the northern region of Australia, and a large swath of the South Pacific and dramatically reducing mortality in Sri Lanka and India (Harrison, 1978). However, widespread agricultural use led to resistant insect populations. In many areas, early victories partially or completely reversed, and in some cases rates of transmission even increased (Chapin & Wasserstrom,1981). The program was successful in eliminating malaria only in areas with "high socio-economic status, well-organized health-care systems, and relatively less intensive or seasonal malaria transmission" (Sadasivaiah et al., 2007). In tropical regions, DDT was less effective due to the continuous life cycle of mosquitoes and poor infrastructure. It was not applied at all in sub-Saharan Africa due to these perceived difficulties.

Moreover, the adverse health effects of DDT versus the health gains in terms of malaria prevention require more attention. For example, a gain in infant survival resulting from malaria control could be partly offset by an increase in preterm birth and decreased lactation, both of which are high risk factors for infant mortality in developing countries. The WHO is con-

http://dx.doi.org/10.5772/53241

ducting a re-evaluation of health risks of DDT, but progress has been slow (PAN, 2012). Nevertheless, in 2006 it approved the use of DDT, particularly indoor residual spraying of walls, in areas endemic for malaria for health-related reasons (WHO, 2006a; WHO, 2006b), although it also carefully drew up major guidelines (WHO 2000). Currently, DDT represents one the main stays to achieve goals of Global Eradication Program launched in 2007 by the Bill and Melinda Gates Foundation, the World Health Organization (WHO) and the Roll Back Malaria association (Roberts & Enserink, 2007; Greenwood, 2008; Khadjavi et al., 2010; Prato et al., 2012). However, in the recent years the possible effects of DDT on human health have been a hot topic of discussion inside malaria research community, as certified by the large number of available publications and intense correspondence among scientists (e.g., Blair et al., 2009; Burton, 2009; van den Berg, 2009; Tren & Roberts, 2010; Bouwman et al., 2011; Tren & Roberts, 2011). The debate is heavily polarized, and three main viewpoints can be identified, as suggested by Bouwman et al. (Bouwman et al., 2011): anti-DDT, centrist-DDT, and pro-DDT.

6.1. Anti-DDT point of view

DDT opponents usually claim for DDT elimination because of environmental and health concerns. However, Tren & Roberts (Tren & Roberts, 2011) pointed that the "activist groups currently promote an anti-DDT agenda routinely hyping supposed human health and environmental harm from DDT and ignoring studies that find no association between DDT and such harm". As an example, Tren & Roberts mentioned the Biovision's "Stop DDT" project engaged to achieve a world-wide ban on DDT (Biovision, 2011), which apparently was connected to the Secretariat of the Stockholm Convention's promotion of an arbitrary deadline for cessation of DDT production by 2020 (United Nations Environment Programme, 2007). Another representative example of a recent anti-DDT action is given by a court case occurred in Uganda (Lewis, 2008): a petition filed in Kampala's High Court accused the Ugandan government of not following DDT spraying guidelines, whether those of the WHO or those of Uganda's National Environment Management Authority. In that case, it appears evident that the big matter was not DDT itself as a molecule, but its incorrect use. In this context, a major point questioned by anti-DDT scientists is that also IRS workers are highly exposed to DDT, since prescribed personal protection procedures and safe practices are not always followed, because of uncomfortable working conditions. Not wearing masks or gloves and frequent wiping of sweaty faces with the same cloth increases dermal and inhalation uptake leading to very high exposure (Bowman et al., 2011). Indeed, DDT serum levels in IRS workers in South Africa were high compared with the general population living in DDT-sprayed houses (Bouwman et al., 1991). On the other hand, Bimenya et al. (Bimeneya et al., 2010) did not found any DDT increase in serum of Ugandan DDT applicators over an entire spray season, stating that effective exposure reduction is possible when protective clothing is used and strict adherence to WHO guidelines (WHO, 2000) is observed. Nevertheless, the WHO's review of human health aspects of DDT use in IRS concluded that "for households where IRS is undertaken, there was a wide range of DDT and DDE serum levels between studies. Generally, these levels are below potential levels of concern for populations" (WHO, 2011b), and none of the thousands of studies conducted to find possible human health effects of

DDT satisfied even the most basic epidemiological criteria to prove a cause-and-effect relationship (Tren & Roberts, 2011).

6.2. Centrist-DDT point of view

According to Bouwman et al. (Bouwman et al., 2011), "the centrist-DDT point of view adopts an approach that pragmatically accepts the current need for DDT to combat malaria transmission using indoor residual spraying (IRS) but at the same time recognizes the risks inherent in using a toxic chemical in the immediate residential environment of millions of people". Thus, scientists sharing a centrist-DDT point of view such as Bouwman and colleagues suggest caution in using DDT because of insufficient investigation whether DDT is safe or not; however, they do recognize its undoubted benefits in areas endemic for malaria and its major role as a life-saving tool. In this context, DDT-centrists call for alternative chemicals, products, and strategies, eventually in order to terminate in the future any use of DDT in IRS for malaria control. As it will be discussed in paragraph 6, some vector control methods are already available as alternatives to DDT. Two of these, the use of alternative insecticides in IRS and the use of insecticide-treated bed nets (ITNs), are mainstreamed because of their proven impact on the malaria burden; other alternatives are receiving limited attention to date, but may play an important role in the future (van den Berg, 2009).

6.3. Pro-DDT point of view

DDT supporters consider DDT safe to use in IRS when applied correctly, and promote DDT to be used for IRS in malaria control where it is still effective. In their perspective, in a risk-benefit comparison, the eventual toxic effects of DDT would be far less than those caused by malaria (Africa Fighting Malaria, 2010; Roberts et al., 1997). Apparently, this is the point of view of WHO itself, since it approved in 2006 the use of DDT, particularly indoor residual spraying of walls, in areas endemic for malaria for health-related reasons (WHO, 2006a; WHO, 2006b), although it also carefully drew up major guidelines (WHO 2000). Moreover, several national malaria control programs and ministers of health repeatedly proclaimed the importance of DDT for disease control programs in countries with high incidence of malaria. These include Namibia and the Southern African Development Community (SADC), which recently reasserted that DDT is a major tool for malaria vector control and announced their intention to produce DDT locally (SADC, 2011). Similarly, the 35 heads of state of the countries members of the African Leaders Malaria Alliance (ALMA) recently endorsed use of DDT in indoor residual spraying (IRS) (ALMA 2010). As a matter of fact, as a consequence of the global eradication program recently launched by charity foundations, which invested relevant amounts of money in DDT-based vector control (Roberts & Enserink, 2007; Greenwood, 2008; Khadjavi et al., 2010; Prato et al., 2012), in 2010 World Health Organization (WHO) officially registered - for the first time in the last decade - a decline in estimated malaria cases and deaths, with 655.000 deaths counted among more than 200 million clinical cases worldwide (WHO 2011a).

http://dx.doi.org/10.5772/53241

7. Studies on DDT toxicity

Despite the concerns of DDT opponents (see par. 6.1), to date there is no consistent evidence that DDT or its metabolite DDE can be toxic for humans. Indeed, despite the large number of studies performed in this context, results are highly contradicting, probably due to different analytical conditions and approaches used by different researchers. On the other hand, DDT toxic effects on animals have been demonstrated quite convincingly. This should be taken in account in the context of general environmental issues (par. 5.5) which led to DDT ban in malaria-free countries. In the following sub-sections, current knowledge on DDT effects on animal and human health will be reviewed.

7.1. Animals

Due to its lipophilicity, DDT readily binds with fatty tissue in any living organism, and because of its chemical stability, bioconcentrates and biomagnifies with accumulation of DDT through the food chain, in particular in predatory animals at the top of the ecological pyramid (Jensen et al., 1969). By the mid 1950s, experimental studies on animals have demonstrated chronic effects on the nervous system, liver, kidneys, and immune systems in experimental animals attributable to DDT and DDE (Turusov et al., 2002), and it quickly became apparent that this could extend to the broader environment (Ramade, 1987). However, dose levels at which effects were observed are at very much higher levels than those which may be typically encountered in humans.

DDT is highly toxic to fish. The 96-hour LC50 (the concentration at which 50% of a test population die) ranges from 1.5 mg/litre for the largemouth bass to 56 mg/litre for guppy. Smaller fish are more susceptible than larger ones of the same species. An increase in temperature decreases the toxicity of DDT to fish (PAN, 2012).

DDT and its metabolites can lower the reproductive rate of birds by causing eggshell thinning which leads to egg breakage, causing embryo deaths. Sensitivity to DDT varies considerably according to species. Predatory birds and fish-eating birds at the top of the food chain are the most sensitive. The thickness of eggshells in peregrine falcons was found to have decreased dramatically following the pesticide's introduction (Ratcliffe, 1970), likely due to hormonal effects and changes in calcium metabolism (Peakall, 1969). Colonies of brown pelicans in southern California plummeted from 3000 breeding pairs in 1960 to only 300 pairs and 5 viable chicks in 1969. In the US, the bald eagle nearly became extinct because of environmental exposure to DDT. According to research by the World Wildlife Fund and the US EPA, birds in remote locations can be affected by DDT contamination. Albatross in the Midway islands of the mid-Pacific Ocean show classic signs of exposure to OCs chemicals, including deformed embryos, eggshell thinning and a 3% reduction in nest productivity. Researchers found levels of DDT in adults, chicks and eggs nearly as high as levels found in bald eagles from the North American Great Lakes (PAN, 1996).

7.1.1. Reproductive and teratogenic effects (birth defects)

DDT causes adverse reproductive and teratogenic effects in test animals. In one rat study, oral doses of 7.5 mg/kg/day for 36 weeks resulted in sterility. In rabbits, doses of 1 mg/kg/day administered on gestation days 4-7 resulted in decreased foetal weights. In mice, doses of 1.67 mg/kg/day resulted in decreased embryo implantation and irregularities in the oestrus cycle over 28 weeks (Agency for Toxic Substances and Disease Registry, 1994). Many of these observations may be the result of disruptions to the endocrine (hormonal) system.

In mice, maternal doses of 26 mg/kg/day DDT from gestation through to lactation resulted in impaired learning in maze tests.

7.1.2. Cancer

The evidence relating to DDT and carcinogenicity provides uncertain conclusions. It has increased tumour production, mainly in the liver and lungs, in test animals such as rats, mice and hamsters in some studies, but not in others. In rats, liver tumours were induced in three studies at doses of 12.5 mg/kg/day over periods of 78 weeks to life, and thyroid tumours were induced at doses of 85 mg/kg/day over 78 weeks. Tests have shown laboratory mice were more sensitive to DDT. Life time doses of 0.4 mg/kg/day resulted in lung tumours in the second generation and leukaemia in the third generation, and liver tumours were induced at oral doses of 0.26 mg/kg/day in two separate studies over several generations (PAN, 2012).

7.2. Humans

The US Department of Health and Human Services (DHHS) has determined that "DDT may reasonably be anticipated to be a human carcinogen". DHHS has not classified DDE and DDD, but the US Environmental Protection Agency (EPA) has stated that they are probable human carcinogens (PAN, 2012), suspecting DDT, DDD and DDE of being environmental endocrine disrupters (Colburn et al., 1996) which may affect human health. Based on the results of animal studies, DDT was suspected to cause cancer, diabetes, neurodevelopmental deficits, pregnancy and fertility loss (Beard, 2006). However, available epidemiological studies reject DDT contribution in the development of these diseases and results are still unclear (Beard, 2006).

7.2.1. Reproductive disorders

In vitro studies have shown DDT and its metabolites to have human estrogenic activity (Chen et al., 1997) and DDE to act as an androgen antagonist (Kelce et al., 1995). Some researchers have also hypothesized a trend for decreasing semen quality in the general human community following the introduction of DDT (Carlsen et al., 1992; Sharpe & Skakkebaek, 1993) suggesting that environmental exposure to OCs may be causing human endocrine disruption. However, the observed patterns may simply reflect geographic variations and lifestyle factors (Hauser et al., 2002).

http://dx.doi.org/10.5772/53241

Much of the epidemiologic research about the possible influence of pesticide exposure in general on pregnancy outcome suffers from significant methodological problems. The largest and most rigorous study of DDT and adverse reproductive outcomes was conducted in a US perinatal cohort of over 44,000 children born between 1959 and 1966 (Longnecker et al., 2001). DDE concentration was estimated in stored serum taken during pregnancy from mothers of 2380 children. Increasing concentrations of serum DDE were statistically and significantly related to preterm births, intra-uterine growth retardation (Siddiqui et al., 2003) and maternal diastolic blood pressure (Siddiqui et al., 2002). On the other hand, other studies have failed to find any relationship between maternal DDT exposure and birth weight (Gladen et al., 2003).

Both animal models and early human studies have suggested a link with exposure to the DDT and the most common adverse pregnancy outcome (spontaneous abortion) (Saxena et al., 1980). However, the results of recent research are inconsistent. One small case-control study nested in a longitudinal study of Chinese textile workers found significantly higher levels of DDE in women with spontaneous abortion than full term controls. (Korrick et al., 2001) On the other hand, other studies have been unable to find an association (Gerhard et al., 1998). Unclear findings have been identified about the impact of DDT on fertility (Cohn et al., 2003): the probability of daughters' pregnancy fell with increasing levels of DDT in maternal serum, but it increased with increasing levels of DDE. Finally, OCs appear to transfer freely across the placenta from mother to foetus and could be also excreted in human milk (PAN, 2012).

In the late 1960s, concentrations of DDE in animals and first-trimester human fetal tissues correlated with reproductive abnormalities in male offspring such as hypospadias and undescended testes (Gray et al., 2001). A case-control study nested in a US birth cohort (1959–1966) (Longnecker et al., 2002) showed small increases in crypt-orchidism, hypospadias, and polythelia among boys with the highest DDE maternal serum levels when compared with those with the lowest maternal levels, although none of these were statistically significant. On the other hand, other studies failed to find a significant association between influence of DDT exposure on hormone levels in adult men, or DDT levels and sperm concentration/mobility in male partners of sub-fertile couples (Hauser et al., 2003).

7.2.2. Other endocrine conditions

Bone mineral density, which is regulated by the antagonistic effect of androgens and oestrogens, may be another possible target of endocrine disruption. DDT has been shown to modulate trophoblast calcium handling functions *in vitro* (Derfoul et al., 2003) and two small cross-sectional studies have suggested there may be a weak association between serum DDE levels and reduced bone mineral density (Beard et al., 2000; Glynn et al., 2000). However, a third study failed to demonstrate any correlation (Bohannon et al., 2000).

In vitro studies suggest that DDT and its metabolites do not influence thyroid metabolism (Langer et al., 2003; Rathore et al., 2002). Other research has failed to find a significant association with endometriosis, a hormone dependant pelvic inflammatory disease (Lebel et al., 1998).

7.2.3. Cancer

Breast cancer has been studied most rigorously; even though the majority of results showed no causative association with DDT exposure (Beard et al., 2006), the latest evidence indicates an increased risk in women who were exposed at a young age. It was hypothesised that DDT co-genres and metabolites might act as tumour promoters in hormonally sensitive cancers due to their oestrogenic and anti-androgenic properties (Iscan et al., 2002). More recently, larger and better designed studies have generally not supported this hypothesis (Calle et al., 2002; Snedeker, 2001). Other hormonally sensitive cancers include cancer of the endometrium and prostate. Two case-control studies have explored the possibility that DDT may be related to endometrial cancer with neither finding a significant association (Sturgeon et al., 1998; Weiderpass et al., 2000). On the other hand, an Italian hospital-based multisite case-control study of prostate cancer found an increased risk among farmers exposed to DDT (Settimi et al., 2003), although exposure assessment in this study relied on self-report, leaving these findings susceptible to recall bias. Rates of prostate cancer were also found to be increased among male applicators using chlorinated pesticides in the Agricultural Health Study cohort (Alavanja et al., 2003) and in a Swedish cohort of pesticide applicators (Dich & Wiklund, 1998).

Pesticides have been associated with pancreatic cancer (Beard, 2006). A large Norwegian prospective study of lifestyle factors and pancreatic cancer identified a higher risk among men occupied in farming, agriculture or forestry (Nilsen & Vatten, 2000). Recent research lends a physiological plausibility to a possible association between DDT and pancreatic cancer by suggesting that DDT may modulate oncogene expression or provide a growth advantage to mutated cells, for example, through its actions as an endocrine disrupter (Porta et al., 1999).

Case control studies using self-reported exposure have found significant associations between DDT exposure and lung cancer, leukaemia and non-Hodgkins lymphoma (NHL) (Beard, 2006). However a nested case-control study using stored serum identified a dose response relationship for NHL with PCB exposure but not DDT. A small case-control study using serum levels drawn at diagnosis has suggested an association between DDT exposure and colorectal cancer.

7.2.4. Nervous system

Animal studies have suggested DDT may cause central nervous system (CNS) toxicity (Eriksson & Talts, 2000). Exposure to DDT may be associated with a permanent decline in neurobehavioral functioning and an increase in psychiatric symptoms, but the few studies and limited exposure information made it impossible to be confidant about this potential relationship (Colosio et al., 2003). These findings are also complicated by potential confounding from exposure to other pesticides, such as organophosphates, that are known to have neurological effects. One recent case study suggested that DDT may be related to neurological impairment (Hardell et al., 2002). Another recent study of retired malaria-control workers found various neurobehavioral functions and performance deteriorated significantly with increasing years of DDT application (van Wendel de Joode et al., 2001). Subjects ex-

http://dx.doi.org/10.5772/53241

posed to pesticides including DDT also scored worse than non-exposed subjects on a self-reported neuropsychological questionnaire of surviving members of a historical cohort of pesticide applicators (Beard, 2006).

7.2.5. Immune system

At least one cross-sectional study has associated DDT and other pesticide exposures with suppression or induction of several immune parameters (Daniel et al., 2002).

7.2.6. Diabetes

Diabetes has been associated with OC exposure in at least one study. An Australian cohort study of mortality in staff working as part of an insecticide application program also found increased mortality from pancreatic cancer in DDT-exposed subjects and from diabetes in subjects working with any pesticide (Beard, 2006).

7.3. Epidemiological studies

It is only in the last 25 years that more rigorous epidemiological research has focused on the possible adverse effects of exposure to DDT in humans. Unfortunately, they are not easily answered since epidemiologic research in this field is plagued by methodological challenges (Blondell, 1990). Fewer early human studies have been undertaken specifically on DDT, moreover they were small and limited in scope. A major methodological challenge is the difficulty in getting accurate information on subject exposure since many of the possible adverse effects of DDT (for example, cancer) may not become evident until many years after a causative exposure. Moreover, since it is rare for past exposure to have been accurately recorded at the time, exposure estimation has often been based on the response by subjects to questioning. However, subjects may have been unaware of significant past exposures to DDT through the food chain and even occupationally exposed subjects are unlikely to accurately remember and quantify exposures faced 20–30 years in the past. In the absence of a recorded exposure history, biological sampling of subjects may give some measure of their past exposure. Unlike other pesticides, DDT and DDE are only very slowly eliminated, making biological monitoring a relatively accurate, easy and cheap means of assessing past exposure. Serum levels of DDT and DDE are closely correlated with levels in adipose tissue and thus provide a relatively non-invasive measure (Mussalo-Rauhamaa, 1991). Unfortunately, biological monitoring of DDT presents its own potential for epidemiological bias since levels can also be influenced by factors that relate directly to the outcome of interest, in particular weight change.

Since DDT and its metabolites are so persistent in the environment and human tissues, humans are not excluded from this ecological trends raising questions about the possible impact of widespread pesticide exposure on human communities. Biological sampling near the time of peak use during the 1960s showed increasing DDT levels in most human communities, mainly due to exposure to residues in food. High levels of human exposure to DDT among those living in sprayed houses, most of whom are living under conditions of poverty

and often with high levels of immune impairment, have been found in studies in South Africa and Mexico (Aneck-Hahn et al., 2007; Bouwman et al., 1991; De Jager et al., 2006; Yanez et al., 2002), but contemporary peer-reviewed data from India, the largest consumer of DDT, are lacking. The simultaneous presence of, and possible interaction between, DDT, DDE and PYs in human tissue is another area of concern (Bouwman et al., 2006; Longnecker, 2005). In North America, rather high levels of exposure have been recorded in biological samples collected in the 1960s (Eskenazi et al., 2009). DDT accumulates in fatty tissue and is slowly released. The half-life of DDT in humans is > 4 years; the half-life for DDE is probably longer (Longnecker, 2005).

8. Possible alternatives to DDT

Several vector control methods are currently available as alternatives to DDT, while others are under development. As previously stated, the use of alternative insecticides in IRS and the use of insecticide-treated bed nets (ITNs), are mainstreamed because of their proven impact on the malaria burden. Moreover, several non-chemical approaches could play a pivotal role in the future. Table 1 summarizes some possible alternative methods to DDT.

Alternatives to DDT	Chemical (yes/no)	Vector stage	Availability	Delivery/Resources	Risk
attractants	yes	adult	under development	local, private sector	resistance, toxicity
botanicals	no	larva adult	available	local	toxicity
chemical larviciding	yes	larva	available	spray teams	resistance, effect on ecosystems
design of irrigation structures	no	larva	available	irrigation sector	negligible
elimination of breeding sites	no	larva	available	local	negligible
fungi	no	adult	under development	not applicable	negligible
genetic methods	no	adult	under development	not applicable	to be studied
habitat manipulation	no	larva	available	local, agricolture sector	negligible
house improvement	no	adult	available	local, development programs	resistance

http://dx.doi.org/10.5772/53241

Alternatives to DDT	Chemical (yes/no)	Vector stage	Availability	Delivery/Resources	Risk
indoor residual spraying	yes	adult	available	spray teams	resistance, toxicity
insecticide-treated bednets	yes	adult	available	free distribution, social marketing, private sector	resistance, toxicity
irrigation management	no	larva	available	local, irrigation sector	negligible
microbial larvicides	no	larva	available	programs, private sectors	resistance
polystyrene beads	no	larva	available	local	negligible
predation	no	larva	available	local, programs, agriculture sector	negligible
repellents	yes	adult	under development	local, private sector	resistance, toxicity

Table 1. Alternative methods for malaria vector control. Adapted from (van den Berg, 2009)

8.1. Chemical methods

The strength of IRS with insecticides lies in its effect on shortening the life span of adult mosquitoes near their human targets (MacDonald, 1957). Two new approaches are currently being developed with regard to IRS, including some existing insecticides not currently available for public health (chlorfenapyr and indoxacarb), potentially effective in areas with pyrethroid resistance (N'Guessan et al., 2007a; N'Guessan et al., 2007b), and new formulations of existing insecticides with prolonged residual activity (Hemingway et al., 2006).

The main alternative to IRS are ITNs, which have been shown convincingly to substantially reduce all-cause child mortality, under both experimental (Lengeler, 2004) and operational conditions (Schellenberg et al., 2001; Fegan et al., 2007). Various new developments in ITN technology have spread recently. At least one nonpyrethroid insecticide with novel chemistry has been developed for ITNs (Hemingway et al., 2006) to cope with the problem of resistance; however, safety issues are still a concern. Other new ITN products are not expected to come to market in the short term.

Chemical insecticides as larvicides can play an important role to control mosquito breeding in urban settings, but they are a concern to the integrity of aquatic ecosystems.

Moreover, in order to push away mosquitoes, which usually are attracted by the moisture, warmth, carbon dioxide or estrogens from human skin, a large spectrum of repellents have been developed and are currently used; these substances, manufactured in several forms, including aerosols, creams, lotions, suntan oils, grease sticks and cloth-impregnating laundry emulsions, are usually applied on the skin or clothes, and produce a vapor layer characterized by bad smell or taste to insects (Brown & Hebert, 1997). The ideal repellent should satisfy several criteria: a) have long-lasting effectiveness; b) do not irritate human skin; c) have

a bad odor only to mosquitoes but not to people; d) have no effects on clothes; e) be inert to plastics commonly used, such as glasses or bracelets; f)be chemically stable; and g) be economical (Brown & Hebert, 1997). The list of main insect repellents, some of which are also used as insecticides, includes N,N-diethyl-3-methylbenzamide (DEET), permethrin, picaridin, indalone, and botanicals (Prato et al., 2012). Additionally, innovative work is in progress on the attractiveness of human odors to malaria vectors, with potential applications as mosquito attractants and repellents for use in trapping and personal protection (Zwiebel & Takken, 2004).

8.2. Nonchemical methods

The development of non-chemical strategies alternative to insecticides and repellents is already available or currently on study. Before the advent of synthetic insecticides, vector control depended primarily on environmental management, and a meta-analysis of data mostly from that period indicated that it substantially reduced malaria risk (Keiser et al., 2005).

Elimination of vector-breeding habitats and managements of water bodies plays a key role in vector suppression, (Walker & Lynch, 2007). In irrigated agriculture, vector breeding can be controlled, through land leveling and intermittent irrigation (Keiser et al., 2002).

The role of aquatic predators as control agents of malaria vectors is potentially enhanced through conservation or through the introduction of agents from outside. Larvivorous fish have frequently been reared and released for controlling vector breeding in small water tanks and wells, but successes have generally been limited to more or less permanent water bodies (Walker & Lynch, 2007).

Microbial larvicides such as *Bacillus thuringiensis israelensis* and *Bacillus sphaericus* produce mosquito-specific toxins associated with a low risk of resistance development (Lacey, 2007). Recent field trials and pilot projects have shown good potential of both bacteria to manage mosquito breeding and to reduce biting rates in certain settings (Fillinger et al., 2008).

Also, insect pathogenic fungi have shown promising results for controlling adult *Anopheles* mosquitoes when sprayed on indoor surfaces and have potential to substantially reduce malaria transmission (Scholte et al., 2005).

Novel methods under development are genetically engineered mosquitoes and the sterile insect technique (Catteruccia, 2007). Genetic control appears a promising tool, comprising all methods by which a mechanism for pest or vector control is introduced into a wild population through mating. These include the sterile insect release method or the sterile insect technique (SIT), through which males are sterilized by irradiation or other means and released to mate with wild females, leading them to lay sterile eggs. Additionally, the introduction of genetic factors into wild populations aimed to make pests harmless to humans might be relevant (Pates & Curtis, 2005).

Finally novel approaches against vector borne diseases include transgenesis and paratransgenesis to reduce vector competence (Coutinho-Abreu et al., 2010). For vector transgenesis, the goal is to transform vectors with a gene (or genes) whose protein(s) impair pathogen de-

http://dx.doi.org/10.5772/53241

velopment. Several mosquito species vectors of different parasites and viruses have been transformed. Some of the transformed mosquitoes were shown capable of blocking pathogen development via tissue-specific expression of molecules impairing the pathogen attachment to the midgut (Ito et al., 2002), or activating some biochemical pathways detrimental to pathogen survival (Franz et al., 2006). Paratransgenesis aims to reduce vector competence by genetically manipulating symbionts. Transformed symbionts are spread maternally or via coprophagy across an insect population (Durvasula et al., 1997).

Unfortunately, although these approaches are potentially promising, they remain a complex approach with a limited use (Coutinho-Abreu et al., 2010). Also, data on the cost-effectiveness of nonchemical methods are scarce. In a retrospective analysis of data from Zambia, environmental management was as cost-effective as ITNs (Utzinger et al., 2001). Moreover, environmental management can benefit from local resources, reducing the need for external funds.

9. Conclusion

To date, DDT represents a major tool for vector control in areas endemic for malaria, and in 2010 it was the main stay contributing to reduce malaria burden. Despite the big ongoing debate whether improve or ban its use, no convincing evidence on long-term toxic effects of DDT on humans is currently available. In the future, further constructive research aimed at ascertaining DDT effects on human health will be certainly welcome; also, the concurrent use of safe DDT alternatives (as long as they are effective as DDT, of course), should not be neglected. Nevertheless, DDT benefits appear self-evident up to now, thereby justifying its current use as an effective anti-malaria tool.

Author details

Mauro Prato[1,2], Manuela Polimeni[1] and Giuliana Giribaldi[1]

1 Dipartimento di Genetica, Biologia e Biochimica, Facolta' di Medicina e Chirurgia, Universita' di Torino, Italy

2 Dipartimento di Neuroscienze, Facolta' di Medicina e Chirurgia, Universita' di Torino, Italy

References

[1] Africa Fighting Malaria (2010). Africa Fighting Malaria. Indoor Residual Spraying and DDT. Available from http://www.fightingmalaria.org/pdfs/Africa%20Fighting %20Malaria% 20IRS%20DDT%20issues.pdf

[2] Agency for Toxic Substances and Disease Registry. (1994). *Toxicology Profile for 4,4'-DDT, 4,4'-DDE, 4,4'DDD*, Public Health Service, Atlanta, GA.

[3] Agency for Toxic Substances and Disease Registry. (September 2002). *Toxicological Profile: for DDT, DDE, and DDE*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service, Retrieved from http://www.atsdr.cdc.gov/toxprofiles/tp35.pdf

[4] Alavanja, M.C., Samanic, C., Dosemici, M., Lubin, J., Tarone, R., Lynch, C., Knott, C., Thomas, K., Hoppin, J.A., Barker, J., Coble, J., Sandler, D.P. & Blair, A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *The American Journal of Epidemiology*, Vol.157, No.9, pp. 800–814, ISSN 1476-6256

[5] ALMA (African Leaders Malaria Alliance) (2010). Report to ALMA Heads of State and Government. ALMA.

[6] Aly, A.S., Vaughan, A.M. & Kappe, S.H. (2009). Malaria parasite development in the mosquito and infection of the mammalian host. *Annual Reviews of Microbiology*, Vol. 63, No.10, pp. 195-221, ISSN 0066-4227

[7] Aneck-Hahn, N.H., Schulenburg, G.W., Bornman, M.S., Farias, P. & De Jager, C. (2007). Impaired semen quality associated with environmental DDT exposure in young men living in a malaria area in the Limpopo Province, South Africa. *Journal of Andrology*, Vol.28, pp. 423–434, ISSN 1939-4640

[8] Arbuckle, T.E. & Sever, L.E. (1998). Pesticide exposures and fetal death: a review of the epidemiologic literature. *Critical Reviews in Toxicology*, Vol.28, pp. 229–270, ISSN 1547-6898

[9] Attaran, A. & Maharaj, R. (2000). Doctoring malaria, badly: the global campaign to ban DDT. *British Medical Journal*, Vol.321, pp. 1403–1405, ISSN 0007-1447

[10] Banting, G., Benting, J. & Lingelbach, K. (1995). A minimalist view of the secretory pathway in *Plasmodium falciparum*. *Trends in Cell Biology*, Vol.5, pp 340-343, ISSN 0962-8924

[11] Beard, J. (2006). DDT and human health. Science of the Total Environment, Vol.355, pp. 78– 89, ISSN

[12] Beard, J., Marshall, S., Jong, K., Newton, R., Triplett-McBride, T., Humphries, B. & Bronks, R. (2000). 1,1,1-Trichloro-2,2-bis (p-chlorophenylethane (DDT) and reduced bone mineral density. *Archives of Environmental Health*, Vol.55, pp. 177–180, ISSN 0003-9896

[13] Beier, J.C. (1998). Malaria parasite development in mosquitoes. *Annual Review of Entomology*, Vol.43, pp. 519-543, ISSN 0066-4170

[14] Bimenya, G.S., Harabulema, M., Okot, J.P., Francis, O., Lugemwa, M. & Okwi, A.L. (2010). Plasma levels of DDT/DDE and liver function in malaria control personnel 6

months after indoor residual spraying with DDT in Uganda, 2008. *South African Medical Journal*, Vol.100, No.2, pp.118–121, ISSN 0256-9574

[15] Biovision (2011). Projects: International. Stop DDT: Promoting Effective and Environmentally Sound Alternatives to DDT, Available from http://www.biovision.ch/fileadmin/pdf/e/projects/2011/International/BV_Factsheet_Stop_DDT_2011_E.pdf

[16] Blair, A., Saracci, R., Vineis, P., Cocco, P., Forastiere, F., Grandjean, P., Kogevinas, M., Kriebel, D., McMichael, A., Pearce, N., Porta, M., Samet, J., Sandler, D.P., Costantini A.S. & Vainio, H. (2009). Epidemiology, public health, and the rhetoric of false positives. *Environmental Health Perspectives*, Vol.117, No.12, pp. 1809–1813, ISSN 0091-6765

[17] Blondell, J. (1990). Problems encountered in the design of epidemiologic studies of cancer in pesticide users. *La Medicina del Lavoro*, Vol.81, pp. 524–529, ISSN 0025-7818

[18] Bohannon, A.D., Cooper, G.S., Wolff, M.S. & Meier, D.E. (2000). Exposure to 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDT) in relation to bone mineral density and rate of bone loss in menopausal women. *Archives of Environmental Health*, Vol.55, pp. 386–391, ISSN 0003-9896

[19] Bouwman, H., Cooppan, R.M., Botha, M.J. & Becker P.J. (1991). Serum levels of DDT and liver function of malaria control personnel. *South African Medical Journal*, Vol.79, No.6, pp.362–329, ISSN 0256-9574

[20] Bouwman, H., van den Berg, H. & Kylin, H. (2011). DDT and Malaria Prevention: Addressing the Paradox. *Environmental Health Perspectives*, Vol.119, No.6, pp. 744-747, ISSN 0091-6765

[21] Bouwman, H., Cooppan, R.M., Becker, P.J. & Ngxongo, S. (1991). Malaria control and levels of DDT in serum of two populations in Kwazulu. *Journal of Toxicology and Environmental Health*, Vol.33, pp. 141–155, ISSN 1087-2620

[22] Bouwman, H., Sereda, B. & Meinhardt, H.M. (2006). Simultaneous presence of DDT and pyrethroid residues in human breast milk from a malaria endemic area in South Africa. *Environmental Pollution*, Vol.144, pp. 902–917, ISSN 0269-7491

[23] Breman, J.G. (2001). The ears of the hippopotamus: manifestations, determinants and estimates of the malaria burden. *American Journal of Tropical Medicine and Hygiene*, Vol.64, No.1-2Suppl, pp. 1–11, ISSN 0002-9637

[24] Brown, M. & Herbert, A.A. (1997). Insect repellents: An overview. *Journal of the American Academy of Dermatology*, Vol.36, No.2Pt1, pp. 243-249, ISSN 1097-6787

[25] Burton, A. (2009). Toward DDT-free malaria control. *Environmental Health Perspectives*, Vol.117, No.8, pp. A344, ISSN 0091-6765

[26] Calle, E.E., Frumkin, H., Henley, S.J., Savitz, D.A. & Thun, M.J. (2002). Organochlorines and breast cancer risk. *CA a cancer journal for clinicians*, Vol.52, pp. 301–309, ISSN 1542-4863

[27] Carlsen, E., Giwercman, A., Keiding, N. & Skakkebaek, N. (1992). Evidence for decreasing quality of semen during past 50 years. *British Medical Journal*, Vol.305, pp. 609–612, ISSN 0007-1447

[28] Catteruccia, F. (2007). Malaria vector control in the third millennium: progress and perspectives of molecular approaches. *Pest Management Science*, Vol.63, pp. 634–640, ISSN 1526-4998

[29] CDC. (2009). Malaria - Vector Control. In: Center for disease control and prevention, 21 April 2009, Available from http://www.cdc.gov/malaria/ control_prevention/ vector_control.htm.

[30] Chapin, G. & Wasserstrom, R. (1981). Agricultural production and malaria resurgence in Central America and India. *Nature*, Vol.293, No.5829, pp. 181-185, ISSN 0028-0836

[31] Chen, C., Hurd, C., Vorojeikina, D., Arnold, S. & Notides, A. (1997). Transcriptional activation of the human estrogen receptor by DDT isomers and metabolites in yeast and MCF-7 cells. *Biochemical Pharmacology*, Vol.53, pp. 1161–1172, ISSN 0006-2952

[32] Cohn, B.A., Cirillo, P.M., Wolff, M.S., Schwingl, P.J., Cohen, R.D., Sholtz, R.I., Ferrara, A., Christianson, R.E., van den Berg, B.J. & Siiteri, P.K. (2003). DDT and DDE exposure in mothers and time to pregnancy in daughters. *The Lancet*, Vol.361, pp. 2205–2206, ISSN 1474-547X [erratum appears in Lancet 2003, Vol.362, No.9394, pp. 1504]

[33] Colburn, T., Dumanoski, D. & Meyers, J.P. (1996). Our Stolen Future, Penguin Books, New York, US.

[34] Colosio, C., Tiramani, M. & Maroni, M. (2003). Neurobehavioral effects of pesticides: state of the art. *Neurotoxicology*, Vol.24, pp. 577–591, ISSN 0161-813X

[35] Coutinho-Abreu, I.V., Zhu, K.Y. & Ramalho-Ortigao, M. (2010). Transgenesis and paratransgenesis to control insect-borne diseases: Current status and future challenges. *Parasitology International*, Vol.59, No1, pp. 1–8, ISSN 1873-0329

[36] Cowman, A.F. & Crabb, B.S. (2006). Invasion of Red Blood Cells by Malaria Parasites. Cell, Vol.124, No.4, pp. 755–766, ISSN 0092-8674

[37] D'Alessandro, U., Olaleye, B.O., McGuire, W., Thomson, M.C., Langerock, P., Bennett, S. & Greenwood, B.M. (1995). A comparison of the efficacy of insecticide-treated and untreated bed nets in preventing malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, Vol.89, No.6, pp. 596–598, ISSN 1878-3503

[38] Daniel, V., Huber, W., Bauer, K., Suesal, C., Conradt, C. & Opelz, G. (2002). Associations of dichlorodiphenyltrichloroethane (DDT) 4.4 and dichlorodiphenyldichloroethylene (DDE) 4.4 blood levels with plasma IL-4. *Archives of Environmental Health*, Vol.57, pp. 541–547, ISSN 0003-9896

[39] De Jager, C., Farias, P., Barraza-Villarreal, A., Avila, M.H., Ayotte, P., Dewailly, E., Dombrowski, C., Rousseau, F., Sanchez, V.D. & Bailey, J.L. (2006). Reduced seminal parameters associated with environmental DDT exposure and *p,p'*-DDE concentrations in men in Chiapas, Mexico: a cross-sectional study. *Journal of Andrology*, Vol.27, pp. 16–27, ISSN 1939-4640

[40] Denholm, I., Devine, G.J. & Williamson, M.S. (2002). Evolutionary genetics. Insecticide resistance on the move. *Science*, Vol.297, No.5590, pp. 2222–2223, ISSN 1095-9203

[41] Derfoul, A., Lin, F.J., Awumey, E.M., Kolodzeski, T., Hall, D.J. & Tuan, R.S. (2003). Estrogenic endocrine disruptive components interfere with calcium handling and differentiation of human trophoblast cells. *Journal of Cellular Biochemistry*, Vol.89, pp. 755–770, ISSN 1097-4644

[42] Diabate, A., Baldet, T., Chandre, F., Akoobeto, M., Guiguemde, T.R., Darriet, F., Brengues, C., Guillet, P., Hemingway, J., Small, G.J. & Hougard, J.M. (2002). The role of agricultural use of insecticides in resistance to pyrethroids in Anopheles gambiae s.l. in Burkina Faso. *American Journal of Tropical Medicine and Hygiene*, Vol.67, No.6, pp. 617–622, ISSN 0002-9637

[43] Dich, J. & Wiklund, K. (1998). Prostate cancer in pesticide applicators in Swedish agriculture. Prostate, Vol.34, pp. 100–112, ISSN

[44] Durvasula, R.V., Gumbs, A., Panackal, A., Kruglov, O., Aksoy, S., Merrifield, R.B., Richards, F.F. & Beard, C.B. (1997). Prevention of insect-borne disease: an approach using transgenic symbiotic bacteria. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.94, No.7, pp. 3274–3278, ISSN 1091-6490

[45] Eriksson, P. & Talts, U. (2000). Neonatal exposure to neurotoxic pesticides increases adult susceptibility: a review of current findings. *Neurotoxicology*, Vol.21, pp. 37–47, ISSN 0161-813X

[46] Eskenazi, B., Chevrier, J., Rosas, L.G., Anderson, H.A., Bornman, M.S., Bouwman, H., Chen, A., Cohn, B.A., de Jager, C., Henshel, D.S., Leipzig, F., Leipzig, J.S., Lorenz, E.C., Snedeker, S.M. & Stapleton, D. (2009). The Pine River statement: human health consequences of DDT use. *Environmental Health Perspectives*, Vol.117, pp. 1359–1367, ISSN 0091-6765

[47] Fegan, G.W., Noor, A.M., Akhwale, W.S., Cousens, S. & Snow, R.W. (2007). Effect of expanded insecticide-treated bednet coverage on child survival in rural Kenya: a longitudinal study. *The Lancet*, Vol.370, pp. 1035–1039, ISSN 0140-6736

[48] Fillinger, U., Kannady, K., William, G., Vanek, M.J., Dongus, S., Nyika, D., Geissbühler, Y., Chaki, P.P., Govella, N.J., Mathenge, E.M., Singer, B.H., Mshinda, H., Lindsay, S.W., Tanner, M., Mtasiwa, D., de Castro, M.C. & Killeen, G.F. (2008). A tool box for operational mosquito larval control: preliminary results and early lessons from the Urban Malaria Control Programme in Dar es Salaam, Tanzania. *Malaria Journal*, Vol. 7, pp. 20, ISSN 1475-2875

[49] Franz, A.W., Sanchez-Vargas, I., Adelman, Z.N., Blair, C.D., Beaty, B.J., James, A.A. & Olson, K.E. (2006). Engineering RNA interference-based resistance to dengue virus type 2 in genetically modified Aedes aegypti. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.103, No11, pp. 4198–203, ISSN 1091-6490

[50] Gerhard, I., Daniel, V., Link, S., Monga, B. & Runnebaum, B. (1998). Chlorinated hydrocarbons in women with repeated miscarriages. *Environmental Health Perspectives*, Vol.106, pp. 675–681, ISSN 0091-6765

[51] Gladen, B.C., Shkiryak-Nyzhnyk, Z.A., Chyslovska, N., Zadorozhnaja, T.D. & Little, R.E. (2003). Persistent organochlorine compounds and birth weight. *Annals of Epidemiology*, Vol.13, pp. 151–157, ISSN 1047-2797

[52] Glynn, A.W., Michaelsson, K., Lind, P.M., Wolk, A., Aune, M., Atuma, S., Darnerud, P.O. & Mallmin, H. (2000). Organochlorines and bone mineral density in Swedish men from the general population. *Osteoporosis International*, Vol.11, pp. 1036–1042, ISSN 1433-2965

[53] Gray, L.E., Ostby, J., Furr, J., Wolf, C.J., Lambright, C., Parks, L., Veeramachaneni, D.N., Wilson, V., Price, M., Hotchkiss, A., Orlando, E. & Guillette, L. (2001). Effects of environmental antiandrogens on reproductive development in experimental animals. *Human Reproduction Update*, Vol.7, pp. 248–264, ISSN 1460-2369

[54] Greenwood, BM. (2008). Control to elimination: implications for malaria research. *Trends in Parasitology*, Vol.24, No.10, (October 2008), pp. 449-454, ISSN 1471-5007

[55] Hardell, L., Lindstrom, G. & Van Bavel, B. (2002). Is DDT exposure during fetal period and breast-feeding associated with neurological impairment? *Environmental Research*, Vol.88, pp. 141–144, ISSN 0013-9351

[56] Harrad, S. (2001). Persistent Organic Pollutants: Environmental Behaviour and Pathways of Human Exposure. Dordrecht, the Netherlands:Kluwer Academic Publishers

[57] Harrison, G. (1978). Mosquitoes, Malaria, and Man: A History of the Hostilities Since 1880, John Murray, ISBN 0-71953-780-8, London, UK.

[58] Hauser, R., Altshul, L., Chen, Z., Ryan, L., Overstreet, J., Schiff, I. & Christiani D.C. (2002). Environmental organochlorines and semen quality: results of a pilot study. *Environmental Health Perspectives*, Vol.110, pp. 229–233, ISSN 0091-6765

[59] Hauser, R., Chen, Z., Pothier, L., Ryan, L. & Altshul, L. (2003). The relationship between human semen parameters and environmental exposure to polychlorinated biphenyls and p,pV-DDE. *Environmental Health Perspectives*, Vol.111, pp. 1505–1511, ISSN 0091-6765

[60] Hemingway, J. & Ranson, H. (2000). Insecticide resistance in insect vectors of human disease. *Annual Review of Entomology*, Vol.45, pp. 371–391, ISSN 1545-4487

[61] Hemingway, J., Beaty, B.J., Rowland, M., Scott, T.W. & Sharp, B.L. (2006). The Innovative Vector Control Consortium: improved control of mosquito-borne diseases. *Trends in Parasitology*, Vol.22, pp. 308–312, ISSN1471-4922

[62] Iscan, M., Coban, T., Cok, I., Bulbul, D., Eke, B.C. & Burgaz, S. (2002). The organochlorine pesticide residues and antioxidant enzyme activities in human breast tumors: is there any association? *Breast Cancer Research and Treatment*, Vol.72, pp. 173–182, ISSN 0167-6806

[63] Ito, J., Ghosh, A., Moreira, L.A., Wimmer, E.A. & Jacobs-Lorena, M. (2002). Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite. *Nature*, Vol. 417, No.6887, pp. 452–455, ISSN 0028-0836

[64] Jensen, S., Johnels, A., Olsson, M. & Otterlind, G. (1969). DDTand PCB in marine animals from Swedish waters. *Nature*, Vol.223, No.5216, pp. 753–754, ISSN 0028-0836

[65] Keiser, J., Utzinger, J. & Singer, B.H. (2002). The potential of intermittent irrigation for increasing rice yields, lowering water consumption, reducing methane emissions, and controlling malaria in African rice fields. *Journal of the American Mosquito Control Association*, Vol.18, pp. 329–340, ISSN 1046-3607

[66] Keiser, J., Singer, B.H. & Utzinger, J. (2005). Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review. *The Lancet Infectious Diseases*, Vol.5, pp.695–708, ISSN 1473-3099

[67] Kelce, W., Stone, C., Laws, S., Gray, L., Kemppainen, J. & Wilson, E. (1995). Persistent DDT metabolite, p,pV-DDE is a potent androgen receptor antagonist. *Nature*, Vol. 375, pp. 581–585, ISSN 0028-0836

[68] Khadjavi, A., Giribaldi, G. & Prato, M. (2010). From control to eradication of malaria: the end of being stuck in second gear? *Asian Pacific Journal of Tropical Medicine*, Vol.3, No.5, pp. 412-420, ISSN 1995-7645

[69] Korrick, S.A., Chen, C., Damokosh, A.I., Ni, J., Liu, X., Cho, S.I., Altshul, L., Ryan, L. & Xu, X. (2001). Association of DDT with spontaneous abortion: a case-control study. *Annals of Epidemiology*, Vol.11, pp. 491–496, ISSN 1047-2797

[70] Lacey, L.A. (2007). *Bacillus thuringiensis* serovariety *israelensis* and *Bacillus sphaericus* for mosquito control. *Journal of the American Mosquito Control Association*, Vol.23 (suppl 2), pp. 133–163, ISSN 1046-3607

[71] Langer, P., Kocan, A., Tajtakova, M., Petrik, J., Chovancova, J., Drobna, B., Jursa, S., Pavuk, M., Koska, J., Trnovec, T., Sebokova,E. & Klimes, I. (2003). Possible effects of polychlorinated biphenyls and organochlorinated pesticides on the thyroid after long-term exposure to heavy environmental pollution. *Journal of Occupational & Environmental Medicine*, Vol.45, pp. 526–532, ISSN 1536-5948

[72] Lebel, G., Dodin, S., Ayotte, P., Marcoux, S., Ferron, L.A. & Dewailly, E. (1998). Organochlorine exposure and the risk of endometriosis. *Fertility and Sterility*, Vol.69, pp. 221–228, ISSN 1556-5653

[73] Lengeler, C. (2004). Insecticide-treated bednets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews*, Vol.2, pp. CD000363, ISSN 1469-493X

[74] Lewis, K. (2008). DDT stalemate stymies malaria control initiative. *Canadian Medical Association Journal*, Vol.179, No.10, pp. 999–1000, ISSN 1488-2329

[75] Lines, J. (1996). Mosquito nets and insecticides for net treatment: a discussion of existing and potential distribution systems in Africa. *Tropical Medicine & International Health*, Vol.1, No.5, pp. 616–632, ISSN 1365-3156

[76] Longnecker, M.P. (2005). Invited commentary: why DDT matters now. *The American Journal of Epidemiology*, Vol.162, pp. 726–728, ISSN 1476-6256

[77] Longnecker, M.P., Klebanoff, M.A., Brock, J.W., Zhou, H., Gray, K.A., Needham, L.L. & Wilcox, A.J. (2002). Maternal serum level of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene and risk of cryptorchidism, hypospadias, and polythelia among male offspring. *The American Journal of Epidemiology*, Vol.155, pp. 313–322, ISSN 1476-6256

[78] Longnecker, M.P., Klebanoff, M.A., Zhou, H. & Brock, J.W. (2001). Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *The Lancet*, Vol.358, pp. 110–114, ISSN 1474-547X

[79] MacDonald G. (1957). The Epidemiology and Control of Malaria. London, Oxford University Press.

[80] Martinez Torres, D., Chandre, F., Williamson, M.S., Darriet, F., Bergé, J.B., Devonshire, A.L., Guillet, P., Pasteur, N. & Pauron, D. (1998). Molecular characterization of pyrethroid knockdown resistance (kdr) in the major malaria vector Anopheles gambiae s.s. *Insect Molecular Biology,* Vol.7, No.2, pp. 179–184, ISSN 1365-2583

[81] Ménard, R. (2005). Medicine: knockout malaria vaccine? *Nature*, Vol.13, No.433, pp. 113-114, ISSN 0028-0836

[82] Metcalf, R.L. (1989). Insect Resistance to Insecticides. *Pesticide Science*, Vol.26, pp. 333-358, ISSN 1096-9063

[83] Munga, S., Vulule, J. & Allan, R. (2009). Evaluation of insecticide treated wall lining materials used in traditional rural African houses, Proceedings of 5th MIM Pan-African malaria conference, Nairobi, Kenya, November 2009, Poster No. 734, pp. 200

[84] Mussalo-Rauhamaa, H. (1991). Partitioning and levels of neutral organochlorine compounds in human serum, blood cells, and adipose and liver tissue. *Science of the Total Environment*, Vol.103, pp. 159–175, ISSN 0048-9697

[85] N'Guessan, R., Boko, P., Odjo, A., Akogbeto, M., Yates, A. & Rowland, M. (2007a). Chlorfenapyr: a pyrrole insecticide for the control of pyrethroid or DDT resistant *Anopheles gambiae* (Diptera: Culicidae) mosquitoes. *Acta Tropica*, Vol.102, pp. 69–78, ISSN 0001-706X

[86] N'Guessan, R., Corbel, V., Bonnet, J., Yates, A., Asidi, A., Boko, P., Odjo, A., Akogbéto, M. & Rowland, M. (2007b). Evaluation of indoxacarb, an oxadiazine insecticide for the control of pyrethroid-resistant *Anopheles gambiae* (Diptera: Culicidae). *Journal of Medical Entomology*, Vol.44, pp. 270–276, ISSN 0022-2585

[87] Nilsen, T. & Vatten, L. (2000). A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. *Cancer Causes & Control*, Vol.11, pp. 645–652, ISSN 1573-7225

[88] PAN (Pesticide Action Network). (2012). Available from http://www.pan-uk.org/

[89] PANUPS (Pesticide Action Network North America) (1996). Global Distribution of organochlorines,, San Francisco, US.

[90] Pates, H. & Curtis, C. (2005). Mosquito behavior and vector control. *Annual Review of Entomology*, Vol.50, pp. 53–70, ISSN 1545-4487

[91] Peakall, D.B. (1969). Effect of DDT on calcium uptake and vitamin D metabolism in birds. *Nature*, Vol.224, pp. 1219–1220, ISSN 0028-0836

[92] Porta, M., Malats, N., Jarriod, M., Grimalt, J.O., Rifa, J., Carrato, A., Guarner, L., Salas, A., Santiago-Silva, M., Corominas, J.M., Andreu, M. & Real FX. (1999). Serum concentrations of organochlorine compounds and K-ras mutations in exocrine pancreatic cancer. *The Lancet*, Vol.354, pp. 2125–2129, ISSN 1474-547X

[93] Prato, M., Khadjavi, A., Mandili, G., Minero, V.G. & Giribaldi, G. (2012). Insecticides as Strategic Weapons for Malaria Vector Control, In: *Insecticides - Advances in Integrated Pest Management*, Perveen, F. (Ed.), pp.91-114, InTech, ISBN: 978-953-307-780-2, Rijeka, Croatia, Available from http://www.intechopen.com/books/insecticides-advances-in-integrated-pest-management/insecticides-as-strategic-weapons-for-malaria-vector-control

[94] Ramade, F. (1987). Ecotoxicology. New York, John Wiley & Sons.

[95] Ratcliffe, D. (1970). Changes attributable to pesticides in egg breakage frequency and eggshell thickness in some British birds. *Journal of Applied Ecology*, Vol.7, pp. 67–115, ISSN 0021-8790

[96] Rathore, M., Bhatnagar, P., Mathur, D. & Saxena, G.N. (2002). Burden of organochlorine pesticides in blood and its effect on thyroid hormones in women. *Science of the Total Environment*, Vol.295, pp. 207–215, ISSN 0048-9697

[97] Ritter, L., Solomon, K.R., Forget, J., Stemeroff, M. & O'Leary, C. (1995). Persistent Organic Pollutants. Geneva: International Programme on Chemical Safety

[98] Roberts, D., Laughlin, L.L., Hsheih, P. & Legters, L.J. (1997). DDT, global strategies, and a malaria control crisis in South America. *Emerging Infectious Diseases*, Vol.3, No. 3, pp.295–302, ISSN 1080-6059

[99] Roberts, L. & Enserink, M. (2007). Did they really say… eradication? *Science*, Vol.318, No.5856, pp. 1544-1545, ISSN 1095-9203

[100] Rogier, C. & Hommel, M. (March 2011). *Plasmodium* life-cycle and natural history of malaria, In: Impact malaria sanofi Aventis' commitment, 9 March 2011, Available from http://www.impact-malaria.com/iml/cx/en/layout.jsp?cnt=2FAECA4C-CA72-4C97-9090-B725867E1579

[101] Sadasivaiah, S., Tozan, Y. & Breman, J.G. (2007). Dichlorodiphenyltrichloroethane (DDT) for Indoor Residual Spraying in Africa: How Can It Be Used for Malaria Control? *American Journal of Tropical Medicineand Hygiene,* Vol.77, No.6, pp. 249–263, ISSN 0002-9637

[102] SADC (Southern African Development Community) (2011). Letter from SADC to A Steiner, Executive Director, United Nations Environment Programme, Notification of SADC Countries Respecting DDT Use and Production, 5 April 2011, Available from http://www.fightingmalaria.org/pdfs/sadclettertounep.pdf

[103] Saxena, M., Siddiqui, M., Bhargava, A., Seth, T., Krishnamurti, C. & Kutty, D. (1980). Role of chlorinated hydrocarbon pesticides in abortions and premature labour. *Toxicology*, Vol.17, pp. 323–331, ISSN 0300-483X

[104] Schellenberg, J.R.M., Abdulla, S., Nathan, R., Mukasa, O., Marchant, T.J., Kikumbih, N., Mushi, A.K., Mponda, H., Minja, H., Mshinda, H., Tanner, M. & Lengeler, C. (2001). Effect of large-scale social marketing of insecticide-treated nets on child survival in rural Tanzania. *The Lancet*, Vol.340, pp.1241–1247, ISSN 0140-6736

[105] Scholte, E.J., Ng'habi, K., Kihonda, J., Takken, W., Paaijmans, K., Abdulla, S., Kelleen, G.F. & Knols, B.G. (2005). An entomopathogenic fungus for control of adult African malaria mosquitoes. *Science.* Vol.308, pp. 1641–1642, ISSN 0036-8075

[106] Settimi, L., Masina, A., Andrion, A. & Axelson, O. (2003). Prostate cancer and exposure to pesticides in agricultural settings. *International Journal of Cancer*, Vol.104, pp. 458–461, ISSN 1097-0215

[107] Sever, L.E., Arbuckle, T.E. & Sweeney, A. (1997). Reproductive and developmental effects of occupational pesticide exposure: the epidemiologic evidence. *Occupational Medicine*, Vol.12, pp. 305–325, ISSN 1471-8405

[108] Sharpe, R. & Skakkebaek, N. (1993). Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *The Lancet*, Vol.341, pp. 1392–1395, ISSN 1474-547X

[109] Siddiqui, M.K., Nigam, U., Srivastava, S., Tejeshwar, D.S. & Chandrawati R. (2002). Association of maternal blood pressure and hemoglobin level with organochlorines in human milk. *Human & Experimental Toxicology*, Vol.21, No.1, pp. 1–6, ISSN 1477-0903

[110] Siddiqui, M.K., Srivastava, S., Srivastava, S.P., Mehrotra, P.K., Mathur, N. & Tandon, I. (2003). Persistent chlorinated pesticides and intra-uterine foetal growth retardation: a possible association. *International Archives of Occupational and Environmental Health*, Vol.76, pp. 75–80, ISSN 1432-1246

[111] Snedeker, S.M. (2001). Pesticides and breast cancer risk: a review of DDT, DDE, and dieldrin. *Environmental Health Perspectives*, Vol.1, pp. 35–47, ISSN 0091-6765

[112] Sturgeon, S.R., Brock, J.W., Potischman, N., Needham, L.L., Rothman, N., Brinton, L.A. & Hoover, R.N. (1998). Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). *Cancer Causes & Control*, Vol.9, pp. 417–424, ISSN 1573-7225

[113] Tren, R. & Roberts, D. (2010). DDT and malaria prevention. *Environmental Health Perspectives*, Vol.118, No.1, pp.A 14–15, author reply pp. A15-16, ISSN 0091-6765

[114] Tren, R. & Roberts, D. (2011). DDT paradox. *Environmental Health Perspectives*, Vol. 119, No.10, pp. A423-424, author reply pp. A424-425, ISSN 0091-6765

[115] Trieu, A., Kayala, M.A., Burk, C., Molina, D.M., Freilich, D.A., Richie, T.L., Baldi, P., Felgner, P.L. & Doolan, D.L. (2011) Sterile protective immunity to malaria is associated with a panel of novel P.falciparum antigens. *Molecular and Cellular Proteomics*, Vol. 10, No.9, pp.M111.00794, ISSN 1535-9484

[116] Turusov, V., Rakitsky, V. & Tomatis, L. (2002). Dichlorodiphenyltrichloroethane (DDT): ubiquity, persistence, and risks. *Environmental Health Perspectives*, Vol.110, No.2, pp. 125–128, ISSN 1552-9924

[117] United Nations Environment Programme (UNEP). (1997). Governing Council, 19th session, see also UNEP GC decisions 18/32, 18/31

[118] United Nations Environment Programme (UNEP). (1997). Status Report on UNEP's and other related activities on POPs

[119] United Nations Environment Programme (2007). Future Plans for Work on DDT Elimination. A Stockholm Convention Secretariat Position Paper, November 2007. Geneva: Secretariat of the Stockholm Convention, Available from http://chm.pops.int/Portals/0/Repository/DDT-general/UNEP-POPS-DDT-PROP-SSCPP.English.PDF

[120] Utzinger, J., Tozan, Y. & Singer, B.H. (2001). Efficacy and cost-effectiveness of environmental management for malaria control. *Tropical Medicine & International Health*, Vol.6, pp. 677–687, ISSN 1365-3156

[121] van den Berg H. (2009). Global status of DDT and its alternatives for use in vector control to prevent disease. *Environmental Health Perspectives*, Vol.117, No.11, pp. 1656–1663, ISSN 0091-6765

[122] van Wendel de Joode, B., Wesseling, C., Kromhout, H., Monge, P., Garcia, M. & Mergler, D. (2001). Chronic nervous-system effects of longterm occupational exposure to DDT. *The Lancet*, Vol.357, pp. 1014–1016, ISSN 1474-547X

[123] Varca, L.M. & Magallona, E.D. (1994). Dissipation and degradation of DDT and DDE in Philippine soil under field conditions. *Journal of Environmental Science and Health*, Vol.29, pp. 25–35, ISSN 0360-1234

[124] Walker, K. (2000). Cost-comparison of DDT and alternative insecticides for malaria control. *Medical and Veterinary Entomology* Vol.14, No.4, pp. 345-354, ISSN 0269-283X

[125] Walker, K. & Lynch, M. (2007). Contributions of *Anopheles* larval control to malaria suppression in tropical Africa: review of achievements and potential. *Medical and Veterinary Entomology*, Vol.21, pp.2–21, ISSN 1365-2915

[126] Wandiga, S.O. (2001). Use and distribution of organochlorine pesticides. The future in Africa. *Pure and Applied Chemistry*, Vol.73, pp. 1147–1155, ISSN 1365-3075

[127] Weiderpass, E., Adami, H.O., Baron, J.A., Wicklund-Glynn, A., Aune, M., Atuma, S. & Persson, I. (2000). Organochlorines and endometrial cancer risk. *Cancer Epidemiology, Biomarkers & Prevention*, Vol.9, pp. 487–493, ISSN 1538-7755

[128] WHO (World health Organization) (1996). The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 1996-1997, UNEP, ILO, WHO, Geneva, Switzerland

[129] WHO (2000). Manual for indoor residual spraying. Geneva:World Health Organization.

[130] WHO (2005). Regional strategic framework for scaling up the use of insecticide-treated nets, In: *Insecticides treated materials*, n.d., Available from http://www.searo.who.int/LinkFiles/ Reports_MAL-239_&_VBC-87.pdf.

[131] WHO (2006a). WHO gives indoor use of DDT a clean bill of health for controlling malaria, In: *World Health Organization*, (20 September 2006), Available from http://www.who.int/mediacentre/ news/releases/2006/pr50/en/print.html

[132] WHO (2006b). Indoor residual spraying, use of indoor residual spraying for scaling up global malaria control and elimination, In: *Indoor residual spraying,* World Health Organization, (11 December 2006), Available from http://www.who.int/malaria/vector_control/irs/en/

[133] WHO (2011a). World malaria report 2011 Available from http://www.who.int/malaria/world_malaria_report_2011/en

[134] WHO (2011b) DDT in Indoor Residual Spraying: Human Health Aspects. Environmental Health Criteria 241. Geneva:WHO. Available from http://www.who.int/ipcs/publications/ehc/ehc241.pdf

[135] Yanez, L., Ortiz-Perez, D., Batres, L.E., Borja-Aburto, V.H. & Diaz-Barriga, F. (2002). Levels of dichlorodiphenyltrichloroethane and deltamethrin in humans and environmental samples in malarious areas of Mexico. *Environmental Research*, Vol.88, pp. 174–181, ISSN 0013-9351

[136] Zwiebel, L.J. & Takken, W. (2004). Olfactory regulation of mosquito-host interactions. *Insect Biochemistry and Molecular Biology*, Vol.34, pp.645–652, ISSN 0965-1748