



## **AFRICA FIGHTING MALARIA BULLETIN #6**

**January 31, 2011**

### **Recognizing the way insecticides work in malaria control – the critical importance of WHO's position on DDT**

#### **Introduction**

The only proven and consistent method of insect-borne disease prevention (where a vaccine does not exist) is vector control – suppressing contact between disease-spreading vectors (mosquitoes, fleas, lice, and other insects) and humans in order to interrupt disease transmission.

Vector control is the most important method of prevention for insect-borne diseases like malaria. Yellow fever is the only major insect-borne disease for which an effective vaccine is currently in use. But even when a vaccine is available and effective, insufficient vaccination rates can lead to disease outbreaks that require vector control for containment. Insecticides remain the most important element in vector control for malaria and other important insect-borne diseases. Indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs) are proven vector control interventions that rely heavily on safe, effective, and long-lasting insecticides.

The World Health Organization (WHO) currently recommends 12 insecticides for IRS. DDT is the oldest of these insecticides and the only one not initially developed for use in agriculture. DDT is also unique because it is the only insecticide that has three distinct modes of action, namely spatial repellency, contact irritancy and toxicity.

Although toxic resistance to DDT has been noted, even after decades of public health use, it is still one of the best and most widely used chemicals for preventing malaria transmission inside houses. The powerful spatial repellent action prevents or slows the selection of resistance in mosquitoes when used for malaria control.<sup>1</sup> In fact, DDT is the only chemical recommended for malaria control that stops mosquitoes from even entering houses and thus transmitting disease.<sup>2</sup> But for decades people have thought that the only good mosquito is a dead mosquito, and that DDT functions only by killing mosquitoes; both of which are seriously flawed concepts.

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<sup>1</sup> Grieco JP, Achee NL, Chareonviriyaphap T, Suwonkerd W, Chauhan K, et al. 2007 A New Classification System for the Actions of IRS Chemicals Traditionally Used For Malaria Control. PLoS ONE 2(8): e716  
doi:10.1371/journal.pone.0000716. Available:

<http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0000716>

<sup>2</sup> Grieco JP, Achee NL, Chareonviriyaphap T, Suwonkerd W, Chauhan K, et al. 2007 A New Classification System for the Actions of IRS Chemicals Traditionally Used For Malaria Control. PLoS ONE 2(8): e716  
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## First evidence of DDT's mode of action

Evidence exists as far back as the 1940s showing DDT also acts first as a spatial repellent, second as a contact irritant and, with prolonged physical contact, a toxin. A spatial repellent is a chemical that induces directed movement away from a chemical source without physical contact, while a contact irritant is one that causes agitation and movement following physical contact with the chemical.

From 1943-44, R.L. Metcalf et al studied the differences in numbers of mosquitoes resting in DDT-treated barns, houses, and nail kegs.<sup>3</sup> They discovered that mosquitoes were not entering DDT-sprayed structures and not resting on DDT-sprayed surfaces, thereby displaying a level of irritant and/or repellent action.

Also in 1944, USDA entomologists, J.B. Gahan and A.W. Lindquist, measured the relative numbers of mosquitoes in treated versus untreated areas by placing nail kegs near, but outside of, DDT-sprayed and unsprayed buildings.<sup>4</sup> They found no meaningful differences in numbers of mosquitoes resting in kegs around sprayed buildings compared to unsprayed buildings, but the numbers of mosquitoes resting inside buildings were reduced by 99% in heavily treated buildings and by 91% in lightly treated buildings. Their findings suggest that DDT had powerful repellent properties that kept mosquitoes out of sprayed buildings but did not kill them or reduce overall mosquito-population numbers.

From 1944-47, two scientists with the Communicable Disease Center, C.M. Tarzwell and F.W. Fisk, conducted a study of malaria mosquitoes in DDT-treated and untreated buildings.<sup>5</sup> They discovered that DDT would kill mosquitoes after prolonged contact, that the insecticide would remain active for over 11 months, and that there was a “reduction of the number of resting mosquitoes in a treated building.” This provided clear demonstration that the complex repellent and irritant actions of DDT essentially preempted any impact from DDT toxicity.

Since these studies in the 1940s, studies conducted around the world in different settings, employing diverse methodologies and with different mosquito species, have consistently shown that DDT acts to quickly reduce malaria by modifying disease transmission behaviors of major vector species.

The most recent study, conducted in 2007 by J.P. Grieco et al, consisted of highly replicated laboratory studies and experimental hut studies, demonstrating that DDT acts first as a repellent,

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<sup>3</sup> Metcalf RL, et al. 1945 Observations on the use of DDT for the control of *Anopheles quadrimaculatus*. Pub Hlth Rep 60(27):753-74.

<sup>4</sup> Gahan JB and Lindquist AW. 1945 DDT residual sprays applied in buildings to control *Anopheles quadrimaculatus*. J Econ Entomol 38(2):223-30.

<sup>5</sup> Tarzwell CM and Fisk FW. 1947 Observations on the nighttime resting and biting habits of anopheline mosquitoes in DDT-treated and –untreated buildings. Publ Hlth Rep 62:84-94.



then as an irritant, and lastly as a toxicant.<sup>6</sup> However, there were, and still are, those who believe mosquitoes must be killed to be controlled; this was, until recently, the official opinion of the WHO.

### **Mosquitoes must be killed**

The WHO's Global Malaria Eradication Program of the 1950's and 60's had as its foundation the idea that mosquitoes had to be killed, based on a mathematical model developed by G. Macdonald and G. Davidson.<sup>7</sup> The model described the major components of malaria transmission and malaria epidemiology, and treated DDT as an insecticide that only killed mosquitoes. WHO based all its major initiatives on the model's fundamentally erroneous assumptions; that DDT killed malaria mosquitoes and, as a result, reduced overall mosquito population longevity below the number of days for completing development of malaria parasites in the mosquito.

Macdonald did recognize that DDT had a repellent action, but he considered that this characteristic compromised malaria eradication.<sup>8</sup> His opinion carried great weight and his views were adopted and repeated by many in the malaria-control community. In fact, his beliefs were so deeply entrenched that any mechanism of chemical action that did not result in mosquito death was often considered undesirable. As a result, many malariologists adopted the view that the repellent action would undermine malaria control.

### **DDT's spatial repellency**

The recognition of DDT's spatial repellency as a hugely valuable tool for malaria control has rarely existed despite the evidence. In 1947, J.S. Kennedy performed laboratory studies to quantify repellency as a mode of DDT action.<sup>9</sup> Kennedy presented data showing that DDT residues, at sublethal concentrations, strongly repelled mosquitoes and that specimens often recovered completely after showing preliminary symptoms of poisoning. He concluded that "DDT must be regarded as acting in two contradictory ways simultaneously. It acts as a lethal agent on the one hand, and as an excitant and thereby sometimes a repellent on the other."

In 1949, the malaria-control specialist, A. Gabaldon, used DDT to control malaria in Venezuela with great success.<sup>10</sup> In his presentation before the Royal Society of Tropical Medicine and Hygiene, Gabaldon explained that "as soon as DDT is sprayed anophelines disappear from the

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<sup>6</sup> Grieco JP et al. 2007 A new classification system for the actions of IRS chemicals traditionally used for malaria control. PLoS ONE 2(8): e716. doi:10.1371/journal.pone.0000716.

<sup>7</sup> Macdonald G and Davidson G. 1953 Dose and cycle of insecticide application in the control of malaria. Bull Wld Hlth Org 9:785-812.

<sup>8</sup> Gabaldon A. 1949 The Nation-wide campaign against malaria in Venezuela. Part II. Trans Roy Soc Trop Med Hyg 43(2):133-64.

<sup>9</sup> Kennedy J. 1947 The excitant and repellent effects of mosquitoes of sub-lethal contacts with DDT. Bull Entomol Res 37:593-607.

<sup>10</sup> Gabaldon A. 1949 The Nation-wide campaign against malaria in Venezuela. Part II. Trans Roy Soc Trop Med Hyg 43(2):133-64.



houses. This may be the consequence of what seems to be its repellent action.” He also noted that “this repellent action, however, should not be confused with the effect apparently produced by DDT in some species, which may inhibit the mosquitoes from remaining on sprayed surfaces, forcing them to leave the house.” This observation referred to two actions of DDT on mosquito behavior: a contact-irritant action and a non-contact, spatial-repellent action.

Unfortunately, the appearance of DDT resistance and the formal startup of the global program helped change research emphasis from testing the efficacy of DDT in control programs to resistance testing and monitoring in spray programs. There was never a coordinated effort to define DDT’s mode of action. Some prominent malariologists, such as J. Zulueta, tried to change opinions about the importance of DDT’s complex actions against malaria. But, after many years of extensive DDT use in malaria control, reports on DDT resistance had accumulated and the view remained strong that DDT resistance meant that DDT would no longer be effective in affected areas. Regardless, as a result of his research, Zulueta embraced the idea of three separate DDT actions: toxic, contact irritant, and non-contact repellent.

However, A. Smith,<sup>11</sup> who was involved in WHO’s global search for DDT substitutes, later concluded that Zulueta and co-author Cullen’s data<sup>12</sup> did not constitute proof that the malaria vectors were greatly deterred from entering treated huts. It was not until they conducted their own investigation, that Smith and D.J. Webley<sup>13</sup> recognized that Zulueta and Cullen had been correct; DDT functioned as both a repellent and irritant. Unfortunately, their paper was not widely read and the popular belief that DDT functions by killing mosquitoes persisted as an official guiding policy of the WHO, until recently.

### **WHO’s recognition of spatial repellency and the way forward**

In its 2007 position statement, the WHO recognized DDT’s mode of action, stating:

DDT has a spatial repellency and an irritant effect on malaria vectors that strongly limit human-vector contact. Vector mosquitoes that are not directly killed by DDT are repelled and obliged to feed and rest outdoors, which contributes to effective disease-transmission control.<sup>14</sup>

WHO’s official recognition of DDT’s spatial repellency is welcomed and is an important step forward, but much more needs to be done. The scientific community must also recognize that modes of action other than toxicity are beneficial to disease control. Perhaps the greatest shortfall of past and present public health insecticide research and development efforts has been failure to focus on the multiple modes of chemical actions (especially non-contact repellent

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<sup>11</sup> Smith A. 1963 Deterrent effect of insecticides on malaria vectors (rebuttal). *Nature* 200:861-62.

<sup>12</sup> Zulueta J and Cullen JR. 1963 Deterrent effect of insecticides on malaria vectors. *Nature* 200:860-61.

<sup>13</sup> Smith A and Webley DJ. 1969 A verandah-trap hut for studying the house-frequenting habits of mosquitoes and for assessing insecticides. III. The effect of DDT on behavior and mortality. *Bull Entomol Res* 59:33-46.

<sup>14</sup> World Health Organization. Global Malaria Programme. The use of DDT in malaria vector control. WHO position statement. Available: [http://www.who.int/ipcs/capacity\\_building/who\\_statement.pdf](http://www.who.int/ipcs/capacity_building/who_statement.pdf)



action) that serve to interrupt human-vector contact and prevent disease transmission inside houses. This should become common knowledge through evidence-based research, which requires funding agencies to acknowledge that varying chemical characteristics exist with the potential to reduce disease transmission. If we are to improve vector control, we must elevate the role of breaking man-vector contact above the goal of killing mosquitoes. In other words, measures that stop mosquitoes from entering houses are more important than measures that reduce numbers of mosquitoes through toxic actions. This prioritization does not necessarily eliminate the need for toxic actions. Indeed, an optimal approach might be to use a killing agent (an insecticide) to deal with subpopulations of mosquitoes that enter houses in spite of active repellency. Combined actions can be obtained either in the form of a single compound that has multiple modes of action, as with DDT, or as a combination of repellent and toxic chemicals. In case of separate chemicals, the insecticide could potentially be used in rotation with a potentially non-toxic spatial repellent to reduce selective pressure for insecticide resistance.

The next step is to encourage investment into true alternatives to DDT that are also spatial repellents. Historically, investment in public health insecticides has been limited to reformulating agricultural pesticides for use in public health, rather than finding new public health insecticides; this must change.

Aside from a \$50 million grant from the Bill and Melinda Gates Foundation to the Innovative Vector Control Consortium (IVCC), no new investment of any significance has been made in the search for public health insecticides. The IVCC is an important and highly valuable consortium. Nevertheless, there is a profound and urgent need to fund many more research projects and to far greater levels in order to develop new public health insecticides and make them available to public health programs.

*More detailed information on this topic can be found in "The Excellent Powder: DDT's Political and Scientific History," available for purchase at <http://www.theexcellentspowder.org/>*