

KILLING MOSQUITOES TO PREVENT MALARIA

DDT and Africa

HISTORY OF DDT USE AND BANS

The insecticide dichlorodiphenyltrichloroethane (DDT) was used widely throughout the world for agricultural pest control beginning in 1940 and for disease vector control beginning in 1944.(1) Vectors targeted with DDT included mosquitoes, lice, and fleas responsible for typhus, plague, yellow fever, and malaria. Its use increased after World War II to include protection of crops, and peaked in the United States in 1959.(2)

Bans on DDT began in Hungary in 1968.(3) By 1972, mostly environmental concerns over the use of DDT led to a restriction of its use as a general pesticide in the United States.(4) Bans were also implemented in Norway and Sweden in 1970, and throughout the developed world until 1984, when DDT was banned in the United Kingdom.(5) Bans in the rest of the world followed, and in 2001, the Stockholm Convention on Persistent Organic Pollutants restricted the use of DDT for disease vector control.(1)

As a result of these severe restrictions, much of the DDT originally present in the environment now exists as one of its metabolites, most commonly dichlorodiphenyldichloroethylene (DDE), which is formed when a HCl is eliminated from DDT. Where DDE:DDT ratios are less than one in the environment, such as those found recently in fish species in Côte d'Ivoire, recent DDT use can be inferred.(6) With regard to those environmental concerns, DDT's use in a more limited role as a vector control agent continues in many parts of the world.

Recent vector control efforts in Africa focus on indoor residual spraying (IRS) in areas where malaria is endemic. The cost-effectiveness of DDT reported by a 2007 study was cited as a measure of superiority for malarial vector control over other insecticides.(1) A variety of other organophosphate, carbamate, and pyrethroid insecticides are recommended by the WHO for indoor residual spraying, and varying resistance in mosquitoes to all insecticides affects insecticide choice by region.(1)

The WHO guidelines for indoor residual spraying include considerations for insecticide susceptibility

Road from Nairobi to Nakuru, in the malaria-endemic Rift Valley of Kenya. Photo WAW.



"In DDT therefore, we also possess an extremely valuable remedy in the fight against malaria, this the most widespread of all contagious diseases which yearly affects about 300,000,000 people and causes a yearly death rate of at least 3,000,000. In the cases of many other diseases spread by insects, diseases such as plague, murine typhus and yellow fever, significant results have been obtained."

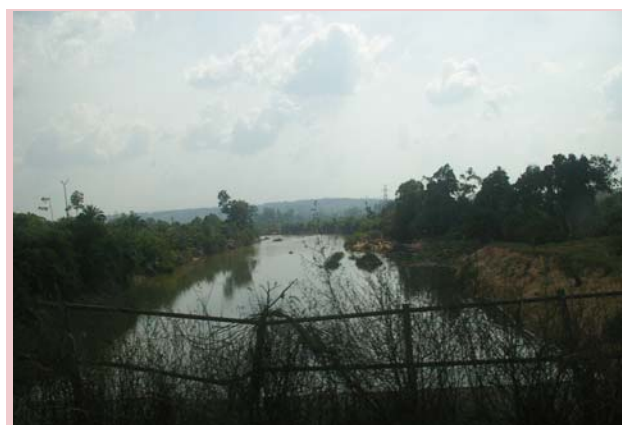
Speech by Professor G Fischer, member of the Staff of Professors of the Royal Caroline Institute, as he presented to the King of Sweden the 1948 Nobel Laureate in Physiology or Medicine, chemist Dr Paul Mueller, who identified the antimalarial properties of DDT.

and vector behavior, safety for humans and the environment, efficacy and cost-effectiveness, as well as sustained political support.(7)

DOES DDT ALTER MORBIDITY OR MORTALITY?

In addition to its cost-effectiveness, there is a relative lack of health concerns in humans that have resulted from using DDT in vector control. Possible concerns include neurological delays in breastfeeding babies, abbreviated lactation, higher incidence of preterm births, and impaired fertility, though hard evidence proving that these effects lead to increased mortality and morbidity is difficult to find.(1,8,9)

Most studies conclude there is no adverse effect in humans living in areas where widespread DDT use was once employed.(10,11) Vector control strategies, such as indoor residual spraying, also do not appear to cause harm to humans.(1) Liver function was unaffected not only in those benefiting from an indoor residual spraying program in South Africa, but also in those charged with applying DDT to households participating in an indoor residual spray-



River in Edo State, Nigeria. Globally, Nigeria suffers the greatest burden of malaria. Photo courtesy of Jessie Egoro.

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House in Lagos. Mosquitoes breed in clean water that pools in banana leaves, on tops of walls, particularly in broken glass bottles that are embedded on tops of walls for security. Photo WAW.

ing program.(12,13) A meta-analysis of studies attempting to correlate incidence of breast cancer with DDT exposure found no increased risk from DDE load.(14)

Even when adverse effects from DDT exposure are found, they are limited in their scope and severity. A 2006 study of neurodevelopment of Mexican-American children exposed to DDT found limited evidence of psychomotor and mental delays in children up to 2 years of age that correlated with exposure to DDT.(15) However, correlations between DDT and DDE and psychomotor and mental development were often insignificant at 95% confidence intervals, and were only 0.2 standard deviations or less when they were significant.

More recent environmental studies also support these assertions. Studies of Nile perch and tilapia from Lake Victoria in Uganda in 1998 found total DDT at 8% of the Australian maximum residue limits for DDT.(16) The Australian standard was the

strictest cited. United States Food and Drug Administration action concentrations were 5 times higher than the Australian standard.(16)

Studies of juvenile tilapia from the Tana River in Kenya from 1998 to 1999 measured concentrations of DDT that were below detection limits.(17) Concentrations of DDT in water samples from the Sabaki River in Kenya also had DDT levels that were below detection limits.(17) While DDE levels were considerably higher in fish samples from the Tana River, they were still only 14% of the Australian limit cited in the Ugandan study.(16,17) Concentrations of DDE in the Sabaki River were less than half that measured in the Tana River. In the Kenyan study, as well as most other DDT studies, analysis of other metabolites of DDT was included.

Even where DDT levels are considered high, the health risk is questionable. A 2006 study concluded that the Ouémé River catchment in Bénin "exceeded environmental quality standards".(18) However, a concomitant study concluded that the consumption of pesticides from fish in the Ouémé River did "not present an immediate risk".(19) A 2003 study of North American and African infant mortality concluded that the increased risk of death to infants from DDT application was comparable to the decrease in risk of infant death from malaria.(20)

Less obvious concerns, such as the effect of DDT on other drugs merit further study. A 2002 study of breastfeeding mothers using the non-steroidal anti-inflammatory drug paracetamol in Zimbabwe found that drug's half-life to be significantly reduced in those mothers as DDT concentrations in their milk increased.(20)

The mechanism of action of DDT has long been theorized to depend on the shape and size of the DDT molecule and the way it fits into voltage-gated sodium channels.(21) The molecule is believed to be of the appropriate size and shape to hold voltage-gated sodium channels of nerve cells in an open conformation, thereby slowing voltage gradient repolarization and encouraging repetitive discharges. Insects exposed to DDT exhibit hyperactivity and convulsions, consistent with this neurological hypothesis.(21)

RESISTANCE TO DDT

Mutations in the DDT target receptor at key amino acids have been shown to confer DDT resistance. The threonine to isoleucine or valine mutation at position 929 (T929I, T929V) and the leucine to phenylalanine or serine mutation at position 1014 (L1014F, L1014S) have been shown to desensitize insects to DDT.(22,23) Additionally, mutations at V410M, L925I, L932F, and S1032F have been implicated in DDT resistance mechanisms.(22,23) Three

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amino acid residues (C933, I936, F1530) which form hydrophobic binding contacts for DDT and are not conserved between arthropods and non-arthropods could be the source of selectivity for insect toxicity.(22) Insects are especially susceptible to DDT because it is readily absorbed through the insect cuticle.(21)

A 2006 modeling study of housefly sodium channels and homologous potassium channels identified several protein alpha-helices (IS6, IIS5, IIS6, IIIS6) within domains I, II, and III where these mutations are concentrated.(22) When the protein is folded, these helices come together to form the inner surface of the channel through which monovalent cations pass. The concentration of these mutations at amino acid positions which line the pore lend further evidence to the proposed mechanism of DDT action.

In addition to mutations in the target receptor, resistance to DDT is attributable in insects to more robust glutathione S-transferases (GSTs).(24) This class of enzyme transfers a tripeptide to its substrate, making the resulting product more water soluble and excretable. Given the high fat-solubility of DDT coupled with its chemical stability, GSTs add significantly to a mosquito's ability to excrete DDT from its system by giving them a more accessible pathway for elimination. Other enzymes with the ability to metabolize DDT, such as the mono-oxygenase p450, also have been implicated in DDT resistance.(25,26)

Though there are several pathways by which *Anopheles* could acquire DDT resistance, a search of recent literature gave limited evidence that they are resistant to DDT in the wild. A survey of *Anopheles arabiensis* and *Anopheles gambiae* mosquitoes from 11 sites in Mozambique from 2000 to 2002 showed 100% mortality after 24 hours after 1 hour exposure to 4% DDT, though limited resistance to other pyrethroids was noted.(26) Altered acetylcholinesterase activity in some of these mosquitoes suggested a low organophosphate and moderate carbamate resistance which would also favor the use of DDT. Resistance to DDT was noted more recently in Burkina Faso, where mosquitoes were also found to be resistant to pyrethroids, though these mosquitoes appear to represent the exception instead of the rule.(27)

CONCLUSIONS

The human health risks from use of DDT in IRS appear to be, at worst, a break-even proposal in infants, and include the possibility of mild neurodevelopmental delays. Data from non-infant populations suggest strongly that DDT poses a mild to insignificant health risk compared to risk of death

and debilitation from malaria, though further study may be warranted to determine DDT's effects in the presence of other drugs or chemicals. Its high toxicity to *Anopheles* mosquitoes, low toxicity to humans, and superiority over other pesticides in combating malaria should encourage health authorities to pursue its use in indoor residual spraying, making alternative pesticide choices only when insect DDT resistance rises or particular human individuals or populations exhibit increased sensitivity to its use.

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