

Health risks and benefits of bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT)

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DDT (bis[4-chlorophenyl]-1,1,1-trichloroethane) is a persistent insecticide that was used worldwide from the mid-1940s until its ban in the USA and other countries in the 1970s. When a global ban on DDT was proposed in 2001, several countries in sub-Saharan Africa claimed that DDT was still needed as a cheap and effective means for vector control. Although DDT is generally not toxic to human beings and was banned mainly for ecological reasons, subsequent research has shown that exposure to DDT at amounts that would be needed in malaria control might cause preterm birth and early weaning, abrogating the benefit of reducing infant mortality from malaria. Historically, DDT has had mixed success in Africa; only the countries that are able to find and devote substantial resources towards malaria control have made major advances. DDT might be useful in controlling malaria, but the evidence of its adverse effects on human health needs appropriate research on whether it achieves a favourable balance of risk versus benefit.

DDT (bis[4-chlorophenyl]-1,1,1-trichloroethane, also called dichlorodiphenyl trichloroethane) was first synthesised in 1874, and its insecticidal properties were described by Paul Müller in the late 1930s.¹ It was first used to protect military areas and personnel against malaria, typhus, and other vector-borne diseases. Commercial sales began in 1945, and DDT became widely used in agriculture to control insects, such as the pink boll worm on cotton, codling moth on deciduous fruit, Colorado potato beetle, and European corn borer. The compound was also used in silviculture and, in a powder form, as a directly applied louse-control substance in people. In the USA, use of DDT rose until 1959 (35 771 tonnes), after which it declined gradually (11 316 tonnes in 1970).¹⁻³ The eighth World Health Assembly in 1955 adopted a Global Malaria Eradication Campaign based on widespread use of DDT indoor and outdoor spraying against adult mosquitoes, and by 1967 endemic malaria was eradicated in developed countries and many subtropical Asian and Latin American countries. However, few African countries participated in the campaign. The 22nd World Health Assembly in 1969 ended the campaign after authorities realised that the infrastructure necessary to support global eradication did not exist. Additionally, mosquitoes were becoming resistant to DDT.⁴

Sweden banned DDT in 1970, the USA in 1972, and the UK in 1986, largely on the basis of ecological considerations, including persistence in the environment and sufficient bioaccumulation and toxic effects to interfere with reproduction in pelagic birds (ie, eggshell thinning).^{1,3,5,6} Toxic effects in human beings did not have a role in bans enacted during the 1970s. During the next 30 years, a combination of research findings and public concern led to bans of many other persistent chlorinated compounds, such as the cyclodiene pesticides (ie, dieldrin and mirex) and polychlorinated biphenyls. Before the Stockholm Convention on Persistent Organic Pollutants proposed a global ban of DDT and 11 other persistent organic pollutants in 2001,

some senior malaria experts objected, citing the rising burden of malaria in sub-Saharan Africa, the historical effectiveness of DDT against malaria vectors, and the absence of obvious toxic effects caused by DDT in human beings.⁷⁻⁹ More than two dozen countries, mostly in sub-Saharan Africa, requested exemption from the ban for DDT use in malaria vector control.¹⁰ However, adverse effects of DDT on human health have been reported, and these will probably affect the decision. Since the Stockholm Convention was to be effective from May, 2004,¹¹ a review of the currently available evidence was appropriate. We discuss some of the advances in knowledge about the toxic effects of DDT, especially chronic or delayed toxic effects occurring at low doses, including neurological, carcinogenic, reproductive, and developmental effects. Where possible, we review the potential for such toxic effects to take place at exposures expected to result from modern insect-control practices. We also consider the problem of the measurement and comparison of possible benefits of DDT in the reduction of malarial mortality, and the possible harm from an increase in non-malarial infant deaths.

DDT exposure and concentration in human tissues

Technical-grade DDT contains 65–80% p,p'-DDT, 15–21% o,p'-DDT, and up to 4% p,p'-DDD (bis[4-chlorophenyl]-1,1,1-dichloroethane).² When sprayed, DDT

Search strategy and selection criteria

We did a search of PubMed from the mid-1960s to February, 2005, for the use, body burden, and toxic and health effects of DDT. We used the keywords "DDT" and "DDE" and any of "malaria", "mosquito", "drug resistance", "toxicity", "health", "cancer", "reproduction", "oestrogen", "neurological", and "development". Of 3650 reports published on DDT, we gave preference to studies in the past 5 years on human health effects of DDT.

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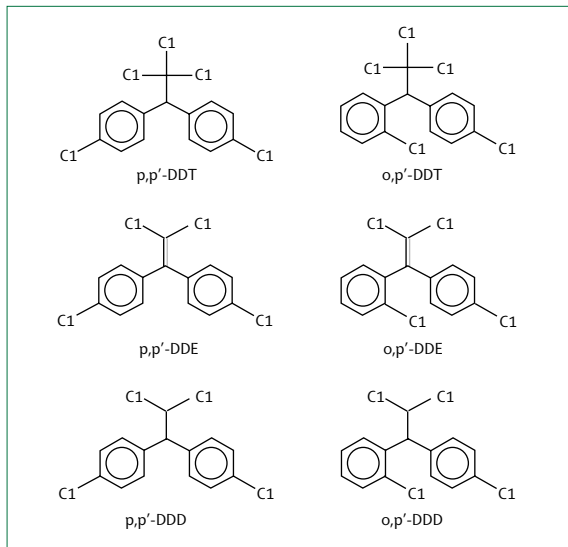


Figure 1: Chemical structures of isomers of DDT, DDE, and DDD

can drift, sometimes for long distances. In the soil, the compound can evaporate or attach to wind-blown dust. In the environment, DDT breaks down to *p,p'*-DDE (bis[4-chlorophenyl]-1,1-dichloroethene),¹ an extremely stable compound that resists further environmental breakdown or metabolism by organisms. DDE is the form usually found in human tissue in the highest concentration, especially in areas where there has been no recent use of the parent compound. Figure 1 shows the chemical structures of these DDT isomers. The general population is exposed to DDT mainly through food, whereas occupational exposures are mainly through inhalation and dermal contact. DDT and DDE can also be transferred from the placenta and breastmilk to fetuses and infants. Although some ingested DDT is converted to DDA (bis[4-chlorophenyl]-acetic acid) and excreted, any non-metabolised DDT and any DDE produced is stored in fat, as is all absorbed DDE, which cannot be metabolised. DDT and DDE are highly soluble in lipid; their concentrations are much higher in human adipose tissues (about 65% fat) than in breastmilk (2.5–4% fat), and higher in breastmilk than in blood or serum (1% fat).¹² The half-life of DDE is about 7–11 years.¹³ DDT and DDE concentrations increase with age.¹²

With the use of DDT declining since the 1970s, concentrations of DDT and its metabolites in human tissue have fallen greatly worldwide.^{14,15} Currently, people in Europe, the USA, Canada, Australia, New Zealand, and Japan have lower concentrations of DDT compounds in their tissues than previously. For example, in Sweden, the total DDT concentration in breastmilk fat was 2.9 µg/g in 1972 and 0.3 µg/g in 1992. However, in Central and South America, Mexico, Africa, and some Asian countries, where DDT has been used for vector control in the past 5–10 years, DDT concentrations in human tissues remain high. For

example, in Mexico, the total DDT concentration in breastmilk fat was 5.7 µg/g in 1994–95 and 4.7 µg/g in 1997–98.¹⁶ In South Africa, continuous DDT spraying has resulted in a median DDE concentration range of 5.2–7.7 µg/g in breastmilk fat in the treated area, compared with a much lower 0.4–0.6 µg/g in the untreated area.¹⁷ In South Africa, the mean concentration of serum DDE in a DDT-treated area was 103 (SD 85) µg/L whereas in an untreated area the value was 6 (7) µg/L.¹⁸ In countries with DDT use in the past 5–10 years, the DDT-to-DDE concentration ratio, which can approach 100% in these areas, is much higher than that in Europe or the USA (2–20%).¹⁴

Workers using DDT to control mosquitoes have very high DDT concentrations. Mexican data revealed that the geometric mean of total DDT was 104.48 µg/g in adipose tissue of 40 DDT sprayers in 1996;¹⁹ whereas in Finland, the USA, and Canada, the value was less than 1 µg/g in adipose tissue in the general population.¹⁴ In another Mexican study, the serum concentration of *p,p'*-DDE was much higher in DDT sprayers (188 µg/L) than in children (87 µg/L) and in adults (61 µg/L) who lived in sprayed houses but were not otherwise exposed to DDT.²⁰

Toxic effects of DDT

Toxic effects of DDT and its analogues have been extensively studied in laboratory animals. Acute exposure to a high dose of DDT can cause death.¹² Exposure to DDT or DDE increases liver weight, induces liver cytochrome P450 (CYP) 2B and 3A and aromatase,^{21–23} and causes hepatic-cell hypertrophy and necrosis.¹² DDT is insecticidal because of its neurological toxic effects. In laboratory animals, DDT causes hyperactivity, tremor, and seizures. DDT is carcinogenic in mice and rats, mainly causing liver tumours,¹² although negative results are also seen,²⁴ and the compound is carcinogenic in non-human primates.²⁵ The *o,p'*-DDT isomer is the most oestrogenic component of the DDT complex (having a relative binding affinity to oestrogen receptors of 2.9×10^{-3} relative to 17-β oestradiol),²⁶ with *p,p'*-DDT being much less oestrogenic than its *o,p'* isomer. The *p,p'*-DDE isomer is anti-androgenic by inhibitive binding to androgen receptors (with a relative binding affinity to androgen receptors of 3.1×10^{-3} relative to dihydrotestosterone),^{27,28} Prenatal exposure to DDT in early pregnancy in rabbits can reduce overall fetal bodyweight and brain and kidney weight in offspring.²⁹ Immunosuppressive effects of DDT have been shown in rats and mice.^{30,31}

In people, DDT use is generally safe; large populations have been exposed to the compound for 60 years with little acute toxicity apart from a few reports of poisoning.¹² Doses as high as 285 mg/kg taken accidentally did not cause death, but such large doses did lead to prompt vomiting. One dose of 10 mg/kg can result in illness in some people.¹² Subclinical and subtle

functional changes have not been meticulously sought until the past few decades.

Neurobehaviour

DDT poisoning usually results in paresthesia, dizziness, headache, tremor, confusion, and fatigue.¹² Occupational exposure to DDT was associated with reduced verbal attention, visuomotor speed, sequencing, and with increased neuropsychological and psychiatric symptoms in a dose-response pattern (ie, per year of DDT application) in retired workers aged 55–70 years in Costa Rica.³² Although DDT or DDE concentrations were not determined in this study, they probably were very high. People who regularly consumed fish from the American Great Lakes were reported to have higher serum DDE concentrations (median 10 µg/L) than those who did not eat fish (5 µg/L), but they did not show impaired motor function,³³ impaired executive and visuospatial function, or reduced memory and learning.³⁴

Cancer

Although extensively studied, there is no convincing evidence that DDT or its metabolite DDE increase human cancer risk. Mainly on the basis of animal data, DDT is classified as a possible carcinogen (class 2B) by the International Agency for Research on Cancer (IARC)³⁵ and as a reasonably anticipated human carcinogen by the US National Toxicology Program.³⁶

Breast cancer has been examined most closely for an association with p,p'-DDE. In a study in 1993,³⁷ breast cancer patients had higher serum DDE concentrations (11.8 µg/L) than controls (7.7 µg/L), and results from several subsequent studies supported such an association.^{38–41} However, large epidemiological studies^{13,42–49} and subsequent pooled and meta-analyses^{50–52} failed to confirm the association. Most of these studies have been analysed, accounting for several factors including sample size, exposure, and odds ratios. Good evidence now indicates that, in white women in North America or Europe, DDE does not raise breast cancer risk, irrespective of oestrogen receptor status in the tumour or polymorphisms in host metabolic enzymes (glutathione-S-transferase, CYP).⁵³ The role of o,p'-DDT—the most oestrogenic isomer—in areas of recent DDT use still needs further investigation.^{52,53}

With detailed work history of chemical manufacturing workers to estimate DDT exposure, a nested case-control study⁵⁴ reported occupational DDT exposure associated with increased pancreatic cancer risk. A weak association of self-reported DDT use with pancreatic cancer was reported in another case-control study.⁵⁵ A report indicated a higher standardised mortality ratio for pancreatic cancer in outdoor workers with a history of DDT exposure of less than 3 years, but the standardised mortality ratio of DDT workers with exposure of 3 years or more was not significantly raised.⁵⁶ The association of serum DDE concentrations (median 1.3 µg/g and

1.0 µg/g lipid in cases and controls, respectively) with pancreatic cancer was not clearly shown in another study when co-exposure to polychlorinated biphenyls was taken into account.⁵⁷ Although one study reported higher DDT and DDE concentrations in *K-ras*-mutated pancreatic cancer patients than in controls,⁵⁸ this finding was not reported from another study.⁵⁹

Previous case-control studies have suggested that a history of DDT use was associated with a raised risk of non-Hodgkin's lymphoma,^{60,61} but subsequent studies⁶² using measurements of total DDT concentrations in serum did not find such increased risk. Two other studies^{63,64} using the history of DDT application as the exposure measure and one⁶⁵ using adipose DDE concentration reported a slightly raised risk associated with DDT or DDE, but the effect disappeared if data were adjusted for history of use or concentration of other pesticides.

Data from an Italian study⁶⁶ of malaria workers showed that, although those directly exposed to DDT had raised risk of liver and biliary tract cancers, workers who did not have direct occupational contact with DDT also showed increased risk.⁶⁶ Another ecological study in 22 US states indicated a correlation between adipose DDE amounts and age-adjusted liver-cancer mortality rates in white men in a multivariate analysis, but not in white women or black men.⁶⁷ In both studies no individual measure of DDT exposure was available, thus making interpretation difficult.

Association of DDT with multiple myeloma,^{66–68} prostate and testicular cancer,^{69,70} endometrial cancer,^{71–73} and colorectal cancer⁷⁴ was sought but results have been inconclusive or generally do not support an association.

Reproductive health

Various reproductive and hormonal endpoints have been examined in both men and women, and although associations have been recorded, causal links have not been confirmed. In Chiapas, Mexico, where DDT was sprayed for malaria control, serum p,p'-DDE concentrations were inversely correlated with semen volume, sperm count, and bioavailable-to-total testosterone ratios in 24 young men not occupationally exposed to DDT.⁷⁵ However, results from another study of South African malaria workers did not confirm these findings although their exposure was nearly as high as that previously reported.^{76,77} Studies of populations with a much lower exposure than that seen in current malaria-endemic areas have shown only weak, inconsistent associations between DDE and testosterone amounts, semen quality, and sperm DNA damage.^{78–84}

An increase of 15 µg/L of DDE in maternal serum was associated with a 1-year advance of the age at menarche in daughters.⁸⁵ One cross-sectional study in Laotian immigrants to the USA with high DDT (mean 2 µg/L) and DDE (21 µg/L) concentrations indicated that the highest quartiles of concentration were associated with a

reduction of 1.5 days in the mean luteal-phase length of menstrual cycles.⁸⁶ Data from the large US Collaborative Perinatal Project undertaken in 1959–66 did not show any association between DDE concentration and menstrual-cycle length.⁸⁷ Raised DDE concentration was associated with earlier natural menopause in two studies.^{88,89}

With respect to time to pregnancy, an increase of 10 µg/L of p,p'-DDT in maternal serum was reported to reduce daughters' probabilities of pregnancy by 32%, whereas the same increase in p,p'-DDE concentrations raised the probability by 16%.⁹⁰ The discrepancy of DDT and DDE effect cannot be easily explained by any known mechanism, and these results need confirmation. Spouses of DDT users were shown to have a non-significantly lower probability of pregnancy than those unexposed.⁹¹

Data from the US Collaborative Perinatal Project indicated that DDE correlated with the risk of spontaneous abortion,⁹² which were consistent with findings from four small studies.^{93–96} However, two other studies^{97,98} did not show these results. A study⁹⁹ of 45 recurrent miscarriage cases and 30 controls showed no increased risk associated with DDE, but the DDE concentrations were much lower than those in previous studies.

Raised serum concentration of DDE correlated with risk of preterm delivery in the US Collaborative Perinatal Project data, with odds ratios of 1.5–3.1 for DDE amounts of 15 µg/L or more compared with those less than 15 µg/L,¹⁰⁰ in accordance with several small studies.^{94,97,101,102} Another US study did not show the same results,¹⁰³ although the median DDE concentration was only 1.4 µg/L in that study (much lower than the concentration in the Collaborative Perinatal Project¹⁰⁰). DDE has also shown an association with small-for-gestational-age in data from the US Collaborative Perinatal Project,¹⁰⁰ low birthweight in a study of fish eaters in the Great Lakes,¹⁰⁴ and intrauterine growth restriction in a small Indian study.¹⁰⁵ However, other studies in North Carolina, USA,¹⁰⁶ Greenland,¹⁰⁷ Ukraine,¹⁰⁸ and Michigan, USA,¹⁰⁹ with various DDE or DDT concentrations, failed to find this association.

Low incidence of birth defects reduces the power of studies examining the causal effect of DDT. The US Collaborative Perinatal Project data have been consistent with a small increase in risk for cryptorchidism, hypospadias, and polythelia with very high concentrations of DDE in maternal serum DDE (>60 µg/L), but the results are inconclusive,¹¹⁰ similar to another study.¹¹¹ Two other studies found no association between concentrations of DDT and DDE and hypospadias¹¹² or cryptorchidism.¹¹³ In a study of Mexican anti-malaria workers, high paternal DDE concentration (>61 µg/g lipid) was associated with a raised risk of birth defects, but these birth defects were few and mostly arose in the nervous system.¹¹⁴

High DDE concentration in breastmilk has shown an association with a shortened duration of lactation.^{115,116} In

858 women, those with the highest concentration of DDE in milk (>6 µg/g lipid) weaned at an average of 2.5 months, whereas those with the lowest concentration (<1 µg/g lipid) weaned at 6.5 months.¹¹⁵ In 229 Mexican women, rising DDE amounts in breastmilk (from <2.5 µg/g to >12.5 µg/g lipid) were associated with a reduction in the mean duration of lactation (from 7.5 months to 3 months).¹¹⁶ The table summarises the overall findings of reproductive outcomes and DDT exposure amounts in different populations.

Infant and child development

Although infant and child growth and neuro-development have been studied, no study has been large enough to show an effect on infant and child survival. In a German study,¹¹⁷ girls with the highest quartile of DDE concentration (>0.44 µg/L whole blood) were an average of 1.8 cm shorter at age 8 years than girls with the lowest quartile of DDE; the difference narrowed at age 9 years and disappeared at age 10 years. However, no such effect was seen in boys. Another study did not show any association between maternal serum DDE and anthropometric and pubertal measures in boys.¹¹⁸ However, follow-up of children in North Carolina showed that at age 12–14 years, the height of boys (but not girls) at puberty rose with transplacental exposure to DDE. Age at pubertal stages, which was mostly assessed prospectively, was unaffected by any measure of DDE exposure.¹¹⁹ Serum concentration of p,p'-DDE (>1 µg/L) was associated with precocious puberty in one unconfirmed study.¹²⁰

DDE concentration in the blood serum of the umbilical cord was negatively associated with mental and psychomotor development of children assessed at 13 months of age.¹²¹ A longitudinal study^{122–124} showed no association between transplacental or lactational DDE exposure and children's cognitive or motor development at age 12–60 months or school reports at age 10 years. The Program for International Student Assessment study¹²⁵ showed that high DDT concentration in human milk could be inversely associated with mental capacities at age 15 years.

Immunology and DNA damage

Increased plasma concentrations of DDE were associated with raised IgA in one study¹²⁶ and with reduced IgG in another.¹²⁷ Plasma p,p'-DDE was inversely associated with in-vitro secretion of tumour necrosis factor (TNF) α by umbilical cord-blood mononuclear cells.¹²⁸ Do these effects translate into immunological disorders with clinical consequences? One study suggested that raised prenatal exposure of p,p'-DDE increased the risk of otitis media in Inuit infants,¹²⁹ but this association was not seen in another study.¹¹⁵ In Mexican women, blood concentrations of DDT, DDE, and DDD were associated with DNA damage in blood cells measured by comet assays,¹³⁰ but data from US residents living near a

pesticide dump site did not indicate any such relation between plasma DDE and lymphocyte micronuclei, although DDE was associated with reduced mitogen-induced lymphoproliferative activity.¹²⁶

Efficacy and effectiveness of DDT for malaria control

Convincing historical evidence has shown that indoor residual house-spraying with DDT was the main method by which malaria was eradicated or greatly reduced in many countries worldwide in the 1940s to 1960s. However, these programmes had not been aimed to rigorously investigate the efficacy of individual components nor of local factors that might modify their effects. In sub-Saharan Africa, early pilot projects of malaria eradication also showed that the disease is highly responsive to vector control by DDT and to aggressive treatment campaigns to eliminate residual foci of transmission. Despite reductions in anopheline vectors and malaria cases, transmission could not be interrupted in the endemic tropical and lowland areas of sub-Saharan Africa.¹³¹ Subsequently, international interest in malaria and funding for malaria research and control waned in most countries on the continent. As a result, residual spraying was not used in sub-Saharan Africa, apart from southern Africa and some islands such as the Reunion, Mayotte, Zanzibar, Cape Verde, and São Tome. In southern Africa, the countries that have developed national malaria control programmes have built up human, financial, and organisational resources for great advances in malaria control.¹³²

However, the effectiveness of DDT can be compromised by insecticide resistance and social resistance to DDT indoor spray. Because of the irritating, excito-repellent nature of the DDT residue, some mosquitoes tend to leave before they have absorbed a lethal dose, or tend to avoid entering the house or resting on the wall at all.¹³¹ By the end of Global Malaria Eradication Campaign, some mosquito species had developed resistance to DDT, especially in India and Sri Lanka.¹ In 1968, high amounts of resistance to DDT in *Anopheles gambiae* was reported in Upper Volta (now Burkina Faso); shortly thereafter, DDT had no effect on mosquito mortality, biting frequency, or resting in houses in trials undertaken in Togo and Senegal.¹³¹ In the 1980s when DDT was judged to control the resurgence of malaria in Zanzibar after the DDT spraying programme finished in 1968, resistance was found in *A gambiae* ss and *A arabiensis*.¹³³ In 2002, 2 years after DDT residual spraying was reintroduced in KwaZulu-Natal to control the increase of malaria cases, resistance was recorded in *A arabiensis*, although *A funestus* was still susceptible to DDT.¹³⁴ Social resistance to DDT indoor sprays occurs because bedbugs are resistant to DDT, and DDT leaves stains on walls, which residents then replaster.¹³² In practice, the efficacy of DDT spraying for vector control depends on the

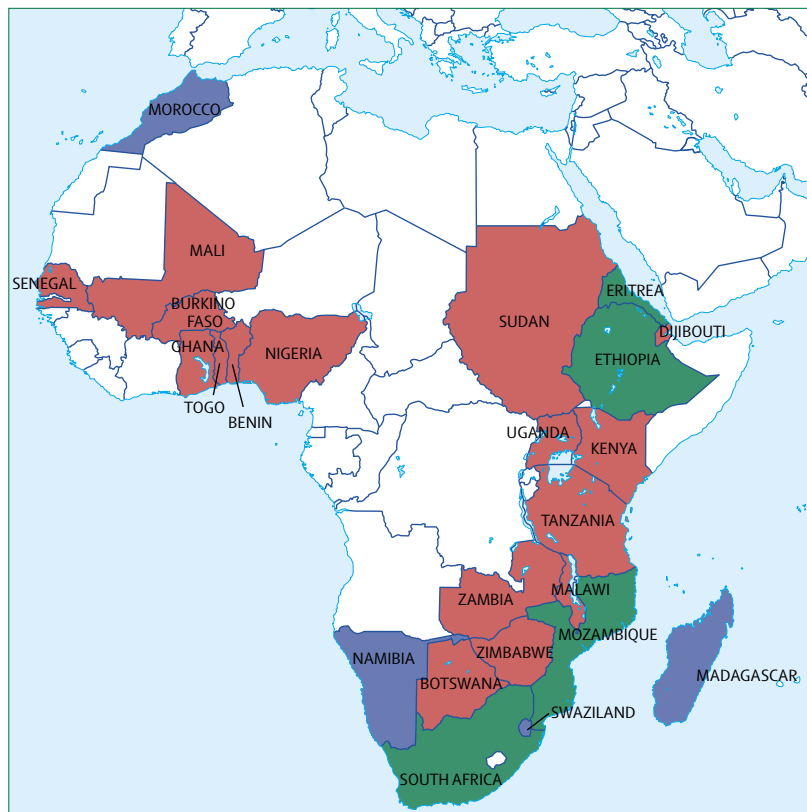


Figure 2: Roll Back Malaria strategic plans in African countries

Countries are coloured if their national strategic plan is to use insecticide residual spraying (blue), insecticide-treated bed nets (red), or both (green). Countries with undetermined plans are not coloured. Adapted from reference 137, with permission from Elsevier.

coverage of spraying, mosquito species, and resistance to DDT. Climate—especially rainfall, temperature, and latitude—could affect the stability of transmission, and thus also affect DDT efficacy. WHO points out that DDT spraying is “most effective in reducing the overall malaria burden in unstable transmission areas, areas with marked seasonal transmission peaks and disease outbreaks, and highland areas”.¹³⁵

A report from Chingola and Chiliabombwe, Zambia, showed that spray coverage of all houses with DDT (80%) or pyrethroid (20%) between peak transmission in 2000 resulted in a 35% fall in malaria incidence in the subsequent 6 months compared with 2 years before spraying.¹³⁶ Currently in Africa, indoor residual spraying (mainly with DDT) has become part of the national Roll Back Malaria strategic plan in several countries (figure 2).¹³⁷ Data for the efficacy of DDT are increasing and will be used to assess the efficacy of DDT spraying.

Debate and decision-making

Since evidence now indicates that DDT might have adverse effects on human health, it is prudent to consider currently available evidence of benefits and possible risks of DDT use in the context of modern malaria control.

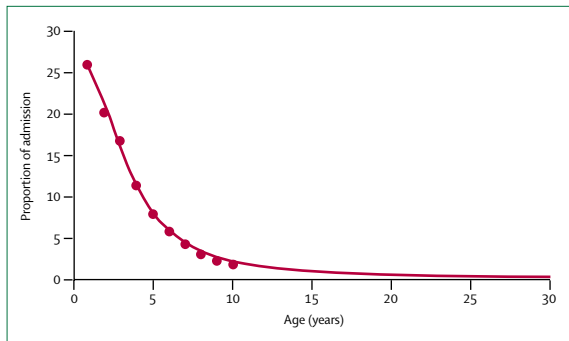


Figure 3: Predicted proportional age-specific malaria mortality in Africa, by admission
Adapted from reference 138, with permission.

Infants are generally known to bear the burden of mortality from malaria worldwide (figure 3);¹³⁸ most such mortality occurs in the first 5 years of life and in areas south of the Sahara (figure 4).¹³⁹ The decision to use DDT would be straightforward if we had data from trials in sub-Saharan Africa showing larger reductions in infant mortality in houses treated with DDT than reductions in houses treated with a different insecticide or where bed nets are used. However, such data are unavailable, and thus any such decision will need several assumptions.

Benefits of DDT spraying in sub-Saharan Africa

The success of the Malaria Eradication Campaign in 1955–69 was attributed to DDT.¹ However, these programmes often included other components, such as

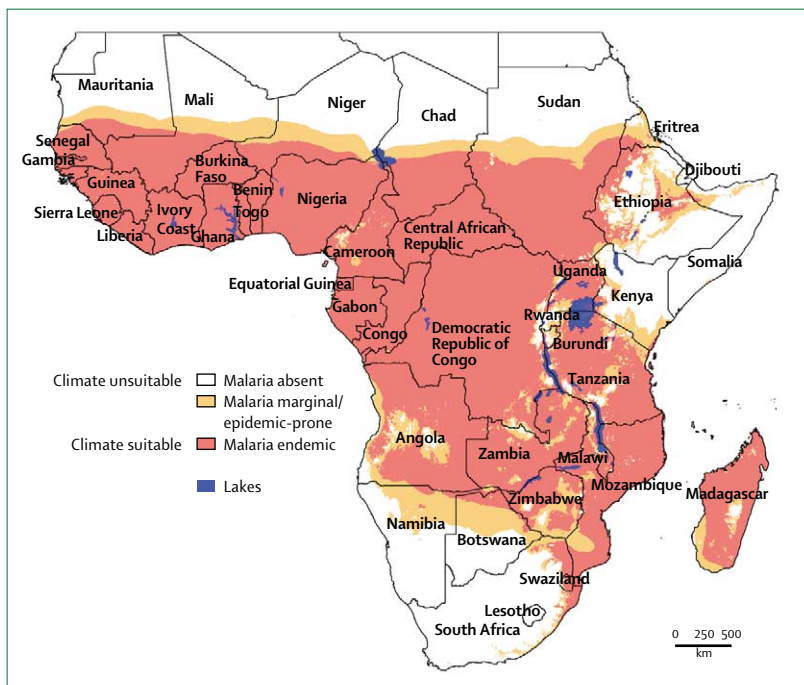


Figure 4: Distribution of endemic malaria in Africa
Adapted from reference 139, with permission.

provision of basic medical care, and were not designed to allow investigation of their individual parts. Thus, Giglioli¹⁴⁰ showed large improvements in infant and all-cause mortality during three decades for employees of the sugar plantations in South America, but the quantitative role of DDT is impossible to specify. Without the appropriate controls, the effects of secular trends also cannot be disentangled.¹⁴¹ Moreover, effective malaria prevention programmes can be associated with a fall in infant mortality that is larger than can be accounted for if malaria is eliminated entirely as a cause of death. This problem could be due to malaria’s ability to produce anaemia and immunodeficiency in both mother and child (rendering them susceptible to death from other causes) or due to other interventions.¹⁴² Because poverty, malnutrition, diarrhoea, and respiratory diseases account for most infant mortality in sub-Saharan Africa, the benefits of DDT use could be dwarfed by interventions to improve nutrition, vaccination, sanitation, personal hygiene, and medication accessibility.

Snow and colleagues¹⁴³ attempted to estimate malaria mortality for African children in the subcontinent. They reported that the median number of deaths from malaria in children aged 0–4 years in population-based studies was nine in 1000 per year; on the basis of deaths occurring in hospital, four in 1000; and in children aged up to 59 months attributable to malaria from intervention studies, seven in 1000. These numbers might not have included all infant deaths that could be avoided by malaria prevention, such as those from preterm delivery and with low birthweight caused by maternal malaria during pregnancy. Maternal malaria was estimated to have caused 3–8% of all infant deaths in areas of Africa with stable malaria transmission.¹⁴⁴ Thus, residual spraying with DDT might end mortality from malaria and reduce overall infant mortality if most or all dwellings are sprayed at least twice a year, if malaria-transmitting mosquitoes do not become resistant, if few people clean or replaster the sprayed wall, and if funding and personnel are always available for residual spraying, among other actions. However, under the actual conditions in sub-Saharan Africa, various technical and logistical barriers hamper the achievement of this goal.

Risks of DDT spraying in sub-Saharan Africa

For indoor residual spraying to effectively prevent infant mortality from malaria, women of child-bearing age, pregnant women, and breastfeeding women will need to be exposed to DDT. Such spraying might be without the ecological effects that caused the ban (although more data are needed), but will unavoidably expose women to amounts of DDT that are associated with forms of toxic effects that might increase infant mortality. Of adverse effects to human health, reproductive outcomes are the major concern (table). Of these, the association of DDE with increased risk of preterm birth and earlier weaning are most relevant to sub-Saharan Africa.^{100,115,116} Although

Ref	Design and population	DDT or DDE concentrations	Effects
Semen quality			
75	24 men from DDT-sprayed area in Mexico (mean age 21 years)	Mean p,p'-DDE 78 µg/g serum lipid	DDE amounts inversely associated with semen volume, sperm count, and testosterone concentration
76,77	47 malaria workers in South Africa (mean age 45 years)	Mean p,p'-DDE 52 µg/g serum lipid	No consistent association with oestradiol, testosterone, or semen quality
78	137 black farmers in the USA (mean age 62 years)	Median p,p'-DDE 1.2 µg/g serum lipid or 7.7 µg/L serum	Only top tenth percentile of DDE associated with reduced testosterone
79	110 Baltic seafood eaters (age range 23–79 years)	Median p,p'-DDE 0.8 µg/g serum lipid	Weak, negative (but non-significant) association with testosterone
80	107 previous malaria workers in Italy (mean age 78 years)	Median p,p'-DDE 0.4 µg/g serum lipid	No association with oestradiol, testosterone, luteinising hormone, follicle-stimulating hormone, and sex-hormone-binding globulin
81,82	212 male partners of subfertile couples in the USA (mean age 37 years)	Median p,p'-DDE 0.2 µg/g serum lipid	Weak association with sperm motility but not with sperm concentration, morphology, and DNA damage
83,84	195 Swedish fishermen (median age 51 years)	Median p,p'-DDE 0.2 µg/g serum lipid	Percentage of sperm DNA fragmentation index rose non-significantly with DDE dose; no association with other semen indices
Menstrual cycle			
89	219 Hispanic women in the USA	Mean p,p'-DDE 36 µg/L serum	High DDE concentration associated with early age at menopause
87	2314 pregnant women in the USA	Mean DDE 30 µg/L	Menstrual cycle irregularity slightly increased, no association with cycle length and bleeding duration
86	50 Laotian immigrants coming to the USA	Mean DDE 21 µg/L serum	Highest quartile of DDE associated with reduced mean luteal-phase length (by 1.5 days) and decreased progesterone during luteal phase
85	151 offspring of anglers in the USA	Maternal DDE range 0–17 µg/L serum	High maternal DDE associated with decreased age at menarche
88	1407 women in a breast cancer case-control study in the USA	Median DDE 3 µg/L plasma	High DDE associated with early age at menopause
Time to pregnancy			
90	289 women born in the early 1960s in the USA	Maternal postpartum median p,p'-DDE 48 µg/L serum, p,p'-DDT 13 µg/L serum	DDE associated with raised probability of pregnancy, and DDT associated with reduced probability of pregnancy
91	Spouses of 105 malaria workers in Italy	Work history	Slightly increased stillbirth rate; reduced male-to-female ratio among offspring and probability of pregnancy in DDT users
Spontaneous abortion			
94	10 cases and 25 controls in India	Mean DDE 164 µg/L (cases) and 13 µg/L serum (controls)	Raised DDE associated with increased risk of spontaneous abortion
92	1717 pregnancy women in the USA	Median DDE 25 µg/L serum	Raised DDE associated with increased fetal loss in previous pregnancies
93	15 cases and 15 controls in China	Mean DDE 22 µg/L (cases) and 12 µg/L serum (controls)	Raised DDE associated with increased risk of spontaneous abortion
98	120 cases and 120 controls in Italy	Mean DDE 5.2 µg/L (cases) and 4.6 µg/L serum (controls)	No associations recorded
96	89 women with repeated miscarriages in Germany	Mean DDE 1.2 µg/L serum	14% of cases with DDE higher than range of previously investigated reference population
99	45 cases and 30 controls in Japan	Mean DDE 0.7 µg/L (cases) and 0.9 µg/L serum (controls)	No associations recorded
Preterm delivery			
94	15 preterm cases and 25 full-term controls in India	Mean DDE 58 µg/L (cases) and 13 µg/L serum (controls)	Cases had higher maternal DDE concentrations than did controls
100	2613 pregnant women in the USA	Median DDE 25 µg/L serum	Raised maternal DDE associated with increased risk of preterm delivery
103	20 preterm cases and 20 full-term controls in the USA	Median DDE 1.3 µg/L (cases) and 1.4 µg/L serum (controls)	No association recorded
102	100 preterm cases and 133 full-term controls in Mexico	Median DDE 0.19 µg/g (cases) and 0.15 µg/g serum lipid (controls)	Suggestive positive relationship between DDE and preterm delivery
Birthweight			
100	2613 pregnant women in the USA	Median DDE 25 µg/L serum	Raised maternal DDE associated with increased risk of small-for-gestational-age
106	912 infants in the USA	Maternal median DDE at birth 13 µg/L serum	Maternal DDE burden not associated with birthweight
105	30 intrauterine growth restriction cases and 24 controls in India	Mean DDE 9 µg/L (cases) and 6 µg/L serum (controls)	Raised maternal DDE associated with increased risk of intrauterine growth restriction
107	178 newborn babies in Greenland	Maternal mean DDE 5 µg/L plasma	No association with birthweight
104	119 frequent fish eaters and 24 infrequent fish eaters in the USA	Median DDE 2 µg/L (frequent eaters) and 1 µg/L serum (infrequent eaters)	Natural log of maternal serum DDE inversely associated with birthweight
108	197 singleton infants in Ukraine	Median DDE 2.5 µg/g breastmilk fat	No association between DDE and birthweight after adjustment for potential confounders
Birth defects			
111	75 cryptorchidism, 66 hypospadias and 283 control babies in the USA	Median DDE 43 µg/L (cryptorchidism and controls) and 41 µg/L (hypospadias)	DDE ≥61 µg/L resulted in slightly raised but non-significant risk for both defects
110	219 cryptorchidism, 199 hypospadias, 167 polythelia, and 552 control babies in the USA	Median DDE 24 µg/L (cryptorchidism, hypospadias, and controls) and 32 µg/L (polythelia)	DDE ≥60 µg/L resulted in slightly raised risk for investigated birth defects, but results were inconclusive
Duration of lactation			
116	229 postpartum women in Mexico	Median DDE 6 µg/g breastmilk fat	Raised DDE associated with reduced duration of lactation
115	858 postpartum women in the USA	Median DDE 2 µg/g breastmilk fat	Raised DDE associated with reduced duration of lactation

Rows are in order of decreasing serum DDE dose.

Table: Summarised DDT and DDE effects on reproductive outcomes

causality has not been established and the studies were done in North America, the methods are not so flawed that the findings can be dismissed by argument.

If we assume that preterm births and early weaning are caused by DDT exposure, that the strength of the association is similar to that observed in North American studies, and that previous weaning or early birth carries a risk of mortality in Africa similar to the risk elsewhere, we would estimate that about 20 excess deaths per 1000 livebirths will result from continuous DDT indoor residual spraying (ie, serum DDE >60 µg/L or breastmilk DDE >5 µg/g lipid).¹⁴⁵ The risk estimate provides a general framework of risk assessment in sub-Saharan Africa, although applicability to a specific country or area depends on the variation in malaria transmission, total infant mortality, DDT spraying strategy, incidence of preterm birth, and duration of lactation.

Balance of benefits and risks from DDT use in malaria control

Malaria remains a difficult problem in Africa. Indoor residual spraying of DDT could be effective in some settings; the procedure is unlikely to lift the entire malaria mortality burden in infants and children. Additionally, if continuous DDT spraying does cause increased preterm births and shortened breastfeeding duration, infant deaths will occur, perhaps to the same extent as the deaths spraying would potentially prevent. Mothers would also carry a body burden of DDT, and even if they were to leave the malaria-protected house, they would still have raised risk of preterm birth and early weaning. Other risks, such as neurological and reproductive effects in spraying staff, might also apply.

Whether such problems do or do not occur is still uncertain, since they cannot be dismissed on grounds of low doses or flawed studies nor can they be reasonably assumed to happen. In areas where DDT is to be introduced, reintroduced, or continuously used for malaria control, caution based on the accumulation of evidence of adverse DDT effects in people is appropriate. Whenever possible, proper controls in the assessment of DDT efficacy and continued parallel research on its effect in human beings should be undertaken. Alternative antimalarial approaches such as use of insecticide-treated bed nets, intermittent presumptive treatment during pregnancy, early diagnosis, artemisinin-based treatment, combination regimen treatment, and health education are all effective.^{146–148} Well-coordinated anti-malarial efforts in combination with efficient health infrastructure should have improved success in malaria control than the sole reliance of disease control on indoor residual spraying of DDT.

Future perspectives

DDT was originally banned because of ecological effects, such as eggshell thinning, and accumulation in the environment and organisms, including human beings.

Although acute toxic effects are scarce, toxicological evidence shows endocrine-disrupting properties; human data also indicate possible disruption in semen quality, menstruation, gestational length, and duration of lactation. The research focus on human reproduction and development seems to be appropriate. DDT could be an effective public-health intervention that is cheap, longlasting, and effective. However, various toxic-effects that would be difficult to detect without specific study might exist and could result in substantial morbidity or mortality. Responsible use of DDT should include research programmes that would detect the most plausible forms of toxic effects as well as the documentation of benefits attributable specifically to DDT. Although this viewpoint amounts to a platitude if applied to malaria research in Africa, the research question here could be sufficiently focused and compelling, so that governments and funding agencies recognise the need to include research on all infant mortality when DDT is to be used.

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