

A risk analysis model with an ecological perspective on DDT and malaria control in South Africa

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Abstract

The Stockholm Convention on Persistent Organic Pollutants granted a controversial exemption for some countries to continue using DDT. DDT has a history of use in malaria control, but widespread concern about health risks led to declining use. A science-based policy analysis of existing published literature was conducted to consider DDT toxicology and malaria risk in South Africa to generate data for a model that tests DDT risks and benefits in relation to infant mortality. This study investigated one aspect of DDT toxicology and risk analysis, and in the process, provided an insight into the effects of scrutinising risks and benefits more carefully than by means of aggregated data. When comparing infant mortality risk from malaria with infant mortality from DDT the results suggested that the net benefit of DDT application relies on certain assumptions associated with the toxicity of DDT. When the analytical model was run based on the best estimates available of the impact of DDT on infant mortality, the costs of DDT application outweighed the potential benefits in areas of low endemicity. According to this analytical method the only situation where DDT for malaria control had a clear net benefit in relation to infant mortality was when the malaria mortality rate was very high (e.g. the equivalent of a malarial epidemic). Our assessment concluded that the net benefits of DDT indoor residual spraying for malaria control are at best marginal and recommends consideration of less toxic, cost effective alternatives such as insecticidal nets.

Keywords: DDT, malaria, risk, infant mortality, South Africa.

Introduction

The Stockholm Convention on Persistent Organic Pollutants (POPs) came into force on the 17th of May 2004, granting a contentious exemption for malaria endemic countries to continue using the pesticide DDT (dichlorodiphenyltrichloroethane) to control malaria carrying mosquitoes (WHO 2004a). This exemption is controversial due to possible links between DDT and animal health (Grey et al. 2001) and human health. The US Department of Health and Human Services classified DDT as “reasonably anticipated to be a human carcinogen” (National Toxicology Program 2002). Critics of the exemption, such as Greenpeace, have focused on the persistent nature of DDT and its possible health implications, often invoking the precautionary principle to justify their claims (Greenpeace 2003). Other critics have warned of potential environmental costs (Wendo 2004). This issue has polarized views and prompted reactions from proponents of the exemption. For example in a recent editorial, Walter Williams insists that DDT saves “crops, forests and livestock,” as well as humans, calling the environmental lobby “extremists [who have] convinced the nation that DDT was not only unsafe for humans but unsafe to birds and other creatures as well. Their arguments have since been scientifically refuted” (Williams 2004). Bate (2004) expresses a similar opinion, calling the ban of DDT the “first example of eco-imperialism.” This debate has been vigorously pursued in both the public sphere and in medical journals (Attaran and Maharaj 2000; Liroff 2001; Chen and Rogan 2004; Roberts et al. 2004) with over 400 scientists signing an open letter in support of DDT (Open Letter 1999).

The Hippocratic Oath compels medical professionals to “abstain from whatever is deleterious” in the prescription of remedies for the good of one’s patients. The Stockholm Convention recognized that POPs “are transported, through the air, water and migratory species, across international boundaries and deposited far from their place of release” (Stockholm Convention on Persistent Organic Pollutants, 2004). Currently, all living organisms on Earth now carry measurable levels of POPs in their tissues and the evidence of POPs contamination in human blood and breast milk has been documented worldwide (Schafer and Kegley 2002). Adverse effects from these synthetic chemicals are being noted in laboratory animal models at dosages below or at former non-observed adverse effect levels, which in some cases overlap with human exposure levels (Gray et al. 2001), and may be relevant to human exposure levels (Shekhar et al. 1997). DDT is considered one of the “dirty dozen” POPs, which have been linked to cancer and damage to the nervous, reproductive, and immune systems (Heath 2004).

In this paper we undertake a science-based policy analysis of the risks and benefits associated with the use of DDT for malaria control in South Africa. The philosophical basis of this analysis rests on an ecological perspective where we assume that the world is interconnected and that biological systems function on the basis of ecological processes such as interdependence, and positive and negative

feedbacks. We also frame this analysis in terms of a critical realist epistemology (Archer et al. 1998), where contra positivism causal mechanisms can exist and one can make policy-relevant statements about them even when the specific mechanism of causality has not been fully understood by science. This approach, which has often been associated with the concept of precaution, is relevant to environmental science which is often concerned with phenomena that are new to the science community (e.g. the endocrine disrupting capability of certain persistent organic pollutants), and/or causal relationships that we do not want to observe in statistically significant quantities (e.g. irreversible adverse health effects). This approach is useful in providing evidence-based information to decision-makers who are required to make difficult decisions that cater for all involved parties.

This paper contributes to the debate concerning the evidence-based evaluation of a compound that is able to be defined as a remedy in terms of its target effects, but also defined by some as a potential health liability in terms of its non-target effects. Of the non-target effects associated with DDT in the scientific and popular literature (e.g. cancer risk, endocrine disruption in humans and wildlife) we focus only on one: a comparison between DDT-induced, and malaria-induced infant mortality.

DDT background

DDT was first synthesized in 1874 (Leonard 1992) with its effective insecticide properties being discovered in 1935 (WHO 2004a). Since then it has been used extensively worldwide. In the US alone approximately 1,350,000,000 lbs were used over a 30-year period (EPA 2002a) before it was banned for general use in 1972 (EPA 2002b) and shortly thereafter in many countries (Turusov et al. 2002). Over much of this period, DDT was used in spite of negative health impacts detected in preliminary animal safety tests (Russell 1999) and isolated cautionary claims first appearing in the national media (New York Times) in 1945 (Gunter and Harris 1998). At least 90 percent of the US population continues to have detectable serum levels of DDT metabolites (Calvert 2004). This is not surprising given that DDE, the major metabolite of DDT, has a clearance half life in the body and the environment of over 65 years (Kelce and Wilson 1997).

The issue at stake in the present study is the best method to control malarial epidemics, which are still occurring today (UN News 2004a,b,c). Globally, 500 million people a year fall ill with malaria and one million of them, mainly children, die as a consequence (Kapp 2000). Initially DDT was considered a wonder chemical receiving praise as WWI's greatest contribution to the future health of the world (Russell 1999) and was focal to the effort to eradicate malaria decided upon at the Eighth World Health Assembly in 1955 (Brown 2002). The campaign was expected to achieve complete eradication within 5 years, but failed to reach this goal. Despite this, the program did result in significant reductions in malaria transmission, and was probably instrumental in eradicating the disease from Europe and North America (WHO 2004a). DDT is a cheap and effective control agent, particularly given the lack of cost-effective alternatives. The Stockholm Convention specifically allows an exemption when "locally safe, effective and affordable alternatives are not available to the party in question" (Stockholm Convention on Persistent Organic Pollutants, 2004), with around twenty-five countries expected to continue use (Kapp 2000).

South Africa provides a useful case study since this country used DDT over an extended period of time with approximately 400 tons used between 1990 and 1999 (Dalvie et al. 2004). The level of DDT in the human population has reached high concentrations, with one localised study measuring a mean of 15,830 µg/kg in milk fat in 1987 (Smith 1999). DDT residues are readily detectable in wildlife (van Wyk et al. 2001) and humans both in areas free from or subject to DDT applications (Bouwman et al. 1990a). South Africa suspended DDT usage in 1996 and switched to pyrethroids (WHO 2004b), resulting in a surge of malarial cases (Feriman 2001). The decision was made to turn once again to DDT because of growing resistance to the pyrethroid insecticides (GCIS 2003). As a result of the reintroduction of DDT and introduction of combination antimalarials for first-line malaria therapy, malarial cases have been cut from 64,622 in 2000 to 8,016 in 2003 (WHO 2004b). As such, South Africa is an ideal environment to investigate the benefits and costs of DDT use.

Until recently it has been assumed that the use of DDT in controlling malaria has saved many lives (Attaran and Maharaj 2000; Feriman 2001) and any adverse effects have been assumed to be outweighed by the benefits. However, a recent study by Chen and Rogan (2003) has quantified the benefits and costs, finding that the benefits of indoor residual spraying (IRS) using DDT on child mortality may in fact equal the costs associated with its use. This study focuses on re-analyzing Chen and Rogan's (2003) model, updating it and applying it to the South African context. Finally, alternatives forms of malaria control in South Africa are examined. To compare the costs and benefits of DDT use, one needs to determine costs associated with malaria, and the effectiveness of DDT at

reducing malarial incidence. A literature search was conducted using the search databases 'Proquest', 'Expanded Academic' and 'PubMed' with keywords combinations including DDT, DDE, DDD, human, health, estrogen, androgen, receptor, lactation, period, preterm, premature, birth, mortality, death, health, infant, child, serum, concentration, and South Africa. In addition, a number of web sites from government and international agencies were searched, including the [South African Department of Health](#), [South African Medical Research Council](#), and the [World Health Organization](#). Program effectiveness was analyzed according to subsequent reduction in malaria prevalence and treatment cost-effectiveness.

Biological mechanisms

Human epidemiological studies have found associations between DDT and endocrine disruption, such as lower testosterone (T) levels (Hagmar et al. 2001). The known mechanisms of endocrine disruption are presented in Table 1. It should be noted that some suggest the risk is negligible (Smith 2000) or dispute the relevance of these studies on the basis of a lack of evidence (Tsuda et al. 2003).

Table 1: Summary of known mechanisms of endocrine disruption for the isomers/metabolites of DDT. Figures indicate the concentrations necessary for 50% displacement or inhibition of AR and ER binding. ND = no data available. Compiled from Kelce *et al.* (1995) and Guillette *et al.* (2000).

DDT isomer/metabolite	Known Disruption Mechanisms and Affinity
ρ , ρ' -DDT	Binds Androgen Receptor(AR), 75 μ M Binds Estrogen Receptor (ER) >1000 μ M
o , ρ' -DDT	Binds AR, 95 μ M Binds ER 5 μ M
ρ , ρ' -DDE	Binds AR, 5 μ M Binds ER, >1000 μ M Estrogen Antagonist
o , ρ' -DDE	Estrogen Agonist
ρ , ρ' -DDD	Binds AR, 90 μ M Binds ER, >1000 μ M
o , ρ' -DDD	ND
o , o' -DDD	ND

Chemicals that block or bind to hormone receptors can cause disruption to natural functioning by either blocking or initiating receptor activated gene transcription respectively (Solomon and Schettler 2000).

A number of studies have found that ρ , ρ' -DDT binds to the ER although this effect still may be relatively weak (see Table 1) (Shekhar et al. 1997; Matthews et al. 2000; Lorenzo et al. 2002). A number of studies have found that o , ρ' -DDT mimics the primary endogenous estrogen - 17 β -estradiol (E_2) (Lorenzo et al. 2002) and can bind to the ER although this affinity is much lower than E_2 (Table 2).

Table 2: Relative binding efficiency (RBE) of o , ρ' -DDT to the ER in comparison to E_2 . Results refer to ER α unless otherwise specified.

	Relative binding efficiency (RBE) to the ER	Source
E_2	100	By convention
o , ρ' -DDT	0.01	Burrow <i>et al.</i> (1999)
	0.00007 - 0.004310345 (Depending on the species tested)	Matthews <i>et al.</i> (2000)
	0.00023 - 0.002 (Depending on the tissue tested)	Loomis and Thomas (1999)
	0.01(ER α) - 0.02 (ER β)	Kuiper <i>et al.</i> (1998)

Studies have also found that ρ , ρ' -DDE can weakly bind to the ER (Klotz et al. 1996; Matthews et al. 2000).

DDT and/or DDE are also suspected to bind to the androgen receptor (Kelce et al. 1995, 1997; Daniel et al. 2002; Frigo et al. 2002), interfere with cytokines (Beard et al. 2000; Daniel et al. 2002), and 16- α -hydroxyestrone (Bradlow et al. 1986, 1995; Jaga 2000; Riza et al. 2001).

Impact of DDT on humans

Estrogen is an important hormone common among tetrapods and plays an important part in the reproductive system (Rosselli et al. 2000) as well as many other body systems such as bone maintenance, the central nervous system and the cardiovascular system (Kuiper et al. 1998). DDT has been implicated in a number of health disorders (Longnecker et al. 1997) such as pancreatic cancer (Garabrant et al. 1992), non-Hodgkin's lymphoma (McDuffie et al. 2001) and breast cancer (Charlier et al. 2003) but many studies have failed to find a significant relationship (Key and Reeves 1994; Rothman et al. 1997; Baris et al. 1998; Aronson et al. 2000; Hoppin et al. 2000; McElroy et al. 2004) with a small minority actually reporting lower levels of DDT in cases than controls (van Veer et al. 1997; Cocco et al. 2000). Longnecker et al. (2002) found that increasing levels of p, p' -DDE were associated with increased risk of polythelia (accessory nipples) and a study by Korrick et al. (2001) suggested the possibility that DDT may increase the risk of spontaneous abortion, although the small sample size ($n=30$) precludes any robust conclusions to be drawn. Due to deficiencies in many studies, contradictory results and the absence of demonstrated biological mechanisms no definitive conclusions to the relevance of DDT to human health can be drawn.

The costs and benefits of DDT use in controlling malaria

DDT concentrations in South Africa

Indoor residual spraying (IRS) with DDT is known to substantially increase the level of DDT found in the environment (Dua et al. 1996; Kashyap et al. 2002). With respect to human contamination, IRS has been found to increase the load of DDT and its metabolites in the human body especially for children (Yáñez et al. 2002) and malarial control workers (Dalvie et al. 2004; Salazar-Garcia et al. 2004). A number of studies in Kwa-Zulu, South Africa, have explored the impact of IRS on DDT concentrations in humans. Bouwman et al. (1990b) found that 6 months after an IRS spray was conducted the DDT concentration in mothers' milk increased from 12.21 mg/kg to 19.49 mg/kg. Bouwman et al. (1990a) reported that mother's milk in DDT treated dwellings had a significantly higher level of DDT (15.83 mg/kg milk fat) than that of control areas (0.69 mg/kg milk fat), suggesting that a "well-founded risk [of harm] to the infants...exists in sprayed areas".

Effect of DDT on lactation period

The effect of estrogen is well known on lactation period. High concentrations of estrogen in maternal blood inhibit lactation by interfering with the action of prolactin on mammary epithelium (Goodman 2003). Studies show that DDT and metabolite levels are associated with a shortened lactation period (Rogan et al. 1987; Gladen and Rogan 1995). Gladen and Rogan (1995) found that in a control population p, p' -DDE levels were 0-2.5 mg/kg (per fat basis), whereas in an exposed population p, p' -DDE levels increased to 5-7.5 mg/kg (approximately the level of increase found in South Africa by Bouwman et al. 1990b). At this level the median lactation period is expected to be 40% to 50% lower than populations with p, p' -DDE levels of 0-2.5 mg/kg (i.e. 3-4 months instead of 7-8 months). On this basis, assuming a 40% reduction in the lactation period at an exposure level of 5-7.5 mg/kg (p, p' -DDE), one would expect the number of infants weaned by 12 months (exposed population) would correspond to the number of infants weaned at 20 months (control population). In South Africa, currently 27.1% of infants are weaned by 12 months, with our calculations predicting this to rise in DDT exposed populations to 62.0% (the current number of infants weaned by 18-19 months under normal conditions) (South Africa Demographic and Health Survey 1998). The duration of lactation is known to have an important impact on the mortality rate of infants, with lower lengths of lactation generally resulting in higher mortality rates as a result of infectious illnesses such as diarrhoea and acute lower respiratory tract infection (Victoria and Barros 2000).

In their study, Chen and Rogan (2003) speculated that if the median lactation period was shortened from 19 to 11-12 months as a result of high DDE concentrations, they would expect the proportion of children weaned before 12 months of age to increase by 25% to 50%. As a consequence, they estimated that this would increase the risk of infant mortality by a percentage they determined using the formula that they developed, namely:

$$\left((p_2 * RR + 1 - p_2) - (p_1 * RR + 1 - p_1) \right) / (p_1 * RR + 1 - p_1)$$

where $p_1 = 25\%$, $p_2 = 50\%$, and RR (risk ratio) = 2. The result is a 20% increase in infant mortality as a result of infectious disease. The formula is based on calculating the control death rate (percent of

babies weaned by 12 months (p_1) multiplied by the risk of death for those babies (RR). The exposed death rate is then calculated by using the same method, but substituting the current number of babies weaned with the expected percent after DDT application (p_2). This is then converted into the percentage difference between the expected death rate and the current death rate.

We used the same model and applied it to the South African data available in the literature to provide an estimate of the impact of DDT and metabolite, resulting from IRS, on infant mortality risk from infectious disease. We ran the model three times, with run (a) using the variables indicated earlier (i.e. $RR=2$, $p_1=0.271$ and $p_2=0.620$), while run (b) reduced the impact of DDT by half (i.e. $RR=2$, $p_1=0.271$ and $p_2=0.446$) and run (c) with DDT having only a minimal impact of 10% (i.e. $RR=2$, $p_1=0.271$ and $p_2=0.306$). The results obtained in runs a, b and c were increases in infant mortality by 27.5%, 13.8% and 0.3% respectively.

Effect of DDT on premature birth rate

DDT is known to pass through the lipid rich placenta (Dorea et al. 2001; Cohn et al. 2003) and previous studies have associated increased DDT concentrations with increasing risk of premature birth (Longnecker et al. 2001). Longnecker et al. (2001) found that in the United States serum DDE levels of > 60 ppb were associated with a 310% increased risk of preterm birth. In Malawi, a study by Sullivan et al. (1999) indicated that preterm births make up 19.7% of all births. Given that the DDE serum range shown in South Africa exceeds that in the study conducted by Longnecker et al. (2001) in the United States, a 310% increase in preterm births was used, resulting in the incidence of preterm birth rate rising from 19.7% to 61.1% of all births. Premature infant birth (defined as a birth before 37 weeks) is associated with a much greater risk of infant death, with data from the United States and Canada showing that mild preterm births (34-36 weeks) are associated with an 2.9 and 4.5 increased risk of death respectively (Kramer et al. 2000). We decided to use the lower limit of this, thereby using a RR of 2.9.

This allowed the calculation of increased numbers of infant deaths by the formula used previously. We ran the model three times with run (a) using the variables indicated earlier (i.e. $RR=2.9$, $p_1=0.197$ and $p_2=0.611$), whilst run (b) reduced the impact of DDT by half (i.e. $RR=2.9$, $p_1=0.197$ and $p_2=0.404$) and run (c) with DDT having only a minimal impact of 10% (i.e. $RR=2.9$, $p_1=0.197$ and $p_2=0.238$). The results obtained in runs a, b and c were increases in infant mortality by 57.3%, 28.6% and 5.7% respectively.

Total infant mortality

Given that the infant mortality rate in South Africa is approximately 60 per 1000 live births (Walker 2001) and that approximately 20% of all deaths are attributable to malaria (Chen and Rogan 2003) this allows us to compare the costs and benefits of DDT use by focusing on a comparable but conservative statistic that does not take into account sub-lethal or chronic potential effects such as disorders of the reproductive and nervous systems, liver damage and cancers. With malaria causing 12 out of every 1000 infant deaths, for DDT to be considered beneficial in any given area it must, at the very least, not lead to an increase in child mortality rates above this background level. Table 3 summarizes the different model permutations used and the hypothetical benefit or cost of DDT application.

As the results show, the net benefit of DDT application relies on the assumptions associated with the toxicity DDT. When the model is run based on the best estimates available on the impact of DDT on infant mortality (i.e. run A in both the lactational and premature birth aspects) the costs of DDT application are clearly large and outweigh the potential benefits of DDT use (50.9 deaths per 1000 live births in DDT exposed populations, compared to 12 deaths per 1000 due to malaria). This net cost remains even if one of the assumed mechanisms DDT effect on infant mortality proves to be false (e.g. if DDT does not influence premature birth), but does in fact influence the lactational period to the extent that we speculate, then the increase of 16.5 deaths per 1000 live births due to DDT still substantially outweighs any potential benefits of DDT. However if DDT is not as toxic as we speculate in run A, then in some cases the benefits of DDT may outweigh our calculated costs. For example if DDT has half our predicted impact on lactation (run B) and only a tenth of our predicted impact on premature birth (run C), then the cost of DDT use will only be 8.5 deaths per 1000, significantly less than the malarial death rate of 12 deaths per 1000 thus producing a net benefit.

We can also manipulate the number of deaths caused by malaria using this model. For example, if the death rate from malaria was to double (for example during an epidemic) then the average of all our

permutations of the model predicts that the potential benefits of DDT application (for this statistic) would outweigh the costs of its use.

Table 3: The predicted costs of DDT application calculated from different permutations of the model. Shaded cells in the two right hand columns indicate a net cost to the use of DDT application. Unshaded cells indicate a net benefit to the use of DDT application.

Lactation Model Used	Preterm Model Used	Increase in Infant Mortality due to DDT (per 1000 births)	Net Benefit for DDT application (12/1000 deaths caused by malaria)	Net Benefit for DDT application (24/1000 deaths caused by malaria)
A	-	16.5	-4.5	7.5
B	-	8.3	3.7	15.7
C	-	0.2	11.8	23.8
-	A	34.4	-22.4	-10.4
-	B	17.2	-5.2	6.8
-	C	3.4	8.6	20.6
A	A	50.9	-38.9	-26.9
A	B	42.7	-30.7	-18.7
A	C	16.7	-4.7	7.3
B	A	42.7	-30.7	-26.9
B	B	25.5	-13.5	-1.5
B	C	8.5	3.5	15.5
C	A	34.6	-22.6	-10.6
C	B	17.4	-5.4	6.6
C	C	3.6	8.4	20.4
Average		18.27	-8.94	3.32

Alternatives to DDT spraying for malaria control

There are many alternatives to DDT available to control malaria such as IRS with different insecticides, use of insecticide treated nets (ITNs) and educational campaigns such as those in the Solomon Islands (Over et al. 2003). An analysis of the relative merits of DDT and alternatives would need to be based on a comparison of the relative effectiveness of the treatments in combating malarial incidence.

DDT has proved highly effective at controlling malaria, but studies often investigate this in absolute rather than comparative terms. For instance, Sharp et al. (1990) found that DDT application in northern Kwa-Zulu killed all *Anopheles arabiensis* mosquitoes within 15 minutes of exposure. Roberts et al. (1997) suggest that a reduction in the quantity of DDT used to control malarial vectors corresponds with a geometric growth in malarial incidence. It appears that DDT excels at controlling malarial epidemics such as that in Madagascar where the use of DDT reduced malarial incidence close to zero (Curtis 2002; Romi et al. 2002).

On the other hand, Goodman et al. (1999) compiled a comprehensive study on the effectiveness of alternatives to DDT for malaria control, noting that existing knowledge on the cost effectiveness of alternatives is sparse. Similarly Goodman and Mills (1999) pointed out that cost effectiveness analysis is not clear cut and depends on the set of assumptions used. Despite this, results from the Goodman et al. (1999) study indicated that the most cost effective options are insecticide treated nets (insecticidal treatment of existing nets), chemoprophylaxis (if an existing network of village health workers was already in place) and improving the compliance of existing programs. Individual residual spraying was not considered particularly cost effective, even if cheaper pesticides were available due to the fixed costs of spraying. ITNs are the most commonly proposed alternative to DDT and merit closer examination.

Pyrethroid-treated nets have often been found to be highly effective in reducing malarial mortality and morbidity (Corbel et al. 2004). A review by Curtis and Mnzawa (2000) concluded that ITNs are at least as efficacious as IRS though more expensive in South Africa. Kamolratanakul et al. (2001) compared

the effectiveness of DDT spraying with the use of ITNs in Thailand, finding that ITNs were much more cost effective than DDT, but had slightly lower effectiveness at reducing malarial incidence. The authors recommended that the use of DDT for vector control operations in Thailand be terminated.

One important study (Goodman and Mills 1999) reported that results obtained from randomized trials indicate that ITNs are effective, though the authors of the study express a reservation that several questions remain unanswered to their cost-effectiveness in large scale practice. ITNs have a number of practical problems associated with their use. Firstly, during the hot seasons they may become uncomfortably hot, reducing their use at a time when malarial vectors are likely to still be present. Secondly, for ITNs to be effective the net must be kept in good repair and retreated with insecticide periodically (Curtis and Mnzawa 2000), meaning that in some situations they will be inappropriate (Whitty et al. 2002). Concerns have also focused on the rise of pyrethroid resistance, which will reduce the effectiveness of ITNs (Hargreaves et al. 2000). However, some studies do show that despite vector resistance, ITNs still retain high mosquito deterrence (but not high mortality) levels (Corbel et al. 2004).

Discussion

Public health is a complicated web of interacting variables that makes it very difficult to ascertain unambiguous findings from much of the data. There are a number of influences that might impact on the results of a study like this. Firstly, often subjects/participants are exposed to a mixture of chemical contaminants (Miller 2004) which makes isolating and determining the impact of a single chemical difficult. How these chemicals interact with each other is still unknown and the subject of much debate (Lancet 1995). When studying endocrine disruptors Arnold et al. (1996) found that rather than a linear response to additional chemicals, there was a non-linear synergistic effect on estrogen receptors. The mixture of two pesticides endosulfan and dieldrin was 150 to 1,600 times more potent than the individual chemicals themselves. It needs to be noted that this study came under severe criticism and its results have failed to be replicated. However a number of other studies have observed synergistic behavior. Shekhar et al. (1997) for example, found, that a single dose of 1.0 μM of either *o,p'*-DDT or *p,p'*-DDT was required to elicit cellular proliferation in MCF-7 cells. However, combined doses with both *o,p'*-DDT or *p,p'*-DDT required concentrations as low as 0.1 μM to illicit a response equivalent to 10 μM of *p,p'*-DDT given singularly.

Another problem is that toxins like DDT can have different effects on different cell and tissue types, depending on the sensitivity of the tissue in question (Lorenzo et al. 2002). Differences in effects arise between subjects, for example, different strains of laboratory rats (O'Connor et al. 1999) as well as at the species level (Matthews et al. 2000).

There is also the issue of chronic sub-lethal toxicology. The effect under consideration in this study was the role of DDT in contributing to the risk of infant mortality through altering lactation period and increasing the risk of premature birth. Infant mortality is an acute and severe risk factor, and even when restricting the analysis to only this aspect of the total spread of potential risks and benefits, the target benefits of DDT for malaria control are significantly challenged by non-target risks. A comprehensive analysis of risks and benefits would need to take all potential target and non-target risks benefits into account, as well as all cost-effective alternatives. For example, malaria also adversely affects the adult human population. On the other hand, if the chronic toxicology of DDT was added to the analysis (e.g. exploring its potential to disrupt the reproductive endocrine system and/or carcinogenicity in adults and children in a longitudinal way) another set of risk factors would need to be added when calculating a risk assessment. A comprehensive risk analysis would also need to evaluate the environmental risks and benefits (e.g. to food chains and wildlife), and the potential feedbacks to the human population (e.g. bio-amplification of this persistent organic pollutant and potential endocrine disruptor in the food chain, and its down-stream effects on top predators including humans).

For instance, we already know that the mechanism of endocrine contaminants is complex, where they have been shown to alter: (a) hormone production at its endocrine source; (b) hormone secretion from the pituitary and hypothalamus; (c) enzymatic metabolism of hormones; and (d) the concentration of serum binding hormones (Guillette and Gunderson 2001). For a few recent examples:

- DDT has been shown to alter the hepatic sexual dimorphism in testosterone metabolism, and decrease the metabolic differences between male and female rats (Sierra-Santoyo et al. 2005).
- DDT exposure to endometrial Ishikawa and human embryonic kidney stimulated the expression of the death ligand, tumor necrosis factor- α (TNF- α), and the release of cytochrome c from the mitochondria and activation of caspase-3/7 eventually leading to cell death (Frigo et al. 2005).

- A study in Italy investigated the reproductive history of the wives of 105 men exposed to DDT in an anti-malarial campaign in the 1940s. It documented the total number of children, sex distribution in the offspring, time-to-pregnancy, and number of spontaneous abortions and stillbirths. Results showed that the exposed population had lower fecundity rates, higher rates of stillbirth, and the reversal of the male/female ratio in the offspring compared with an unexposed population (Cocco et al. 2005).
- The application of DDE to human granulosa has been shown to alter endocrine homeostasis and possibly act as an endocrine toxicant, through altered free calcium ion concentrations in the cytosol ($[Ca^{2+}]$) of cells (Younglai et al. 2004).
- Results from a study exploring the potential effects of organochlorines on the androgen receptor showed that the recent increase in the incidence of human male reproductive disorders could be due to on-going exposure to organochlorine pesticides (Lemaire et al. 2004).

Also, the interactions between the human body and chemical exposure in general is multi-faceted, where nutritional and genetic factors have an impact on human health singularly (one such example is breast cancer (Ambrosone 2004; Bieche et al. 2004), and their interactions with chemicals is as yet undetermined (Calvert 2004). A compounding problem is that accurate data sets on exposure levels are rarely available, and yet the length and timing of exposure also influence the degree of impact of a contaminant (Charlier et al. 2003). For example, serum based studies have shown that it is not the level of hormones in the blood that have the effect per se, rather the concentration of the hormone that reaches the cell in question (Goodman 2003). There can also be long latency periods between cause and effect (Charlier et al. 2003) with persistent contaminants making accurate diagnosis and therefore risk assessments difficult (Veeramachaneni 2000).

The biological mechanisms outlined above suggest that DDT has two main characteristics, firstly it is capable of mimicking estrogen, and secondly appears to exhibit anti-androgen properties. Findings such as reduced lactational period as discussed previously are consistent with the suggestion that DDT mimics E_2 . Much criticism of the plausible link between DDT and human health focuses on the low potency of DDT, for example its low binding affinity to the ER and AR, thereby suggesting that the effect of DDT is negligible. Although this is accurate in a narrow sense, it fails to take into account the long half life of DDT, its lipophilic properties that lead to its propensity to amplify in adipose tissue and its resistance to enzymatic and chemical degradation. These factors may counterbalance the low estrogenic potency of DDT (Shekhar et al. 1997; Romieu et al. 2000). Moreover, these impacts are likely to be profound during the pregnancy period which is associated with increased metabolism of fats (Dorea et al. 2001) and high sensitivity of developmental tissues at certain stages of fetal development.

The difficulties facing those studying or attempting to regulate POPs are amplified by the ethical issues preventing laboratory experimentation on humans when dealing with toxins of this nature (as guided by the Helsinki Declaration). It is in this light that the proposed model of cost benefit analysis can be seen as somewhat simplistic and overly reliant on unproven, and some may argue unfounded claims. There is no doubt though, that in the absence of human experimentation we are compelled to make our best decisions based on the best information available, and this study and the one by Chen and Rogan (2003) helps to clarify and summarize information of value to risk analysis, on the basis of what is known about the toxicology of this form of malaria control.

To sharpen this analytical tool it is important that further research be undertaken to improve the accuracy of this and other similar models and if possible (using animal models or human tissue cultures) more definitively elucidate causal mechanisms in DDT toxicology. To be realistically considered in public health planning, alternative control methods need to be effective and available at a suitably low cost for a less developed country with a limited health budget. Information on the ability of alternatives to meet these demands is often in short supply. A generic analysis cannot be undertaken to determine the suitability of alternatives in controlling DDT due to the importance of site specific conditions. For example, the cost effectiveness of insecticide treated nets (ITNs) relies on a number of factors including the available infrastructures, the proportion of people already owning nets, the existence of a network of village health workers, the level of resistance in local vector populations (Goodman et al. 1999), and the acceptability of among the local people to interventions (Goodman and Mills 1999).

Conclusion

The need for accurate information is fundamental in guiding public health policy decisions. Where a full information set is not available and there is evidence of significant potential harm the precautionary principle becomes relevant. The employment of this principle would need to evaluate the risks of using a potentially harmful solution as well as the risks of not using it. In the context of this study there is a need for policy decisions either in support of the use of DDT in IRS, or its substitution with other vector control methods. Given the lack of comprehensive toxicological data on the alternatives to DDT it may be premature to recommend a complete ban based on the current evidence as suggested by some environmental NGOs. One option is to use less harmful alternatives (e.g. ITNs) where conditions in their favour exist (e.g. where suitable infrastructures exist) and restricting DDT for use in highly endemic or epidemic areas.

An appraisal of a remedy that considers only its target effect but does not evaluate non-target effects, is by definition a narrow reductionist basis for risk assessment. If we understand the world of public health to exist as a network of interdependencies, the horizon for risk assessment by necessity widens to take more into consideration. The challenge for risk assessments of DDT in relation to malaria is to ensure that all relevant variables are factored into the equation so that one can be loyal to the Hippocratic Oath that compels medical professionals to “abstain from whatever is deleterious” in the prescription of remedies for the good of one’s patients. Much of the evidence accumulated to date suggests that risks associated with the continued widespread use of DDT may be significant enough to outweigh the benefits in the face of less toxic and cost-effective alternatives. This should provide a strong impetus for continued targeted toxicological research on DDT and the refinement of alternative malarial control programs. We accept that there will always be those who insist on double-blind, placebo-controlled experiments in statistically significant quantity before they will accept the chronic risk of DDT on human health. The fact that it would probably contravene the Helsinki Declaration and various ethical standards to conduct such experiments on human subjects, means that we are left with *in vitro* analysis, animal proxies and epidemiological studies (circumstantial evidence), and the precautionary principle as a risk management policy tool.

In terms of the latter we recommend the development of a set of standardized measurements for DDT risk analysis (e.g. using lipid corrected blood serum samples or adipose tissue samples), and testing regimes that take into account the relative concentration of all seven DDT isomers/metabolites. We also recommend the establishment of a worldwide “open access” database containing raw data pertinent to malarial control remedies and toxicological research, enabling researchers to gain access to common data sets generated from common research methods. And finally, we recommend that DDT risk assessment databases include data on risks and benefits of both target and non-target effects on humans and non-human wildlife, and risk assessment and cost information for alternative methods of malaria control.

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