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A response to the paper by Riana Bornman, Christiaan de Jager, Zeleke Worku, Paulina Farias and Simon Reif, entitled "DDT and urogenital malformations in newborn boys in a malarial area"

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Introduction

For six decades dichloro-diphenyl-trichloroethane (DDT) has been used successfully in indoor residual spraying programs to control malaria. During the many decades that DDT has been in use, thousands of tonnes of the chemical have been produced and used throughout the world with millions of people coming into direct contact with it in one way or another. One of the main attributes of the pesticide, which contributes to its effectiveness in the fight against malaria, is its long residual action. This attribute vastly improved malaria control when DDT was first introduced in the 1940s. Dr. Paul Müller, who discovered DDT's insecticidal properties, was awarded a Nobel Prize for his work. His discovery proved vitally important for malaria control, as prior to this, insecticides such as natural pyrethrum had to be sprayed approximately every two weeks compared to around once a year with DDT. DDT's persistence made malaria control more effective and cost-effective and protected hundreds of millions of people from this preventable disease. But DDT's persistence has also given rise to the suspicion that the insecticide is harmful to humans.

Over the years, huge numbers of studies have investigated the potential adverse effects of DDT on human health. Yet despite the voluminous research, no scientific study has been able to prove that DDT is harmful to people. Most studies find no evidence of harm or find only weak and un-replicated associations between DDT and possible human health harm. Unfortunately, those weak and un-replicated studies are all too often used by anti-insecticide activists to lobby for restrictions on public health insecticides.

Based on DDT's effectiveness in malaria control and its history of safe use, it is one of a dozen insecticides recommended for use by the World Health Organization. Yet studies attempting to find human health harm from DDT are ongoing, the most recent is found in a study by Bornman et al, published in the British Journal of Urology International, entitled "DDT and urogenital malformations in newborn boys in a malarial area". Studies that provide the public health community with improved understanding of public health interventions should be welcomed by all. However, the research by Bornman and others is neither informative nor instructive and could severely undermine malaria control.

Discussion

We find a number of shortcomings in this study and question the validity of the methodology adopted. Any real world analysis must take into account all the potential mechanisms of developmental harm. For example, conditions of poverty allow and, in some cases, promote a

1150 17th St, NW, Suite 910
Washington, DC 20036
+1 202 223 3298

PO Box 17156, Congella
4013, South Africa
+27 31 206 1416

http://fightingmalaria.org

variety of human disease conditions. Unsanitary conditions that often characterize poverty can promote a variety of infections, such as cytomegalovirus (CMV). The occurrence of CMV infections can cause birth defects, and has not been considered in the analyses of Bornman et al.

The authors also did not control for history of malaria infection. Malaria is mostly a problem of poor rural populations. Poverty and poor nutrition also have severe and adverse affects on a whole spectrum of biological parameters. The study compares populations exposed to DDT with populations not exposed to DDT. Presumably, the unexposed populations do not suffer from malaria; whereas exposed populations have problems with malaria (houses are sprayed with DDT to prevent malaria). Malaria is a cause of severe stress on pregnant women and malaria infections would be a confounding variable for the developing foetus. The authors state that "it is possible that some other unknown factor that differed between people in the sprayed and unsprayed villages could account for some of the associations seen." Indeed, the differences in the counts of birth defects were so small between supposedly exposed and unexposed populations that almost any one of a number of uncontrolled variables could account for those differences.

For example, there is weak evidence that anti-malarial drugs used to treat malaria during pregnancy might have teratogenic action. Chloroquine is recognised to be weakly teratogenic in animal studies but has not shown action in humans, at least not at high risk. A study by Wolfe and Cordero (1985) on birth defects in women taking chloroquine versus birth defects in a control group mostly not exposed to malaria, reported the following observations:

> The proportion of birth defects in the exposed group was not significantly different from that in the control group. This observation must be considered within the limitations of the study, which could detect only a strong teratogenic effect. It could not exclude risks lower than a 5.7-fold increase in the incidence of birth defects when chloroquine was used.
>
> Women using chloroquine during pregnancy for chemosuppression of malaria can be reassured that it is not a strong teratogen, but if it is to be used the risk of developing malaria should be balanced against the lack of data to determine whether it carries a low teratogenic risk.[1]

Regarding the statement that the study on birth defects could not exclude drug-linked risks lower than a 5.7-fold increase, we must emphasize that the highest odds ratio in Bornman's study was just 2.5 – an odds ratio below the 5.7-fold cut-off. Given these potential relationships, to include the risk of birth defects simply as a result of fevers associated with malaria infections, the study would need to look beyond the simplistic assumption that DDT is causing birth defects. Other studies, e.g., Longnecker et al (2002), have not shown that DDT is a cause of hypospadias or any other urogenital birth defect (UGBD) for that matter.[2]

The wealth of funding for ecotoxicology studies has resulted in a laundry list of mechanisms for DDT and metabolites to influence human development. Such mechanisms are often quantified through high and acute doses of DDT and generally identified through animal experimentation. Considerable controversy surrounds the issue of extrapolation of data from animal studies to

humans. What occurs in an animal model is not predictive of what will happen in humans. The problem with the current knowledge base of mechanisms of harm from acute high doses of DDT is that there is almost no evidence that, in the real world, environmental DDT exposures cause development problems for humans. This is reflected in the following two assessments in the Agency for Toxic Substances and Disease Registry's toxicological profile for DDT and metabolites:

1. "In summary, there is no conclusive evidence that DDT/DDE at the levels found in the environment cause developmental effects in humans,"[3]
2. "Collectively, the data do not suggest that DDT and related compounds present a genotoxic hazard at environmentally relevant concentrations."[4]

The authors of the study have an exceptionally poor definition of DDT exposure. They identify mothers as DDT exposed if, according to Malaria Control Programme staff, the village in which the mother reports residing can be classified as "currently sprayed", "sprayed between 1995 and 2003" or "any exposure to DDT". The authors assert that, "The spray history of the various groups of villages is summarized in Table 2; 33.9% (1122) subjects were from currently DDT-sprayed villages." The authors' Table 2 (with the exception of the 'Total' column) is reproduced as Table 1 below.

Table 1: Distribution of maternal village history of DDT spraying in Limpopo Province, South Africa (3310)

DDT sprayed, n (%)	Yes	No	Total
Currently DDT exposed	981 (30)	2,329 (70)	3,310 (100)
Village sprayed 1995-2003	738 (22)	2,572 (78)	3,310 (100)
Any DDT exposure	2,396 (72)	914 (28)	3,310 (100)

Source: Bornman et al (2009)

However, from this table we find that only 30% (981) of individuals are from currently DDT sprayed villages. Nevertheless, a better measure of DDT exposure would be to actually measure the amount of DDT or its metabolite DDE in serum samples of study individuals. In addition, the exposed and unexposed individuals in this study all come from the same regional location. In order for the analysis to be truly informative the authors should have used a control (unexposed) group that was geographically distinct. Their results could therefore simply be picking up a regional confounder.

Table 3 in the Bornman et al study is reproduced as Table 2 below (with the exception of the 'Ever sprayed' and 'Never sprayed' n values). From this table we note that hypospadias was the numerically dominant birth defect (representing 47.9% of all birth defects). More specifically, the rate of hypospadias was actually higher in the unexposed population than in the exposed population, as was the rate of penile cyst. Additionally, rates of individual birth defects with sufficient n values did not differ greatly in exposed and unexposed populations.

Table 2: Distribution of UGBDs in newborn boys by indoor DDT spraying history

Malformation	n (%)	Ever sprayed (n=2,396)	Never sprayed (n=914)
Micropenis	71 (2.2)	53 (2.2)	18 (2.0)
Cryptorchidism	70 (2.4)	58 (2.4)	12 (1.3)
Hypospadias	171 (5.6)	122 (5.1)	49 (5.4)
Chordee	44 (1.4)	38 (1.6)	6 (0.7)
Phimosis	34 (1.1)	26 (1.1)	8 (0.9)
Penile cyst	7 (0.3)	3 (0.1)	4 (0.4)
Any UGBD	357 (11.0)	264 (11.0)	93 (10.2)

Source: Bornman et al (2009)

The authors state, "Associations with a statistical significance of $P \leq 0.15$ were considered in multivariate logistic regression models. In a multivariate model, variables were excluded one at a time, starting with the least significant one. Only variables with $P < 0.05$ or whose exclusion changed the other coefficients by > 10% were kept in the final model." However, the threshold for statistical significance of a cause and effect relationship is set well below what is considered acceptable (p-value equal to or less than 0.05).

The authors do not appear to understand that the 95% confidence interval is a useful approximation of statistical significance for a cause-effect relationship only when the odds ratio is large and widely separated from 1.0. Data presented in this study do not suggest that such relationships exist. One can, in general, interpret a 0.05 level of significance as suggesting that, for a set of 20 parameters, at least one can be expected to show a p-value less than or equal to 0.05. That is to say, the chance of getting a result that is due to chance alone is one in twenty, or 1 to 20. In this study, the authors set their p-value at 0.15. Thus, the probability of getting a result that is due to chance is 1 to 6.7. The authors worked with a set of 7 outcomes, so the chance that one of these outcomes will be significant at the 0.15 level of probability is high—chance being 1 to 7. Reducing the standards of statistical significance when the risk of reaching an incorrect conclusion has a low probability of causing broad human health harm is perhaps acceptable. However, reaching an incorrect conclusion that DDT is harmful imposes very high risks of DDT being withdrawn from disease control programs; therefore high standards of statistical significance should be required.

The authors exclude the variables controlling for consanguinity and maternal age stating that these variables had no influence on the occurrence of UGBDs in this model. Yet, confounding as a result of mother's age is highly important. The rate of chromosome abnormalities increases greatly with the mother's increasing age. Moreover, Nazer et al (2007) found that, "The association between prevalence rates of congenital malformations and maternal age is U shaped with a higher proportion of malformed children among women aged less than 20 years or more than 39 years."[5]

The authors state, "As consanguinity was reported in 3.64% of the cases, the possible effect of inherited factors on the presence of UGBDs needs to be explored in more detail in follow-up studies." Studies have found that the risk of significant birth defects in offspring of first cousin

unions is between 1.7 and 2.8% higher than in the general population.[6] Stoltenberg et al (1999) found that, "For nonconsanguineous parents the risk of a birth defect for the subsequent sib was 15 per 1,000 births (95% confidence interval: 14.5-15.1) if the previous child did not have a birth defect and 33 (95% confidence interval: 30-37) if the previous child had a birth defect. For parents who were first cousins the risk of a birth defect for the subsequent sib was 36 per 1,000 (95% confidence interval: 30-42) if the previous child did not have a birth defect and 68 (95% confidence interval: 33-122) if the previous child had a birth defect. The risk of recurrence of birth defects is higher for subsequent sibs with first-cousin parents than for those with nonconsanguineous parents."[7] These findings also point to the importance of controlling for sequence of births and their demonstrated associations with UGBDs.[8]

Each birth categorized with a UGBD in newborn boys would need to be checked against a family history of consanguinity and included as a potential confounder. The study records UGBDs as discrete events; however, it is possible that a single birth would account for more than one UGBD. Furthermore, the study does not report on any incidence of more than one UGBD in a single family. In the two-year timeframe of the study, it is possible that a mother had more than one child with a UGBD. These events should be singled out and clearly identified. The study should have also reported on any UGBDs born within the family outside the two-year study period.

The authors of the study dismiss maternal alcohol intake and smoking, collected via questionnaire, as factors contributing to UGBDs. More specifically, the authors note, "Only four mothers reported smoking and seven drinking alcohol, so these variables were not considered any further." The authors also state that they did not inquire about paternal smoking and drinking habits, when clearly these may also be contributing factors to UGBDs as well as other factors such as paternal age etc. The authors suggest that other studies have shown that men from these villages seldom smoke or drink. A single study was referenced to back-up this claim, which was conducted by several of the same authors of the study in question.

Table 4 in the Bornman et al study is reproduced as Table 3 below.

Table 3: UGBDs in newborn boys significantly associated (P ≤ 0.15) with DDT exposure and other risk factors

UGBD	Predictor	Odds ratio (95% CI)
UDT	Village ever sprayed	2.1 (1.14 – 3.92)
	Never sprayed (ref)	1.0
	Time lived in village, years	0.96 (0.94 – 0.99)
Occupation	Homemaker	2.4 (1.15 – 4.94)
	Student	2.1 (1.0 – 4.54)
	Employed (ref)	1.0
Hypospadias	Consanguinity	1.6 (0.84 – 3.0)
	No (ref)	1.0
Chordee	Village ever sprayed	2.5 (1.1 – 6.0)
	Never sprayed (ref)	1.0
Any UGBD	Consanguinity	1.5 (0.97 – 2.4)
	No (ref)	1.0
	Time lived in village, years	0.99 (0.98 – 1.0)
Occupation	Homemaker	1.3 (1.1 – 1.7)
	Employed or student (ref)	1.0

Source: Bornman et al (2009)

The authors note, "Some malformations had a slightly higher percentage in places that had been sprayed with DDT than in from places that had never been sprayed. However, only a few of these differences were statistically significant (Table 4) [reproduced as Table 3 above]. For most malformations, the percentages of UGBDs were practically the same for both sprayed and never-sprayed." Only when all the UGBDs were grouped together did the authors find statistical associations. Indeed the authors state, "Grouping the UGBDs as a single variable for male babies provided stronger associations." We propose that grouping variables, as a last ditch effort to achieve some level of statistical significance, is a highly questionable practice. Combining all the UGBD dummy variables into one variable tells us nothing because the authors have already reported that individual UGBDs were not statistically different between exposed and unexposed populations.

The authors claim, "Being a homemaker instead of being employed further significantly increased the risk of having a baby with a UGBD by 41% (odds ratio 1.41, 1.13 – 1.77)." The implication is that being a homemaker increases exposure to DDT. However, a higher odds ratio for children born to homemakers must consider confounding as a result of burning biomass and the release of natural organohalogens within the house – a risk that would be greatest for mothers who are homemakers, opposed to those who work or study outside the house.[9]

In the discussion section of the paper the authors acknowledge, "These findings must be followed up by a case-control study with adequate numbers and consideration of other risk factors for UGBDs, to better evaluate an independent association of UGBDs with DDT and for clearer conclusions."

Conclusion

Given how the data are manipulated in this study in order to get the reported results, and given that the authors have failed to adequately consider all potential confounders and have set the p-value at a non-conventional and scientifically unacceptable level, this study should be classified as highly biased and the conclusion of DDT as a cause of UGBDs invalid. A number of other questions arise as a result of the deficiencies in this study: What is the unemployment rate and socioeconomic status of the individuals in the sample? Why is the unexposed area situated in such close proximity to the exposed area? What are the characteristics of the siblings?

We are unaware of any replicated scientific studies that have found UGBDs in boys born in areas of very heavy DDT use in agriculture and for control of household pests. Such use would have resulted in very high levels of exposure and would have occurred in many developed economies where the advanced health systems would have picked up any occurrences. This fact, along with the points made above, lead us to conclude that the results and conclusion of this study are questionable. Given the immediate and real risks posed by malarial mosquitoes, particularly to young children, this study should in no way be used to argue against the use of DDT in malaria control in South Africa or elsewhere.

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