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DDT AND UROGENITAL MALFORMATIONS IN NEWBORN BOYS IN A MALARIAL AREA

Sir,
The October 22, 2009 paper by Bornman *et al.* [1] reports urogenital birth defects (UGBDs) in South Africa as a result of 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane (DDT) exposure. After obliquely inferring DDT may not be the actual cause of the observed birth defects, the authors asserted that people at risk of malaria should be informed about risks of birth defects if DDT is used. The popular media in South Africa publicised the authors' claims widely, to include rural malarial areas. Public concern has arisen, and consequently the malaria control programme is encountering new obstacles.

Most people would agree that because DDT provides great benefit by protecting people from malaria and other diseases, it does not make sense to alarm people about DDT unless it has been proven to cause harm. Richard Grady addressed this issue in the editorial comment that accompanied the Bornman *et al.* [1] paper. Grady stated that issues of association and causality could not be distinguished in the paper. Given that there are broadly accepted epidemiological criteria, which are described below for defining causation, Grady was right. The claim that DDT causes birth defects does not fulfil any of these criteria and, based on the science, the pronouncement that there is an urgent need to warn people in malarious areas that they are at risk of birth defects if DDT is used, should not have been published. In addition to this destructive and alarmist pronouncement, herein specific examples of selective bias and misrepresentations of science will be described.

Firstly, it is important to consider some basic issues of DDT dosing and availability. Presence of DDT in living organisms is largely confined to fat cells where it is not biologically active. Thus, dosing in *in vitro* studies should account

for differences in actions of chemical from acute dosing vs chemical stored in fat cells. Additionally, dosing based on chemical concentrations in blood serum must differ between estimates of unadjusted (ng/mL) vs adjusted concentrations (ng/g lipid). The former measurement can give estimated concentrations far more than 100-fold less than the latter. This occurs because DDT and its metabolites are in the lipid fraction of blood serum, which comprises only $\approx 0.6\%$ of serum. A 1991 paper classified serum DDT levels in South Africa for people living in DDT sprayed houses as very high (unadjusted concentrations of 140 $\mu\text{g/L}$) [2]. In reality, that level equates to just 0.14 parts per million of sum DDT (1 $\mu\text{g/L}$ = one part per billion and ($\mu\text{g/L}$)/1000 = one part per million). Compare that 'high' level with the concentrations used in animal tests below.

In making their case against DDT as a cause of human birth defects, Bornman *et al.* [1] make several claims from publications that warrant further consideration. They cite a paper by Kelce *et al.* [3] and state that 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) inhibits androgen binding, androgen-induced transcriptional activity, and normal male prepubertal development. They cite a paper by Danzo [4] as demonstrating p,p'-DDE was the most potent of chemicals tested at binding androgen. Bornman *et al.* [1] failed to state that neither of these studies involved humans. The study by Kelce *et al.* [3] was on rats and the investigators dosed rats with 100–200 mg/kg/day of DDE. For comparable dosing of a 68-kg human, such dosage levels would equate to a daily administration of 7 000–14 000 mg of DDE. In the real world, a comparable acute dose of DDE would never be present in a sprayed house, let alone be available in a form that could be consumed daily by a human living in the house. The paper by Danzo consisted of laboratory assays of physiological ligands and the tests were dosed with 100 μmol of DDT, DDE, etc., and with just 7 nmol of ligand. In reality, 100 μM

of DDT equates to an *in vitro* concentration of about 35 parts per million, so the investigators used unrealistically high doses of DDT vs miniscule concentrations of ligand. The point of these examples is that Bornman *et al.* [1] imply these data are relevant to humans. In fact, the data are not relevant to humans because they are performed with rats or are *in vitro* tests. Additionally, the data are based on extraordinarily high acute doses of DDT that humans will not normally, if ever, encounter. Indeed, Danzo [4] specifically stated 'Whether these compounds would act *in vivo* [in living organisms] as agonists or antagonists of androgen action remains to be determined'.

Bornman *et al.* [1] describe the damage of *in utero* exposure of animals to DDT or DDE. They state such exposures are associated with reduced penis size in alligators, and hypospadias and cryptorchidism. For the claim of reduced penis size in alligators, they cite a paper by Guillette *et al.* [5]. In fact, Guillette *et al.* actually renounce the claim in that paper, stating: '[a] recent study from our laboratories demonstrated no relationship between plasma concentrations of various pesticide metabolites and phallus size in juvenile male alligators from Lake Apopka, suggesting that an activational antiandrogenic response to the contaminants studied may not explain phallus size [citation removed]. It is important to note that we still have no data on which, if any, of the pesticides present in alligator tissues act as antiandrogens'.

Bornman *et al.* [1] also refer to a paper by de Jager *et al.* [6] for their statement that *in utero* exposure of animals to DDT causes hypospadias and cryptorchidism. In a similar fashion, their statement is wrong because the paper by de Jager *et al.* was not about *in utero* exposure of animals to DDT. Collectively, their claims reflect, at worst, a purposeful misrepresentation of science, or, at best, a failure to read the literature.

In addition to the problems of interpretation and representation of cited publications, the Bornman *et al.* [1] paper also includes several inconsistencies and shortcomings in design, data analyses and interpretation. Bornman *et al.* [1] find an association and then claim that they have found cause and effect. To prove a claim about the impact of DDT on human health, researchers should satisfy the criteria for proving a cause and effect relationship. These criteria are: (i) Strength of association, the stronger an observed association appears over a series of different studies, the less likely this association is spurious because of bias; (ii) Dose-response effect, the value of the response variable changes in a meaningful way with the dose (or level) of the suspected causal agent; (iii) Lack of temporal ambiguity, the hypothesized cause precedes the occurrence of the effect; (iv) Consistency of the findings, most, or all, studies concerned with a given causal hypothesis produce similar findings; (v) Biological or theoretical plausibility, the hypothesized causal relationship is consistent with current biological or theoretical knowledge; (vi) Coherence of the evidence, the findings do not seriously conflict with accepted facts about the outcome variable being studied; (vii) Specificity of the association, the observed effect is associated with only the suspected cause (or few other causes that can be excluded).

The study by Bornman *et al.* [1] fails to satisfy these criteria. Furthermore, other studies already exist that are not consistent with the authors' findings of DDT as a cause of UGBDs [7,8]. Claiming a cause and effect relationship on the basis of an observational study, such as the one by Bornman *et al.* [1], is not appropriate. History has shown that once a claim of causation is made, over the next several years other studies are performed and that claim is often rejected. This sequence has been repeated with such frequency that it should now be well understood that a correlation between variables, as might result from a cross-sectional study, does not prove causation. Yet, many investigators still succumb to temptation and claim their research proves more than it actually does. In the case of DDT, this has occurred repeatedly with such ills as reduced duration of lactation, various cancers, birth defects, etc. For example, DDT as a cause of reduced duration of lactation was announced in 1985 [9]. This claim was followed by other studies,

eventually leading to a 2003 high-profile suggestion in infectious disease literature that DDT might be too harmful for use in malaria control [10]. Years later, in 2008, a large study disproved that DDT caused reduced duration of lactation [11]. Another example was the claim that DDE caused breast cancer [12]. Anti-DDT activists used the reported association of DDE with breast cancer to campaign against public health use of DDT. A meta-analysis of many studies in 2004 disproved DDE was a cause of breast cancer [13]. A highly damaging part of this cyclic process is that the media report the initial claim but ignore later studies that disprove the original claim of causation. Indeed, as described above, the media in South Africa has widely reported claims of the Bornman *et al.* [1] paper as proof that DDT causes birth defects and to the detriment of the malaria control programme [14].

In addition to the issues described above, inconsistencies in the data used should give serious cause for concern. Bornman *et al.* [1] state that the final dataset for computations consisted of 3310 newborn baby boys. However in Table 1, the summed total of boys listed by maternal age is 3304; the summed total of boys listed by maternal occupation is 3253; and the summed total of boys listed by ethnicity is 3310. Such differences would be irrelevant if differences in UGBDs within exposed and unexposed populations were large; but they were not. The differences in the summed totals of these characteristics are unexplained, and given these differences, it is unclear which denominator values were used in estimating the distribution of UGBDs in Table 3.

The authors state that the final multivariate logistic model included only 3144 baby boys. If the authors started with 3310 boys, which boys expressing which UGBDs were not included in the model in order to get a combination of UGBDs to give a significant model? Such changes in the population would perhaps be less important if investigators had used a rigorous statistical standard for admitting parameters into the model in the first place. However, instead of the standard 0.05 probability level, they used a P -value of 0.15. The authors explain how they arrived at a total sample size of 3310 boys, but do not explain which boys were not included in the model to arrive at a final sample size of 3144 boys.

Other inconsistencies are found in Table 3. The values listed for 'any UGBD' are undefined and are less than the summed total of the six UGBDs in the corresponding column. Table 3 consists of values for six UGBDs in three columns, including 'n', 'ever sprayed', and 'never sprayed'. The summed total of the six UGBDs for the columns 'ever sprayed' and 'never sprayed' are 300 and 97, respectively. The last row of data is 'any UGBD'. It would be expected that the values in this row would be equal to or greater than the summed total of the six UGBDs in the corresponding column (i.e. 300 and 97; but instead the values are 264 and 93, respectively). As the authors refer to this row as representing 'any UGBD', the values could include some conditions not described in the list of six UGBDs. But the values for 'any UGBD' are actually fewer than the summed totals of the six UGBDs. The authors state in their text that any category with a count of <5 would be excluded; therefore, since the values for 'penile cyst' were <5, these were subtracted from the summed totals to determine if the differences were due to the deletion of this data. Subtracting the values (three and four) for 'penile cyst' however, does not account for the differences between the summed totals of the six UGBDs and the values listed for 'any UGBD'. The threshold for statistical significance of a cause and effect relationship ($P \leq 0.15$) is set well below what is considered acceptable ($P \leq 0.05$). The authors do not appear to understand that the 95% CI 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 $P \leq 0.05$. That is to say, the chance of getting a result that is due to chance alone is 1 in 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 in 6.7. The authors worked with multiple variables and outcomes, so the chance that an association will be significant at the 0.15 level of probability is high-chance being 1 in 7. Lowering statistical standards for finding a significant correlation is not good statistical practice; it is particularly unacceptable when an erroneous conclusion may cause harm. In such circumstances, statistical standards should be raised, not lowered.

The percentage of UGBDs in villages never sprayed with DDT is high at 10.2%, and not significantly different from the 11% observed in villages sprayed with DDT. Given the high percentages of UGBDs in both DDT-sprayed and unsprayed communities, research should be undertaken to determine the cause. Yet, it seems clear that a focus on DDT will divert attention away from the real cause(s) and, simultaneously, increase the risk that DDT will be withdrawn from the malaria control programme in South Africa. It was withdrawn once before with disastrous consequences and would be a great public disservice if the Bornman *et al.* [1] paper was the cause of a repeat performance of that disaster.

It seems clear that the Bornman *et al.* [1] paper itself now poses great risks to the health and welfare of people in malarious areas because it may become the cause célèbre for stopping house spray programmes that use DDT.

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