Serum levels of DDT and liver function of malaria control personnel

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Summary

The levels of DDT and metabolites in serum of 23 applicators involved in malaria control operations in Natal were determined using gas chromatography with electron capture detection. The mean levels (μg/l, ppb) were 61,7 DDT, 129,3 DDE, 11,0 DDD and 202,0 ΣDDT. Percentage DDT was 33,4%. These levels were higher than for an age matched sample of the general population in KwaZulu, who are protected by DDT against malaria. Percentage DDT correlated negatively with age ($P < 0,05$) for the applicators, suggesting a change in pharmacodynamics with age. Mean serum albumin, alkaline phosphatase, aspartate transferase and γ-glutamyltransferase (GGT) levels did not differ significantly from an age-matched control group, but the mean GGT value for the applicators was higher than the maximum of the laboratory normal range. Although not clinically significant, the alanine transferase was significantly higher in the applicators than in the control group. These higher levels suggest a possible risk to the health of the sprayers, but uncertainties remain.

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DDT is used in northern Natal and eastern Transvaal as an intradomiciliary applied agent to interrupt malaria transmission.[1] In places where the mosquito vectors have not yet developed resistance to DDT, such as in KwaZulu,[2] it remains the insecticide of choice. In the malaria-endemic areas of KwaZulu and Natal, the annual application of DDT to the dwellings of all residents has been very successful in preventing malaria.[1] This strategy has also been applied in numerous other countries with endemic malaria, and has helped to eliminate this parasitic disease in many others.[3]

The resistant properties of the insecticide to biological degradation and its lipid solubility resulted in DDT being a ubiquitous contaminant. Its use in South Africa has, since 1976, been limited to malaria control operations only.[4] This limited use was brought about by the recognition that agricultural application could result in environmental damage, largely affecting top carnivores, such as pelicans.[5] Its continued use in community health programmes is motivated by the well-documented human safety record of DDT.[6] Although DDT is a carcinogen in animal models,[7] no such effects have been found in people with excessive exposure to DDT, such as pesticide-factory workers.[8] However, impaired liver function,[9] impaired cognitive function,[10] and macular involvement in applicators,[11] and hyporeflexia in infants[12] have been found.

It therefore remains necessary to monitor levels of xenobiotics in people that are exposed to these agents in order to determine whether their activities result in increased exposure and thereby risk. Because application is done between January and March each year, the hottest months, DDT applicators in Natal (RSA — excluding KwaZulu applicators) are not required to wear respirators while applying DDT. Furthermore, the applicators are also required to work the spray pumps manually to attain a constant pressure, assuring effective surface coverage. The compounding discomfort of heat and physical exertion leads to an aversion to wearing respirators. This exposes the applicators to higher than normal levels of DDT. A recent policy change, where the DDT formulation (75% DDT water-wettable powder) is pre-weighed into individual pump-charges by the applicators before the start of the application season, could also have resulted in longer exposure of the applicators to DDT.

Since no previous study of this nature has been done in South Africa, the need exists to collect body burden data of applicators in order to revise policy, if necessary. A study was therefore undertaken to determine levels of DDT in the serum of applicators employed by the Department of National Health and Population Development in Natal and to compare this with levels from a general population protected by DDT. This would establish whether the sprayers were at increased risk due to their intensive exposure compared with the population they protect, considering the occupational circumstances. Serum and whole-blood levels of DDT and its metabolites have proved adequate indicators of exposure and body burden to replace the more laborious fat biopsy.[13-15] Liver function parameters were also determined and compared.

Subjects and methods

Informed consent was obtained from the sprayers using their own language, Zulu. Blood samples (venepuncture) from 23 applicators present at a meeting (representing 72% of all Natal (RSA) applicators) were taken 1 month before the spraying season started (November). Pre-weighing of the DDT had not yet started. This allowed the baseline values to be used as a more stable indicator of exposure. Serum samples (2 ml) were frozen at −10°C in glass containers on the day they were obtained, without the serum coming into contact with rubber or plastic.

Age- and sex-matched data ($N = 23$) from 12 families involved in a study in KwaZulu to determine longitudinal changes in serum levels served as the control.[16] These people were protected against malaria by annual indoor application of DDT, but were not involved in its application. The people selected had been resident in Ubombo, a malaria controlled area, for more than 20 years. The individuals selected were permanently resident at a particular homestead (not migrant labourers) and have had life-long exposure to DDT from malaria control. Dwellings were constructed of mud; residents of cement dwellings, which were treated with a different DDT

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formulation, were excluded. Serum samples from this group were taken during the same month as that from the applicators. The applicator and control groups were both from the coastal plain of northern Natal.

Samples were extracted using a method previously described.[17] Briefly, the serum was placed on a pre-washed column consisting of 3 g of a 1:1 mixture of silica gel and Celite. The organochlorines were eluted with a dual solvent system. The extract was concentrated and analysed using gas chromatography-electron capture detector (GC-ECD). The compounds analysed were p,p'-DDT (1,1,1-trichloro-2,2-di (4-chlorophenyl)ethane) p,p'-DDE (1,1-dichloro-2-2-dichloro-2,2-di (4-chlorophenyl)-ethylene and p,p'-DDD (1,1-dichloro-2,2 (4-chlorophenyl)ethane). The minimum detectable quantity was 0,5 pg per compound. The recoveries, at different levels for different compounds, ranged from 71% to 104%. This method was developed to facilitate recovery of a fraction of the spiked compound that was not extracted after the spiked sample was frozen for longer than 24 hours. Confirmation of peak identities was done by an independent laboratory. Results presented here are not corrected for recovery.

Liver function parameters were determined by the Chemical Pathology Department of King Edward VIII Hospital, Durban.

Results

The applicators were employed in that capacity for a mean of 8 ± 6,3 years and had a mean age of 34,8 ± 9,0 years. The sera of all applicators were positive for DDT and DDE. Only 1 applicator had no detectable residues of DDD. All the control subjects were positive for DDT and DDE, but only 3 had detectable residues of DDD. The results of the analysis are given in Table I. DDT, DDD and ΣDDT-levels were significantly higher in the applicators (using log-transformed data in two-sided *t*-tests), but the percentages DDT and DDE, although higher than for the control group, were not significant.

No significant regression relationship between DDT, DDD, DDE or ΣDDT on age or length of employment was found for the applicators. This was also true for the log-transformed data. The correlation coefficient for the regression of log DDE on age was 0,330 with a standard error of 88,9 ($P > 0,05$). The correlation coefficient for log DDT on age was 0,033 with a standard error of 30,1 ($P >$ 0,05). The only significant regression found for the applicators was for percentage DDT on age (Fig. 1). Percentage DDT had a normal distribution and was not transformed.

Significant regressions of DDE ($P < 0,001$; correlation coefficient = 0,57; standard error = 50,7) and ΣDDT ($P < 0,001$; correlation coefficient = 0,569; standard error = 59,5)

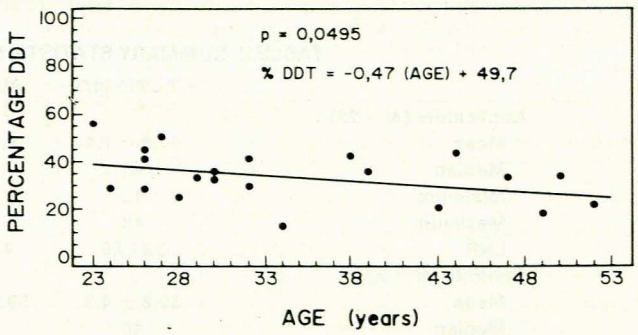

Fig. 1. Linear regression of percentage DDT on age.

on age were obtained for the controls, but not of DDT, DDD and percentage DDT on age.

Only serum alanine aminotransferase (ALT) levels were significantly higher in applicators compared with controls (Table II), but this value was still well within the laboratory normal range (LNR). An outlier γ-glutamyltransferase (GGT) value was not included in Table II because the subject was receiving treatment for cysticercosis. Although the difference in means between applicators and controls was statistically non-significant, the mean GGT value was well above the maximum of the LNR. Liver function results were normally distributed.

Discussion

The breathing space of a DDT applicator can contain concentrations of DDT as high as 7,1 mg/m³ during indoor spraying operations.[18] These levels explain the elevated levels of serum DDT compared with the control subjects. This has also been found by a number of other workers.[10,19,20] Comparing the levels found in this study with these reports show some startling differences. Misra *et al.*[10] found mean values (μg/l) of 212 DDT, 146 DDE, 34 DDD, 401 ΣDDT and 52,9 %DDT in the serum of 17 applicators (mean age 39,3 years, mean length of employment 12,7 years). These applicators were involved in year-long spraying in India and were therefore more exposed. This will also explain the higher percentage DDT, since the baseline values measured in the present study represent exposure 9 months after the end of the previous application. Violante *et al.*[19] analysed serum from 64 workers in Italy and found mean values (μg/l) of 24,2 DDT, 16,4 DDE and a percentage DDT of 67%. No DDD was detected,

TABLE I. SUMMARY STATISTICS OF LEVELS OF DDT AND ITS METABOLITES IN SERUM (μg/l)

	DDT	DDE	DDD	ΣDDT	%DDT
Applicators ($N = 23$)					
Mean	**61,7 ± 29,4***	**129,3 ± 29,0**	**11,0 ± 10,2***	**202,0 ± 120,4****	**33,4 ± 10,2**
Median	**55**	**84**	**8**	**155**	**34**
Minimum	**9**	**21**	**0**	**36**	**12,7**
Maximum	**130**	**358**	**42**	**453**	**55,6**
Controls ($N = 23$)					
Mean	**28,9 ± 17,1***	**105,2 ± 98,4**	**0,2 ± 0,7***	**134,6 ± 114,6****	**27,9 ± 12,9**
Median	**28**	**81**	**0**	**104**	**24**
Minimum	**5**	**6**	**0**	**11**	**8,4**
Maximum	**88**	**424**	**3**	**467**	**60,6**

* $P < 0,0001$.
** $P < 0,05$.
} using log-transformed data.

TABLE II. SUMMARY STATISTICS OF LIVER FUNCTION PARAMETERS

	Albumin (g/l)	ALP (IU/l)	AST (IU/l)	GGT (IU/l)†	ALT (IU/l)
Applicators ($N = 23$)					
Mean	41,8 ± 7,4	65,6 ± 30,7	29,7 ± 16,6	87,6 ± 84,5	12,6 ± 5,0
Median	44	63	29	51	11
Minimum	13	26	15	17	7
Maximum	48	179	85	308	27
LNR	32 - 50	42 - 121	10 - 42	7 - 64	10 - 60
Controls ($N = 23$)					
Mean	39,8 ± 4,3	59,9 ± 24,8	20,9 ± 15,2	59,4 ± 68,7	9,2 ± 1,9*
Median	40	59,5	16	31	9
Minimum	27	5	9	9	5
Maximum	47	139	74	278	14
LNR	32 - 50	42 - 121	10 - 42	7 - 64	10 - 60

* $P < 0,05$.
† Outlier of 1689 excluded.

and no information as to the length of exposure was given. Mpofu[20] detected no DDT residues in serum from people living in DDT-treated dwellings. The applicators in this study, however, had a mean ΣDDT level of 2 200 μg/l (data reported as ΣDDT only). None of these studies reported the use of respirators during the application of DDT.

Although the exposure of the applicators during the spraying season is much higher than the general population, the results suggest that this increased exposure does not result in dramatically higher serum levels.

Differences in respect of the pharmacokinetics between the general population and applicators were noticed. Usually an increase in levels of ΣDDT with age can be expected[21] and this was found for the control group of the present study. The applicators, however, did not show this relationship. The only significant change with age was for %DDT, which decreased significantly. The same analysis was also done by Violante *et al.*[19] for applicator data, but no relationship was found. The argument revolves around the possible changes in pharmacodynamics concerning breakdown of DDT and DDE with age.[19,21] Different rates of elimination for DDT and DDE have been found for people 3 - 20 years and 21 - 67 years of age, exposed to DDT via malaria control applications to their dwellings.[16] The present data suggest that this might be the case at higher levels of exposure as well. The reduction in % DDT found in the present study for the applicators was not noticeable in the controls nor for applicators in which this possibility had been tested.[19] Together with the lack of increase in ΣDDT with age, the present data suggest an enhanced metabolism of DDT to DDE with age at higher levels of exposure, such as applicators involved in malaria control. This is probably the result of induced liver enzyme activity, which has been well documented by other workers.[22-24]

Although the mean ALT level in applicators was significantly higher than in the control group, it was within the LNR. The mean values of the other liver enzymes, except GGT, were also within the LNR. The mean GGT level of the applicator group was higher than the maximum of the LNR, indicating a stimulated liver activity, but the pathogenesis of elevated GGT is not well understood.[25] The mean serum albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and ALT enzyme levels of both groups were within LNR, not indicating progressive liver disease due to exposure to DDT and its metabolites. However, the maximum values of ALP, AST and GGT were more than the maximum of the LNR for both groups suggesting some biologically significant risk from DDT exposure.

Reports on factory formulators,[8,22] usually with greater exposure to DDT than applicators (DDT is not formulated in the RSA), and oral intake studies[24] show the lack of risk, even at very high body burdens. Misra *et al.*,[10] however, reported a possible involvement of DDT in the impairment of cognitive function in DDT applicators. In another study, Misra *et al.*[11] found macular involvement in DDT applicators. A study looking at the possible neurological impairment of infants by DDE in breast-milk, found hyporeflexia significantly associated with an increase in DDE levels.[12] These studies, together with the present study, suggest a possible effect — but the clinical significance is not clear. Although much has been learnt about DDT in the 50 years since its introduction, there still remain aspects, such as improved worker protection and neurological and immunological involvement, that warrant further attention.

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