Malaria control and longitudinal changes in levels of DDT and its metabolites in human serum from KwaZulu

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Blood samples were obtained on four occasions over a 12-month period from individuals living in KwaZulu, South Africa, who had been exposed to DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane) as a consequence of its use in their homes to control transmission of malaria. The longitudinal changes in serum DDT and its major metabolites, DDE and DDD, were determined. No additional risk was considered to have been presented by the increases that occurred following application of the pesticide. There were significant increases in DDT, DDE and ΣDDT (DDT + its metabolites) for the age group ≥21 years, but for the age group 3–20 years a reduction in serum levels occurred over 12 months. Two concurrent processes probably govern the increase and decrease in serum levels, and the relative contributions of each interchange as the individual becomes older. The results suggest that children in KwaZulu experience conditions that differ from those of their parents, as well as from those that affect children in developed countries. In consequence, it is desirable that risk assessments of vector control chemicals consider all sectors of a population.

Introduction

The levels of DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane) and its metabolites in serum and whole blood have received considerable attention (*1–5*). Many studies have been conducted in developed countries and have dealt with occupational exposures to DDT (*6, 7*); however, only a few studies have examined people living in dwellings treated with DDT for malaria control purposes (*8, 9*).

Indoor application of DDT is used with great success to interrupt the transmission of malaria parasites in many developing countries. In South Africa it is employed in the northern and eastern Transvaal and northern KwaZulu, where malaria is endemic (*10*). DDT was applied biannually to all homesteads in these areas between 1957 and 1977; subsequently, regular annual applications have been made between January and March.

DDT can accumulate in biological systems because of its stable, lipophilic properties. In KwaZulu the contribution to the burden of DDT in the human body derived from contaminated fish is negligible (*11*), and there have been no significant changes in DDT levels in fish following its application. The mean intake of ΣDDT (DDT + its metabolites DDE and DDD) from breast milk by infants in KwaZulu exceeds the recommended acceptable daily intake (*12, 13*). The high levels in mothers' milk have resulted in high levels in infants' blood and are also related to maternal parity and infant age (*14*).

A cross-sectional study, which we reported in 1991, found that serum from 71 people aged ≥3 years living in DDT-treated dwellings in KwaZulu had significantly higher mean levels of ΣDDT than that from people in a control area (mean ΣDDT: 140.9 $\mu g.l^{-1}$ and 6.04 $\mu g.l^{-1}$, respectively; $P < 0.005$) (*9*). For exposed people, the mean ΣDDT was significantly higher among 3–10-year-olds than among those aged 20–29 years and 30–39 years (168.6 $\mu g.l^{-1}$, 60.5 $\mu g.l^{-1}$ and 84.2 $\mu g.l^{-1}$, respectively; $P < 0.05$). Statistical analysis suggested that those aged 3–29 years were eliminating DDT (most probably accumulated from contaminated breast milk) faster than they accumulated it. From about 29 years of age, accumulation predominated and the levels began to increase. With regard to the elimination of the metabolite DDE (1,1-dichloro-2,2-bis(4-chlorophenyl)ethene) and DDT, pharmacokinetic differences between the two age groups have been suggested (*9*). An age-related change in elimination rates was also suggested by the results of a study of DDT applicators (*15*).

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The present study was designed to determine longitudinal changes in levels of DDT and its metabolites in the serum of a population protected against malaria by the insecticide, and to examine differences in the rates of change of serum levels of DDT and DDE between younger and older age groups.

Materials and methods

Twelve households, each comprising all the members of a family residing at a specific homestead, were selected in the Mlambongwenya area of Ubombo in northern KwaZulu, where DDT is used for malaria control. At least 10 years' residence at a particular homestead was required for inclusion in the study; homesteads with cement structures were excluded because of the type of DDT formulation applied to them. An inclusion criterion of permanent residence for persons aged ≥3 years was essential because migrant workers were exposed differently.

Two weeks before the initial survey, the informed consent was obtained (in the Zulu language) from participants or, in the case of minors, from their parents, and a questionnaire was completed for each individual. The study design and methods were approved by an ethics committee of the South African Medical Research Council. Local conditions have been described previously (*9*).

Blood samples were collected in November 1986, March 1987, June 1987, and November 1987 by venepuncture and allowed to clot, and 2-ml serum samples were stored in glass vials and frozen on the day of collection. The second survey (March 1987) was carried out, with the assistance of malaria control personnel, 10 days after the application of DDT to the selected homesteads. Each survey took 2 days, during which time sera were obtained from all the participants who could be contacted within a 50-km radius by road. Serum samples were extracted using a supported liquid–liquid extraction technique that has been described previously (*16*).

Results

All members of the selected households agreed to participate. Table 1 shows the numbers of participants sampled on each occasion. During the study two males, aged 6 years and 36 years, died; the cause of the boy's death could not be determined, while the adult died of a urological infection. The ΣDDT levels in both these cases were close to the means for their respective age groups and it appeared unlikely that they would have influenced the overall pattern. Some individuals from whom blood samples were obtained during the initial survey were unavailable during one or more of the subsequent surveys because of hospital visits, family visits, farm work, attendance at school, fishing trips, shopping, or other reasons. The mean age of participants at the start did not differ significantly between surveys. There were

Table 1: **Mean DDE, DDT and ΣDDT levels in serum, by survey and age group**[a]

Survey and age groups	*n*[b]	Concentration in serum (μg.l^{-1}) of: DDE		DDT		ΣDDT	
November 1986							
≤20 years	42	103.9	(76.6)[c]	43.5	(31.0)	147.5	(105.1)
≥21 years	29	102.7	(97.6)	28.2	(17.2)	131.4	(113.9)
Combined	71	103.4	(85.1)	37.3	(27.2)	140.9	(108.3)
March 1987							
≤20 years	39	122.1	(93.0)	53.0	(28.6)	174.2	(110.6)
≥21 years	27	134.3	(113.3)	39.7	(23.6)	175.3	(131.7)
Combined	66	127.1	(101.1)	47.5	(27.3)	174.6	(118.8)
June 1987							
≤20 years	36	111.0	(77.1)	48.4	(30.9)	160.7	(106.0)
≥21 years	22	107.7	(93.3)	32.3	(18.2)	145.3	(111.8)
Combined	58	109.7	(81.8)	42.6	(27.9)	155.4	(107.3)
November 1987							
≤20 years	36	95.4	(65.6)	31.1	(21.5)	127.9	(86.5)
≥21 years	27	124.7	(124.8)	31.9	(21.8)	161.1	(145.0)
Combined	63	107.9	(95.8)	31.4	(21.5)	142.1	(115.4)

[a] ΣDDT = DDT + DDE + DDD.
[b] Numbers of persons sampled.
[c] Values in parentheses are standard deviations.

29 persons in the ≥21-year age group and 42 in the younger age group. Elimination kinetics were calculated separately for each participant and compared pairwise.

The results of the serum analyses are shown in Table 1. DDD (1,1-dichloro-2,2-bis(4-chlorophenyl)-ethane) levels are included in the ΣDDT data and do not appear separately, nor are statistical analyses of DDD levels presented because of their small contribution (±2%) and variation. All concentration parameters were log-normally distributed and were transformed during the statistical analysis.

Changes in the serum levels of contaminants were tested using two-sided, paired Student's *t*-tests and are shown as sequential (successive) changes in Table 2 and summarized in Fig. 1 and 2. Age groups were selected on the basis of the previous observations that under-21-year-olds had a negative DDT balance, i.e., over a 12-month period more ΣDDT was excreted than absorbed, and that older persons had increased ΣDDT levels (*9*). For each parameter, sequential changes between age groups were also compared.

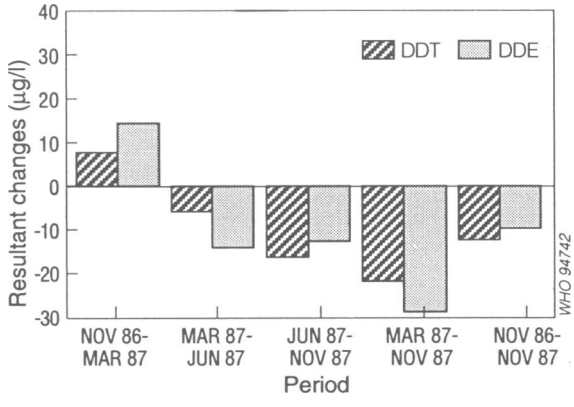
The rates of change in ΣDDT, DDT, and DDE concentrations can be expressed quantitatively as

Table 2: **Resultant mean pairwise changes in ΣDDT, DDT and DDE levels**

Period	Serum concentration (μg.l^{-1}) for age group: ≤20 years	≥21 years	All
November 1986–March 1987			
ΣDDT	21.5	*46.6*[a]	*31.8*
DDT	7.7	*11.8*	*9.3*
DDE	14.6	*34.1*	*22.6*
March–June 1987			
ΣDDT	−17.9	*−28.8*	*−21.6*
DDT	− 5.9	− 7.0	− 6.3
DDE	−14.4	*−25.4*	*−18.5*
June–November 1987			
ΣDDT	*−29.3*[b]	36.2	− 5.8
DDT	*16.4*[b]	2.7	− 9.3
DDE	−12.8[b]	23.1	1.3
March–November 1987			
ΣDDT	*−48.2*	*−26.7*	*−38.9*
DDT	*−22.0*[b]	*− 9.2*	*−16.4*
DDE	*−28.7*	*−47.3*	*−25.7*
November 1986–November 1987			
ΣDDT	−20.7[b]	28.5	0.4
DDT	*−12.3*[b]	3.7	*− 5.4*
DDE	− 9.8[b]	20.8	3.3

[a] Figures in italics are significant ($P<0.05$; Bonferroni adjusted).
[b] Significant difference ($P>0.05$) between the younger and older age groups.

Fig. 1. **Resultant changes in the levels of DDT and DDE residues in sera from the younger age group (≤20 years) for different periods.**



coefficients using first-order reaction kinetics:

$$C = C_o e^{-kt}$$

where

C = final concentration,
C_o = initial concentration,
t = time in years, and
k = rate coefficient.

These coefficients and the results of paired *t*-tests between periods and age groups are shown in Table 3 and summarized in Fig. 3 and 4. No direct comparison of Table 2 and Fig. 1 and 2 (representing resultant changes) with Table 3 and Fig. 3 and 4 (representing absolute values) can be made.

The most notable feature in Table 3 is the increase (negative values) in all parameters for all age groups for the period November 1986 to March

Fig. 2. **Resultant changes in the levels of DDT and DDE residues in sera from the older age group (≥21 years) for different periods.**

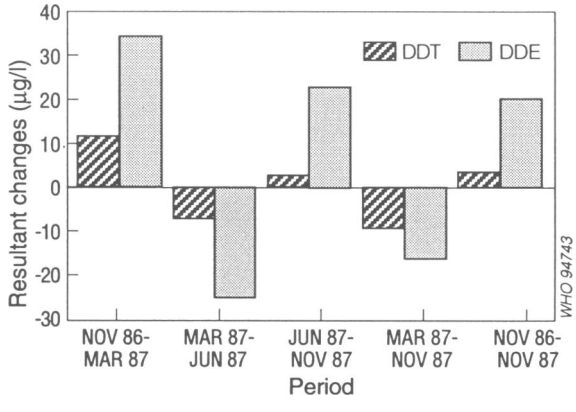


Table 3: **Rate coefficients for ΣDDT, DDT, and DDE, by age group and survey**

Coefficient	Age group	Survey period:[a] Nov86–Nov87	Nov86–Mar87	Mar–Nov87	Mar–Jun87	Jun–Nov87
$k_{\Sigma DDT}$	All	0.0707[b]	–0.2135	0.3359	0.1278[b]	0.1409[b]
$k_{\Sigma DDT}$	≤20 years	(0.2043)[b, c]	–0.1359	0.3909	0.0986[c]	(0.2834)[b]
$k_{\Sigma DDT}$	≥21 years	(–0.1073)[b, d]	–0.3256	0.2639[c]	0.1845[b, c]	(–0.1142)[d]
k_{DDT}	All	0.1776[b]	–0.2755	0.5145	0.1634[b]	0.2986[b]
k_{DDT}	≤20 years	(0.3496)[b, c]	–0.2124	(0.6371)[d]	0.1503[b]	(0.4794)[c, d]
k_{DDT}	≥21 years	(–0.0518)[b]	–0.3668	(0.3541)[c]	0.1875[b, c]	(–0.0088)[b]
k_{DDE}	All	0.0484[b]	–0.1732	0.2681[c]	0.1359[b, c]	0.0902[b]
k_{DDE}	≤20 years	0.1476[b, c]	(–0.0899)	0.2869[b]	0.0735[c]	(0.2026)[b, c]
k_{DDE}	≥21 years	–0.0971[c]	(0.2935)[d]	0.2434[b]	0.2399[b]	(–0.0835)[c, d]

[a] Negative values indicate increases.
[b, c, d] For each compound, rates were significantly different (P <0.05) between periods for the same age group, except those marked by the same character in the same row. Rates in parentheses were significantly different within each period for each parameter between age groups (P <0.05).

1987. Comparison between age groups indicates that the rate coefficients were significantly different only for DDE, the increase for the older group being three times faster than that for the younger group. For ΣDDT and DDT the rates were also faster for the younger age group. The rate coefficients that were significantly different (P <0.05) between age groups in the same period are also shown in Table 3.

All the rate coefficients for the period November 1986 to March 1987 for the same age groups (all ages, ≤20 years and ≥21 years) were significantly different from those for all other periods, except for k_{DDE} for the older age group for the June to November 1987 period (Table 3). None of the coefficients for November 1986 to November 1987 were significantly different from those for June to November 1987. In the March–June 1987 period, only k_{DDE} for the older age group was significantly different from the coefficients for June to November 1987.

The younger age group had faster rates of change (positive or negative) for three periods (November 1986 to November 1987, March to November 1987, June to November 1987), while the older age group had faster rates of change in the remaining periods. Fig. 3 and 4 show that the rate coefficients for DDT were always at least twice those for DDE among the younger age group over the same periods.

The P-values for comparisons of the coefficients between DDE and DDT for the same age groups over the various survey periods are shown in Table 4. For the younger age group, the coefficients were

Fig. 3. **Rate coefficients for DDT and DDE residues in sera from the younger age group (≤20 years) for different periods.**

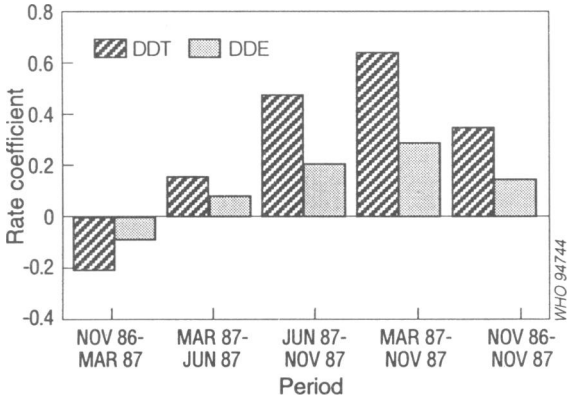


Fig. 4. **Rate coefficients for DDT and DDE residues in sera from the older age group (≥21 years) for different periods.**

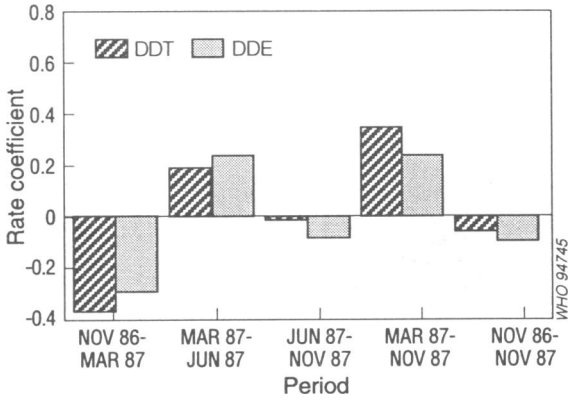


Table 4: **Student's *t*-tests for differences between rates of change for DDE and DDT**

Period	Student's *t*-test for age group:	
	≤20 years	≥21 years
Nov 86–Mar 87	*0.0018*[a](DDT, I)[b]	0.4432 (DDT, I)
Mar–Jun 87	0.1545 (DDT, D)	*0.0418* (DDE, I)
Jun–Nov 87	*0.0000* (DDT, D)	0.1319 (DDE, I)
Mar–Nov 87	*0.0208* (DDT, D)	0.3385 (DDT, D)
Nov 86–Nov 87	*0.0000* (DDT, D)	0.2076 (DDE, I)

[a] Significant differences (P <0.05) are shown in italics.
[b] DDT or DDE level with largest k value; I = increase in serum level of compound with largest value; and D = decrease in serum level of compound with largest value.

significantly different (P<0.05) between DDT and DDE for all the periods under consideration, except March to June 1987. For November 1986 to March 1987 there was a faster rate of increase in DDT than in DDE, and there were decreases in the other three periods for which the differences were significant. There was a significant difference in the rate of change between DDE and DDT for the older age group for March to June 1987, reflecting a faster decrease in the level of DDE.

Discussion

The study subjects experienced no exposure to DDT from any source other than that of malaria control activities. The participants in the study were considered to be representative of the population exposed to DDT in their homes as a result of such activities.

The levels of DDT detected in the first survey in the study area, reported in 1991, were judged not to present a risk to the health of over-3-year-olds (*9*). Also, Morgan & Roan (*17*) found no evidence that high serum levels of DDT and DDE in adult males (52 μg.l^{-1} and 222 μg.l^{-1}, respectively) caused damage to liver cells (*17*). No relationship between overall mortality or cancer mortality and increasing levels of DDT in the serum of DDT formulators has been observed (*18*). Poland et al. found that at a mean ΣDDT level of 1359 μg.l^{-1} in the serum of DDT factory workers, phenylbutazone had a significantly reduced half-life; urinary excretion of 6β-hydroxycortisol was 57% higher than in the control group (mean ΣDDT level = 51 μg.l^{-1}) (*19*). There was no evidence of hepatic disease or liver function abnormalities among 10 factory workers whose mean ΣDDT serum level was 1373 μg.l^{-1} (*20*). Laws et al. could not ascribe any harmful effects to exposure among DDT factory workers (mean ΣDDT serum level = 737 μg.l^{-1}) (*21*). Kreiss et al. found a mean ΣDDT serum level of 159.4 μg.l^{-1} in a cross-sectional study of a community exposed to DDT via contaminated fish, but no association between ΣDDT and any specific illness or ill-health (*5*).

Most comparable studies dealing with malaria control have considered the effect of DDT on people applying it (*2, 22, 23*). Although not referring to malaria control, Agarwal et al. found that the ΣDDT levels in whole blood from the general population in Delhi lay in the range 5–8400 μg.l^{-1} (*24*). No residues were found in a community in Zimbabwe where DDT had been used for malaria control (*8*). In contrast, a mean ΣDDT level of 202 μg.l^{-1} was found in serum from 23 persons who had been applying DDT in Natal (*15*); elevated levels of serum γ-glutamyltransferase in these persons suggested a possible risk to their health.

ΣDDT levels increased significantly after application of the pesticide (Table 2) but, in view of the findings of the studies mentioned above, we do not consider this to present an additional risk to the population. This is consistent with a similar finding on the observed increase in the level of DDT and DDE in the breast milk of breast-feeding mothers in KwaZulu after DDT application (*14*). The infants might, however, have been at an increased risk as a result of the higher levels in breast milk.

Table 1 shows that there was an increase in the mean levels of DDT, DDE and ΣDDT in the whole study group after the first survey, followed by a decrease almost to the initial mean level by the last survey in November 1987. However, the data in Table 2 and Fig. 1 and 2 show that the situation was more complicated. After the application, the increase in DDT, DDE and ΣDDT levels for the younger age group was not significant, but was for the older age group. The increases in the older age group were responsible for the significant increase for all ages (P<0.05).

Table 2 also shows that the increase in the younger age group occurred only directly after DDT application; subsequently the levels fell. In the older age group there was an increase following application, a decrease from March to June 1987, and a further increase from June to November 1987. Despite the significant decrease from March to November 1987, an overall increase occurred between November 1986 and November 1987 in the older group. In contrast, the serum levels of DDT, DDE and ΣDDT all decreased among the younger age group over the latter period. The respective gains and losses among the two age groups cancelled each other out, resulting in almost identical mean levels for November 1986 and November 1987 for the whole study group, for which only DDT showed a significant change. This was caused by the significant decrease in the level of serum DDT in the younger age group over

the 12-month period (Table 2), while the corresponding change in the older group was not significant. It should be borne in mind that DDT comprises only a small proportion of ΣDDT.

The respective gains and reductions in levels in both age groups account for the trend reported previously by Bouwman et al. (*9*). Together with this result, the relatively high levels of DDT and its metabolites in breast milk from the same area (*12*) and in infants (*14*) lead to the conclusion that in young children these compounds are mainly derived from breast-feeding. We have previously suggested that under-20-year-olds eliminate DDT and DDE faster than they accumulate them (*9*). This is supported by the results presented in Table 2 and Fig. 1 and 2.

We hypothesize that two concurrent processes govern the changes in DDT and DDE levels in serum, and that their relative contributions interchange with age. During youth the process governing the increase in serum levels, presumably through uptake, is slower than elimination or dilution. Later in life the two processes transpose, resulting in an increase in serum levels. Confirmation of this requires a comparison of rates rather than of changes in levels.

The reduction of serum DDT levels in the younger age group could also be linked to weight gain after birth, especially in adipose tissue, which would dilute the accumulated stores of DDT. Because of the dynamic equilibrium between DDT in fat and blood (*9*), a gain in weight results in decreased serum levels, since exposure via other routes does not exceed that resulting from discontinuation of breast-feeding. It can therefore be hypothesized that weight gain dilutes both major compounds (DDE and DDT) to the same extent, i.e., if growth dilutes DDE by 50% the same can be expected to apply to DDT. This hypothesis can be tested by comparing the rates of change in DDT and DDE for both age groups; further subdivision can be made into rates of change of the compounds after application, as well as over the 12-month period. The null hypothesis is that exposure to a relatively constant DDE:DDT ratio over long periods will produce rates of change of the two compounds in either age group that do not differ significantly.

The rate coefficients in Table 3 show that the rate of increase in levels was faster for the older than for the younger group between November 1986 and March 1987, and that the difference was significant for DDE. This supports the postulate that two concurrent processes are occurring. The largest rate coefficient was for the decrease in DDT in the younger age group (March to November 1987); its value was almost double that of the corresponding coefficient for the older group. Other indications of this trend were found by making quantitative comparisons of the changes in magnitude of the rates for the younger and older groups between periods.

The significant differences between the rates of change in DDT and DDE levels per period and within age groups are shown in Table 4. Comparison of Fig. 3 and 4 clearly shows that the rate coefficients for DDE and DDT are markedly different for the younger age group. This supports previous suggestions about age-related pharmacokinetic differences for DDT in humans (*5, 9, 15*).

Table 4 shows that, following DDT application, both age groups increased their serum levels of DDT at a faster rate than those of DDE. After March, however, DDT decreased at a faster rate than DDE in the younger group; the difference was significant between June and November 1987. In the older age group, DDE declined at a faster rate, except between March and November 1987, when DDT was eliminated slightly faster than DDE.

Direct comparison with previous investigations cannot be made because of different study designs concerning age-related phenomena, especially in children. Nevertheless, it is worth noting some earlier results that have a bearing on our findings.

Davies et al. analysed whole blood samples from children for DDE and found a general increase in levels (5.3 $\mu g.l^{-1}$ after birth; 15.7 $\mu g.l^{-1}$ for children aged 1–7 years; and 12.6 $\mu g.l^{-1}$ for those aged ≥18 years). There was a very strong age dependency for serum ΣDDT among individuals aged ≤19 years, but not among older people. Both groups exhibited increases in ΣDDT with age. In contrast, the present study found a decrease in ΣDDT levels with increasing age, indicating probable differences in magnitude, route, and exposure regime.

Perron & Barrentine (*22*) analysed three groups of men who were exposed occupationally to DDT. Between April, when exposure began, and August of the same year, the study subjects experienced a fivefold increase in ΣDDT levels (from 25 $\mu g.l^{-1}$ to 130 $\mu g.l^{-1}$). The trend was ascribed to exposure during application of DDT. Subsequently, during exposure to DDT, the serum DDT levels increased faster than DDE levels. Insufficient data were available to permit calculation of the rate coefficients, but the faster rate of increase in serum DDT in Perron & Barrentine's study was also apparent among the older people in the present study. We found the rate of change to be much smaller, probably because of a different exposure regime.

An increase in serum ΣDDT from the age of 3 years onwards has been reported previously (*26*). However, the percentage of DDT decreased with age: for all age groups the mean DDT level lay in the

range 2.1–4.8 μg.l^{-1}; and the mean DDE level ranged from 7.9 μg.l^{-1} for the youngest age group to 26 μg.l^{-1} for those aged 31–60 years. The decrease in the proportion of DDT with age was thus attributable to an increase in DDE levels, but there was almost no change in the level of DDT itself. In our study we observed changes in both DDE and DDT levels, a difference that could again be linked to magnitude, exposure regime and, possibly, route.

A further study involving adults indicated that if DDE is derived from DDT in the body, the mechanisms converting DDT to DDE must be saturated at very low levels (*27*). This was confirmed when it was determined that urinary bis(4-chlorophenyl)-acetic acid (DDA) excretion appeared to account for a larger proportion of the DDT at lower intake levels (*28*). Comparison of these findings with our data is inconclusive, mainly because these last two studies considered oral intake of DDT, whereas we investigated the influence of a single annual application to homesteads.

Morgan & Roan found that in two adult subjects who received oral doses of DDT the individual rates of elimination were different after the final doses, the individual with the higher total dose eliminating DDT faster than the other (*29*). Assuming that all the subjects in our study received essentially the same dose of DDT, a comparison of our findings with those of Morgan & Roan indicates age-related differences in pharmacokinetics. For example, one subject in Morgan & Roan's study who ingested DDE showed no reduction in the levels of this metabolite 8 months after the final dose. This confirms the trend we found for the older group but not that for the younger group. Also, Morgan & Roan found a close correspondence between DDT levels in serum and fat; for DDE the correspondence was less marked. The relationships between the serum and fat levels of compounds (between two individuals ingesting DDT and one ingesting only DDE) were not sufficiently clear to determine the relative rates of change, but the authors concluded that a modest gradient between the serum and fat levels did not interfere with serum-level estimations of the levels in fat. Storage and mobilization apparently respond to the same kinetics.

Keil et al. found that mean levels of DDT and DDE in African-American children aged 6–9 years were 18.5 μg.l^{-1} and 55.2 μg.l^{-1}, respectively, lower than those in the adult reference population of average age 40 years (26.3 μg.l^{-1} and 122.2 μg.l^{-1}, respectively), indicating an age-related increase in levels; a decrease in the proportion of DDT was also evident (*30*).

In a cross-sectional study, no statistically significant changes in serum DDT or DDE levels were found in 192 schoolchildren between the ages of 6 and 9 years (14.5 μg.l^{-1} and 11.7 μg.l^{-1} for DDT; and 41.5 μg.l^{-1} and 38.5 μg.l^{-1} for DDE, respectively). However, it seemed that DDT declined with age at a faster rate than DDE, which is consistent with our findings. Astolfi et al. found that ΣDDT increased with age and that the proportion of DDT in ΣDDT fell with increasing age (from 0–2 years to 14–16 years) (*31*). Although the trend was not consistent, a larger proportion of DDT tended to be present in these 0–16-year-olds than in a previously studied adult group. This was attributed to the lower capacity of children to metabolize DDT. Our findings, however, suggest the opposite, in view of the differences in the rates of change between our two study age groups.

An increase in the proportion of DDE with age has been reported by Kreiss et al. but was not significant when controlled for DDT level (*5*). Comparison between this and the present study is appropriate because both populations were exposed to high levels of DDT, although the sources were different (highly contaminated fish and malaria control, respectively). The population in the study by Kreiss et al. had 86.7% of the serum ΣDDT in the form of *p,p'*-DDE and *o,p'*-DDE, while the dietary fish contained 68% DDD (ΣDDT = 226 μg.l^{-1}). There was a gradual increase in serum levels of ΣDDT with age at a rate indicating that a steady state had not been reached. The gradual increase in DDT levels, which also affected elderly people, suggested that there were age-related changes in absorption, excretion, or partition between fat and serum stores. The highest serum level detected (ΣDDT = 643.3 μg.l^{-1}) involved a 4-year-old boy who was breast-fed for 18 months (*5*). We have previously found that levels are generally higher among Zulu children, resulting from the longer periods of breast-feeding practised (*14*).

Pines et al. have calculated the rate coefficients for DDE and DDT in the serum of people from Israel, without taking age into account (*32*). The values obtained were k_{DDE} = 0.09 and k_{DDT} = 0.40. Differences in study design between this and our own study prevent any meaningful comparison except that the k_{DDT} value was similar to that for March to November 1987 for our older age group.

Three general conclusions can be drawn.

- With the possible exception of the investigation by Keil et al. (*30*), studies dealing with children have found an increase in serum levels with age (*1, 5, 25, 26*). The differences between the results of such studies and our findings could have arisen because of the higher levels to which our study children were previously exposed during breast-feeding and because they were eliminating rather than accumulating ΣDDT.

• Four of the above-mentioned studies reported a rate of change for DDT in children that was less than that for DDE (*5, 26, 30, 31*). The present study examined the opposite situation (a decrease in levels with age) and found that the level of DDT was reduced at a faster rate than that of DDE. These findings, taken together, confirm that the pharmacokinetics of DDT and DDE in children differ from those of older people.

• None of the previous studies offer adequate explanation or support for our findings in adults. Most of these studies also seemed to indicate a decreasing proportion of DDT (*22, 26, 29, 32*). If the mechanisms responsible for converting DDT into DDE are saturated at low levels (*29*), the absence of differences in the dynamics of DDT and DDE might arise, in part, because DDT is being added to a system that produces or takes up DDE at such a rate that it is in equilibrium with DDT at a higher exposure. In turn, this supports the hypothesis that there are pharmacokinetic differences between children (subjected essentially to the same exposure, directly via malaria control and indirectly via alternative routes) and older people.

The observed more rapid reduction in serum DDT by those in the younger age group could perhaps have arisen exclusively from dilution by growth. It is impossible to rule out this "passive" mechanism, but the analysis presented strongly indicates a second mechanism — a true faster rate of reduction in serum DDT—not detected in the older age group. That this mechanism was much more pronounced in our study population suggests that different processes were operating. This can almost certainly be ascribed wholly to the prolonged postnatal exposure to DDT and DDE (malaria control being the only source) via breast milk. In order to determine risk to subgroups of populations, multiple exposures have to be taken into account. DDT will remain in most biological systems for years, even after its use has been discontinued. Furthermore, it should be noted that its replacement with alternative substances would result in multiple exposures, from which breast-feeding infants still receiving DDT from their mothers would not be protected. Erikson et al. have reported changes in the cholinergic muscarinic receptors and behaviour of adult mice exposed to bioallethrin after exposure to DDT (*33*).

Risk assessment of any chemical used against vectors of disease or of any contaminant should include all subgroups of a population and consider them separately, with special reference in developing countries to children and infants, who live under circumstances very different from those of older people, as well as from those experienced by children in developed countries.

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Résumé

Lutte antipaludique et modifications longitudinales des taux de DDT et de ses métabolites dans le sérum humain au KwaZulu

Au KwaZulu (Afrique du Sud), les habitations sont traitées une fois par an par le DDT (1,1,1-trichloro-2,2-bis(4-chlorophényl)éthane) pour lutter contre les vecteurs du paludisme. Des études antérieures ont montré la possibilité d'une différence liée à l'âge en ce qui concerne la pharmacocinétique du DDT et de ses principaux métabolites, le DDE (1,1-dichloro-2,2-bis(4-chlorophényl)éthène) et le DDD (1,1-dichloro-2,2-bis(4-chlorophényl)éthane). Lors de la présente étude, nous avons recherché cette différence en effectuant des prélèvements de sang à quatre reprises sur une période de 12 mois chez des membres des foyers exposés au DDT. Les modifications longitudinales des taux sériques de DDE, de DDD et de DDT ont été déterminées au moyen de techniques d'extraction classiques et d'un chromatographe gazeux équipé d'un détecteur à capture d'électrons.

L'augmentation des taux sériques de DDT après traitement des habitations n'a pas été considérée comme présentant un risque supplémentaire pour les habitants. Une augmentation significative des taux de DDT, DDE et ΣDDT (DDT + métabolites) après application a été observée chez les sujets de plus de 21 ans, tandis que ces taux diminuaient chez les 3–20 ans.

La vitesse de modification des taux sériques de DDT et de ses métabolites, calculée selon une cinétique de premier ordre, différait sensiblement selon le groupe d'âge. Dans le groupe le plus jeune (≤20 ans), les taux de variation du DDT et du DDE étaient significativement différents pour les quatre périodes considérées. Chez tous les sujets de ce groupe, les taux de DDT baissaient plus vite que les taux de DDE. En revanche, dans

le groupe le plus âgé (≥21 ans), les taux de DDE baissaient plus vite que ceux de DDT.

Il semble que deux processus concurrents interviennent dans l'évolution des taux de DDT et de ses métabolites dans le sérum, et que leur importance relative varie selon l'âge. Chez les sujets jeunes, le processus régissant l'augmentation des taux sériques, probablement par absorption, est plus lent que le processus d'élimination. L'analyse présentée ici montre qu'il existe un second processus, par lequel la baisse du DDT sérique est plus rapide chez eux que chez les sujets plus âgés. Le fait que ce mécanisme soit ici beaucoup plus prononcé que dans les études précédentes montre que d'autres processus interviennent dans la population étudiée, notamment l'exposition postnatale prolongée au DDT et au DDE par le lait maternel, résultant exclusivement des activités de lutte antipaludique.

L'évaluation des risques associés à l'utilisation de produits chimiques dans la lutte antipaludique doit prendre en compte tous les secteurs de la population, car nos résultats montrent que les enfants du KwaZulu sont exposés à des conditions différentes de celles qu'ont connues leurs parents ou que connaissant les enfants des pays développés. Les risques pour leur santé pourraient par conséquent être plus prononcés que chez les adultes.

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