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EXPOSURE OF FOREST WORKERS TO 2,4,5-T: CALCULATED DOSE LEVELS

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EXPOSURE OF FOREST WORKERS TO 2,4,5-T: CALCULATED DOSE LEVELS

SUMMARY

This report presents calculated dose levels of 2,4,5-T in workers following application of 2,4,5-T in forestry operations. Experiments were conducted with 19 male and 2 female workers engaged in the application of the propylene glycol butyl ether (PGBE) ester of 2,4,5-T (ESTERON® 245 herbicide) by helicopter (both raindrop nozzle and microfoil boom), by backpack spraying, and by tractor-mounted mist blowers.[1] No special instructions or safety precautions were used. Urine samples were collected following each application and analyzed for 2,4,5-T. The amount of 2,4,5-T absorbed by each worker was calculated by pharmacokinetic analyses of the urinary excretion data using three different methods. The results were classified by the worker's job description and the average dose levels of 2,4,5-T were as follows, calculated as mg 2,4,5-T per kg of body weight. Mixers, 0.073±0.046; backpack sprayers, 0.063±0.034; tractor drivers, 0.045±0.007; supervisors, 0.011±0.011; helicopter flagmen, 0.002±0.003. The two helicopter pilots had average calculated dose levels of 0.007 and 0.048 mg/kg. These dose levels of

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2,4,5-T are far below the 20 mg/kg no effect level for teratogenic or fetotoxic effects. Therefore, we conclude that under these conditions the absorption of 2,4,5-T presents a negligible toxic hazard to forest workers.

INTRODUCTION

Basic toxicological principles require a knowledge both of the inherent toxicity of a chemical and of the quantity actually absorbed into the body in order to assess its possible hazard. The quantity of chemical absorbed may be quite different from the quantity to which workers are exposed under field conditions. Therefore, a proper assessment of the potential hazard to workers during pesticide applications in the field is dependent on reliable estimates of the quantity of pesticide absorbed under these conditions.

The amount of 2,4,5-T absorbed by applicators of 2,4,5-T formulations in forestry operations has never been directly measured. A study was recently conducted by T. L. Lavy (1) which provides urinary excretion data from which estimates can be made of the amount of 2,4,5-T absorbed by forestry workers during the application of 2,4,5-T. Four experiments were conducted with 19 male and 2 female workers engaged in the application of the propylene glycol butyl ether (PGBE) ester of 2,4,5-T (ESTERON® 245 herbicide) by helicopter

(both raindrop nozzle and microfoil boom), by backpack spraying, and by tractor-mounted mist blowers. Total voided urine samples were collected for each worker both prior to and following application, and measurements were made of the amount of 2,4,5-T excreted. The forest applications were made by personnel normally engaged in this type of work and all operations were carried out in the usual manner. No special instructions or safety precautions were used. The field conditions of the studies as well as the results of the analyses are reported in detail by Lavy (1).

The total amount of 2,4,5-T excreted in the urine following exposure represents a minimum estimate of the amount of 2,4,5-T absorbed, since urinary excretion may not be complete at termination of the experiment. However, calculation of the absorbed dose of 2,4,5-T based on pharmacokinetic analysis of urinary excretion data is not dependent on total excretion and can therefore provide a more realistic estimate of the absorbed dose. Furthermore, this approach provides a sound statistical basis for evaluating the adequacy of the pharmacokinetic model to explain the observed data. It is the purpose of this paper to report estimates of the amount of 2,4,5-T absorbed by these workers, based on pharmacokinetic analyses of the amount of 2,4,5-T excreted in the urine.

METHODS

Pharmacokinetic Model

In order to establish an adequate pharmacokinetic model for the absorption and excretion of 2,4,5-T, the following data were considered.

Previous studies with 2,4,5-T ingested by human volunteers at a dose level of 5 mg per kg body weight showed that essentially all of the 2,4,5-T was quickly absorbed and excreted unchanged in the urine (2). Urinary excretion of 2,4,5-T occurred by an apparent first order process with a half life of 23.1 hr (0.96 day). The fecal route of excretion was shown to be negligible for 2,4,5-T in humans.

In rats given a single oral dose of 5 mg/kg, the 2,4,5-T was excreted mainly in the urine by an apparent first order process with a half-life of 13.6 hr (3). In another study, in rats given a single intravenous dose of 5 mg/kg (4), urinary excretion of unchanged 2,4,5-T accounted for 96% of the administered dose and excretion occurred by an apparent first-order process with a half-life of 10.7 hr. Thus, the urinary excretion of 2,4,5-T at this dose level occurs by a first order process that is essentially independent of the route of administration.

A recent study conducted in this laboratory (5) showed that the PGBE ester of 2,4,5-T applied to the shaved skin of rats at a dose level of 5 mg/kg was virtually completely absorbed, and subsequently excreted in the urine as 2,4,5-T per se. Urinary excretion of 2,4,5-T appeared to be a first order process with a half-life of approximately 24 hr, indicating that the dermal absorption process may have been slow in relation to the urinary excretion of 2,4,5-T.

The foregoing data demonstrate that measurement of the urinary excretion of 2,4,5-T can provide a reliable estimate of the amount of 2,4,5-T absorbed. Also, it is apparent that esters of 2,4,5-T are slowly but readily absorbed through the skin and are then excreted in the urine as 2,4,5-T acid. These considerations provide the basis for the pharmacokinetic model shown in Figure 1 for the absorption of 2,4,5-T or its esters and subsequent urinary excretion of 2,4,5-T in humans. A definition of symbols and terms is given in the legend of Figure 1. All calculations have been made on the basis of 2,4,5-T acid equivalents.

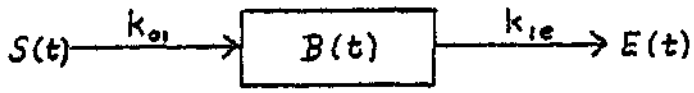


Figure 1. Schematic diagram of the pharmacokinetic model for the absorption of 2,4,5-T or its PGBE ester in humans, followed by urinary excretion of 2,4,5-T acid. S(t) = amount of 2,4,5-T remaining to be absorbed at time t. B(t) = amount of 2,4,5-T in body at time t. E(t) = amount of 2,4,5-T excreted in urine at time t. k_{01} and k_{1e} = first order rate constants for absorption and excretion of 2,4,5-T, respectively.

The differential equations and initial conditions describing the dynamics of the pharmacokinetic model are shown in Figure 2. The half-life for the urinary excretion of 2,4,5-T in humans previously determined as 0.96 day (2) corresponds to an apparent first order elimination rate constant of 0.72 day^{-1}, the value we have used for k_{1e} in the differential equations of Figure 2. The value of S(t) at time zero represents the dose D_o, which is the total quantity of 2,4,5-T absorbed.

Differential Equation	Initial Condition
$\frac{dS(t)}{dt} = -k_{01} S(t)$	$S(o) = D_o$
$\frac{dB(t)}{dt} = k_{01} S(t) - k_{1e} B(t)$	$B(o) = O$
$\frac{dE(t)}{dt} = k_{1e} B(t)$	$E(o) = O$

Figure 2. Differential equations and initial conditions describing the pharmacokinetic model of Figure 1.

Data Base

The urinary excretion data reported by Lavy in Tables 6, 7, 8, and 9 of reference 1 were treated as follows. Since a large amount of diurnal variation was evident in the urine samples collected at 12-hr intervals, the values for successive 12-hr intervals were combined so that each value represents the amount of 2,4,5-T excreted per day. Urine samples collected on the day previous to either the first or the second application date were considered to be pre-exposure samples. The data thus arranged are shown in Table 1, with the same designation used by Lavy for each worker (1).

The amount of 2,4,5-T in the pre-exposure samples fluctuated widely with no apparent pattern, therefore no background corrections were applied. The workers employed as mixers may have been exposed on the day previous to the application date (since the formulations are usually mixed the day before the actual application), but for purposes of pharmacokinetic analysis they were considered to be exposed only on the date of application. The duration of the application procedures ranged from 55 minutes to approximately 4 hours (average 138 minutes). Since this is a short time span relative to the total duration of the experiments (up to seven days), the calculated dose was considered to be a single application to the skin at time zero. These assumptions have either a negligible or a maximizing influence on the calculated dose absorbed.

TABLE 1. Daily and Total Amounts of 2,4,5-T Excreted in the Urine of Forest Workers Following Application of ESTERON® 245[a]

Worker No.[b]	mg 2,4,5-T Excreted[e]							
	Day 0	Day 1[c]	Day 2	Day 3	Day 4	Day 5	Day 6	Total[d]
1A	0.119	0.182	0.210	0.127	0.155	0.085	0.075	0.834
1B	0.039	0.169	0.122	0.167	0.203	0.198	-	0.859
2A	0.398	0.611	1.458	1.460	0.723	0.422	1.212	5.886
2B	0.784	2.067	0.911	0.978	0.646	0.464	-	5.066
3A	nd	0.472	1.100	1.648	0.618	0.218	0.267	4.323
3B	0.246	1.142	0.237	0.515	0.549	0.214	-	2.657
4A	0.146	0.254	0.913	0.421	0.495	0.279	0.494	2.856
4B	0.749	0.402	1.101	0.584	0.506	0.597	-	3.190
5A	0.033	0.133	0.772	0.251	0.222	0.101	0.142	1.621
5B	0.098	0.193	0.367	0.126	0.122	0.074	-	0.882
6A	0.373	0.572	1.027	0.458	0.235	0.214	-	2.506
7A	0.796	0.211	3.701	0.856	0.876	0.760	0.566	6.970
7B	0.314	0.931	0.708	0.368	0.422	0.334	-	2.763
8A	0.088	0.698	0.858	0.579	0.380	0.259	-	2.775
8B	-	-	0.277	0.196	0.146	0.134	-	0.753
9A	0.103	0.343	1.500	0.687	0.599	0.372	-	3.501
9B	0.097	0.644	0.716	0.548	0.478	0.278	-	2.664
10A	0.690	0.709	0.748	0.773	0.761	0.498	-	3.489
10B	0.953	0.889	1.068	0.539	0.892	0.893	-	4.281
11A	0.037	1.246	2.272	1.653	0.629	0.408	-	6.208
11B	-	-	1.632	1.204	0.283	0.279	-	3.398
12A	nd	nd	nd	0.041	nd	nd	-	0.041
12B	nd	0.230	0.310	0.267	0.097	0.084	0.069	1.057
13A	1.894	2.430	1.409	1.827	1.386	1.136	-	8.188
13B	1.362	1.470	1.397	1.344	0.964	0.737	0.773	6.685
14A	nd	nd	0.029	0.109	0.155	0.032	-	0.325
14B	0.012	0.099	0.060	0.038	0.010	0.081	0.031	0.319
15A	0.020	0.008	0.035	nd	nd	0.097	-	0.140
15B	nd	nd	nd	nd	nd	nd	nd	nd
16A	0.026	0.008	0.053	0.107	nd	nd	-	0.168
16B	nd	0.020	0.037	0.014	nd	nd	nd	0.071
17A	0.288	0.467	0.602	0.383	0.409	0.365	0.255	2.481
17B	0.324	0.370	0.812	0.600	0.602	0.455	-	2.839
18A	0.715	1.610	1.229	0.883	0.916	0.804	0.465	5.907
18B	0.960	1.112	3.536	2.229	2.428	1.650	-	10.955
19A	nd	0.014	0.158	0.113	0.073	0.067	0.116	0.541
19B	0.047	0.018	0.057	0.032	nd	nd	-	0.107
20A	nd	0.070	0.079	0.064	0.016	nd	nd	0.229
20B	nd	nd	0.022	nd	nd	nd	-	0.022
21A	nd	nd	0.029	0.033	0.032	nd	0.022	0.116
21B	nd	nd	0.016	0.022	0.011	0.089	-	0.138

[a] Data taken from Lavy (1).

[b] A and B refer to the first and second exposure, respectively.

[c] The beginning of day 1 is designated as the beginning of the exposure.

[d] Excluding the 2,4,5-T excreted on day 0 (the "pre-exposure" sample).

[e] - means no data available; nd means 2,4,5-T below detection limit in urine.

In order to estimate the actual amount of 2,4,5-T absorbed (calculated as mg 2,4,5-T) during each application, the following three methods were used.

Method A

This method is based on pharmacokinetic parameter estimation techniques in which the best parameter estimates are considered to be those that yield the closest fit of the calculated data to the observed data (using the least squares criterion). In this case, parameter estimates were desired for the absorption rate constant (k_{o_1}) and for the total absorbed dose of 2,4,5-T (D_o). The excretion rate constant (k_{1e}) was set at the previously established value of 0.72 day^{-1}, and the observed data consisted of mg 2,4,5-T excreted in the urine per day.

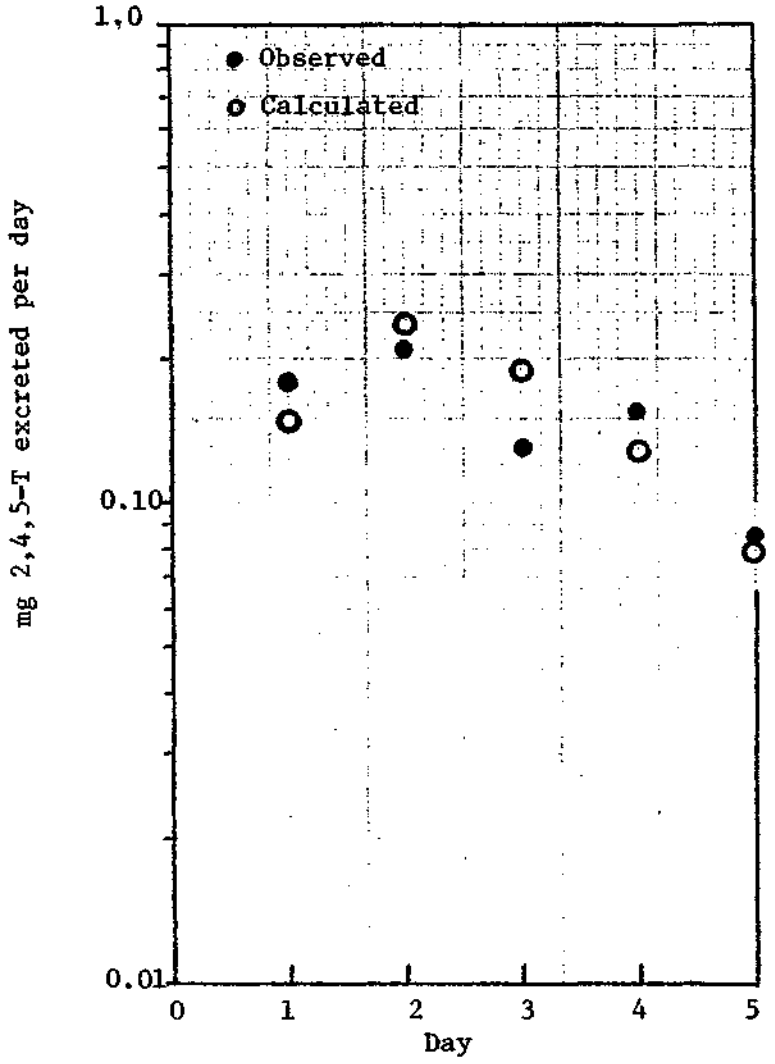
The data for each worker following both exposures were plotted on semi-logarithmic graph paper. Visual inspection of all these plots showed that there were 12 exposures for 10 different workers in which (a) the data were complete (no missing data points), and (b) the time course of urinary excretion of 2,4,5-T followed a kinetically consistent pattern (i.e., a rise following the application date and a subsequent log-linear decline). These data sets were consistent with the model shown in Figure 1.

Pharmacokinetic parameter estimation for these 12 data sets was accomplished with a digital computer, and the average percent variation explained was 69.0% (range 29.5% to 93.5%). The results of these analyses are shown in Figures 3(a) through 3(ℓ) in which the points • and o represent the observed and calculated data points, respectively. As expected, the estimated values of D_o varied considerably between individuals. However, the apparent first-order absorption rate constant k_{o1} was reasonably consistent between individuals, the average value being 0.92 day^{-1} with a standard deviation of 0.21 day^{-1} (n = 12). The foregoing analyses thus provided an estimate of the absorbed dose of 2,4,5-T for 12 of the 41 exposures comprising the complete study. The results are shown in column A of Table 2. Also, the average value of the absorption rate constant determined here was used in the following two methods to obtain further estimates of the absorbed dose.

Method B

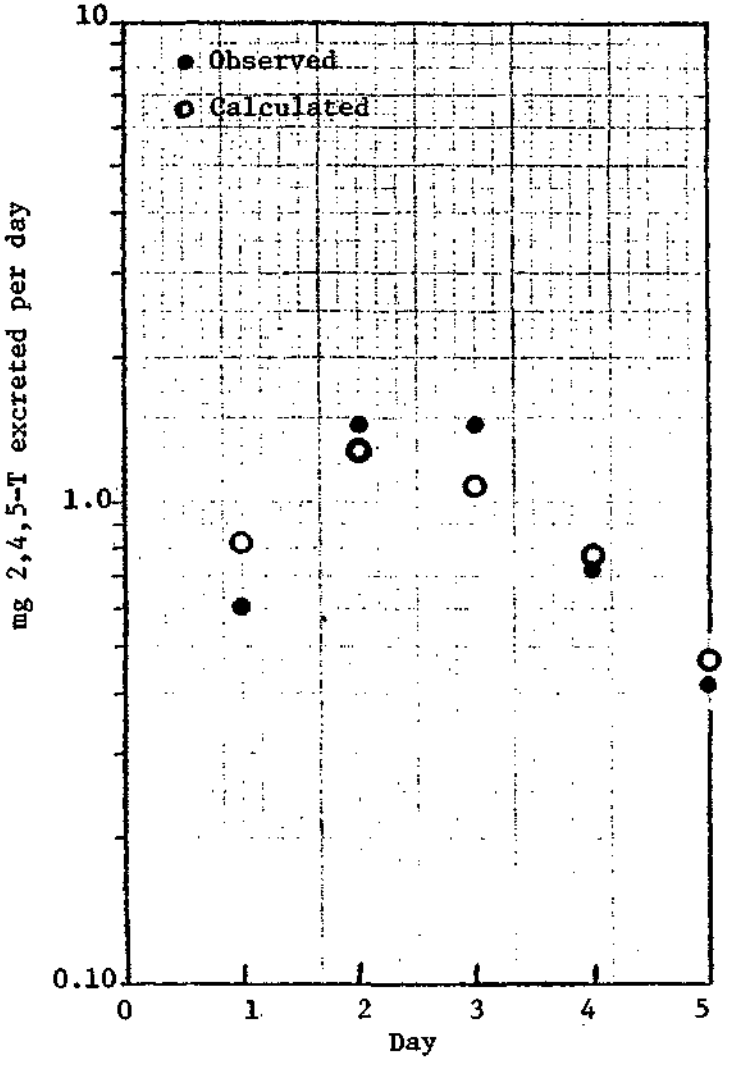
Integration of the differential equations of Figure 2 and solution for the total amount of 2,4,5-T excreted in the urine t days following exposure, designated as E(t), results in equation 1.

$$E(t) = D_o \left\{ t - \frac{k_{1e}\, e^{-k_{o1}t}}{(k_{1e} - k_{o1})} - \frac{k_{o1}\, e^{-k_{1e}t}}{(k_{o1} - k_{1e})} \right\} \qquad (1)$$



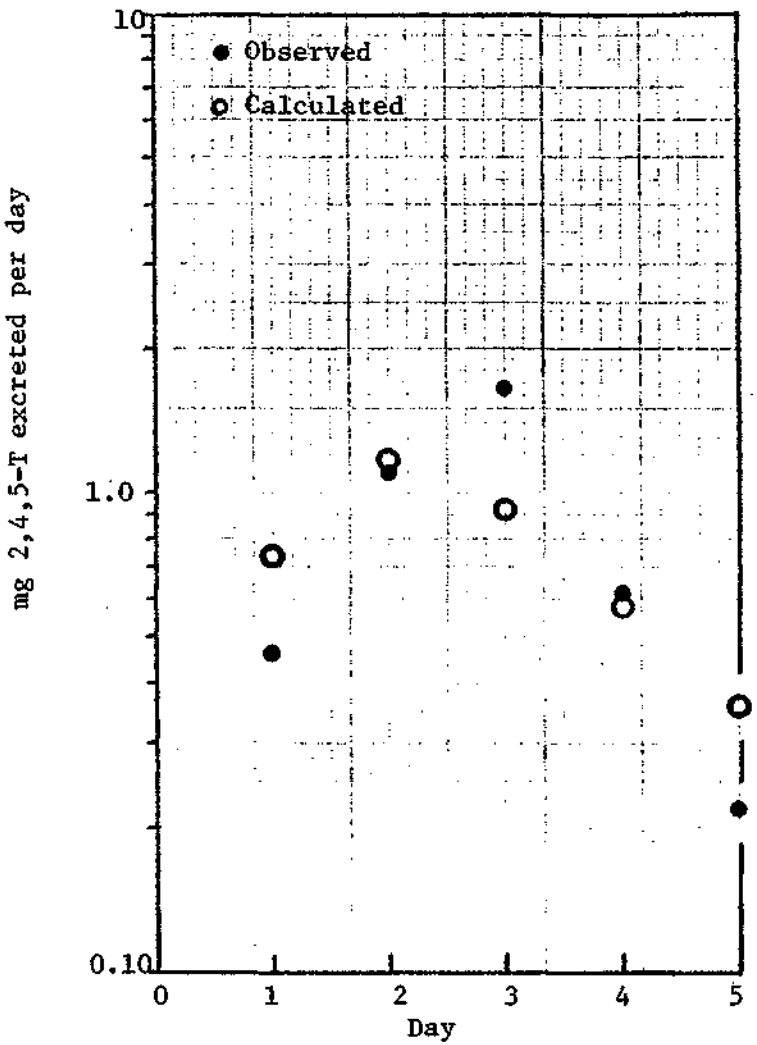
Worker No. 1(A)
D_o (Calc.) = 0.90 mg

Figure 3a



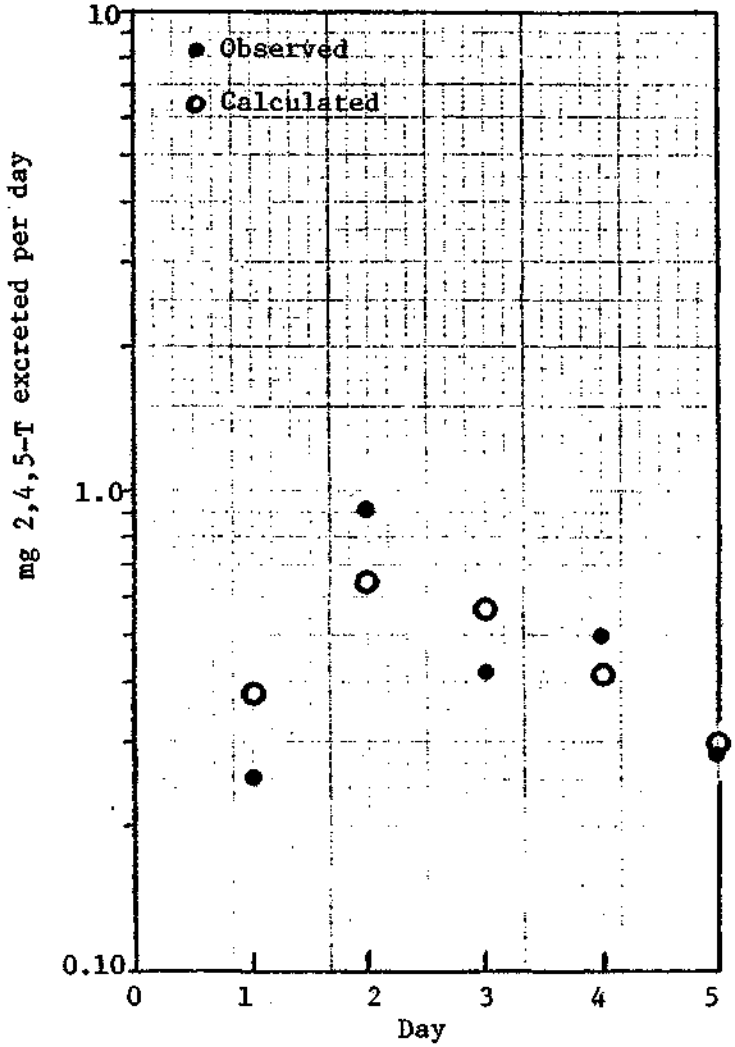
Worker No. 2(A)
D_o (Calc.) = 5.15 mg

Figure 3b



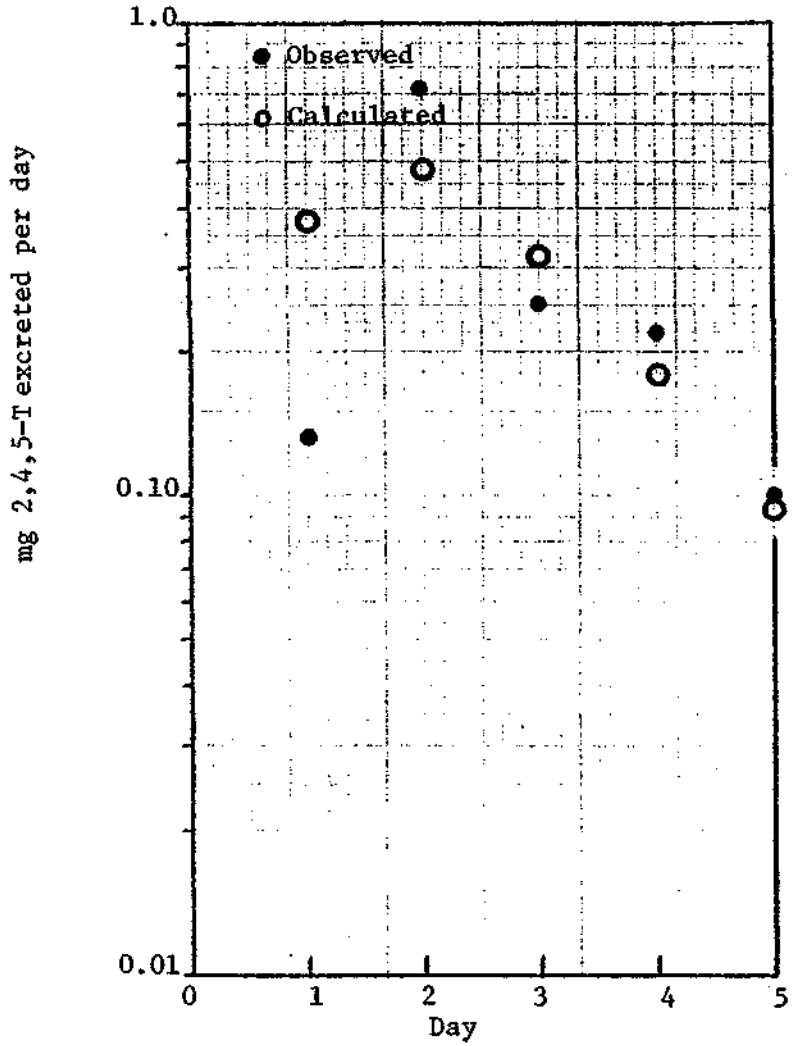
Worker No. 3(A)
D_o (Calc) = 4.26 mg

Figure 3c



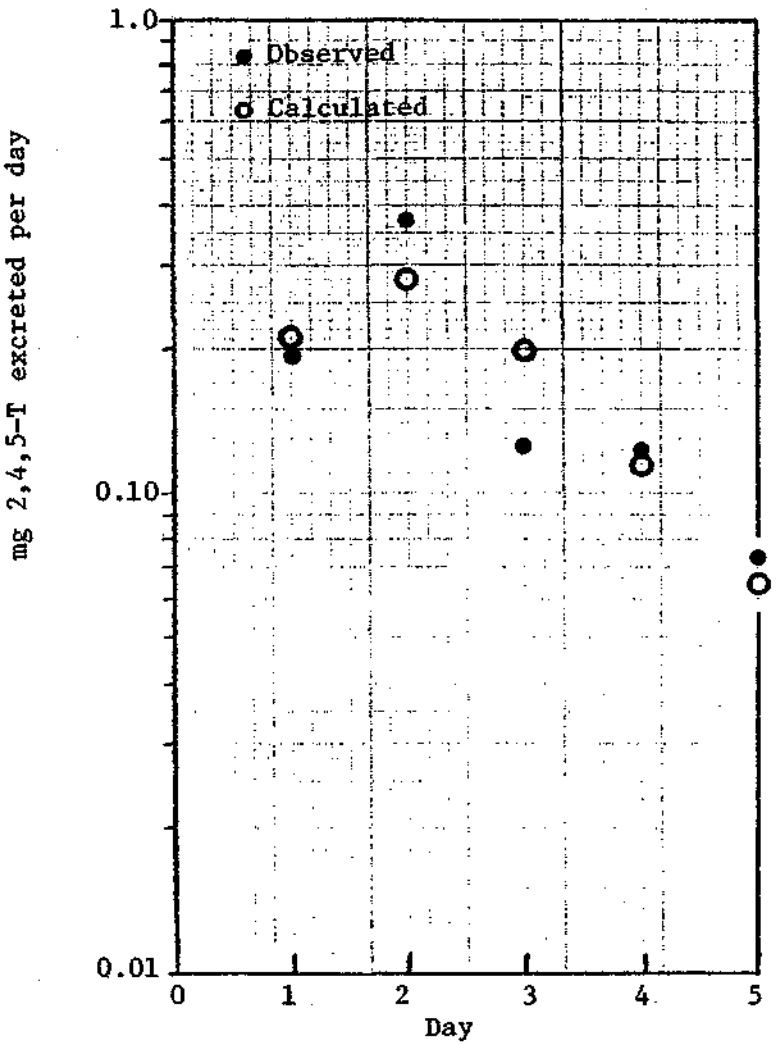
Worker No. 4(A)
D_o (Calc) = 2.76 mg

Figure 3d



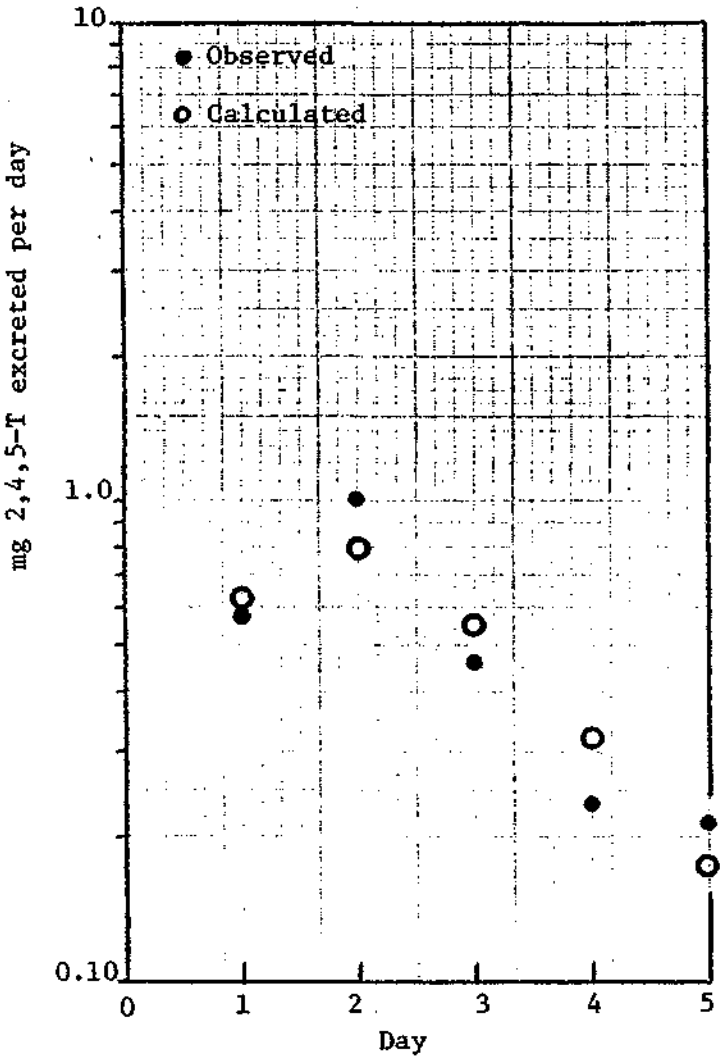
Worker No. 5(A)
D_o (Calc) = 1.56 mg

Figure 3e



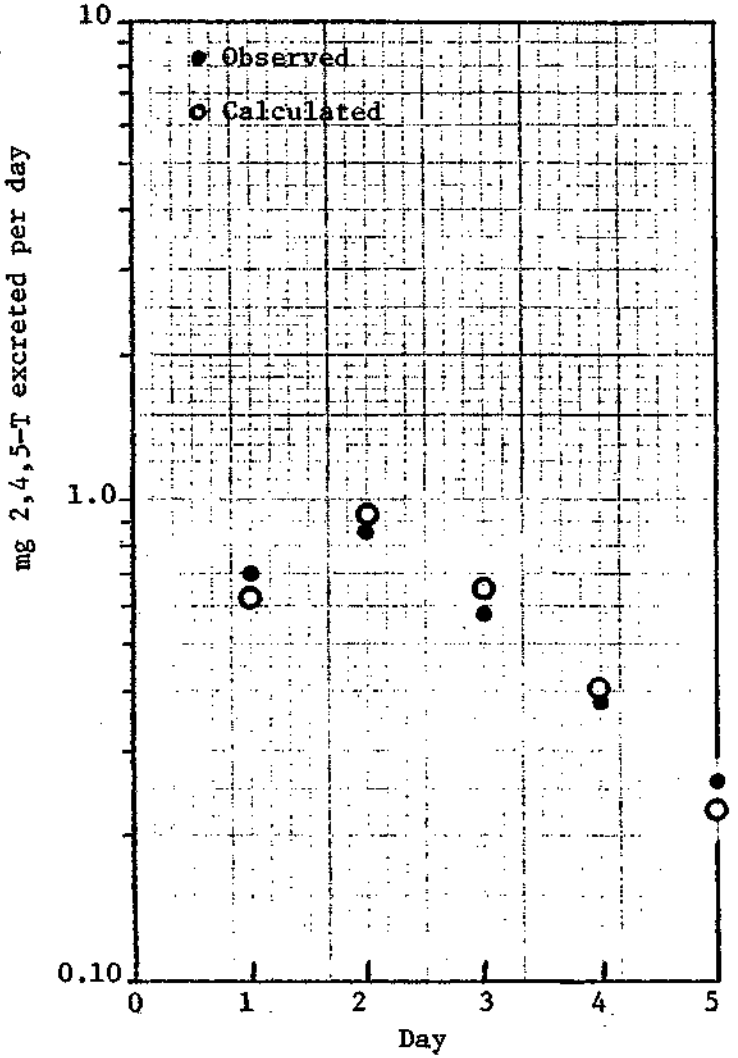
Worker No. 5(B)
D_o (Calc) = 0.95 mg

Figure 3f



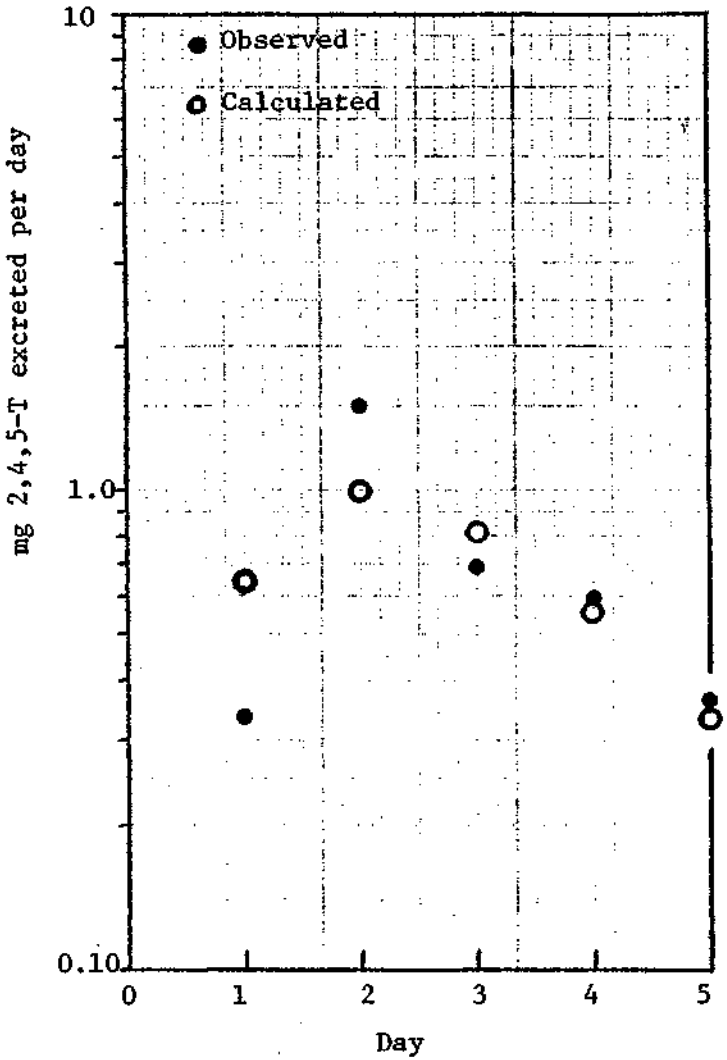
Worker No. 6(A)
D_o (Calc) = 2.64 mg

Figure 3g



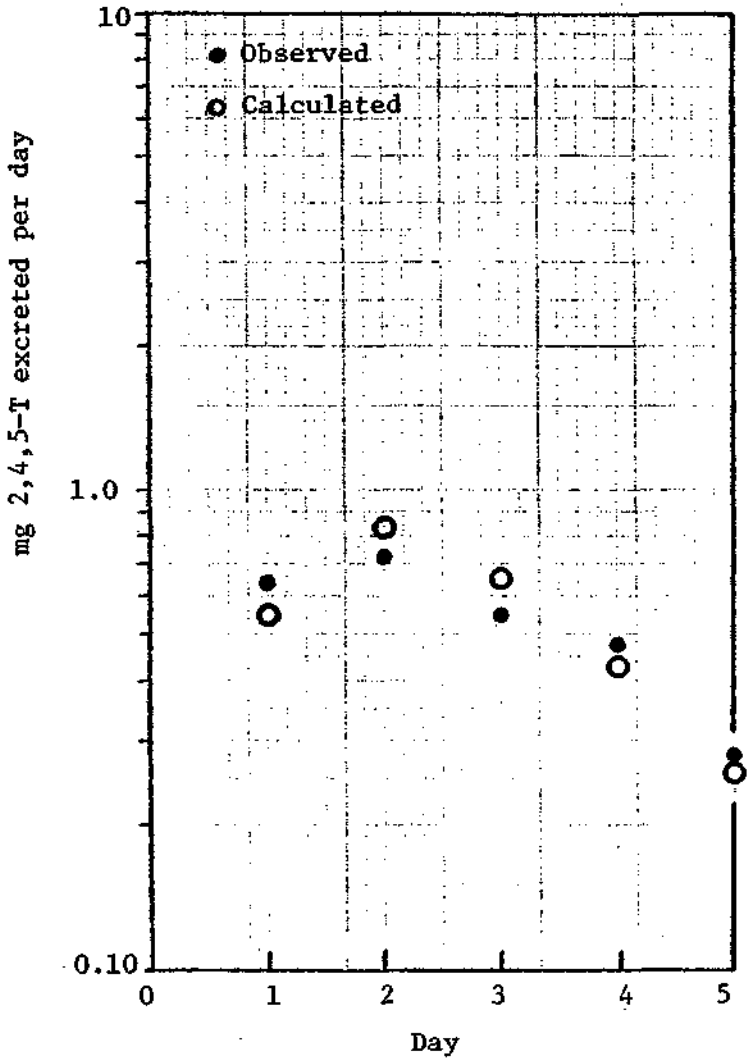
Worker No. 8(A)
D_o (Calc) = 3.09 mg

Figure 3h



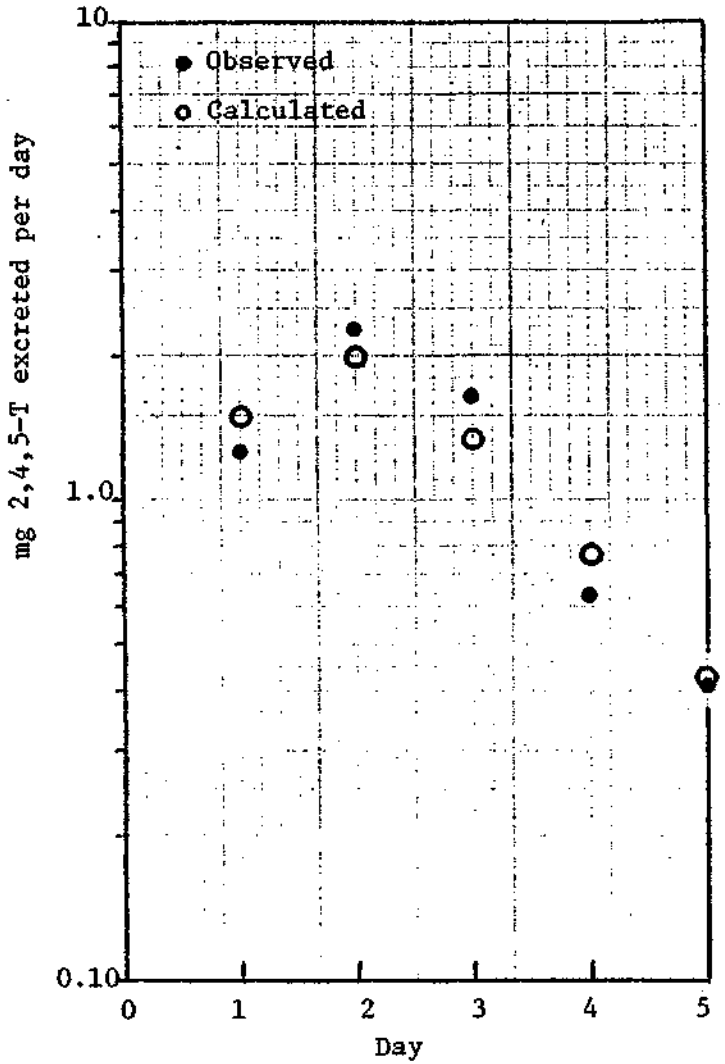
Worker No. 9(A)
D_o (Calc) = 3.84 mg

Figure 3i



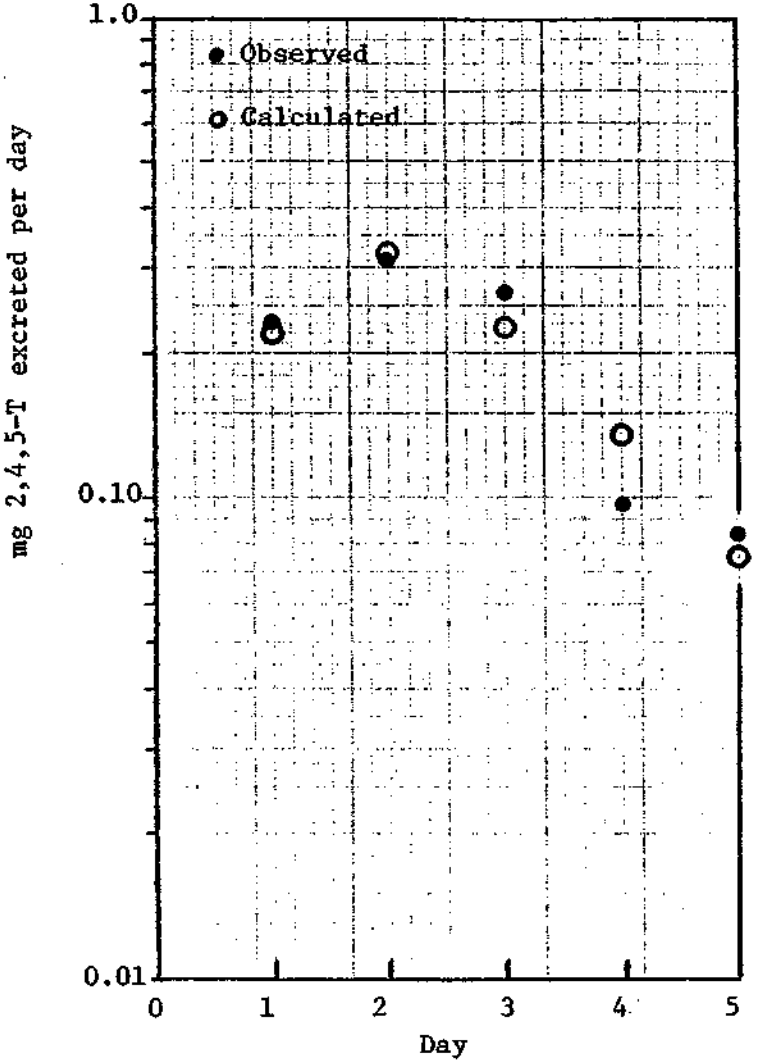
Worker No. 9(B)
D_o (Calc) = 3.09 mg

Figure 3j



Worker No. 11(A)
D_o (Calc) = 6.45 mg

Figure 3k



Worker No. 12 (B)
D_o (Calc) = 1.06 mg

Figure 3ℓ

TABLE: 2. Calculated Amount of 2,4,5-T Absorbed by Forest Workers During Application of ESTERON® 245

Worker No.[a]	Calculated mg 2,4,5-T Absorbed		
	Method A	Method B	Method C[b]
1A	0.898	0.875	1.040 ± 0.408 (6)
1B	-	0.943	1.221 ± 0.833 (5)
2A	5.153	6.175	9.016 ± 9.539 (6)
2B	-	5.564	5.804 ± 2.840 (5)
3A	4.262	4.535	4.585 ± 2.030 (6)
3B	-	2.918	3.173 ± 1.884 (5)
4A	2.755	2.996	4.206 ± 3.720 (6)
4B	-	3.504	4.003 ± 2.175 (5)
5A	1.561	1.701	1.800 ± 1.005 (6)
5B	0.947	0.969	0.941 ± 0.248 (5)
6A	2.644	2.752	2.624 ± 0.719 (5)
7A	-	7.312	6.842 ± 4.667 (6)
7B	-	3.035	3.270 ± 1.260 (5)
8A	3.086	3.048	3.077 ± 0.365 (5)
8B	-	-	1.169 ± 0.373 (4)
9A	3.844	3.845	3.877 ± 1.410 (5)
9B	3.085	2.926	3.088 ± 0.527 (5)
10A	-	3.832	4.369 ± 1.574 (5)
10B	-	4.702	5.766 ± 3.513 (5)
11A	6.450	6.818	6.373 ± 1.449 (5)
11B	-	-	4.240 ± 1.732 (4)
12A	-	0.059	0.190 (1)
12B	1.063	1.109	1.151 ± 0.290 (6)
13A	-	8.993	10.130 ± 3.704 (5)
13B	-	7.013	8.882 ± 4.750 (6)
14A	-	0.357	0.541 ± 0.439 (4)
14B	-	0.335	0.455 ± 0.374 (6)
15A	-	0.154	0.469 ± 0.673 (3)
15B	nd	nd	nd
16A	-	0.241	0.241 ± 0.233 (3)
16B	-	0.102	0.099 ± 0.032 (3)
17A	-	2.603	3.323 ± 1.653 (6)
17B	-	3.118	3.560 ± 1.572 (5)
18A	-	6.197	7.431 ± 2.905 (6)
18B	-	12.032	13.501 ± 6.143 (5)
19A	-	0.568	0.877 ± 0.934 (6)
19B	-	0.153	0.147 ± 0.054 (3)
20A	-	0.275	0.262 ± 0.102 (4)
20B	-	0.112	0.077 (1)
21A	-	0.113	0.251 ± 0.184 (4)
21B	-	0.152	0.345 ± 0.532 (4)

[a] A and B refer to the first and second exposure, respectively.

[b] The number of individual determinations of D_o by Method C is shown in parentheses.

Solution of equation (1) using the previously determined values of k_{o_1} and k_{1e} at successive values of t reveals the cumulative fraction of the absorbed dose of 2,4,5-T that is excreted in the urine following exposure. The values of this fraction obtained from 1 through 7 days following exposure are given in Table 3.

TABLE 3. Cumulative Fraction of the Absorbed Dose of 2,4,5-T Excreted in the Urine

Days Following Exposure	Cumulative Fraction of Dose Excreted
1	0.1956
2	0.4819
3	0.6974
4	0.8326
5	0.9105
6	0.9532
7	0.9760

The absorbed dose D_o was calculated by dividing the cumulative quantity of 2,4,5-T excreted in the urine by the appropriate fraction at that time. This procedure provided a single estimate of the absorbed dose for 39 of the 41 exposures, shown in column B of Table 2.

Method C

By using the integrated form of the equation for the cumulative quantity of a chemical excreted as a function of time, an equation can be derived with which the absorbed dose can be

calculated based on the interval (in this case, daily) amount of 2,4,5-T excreted using the previously established values for k_{01} and k_{1e} (7). This calculation is based on equation 2 where E_i is the amount of 2,4,5-T excreted during the i-th day following exposure, d_i is the length of the collection interval (1 day), and t_i is the total number of days following exposure. The calculation of D_o by this method is independent of the total (cumulative) quantity of urine collected.

$$D_o = E_i (k_{01} - k_{1e}) \left\{ k_{01} e^{-k_{1e} t_i} \left(e^{k_{1e} d_i} - 1 \right) - k_{1e} e^{-k_{01} t_i} \left(e^{k_{01} d_i} - 1 \right) \right\}^{-1} \quad (2)$$

Application of equation 2 therefore provided an estimate of the absorbed dose every day on which urine was collected following each of the 41 exposures comprising the study. The results shown in column C of Table 2 are the average calculated dose (± standard deviation) for each exposure by this method.

RESULTS

Table 2 shows the calculated dose of 2,4,5-T following each exposure to the 21 workers in this study. A comparison of the data in Table 2 reveals similar results by all three methods used to calculate the dose. As expected, these calculated doses are almost always greater than the total mg of 2,4,5-T excreted in the urine at the end of 5 or 6 days following exposure (last column in Table 1).

The maximum (i.e., worst case) estimated dose shown in Table 2 for each exposure was used to calculate the dose in mg 2,4,5-T per kg body weight for each worker. These dose levels are shown in Table 4, 5, 6 and 7 for the four types of spray application included in this study. It is apparent from inspection of these tables that the quantity of 2,4,5-T absorbed by the workers was usually less than 0.1 mg/kg. In fact, only two doses exceeded this level; a backpack sprayer (No. 2, second exposure) with a calculated dose of 0.132 mg/kg, and a mixer (No. 18, second exposure) with a calculated dose of 0.156 mg/kg. The lowest dose level of 0.001 mg/kg was received by flagmen for helicopter applications.

Since there was an obvious correlation between the job descriptions of the workers and the calculated dose levels of 2,4,5-T, the results were grouped on the basis of job descriptions. The average dose levels thus obtained are

TABLE 4. CALCULATED DOSE OF 2,4,5-T TO FOREST WORKERS: BACKPACK SPRAYER APPLICATION

WORKER (sex)	BODY WEIGHT (kg)	JOB DESCRIPTION	EXPOSURE	MAXIMUM CALCULATED DOSE OF 2,4,5-T (mg/kg)
1 (M)	72.6	Mixer/Supervisor	First	0.014
			Second	0.017
2 (M)	68.1	Sprayer	First	0.132
			Second	0.085
3 (F)	49.9	Sprayer	First	0.092
			Second	0.064
4 (M)	95.3	Sprayer	First	0.044
			Second	0.042
5 (F)	52.2	Sprayer	First	0.034
			Second	0.019
6 (M)	65.8	Sprayer	First	0.042
7 (M)	74.9	Sprayer	First	0.098
			Second	0.044

TABLE 5. CALCULATED DOSE OF 2,4,5-T TO FOREST WORKERS:

TRACTOR MOUNTED MIST BLOWER APPLICATION

WORKER (sex)	BODY WEIGHT (kg)	JOB DESCRIPTION	EXPOSURE	MAXIMUM CALCULATED DOSE OF 2,4,5-T (mg/kg)
8 (M)	95.3	Supervisor	First	0.032
			Second	0.012
9 (M)	84.0	Driver	First	0.046
			Second	0.037
10 (M)	106.7	Driver	First	0.041
			Second	0.054
11 (M)	79.5	Mixer	First	0.086
			Second	0.053

TABLE 6. CALCULATED DOSE OF 2,4,5-T TO FOREST WORKERS:

HELICOPTER (MICROFOIL BOOM) APPLICATION

WORKER (sex)	BODY WEIGHT (kg)	JOB DESCRIPTION	EXPOSURE	MAXIMUM CALCULATED DOSE OF 2,4,5-T (mg/kg)
12 (M)	95.3	Pilot	First	0.002
			Second	0.012
13 (M)	109.0	Mixer	First	0.092
			Second	0.081
14 (M)	84.0	Supervisor	First	0.006
			Second	0.005
15 (M)	61.3	Flagman	First	0.008
			Second	nd*
16 (M)	74.9	Flagman	First	0.003
			Second	0.001

*Not detected.

TABLE 7. CALCULATED DOSE OF 2,4,5-T TO FOREST WORKERS:

HELICOPTER (RAINDROP NOZZLE) APPLICATION

WORKER (sex)	BODY WEIGHT (kg)	JOB DESCRIPTION	EXPOSURE	MAXIMUM CALCULATED DOSE OF 2,4,5-T (mg/kg)
17 (M)	72.6	Pilot	First	0.046
			Second	0.049
18 (M)	86.3	Mixer	First	0.086
			Second	0.156
19 (M)	81.7	Supervisor	First	0.011
			Second	0.002
20 (M)	86.3	Flagman	First	0.003
			Second	0.001
21 (M)	95.3	Flagman	First	0.001
			Second	0.002

TABLE 8. AVERAGE CALCULATED DOSES OF 2,4,5-T TO FOREST WORKERS

JOB DESCRIPTION	(N) TOTAL NUMBER OF EXPOSURES	AVERAGE CALCULATED DOSE OF 2,4,5-T (mg/kg) ± Std. Dev.
Mixers	8	0.073±0.046
Backpack Sprayers	11	0.063±0.034
Tractor Drivers	4	0.045±0.007
Supervisors	6	0.011±0.011
Helicopter Flagmen	8	0.002±0.003
Helicopter Pilot (No. 12)	2	0.007
Helicopter Pilot (No. 17)	2	0.048

shown in Table 8. The mixers, backpack sprayers, and tractor drivers had average dose levels of 0.073±0.046, 0.063±0.034, and 0.045±0.007 mg/kg respectively. The average dose level calculated for all the workers in these groups (n=23 exposures) was 0.063±0.036 mg/kg. The supervisors and helicopter flagmen showed average dose levels of 0.011±0.011 and 0.002±0.003 mg/kg respectively. The two helicopter pilots had average dose levels during the two applications of 0.007 and 0.048 mg/kg.

DISCUSSION

The general validity of the linear pharmacokinetic model used to obtain the dose estimates reported here is attested by the reasonable fit of the observed and theoretical data points shown in Figures 3(a) through 3(ℓ). While any of the three methods of calculating D_o should provide a valid estimate, Method C (the use of the interval amounts of 2,4,5-T excreted) is believed to yield the best overall value, since each daily urinary output of 2,4,5-T carries equal weight in calculation of the average dose absorbed for a given exposure. The generally excellent agreement between the three methods of calculating D_o (Table 2) lends further support to the above conclusions.

The pattern of the daily amount of 2,4,5-T excreted in the urine following exposure is characterized by a maximum on day 2, followed by a steady log-linear decline thereafter (see the calculated data points in Figure 3). However, an examination of the data in Table 1 shows that, in many cases, there is a significant increase in the amount of 2,4,5-T excreted after the second day following exposure. These data are inconsistent with the excretion pattern expected from a single exposure (2), and may indicate subsequent exposure to 2,4,5-T or to its ester after the actual application date. The speculation that such exposures might arise from the use of contaminated clothing or footgear should be verified by further experiments and observations. In each case, these increased amounts of urinary 2,4,5-T have the effect of increasing the calculated dose, and therefore result in maximized estimates of the dose absorbed on the application date.

Since the data reported by Lavy (1) indicate clearly that the respiratory route of exposure to 2,4,5-T is virtually negligible, we have assumed that most of the absorbed dose of 2,4,5-T is the result of dermal exposure to ESTERON 245 herbicide formulations. However, the methods used here to calculate the absorbed dose are, in effect, independent of the actual route of administration and will reflect the total amount of 2,4,5-T absorbed by all possible routes.

The pharmacokinetic model describing the absorption and excretion of 2,4,5-T in humans can also be used to predict the accumulated body burden of 2,4,5-T that would result from repeated daily exposures (6). The results of this mathematical simulation are shown by the solid line in Figure 4. These simulated data predict that the maximum accumulated body burden of 2,4,5-T resulting from repeated daily exposures would be 1.4x the daily dose D_o. In other words, if a worker absorbed a dose of 0.05 mg/kg each day, the maximum body burden attained would be 0.07 mg/kg and this maximum would be reached after approximately 7 daily exposures. However, if the 2,4,5-T remaining to be absorbed were removed 6 hr after each exposure (e.g., by washing or changing clothing), the predicted accumulated body burden would be represented by the dotted line in figure 4. In this case, the maximum body burden would be 0.3x the daily dose D_o, and this maximum would be reached after approximately 3 daily exposures.

In summary, the amount of 2,4,5-T absorbed by forest workers during the application of ESTERON® 245 has been shown to be generally less than 0.1 mg 2,4,5-T per kg of body weight. Since this dose level is far below the no effect level of 20

mg/kg for fetotoxic or teratogenic effects cited by EPA (8), we conclude that under these conditions the absorption of 2,4,5-T presents a negligible toxic hazard to forest workers.

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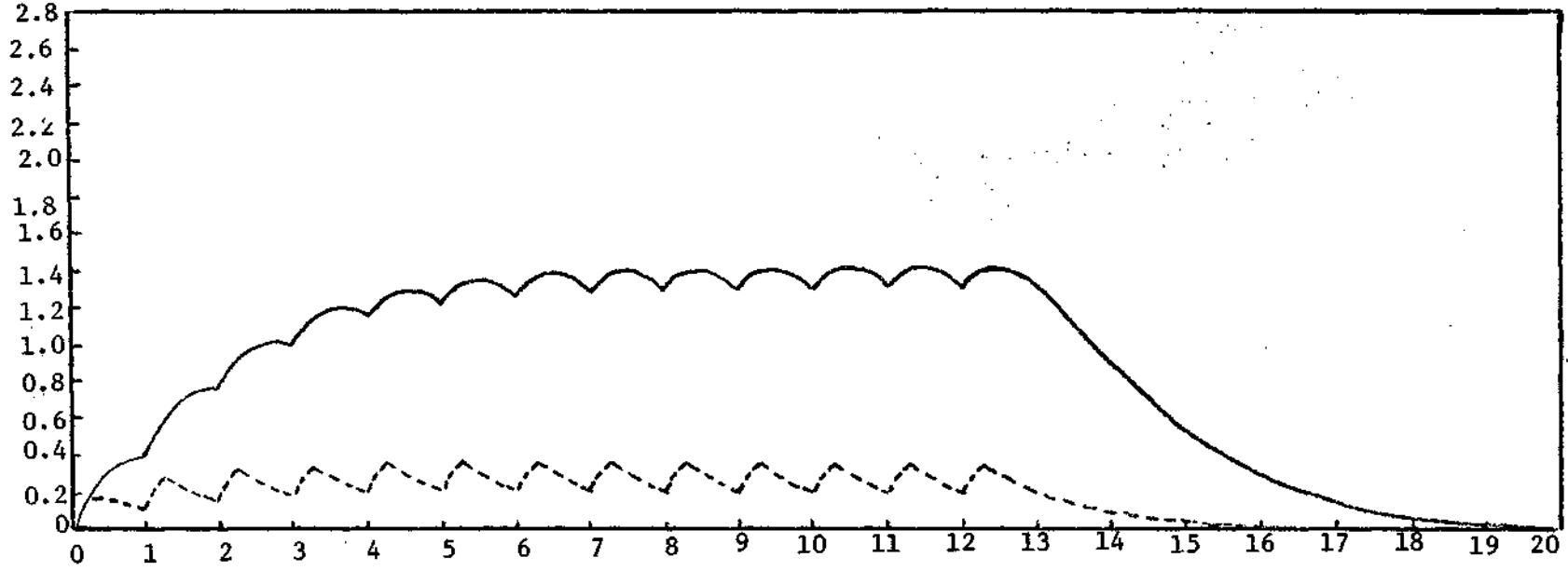

Simulated body burden of 2,4,5-T following 13 repeated daily exposures in units of the daily dose D_o .

Solid Line=body burden if 2,4,5-T continuously absorbed.

Dotted Line=body burden if 2,4,5-T remaining to be absorbed is removed 6 hours after each exposure.

Figure 4

REFERENCES

(1) T. L. Lavy. Measurement of 2,4,5-T Exposure of Forest Workers. Project Completion Report to National Forest Products Association. November, 1978.

(2) P. J. Gehring, C. G. Kramer, B. A. Schwetz, J. Q. Rose, and V. K. Rowe. The Fate of 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) Following Oral Administration to Man Tox. Appl. Pharmacol. 26, 352-361 (1973).

(3) W. N. Piper, J. A. Rose, M. L. Leng, and P. J. Gehring. The Fate of 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) Following Oral Administration to Rats and Dogs. Tox. Appl. Pharmacol. 26, 339-351 (1973).

(4) M. W. Sauerholf, W. H. Braun, G. E. Blau, and P. J. Gehring. The Dose-Dependent Pharmacokinetic Profile of 2,4,5-Trichlorophenoxyacetic Acid Following Intravenous Administration in Rats. Tox. Appl. Pharmacol 36, 491-501 (1976).

(5) J. D. Young, J. C. Ramsey, and W. H. Braun. Pharmacokinetics of 2,4,5-T PGBE Ester Applied Dermally to Rats. The Dow Chemical Company, Midland, Mich. Manuscript in Preparation -

(6) Continuous System Modeling Program III. Program Reference Manual. IBM No. SH 19-7001-2. 1972.

(7) J. C. Ramsey, G. E. Blau, and P. J. Gehring. Pharmacokinetic Modeling Based on Interval Excretion Data. The Dow Chemical Company, Midland, Mich. Manuscript in Preparation.

(8) EPA. Rebuttable Presumption Against Registration and Continued Registration of Products Containing 2,4,5-T. Federal Register 43(78), 17116-17157, April 21, 1978.