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Trichlorfon (TCF)

Caswell No. 385
(EPA Registration 3125-9)

DATA EVALUATION RECORD

STUDY TYPE: Three-generation Reproduction Assay - Rats (Feed)

ACCESSION NUMBER: 244915

MRID NUMBER: (Not assigned)

SPONSOR: Chemagro Agricultural Division, Mobay Chemical Corporation, Report #24855, submitted March 24, 1981.

CITATION: "Bay 15 922-General Study on Rats," Dr. rer. nat. Eckhard Löser.

CONTRACTING LAB: Farbenfabriken Bayer AG Institut Für Toxikologie, Wuppertal-Elberfeld, Report No. 1195.

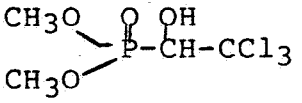
DATE: January 23, 1969.

TEST MATERIAL: Technical TCF, 98.3% purity.

REVIEWED BY: Irving Mauer, Ph.D., Geneticist (HED/TB) 04-15-83

DATE OF REVIEW: April 11, 1983

PROTOCOL: Bay 15 922 (trichlorfon) is an insecticidal compound, with the following structural formula:



Trichlorfon

(0,0-dimethyl-(2,2,2-trichlorohydroxyethyl)-phosphonate)

Acute oral toxicity testing was conducted in rats [sex and strain unspecified] "...at the start of, during and at the end of the study....," according to the report; the values (7-days observation) were reportedly "...all within the normal range." [No data were presented in this report, however.]

Five groups of male and female strain FB 30 rats each ("Elberfeld breed" - [presumably, but not stated, of Long-Evans derivation]-), 33 days old and averaging 45 to 55 g at the start, were fed "Altromin R" powder feed containing TCF

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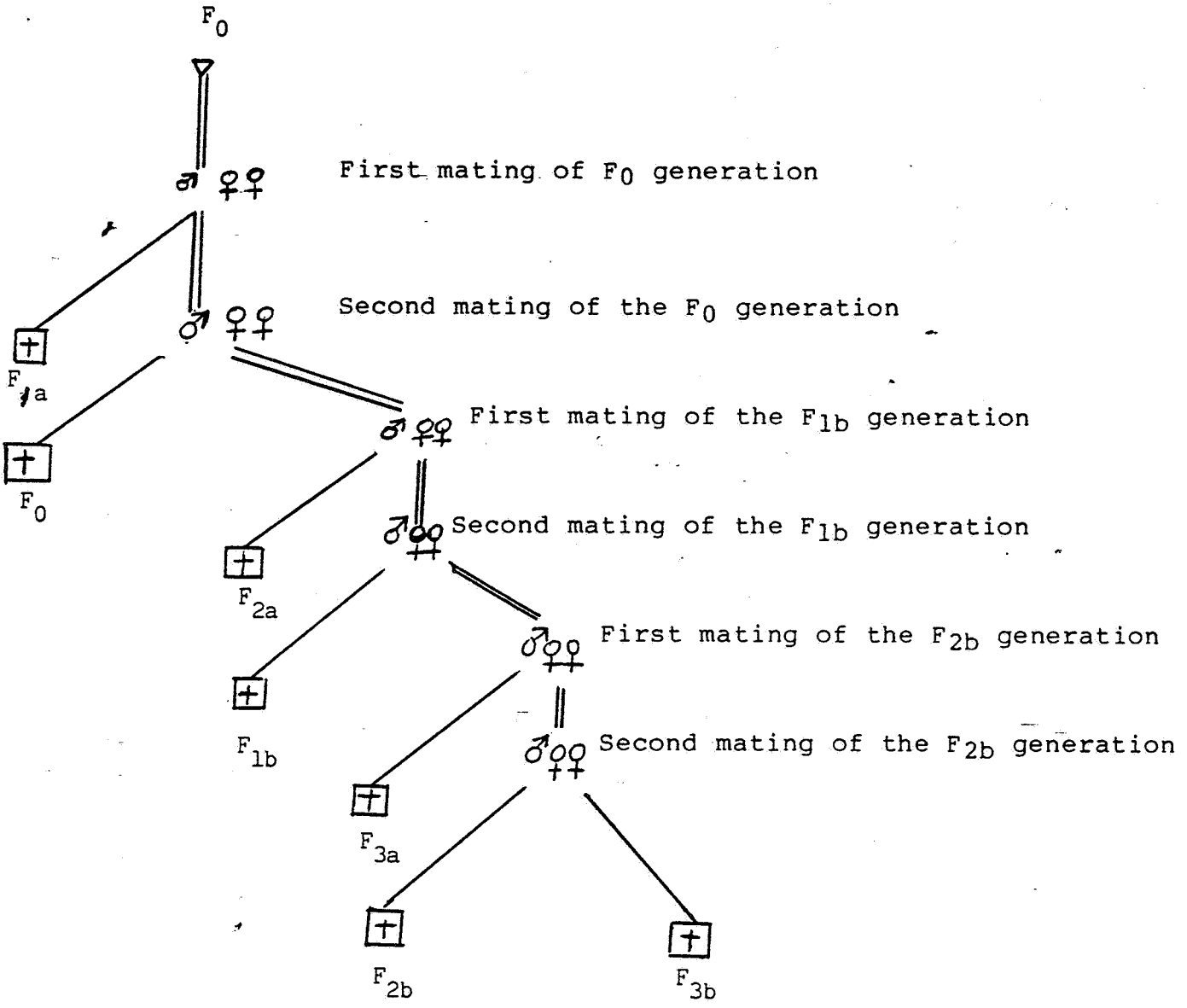
at concentrations of 0 (= control), 100, 300, 1000 and 3000 ppm (approximate intake = 5, 15, 50 and 150 mg/kg) commencing 70 days prior to first mating, through three generations of matings, according to the then current standardized protocol (1969), as schematized below:



Adult rats were weighed weekly; pups at parturition, 5 and 7 days postnally, weekly thereafter. During mating (age, 100 days), 2 females were housed with one male for 19 or 20 days, and males interchanged such that each female was caged with 3 different males for a period longer than one estrus cycle.

Litter sizes were recorded at birth, and reduced to no more than 10 offspring on the fifth postnatal day. Lactation was permitted up to 4 weeks, following which the offspring of each first mating ($F_{1a}$, $F_{2a}$, $F_{3a}$) were sacrificed.

Offspring from second mating were weaned at 4 weeks, 10 males and 20 females of the $F_{1b}$, $F_{2b}$ and $F_{3b}$ were mated (1 male: 2 females) at 3 months, following which $F_0$, $F_{1b}$ and $F_{2b}$ animals were sacrificed.

All newborn were examined for gross malformations; juveniles were also re-examined during lactation. All moribund and dead animals were autopsied to establish cause.

At the end of the study, all three-week old $F_{3b}$ rats were sacrificed, and the following organs examined for any gross pathology: Lungs, heart, liver, spleen, kidneys, adrenals and gonads.

All recorded treated group mean values were compared to controls by the Wilcoxon non-parametric rank test.

RESULTS:

$F_0$ (Parental) Generation:

Significantly lower body weight (gains) than control values were recorded among 300 ppm-treated males (but not at higher levels), as well as among females fed 1000 and 3000 ppm TCF [Figure 2 of report]. Although fertility was apparently not affected during the first mating [Table 1 records pregnancy rates for the 5 dosage groups as 100, 90, 85, 85 and 95%, respectively], the average litter size was significantly

smaller than controls in the 1000 and 3000 ppm group, as summarized in Table 2 of the report below:

| Dose (ppm) | Average number of pups/litter ($F_{1a}$) | |
|---|---|---|
| | At birth (total litter) | At 5 days, after reduction to 10 pups/litter |
| 0 | 22.10 | 9.30 |
| 100 | 11.33 | 8.77 |
| 300 | 13.41 | 9.41 |
| 1000 | 9.94* | 8.64 |
| 3000 | 9.11* | 5.82* |

* Significantly different from control ($p < 0.01$)

Lactation performance rates in all treated groups except the HDT (3000 ppm) were not different from control; dams fed 3000 ppm TCF, however, nourished fewer pups, as indicated in the report's Table 3 (below):

| Dose (ppm) | ($F_{1a}$) generation | | |
|---|---|---|---|
| | Total number of young after reduction to 10 pups per litter | Young lactated for up to 4 weeks | |
| | | Number | % |
| 0 | 186 | 184 | 98.9 |
| 100 | 158 | 153 | 96.3 |
| 300 | 160 | 147 | 91.8 |
| 1000 | 147 | 145 | 98.6 |
| 3000 | 99 | 54 | 54.5 |

The average body weight of $F_{1a}$ pups from dams fed 3000 ppm was also significantly reduced ($p < 0.01$), both at birth, as shown in Table 4 of the report (5.29 g, compared to 6.14, 6.33, 5.82, and 6.12 g for the 0, 100, 300 and 1000 ppm groups, respectively), as well as throughout the (4 week) lactation period (Figure 3 of report); no malformed offspring were observed, however.

Dose-related reduced fertility was recorded from the second mating ($F_{1b}$ generation) at the two highest dosages (Table 5 of the report records pregnancy rates of 100, 89.5, 95, 80 and 65%, respectively), as well as reduced litter size at the HDT, as recorded in Table 6 (below),

| Dose (ppm) | Average number of pups/litter ($F_{1b}$) | |
|---|---|---|
| | At birth (total litter) | At 5 days, after reduction to 10 pups/litter |
| 0 | 11.40 | 8.40 |
| 100 | 12.47 | 8.82 |
| 300 | 12.68 | 9.00 |
| 1000 | 12.18 | 9.50 |
| 3000 | 7.38* | 3.77* |

* Significantly different from control ($p < 0.01$)

and these dams raised fewer young as indicated by the tabulation of lactation rates (Table 7, below):

| Dose (ppm) | ($F_{1b}$) generation | | |
|---|---|---|---|
| | Total number of young after reduction to 10 pups per litter | Young lactated for up to 4 weeks | |
| | | Number | % |
| 0 | 169 | 147 | 87.0 |
| 100 | 150 | 130 | 80.7 |
| 300 | 171 | 163 | 95.3 |
| 1000 | 152 | 138 | 90.8 |
| 3000 | 49 | 16 | 32.7 |

Average $F_{1b}$ pup weight was comparable in all groups at birth (5.81, 6.12, 6.25, 6.07, and 6.07 g, respectively) [Table 8 of report], but pups from the HDT gained less weight, and were significantly lighter at the end of the (4-week) lactation period (as illustrated in Figure 4).

None of the $F_{1b}$ young showed any gross malformations either at birth or during the lactation period.

The $F_{1b}$ Generation:

Body weight curves for all TCF-treated groups, except that at the HDT, were comparable to the control; both males and females fed 3000 ppm, on the other hand, gained significantly less weight (Figure 4 of report), and none survived to mating. [Consequently, the 3000 ppm dietary concentration was elimnated from the remainder of the study.]

No effect of treatment (up to 1000 ppm) was recorded for either mating ($F_{2a}$ or $F_{2b}$) on:

(i) $F_{1b}$ fertility (Table 9a records 75, 90, 85 and 85% at 0, 10, 300 and 1000 ppm; respectively, for first; and Table 9b = 100, 95, 100 and 100% for second); (ii) average number of pups born or at 5 days when litters were reduced to 10 (Table 10a, for $F_{2a}$ = 9.33 to 10.82 at birth and 8 to 9.8 at 5 days; Table 10b for $F_{2b}$ = 9.6 to 11.5 at birth, and 8.8 to 9.9 at 5 days); (iii) the number weaned, i.e. at the end of lactation (Table 11a for $F_{2a}$ = 96 to 98%; Table 11b for $F_{2b}$ = 93 to 98%); (iv) pup weight at birth (Table 12a for $F_{2a}$ = 6.58 to 6.38 g; Table 12b for $F_{2b}$ = 6.27 to 6.06 g). After weaning (4 weeks), however, both $F_{2a}$ and $F_{2b}$ 1000 ppm-group males and females weighed significantly less ($p < 0.05$) than the controls or other treated groups (Figures 5 and 6 of report).

None of the $F_2$ offspring showed any gross malformations either at birth or during the lactation period (or after sacrifice i.e., the $F_{2a}$).

$F_{2b}$ Generation:

Average body weight of treated $F_{2b}$ animals did not differ significantly from controls at any time before sacrifice (Figure 6); nor in either mating did their fertility (Tables 13a and 13b), litter sizes at birth or at 5 days of age ($F_{3a}$ and $F_{3b}$, Tables 14a and 14b), or at weaning (Tables 15a and 15b). Average body weights of the treated $F_3$ pups at birth were no different than control (Tables 16a and 16b), but significant decreases were recorded for the 1000 ppm males and females of both $F_{3a}$ and $F_{3b}$ during weaning (Figures 7 and 8).

None of the offspring of the $F_{3a}$ and $F_{3b}$ generations showed any signs of malformations either at birth or during the 3-week lactation period.

Post-Mortem Observations: No gross pathological changes were found in any $F_0$, $F_{1b}$ or $F_{2b}$ rats autopsied after mating, nor in any $F_{3b}$ animal sacrificed at 3 weeks of age.

Histopathological examination [detailed path sheets are included in the report] revealed no significant alterations in morphology of any tissue or organ sampled from any treated rat. Occasional small foci of lymphocytic infiltration unrelated to treatment or dosage were observed in the livers of a few rats, and minimal vacuolization in midzonal and periportal hepatic areas of one 300 ppm male. Renal parenchyma of all rats were within normal (and control) limits; a single 300 ppm female presented minimal hydronephrosis.

The author concluded that the 300 (and less) ppm dietary level of TCF for 3 generations had no effect on reproductive performance of rats, 1000 ppm had minimal effects (slower weight gain, lowered fertility during $F_0$ matings), and 3000 ppm had a significantly adverse effect (no $F_1$ animals survived to mating time, 100 days). No dietary level caused any malformations throughout 3 generations (at 1000 ppm)

REVIEWER'S EVALUATION: The protocol and reporting of this study were adequate to generate valid results. It is judged CORE-MINIMUM DATA. From the results reported the NOEL for reproductive effects = 300 ppm (maternal-fetal toxicity), and the LEL = 1000 ppm (feed).