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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

CASWELL NO. 385

MEMORANDUM JUN 3 1983

ACCESSION NOS. 244915/249535

SUBJECT: Trichlorfon (EPA Reg. # 3125-9): Studies submitted for Registration Standard Development. [3(c)(2)(B) Data Call-In].

TO: William H. Miller, PM 16, Registration Division (TS-767c)

THRU: William Butler, Head Section III, Toxicology Branch Hazard Evaluation Division (TS-769c) *William Butler*

REGISTRANT: Mobay Chemical Corporation (Agricultural Chemistry Division), P.O. Box 4913, Hawthorn Road, Kansas City, MO 64120.

ACTION REQUESTED: The following studies (all conducted with the technical, 98-99%) were submitted for Toxicology Branch review:

1. Mobay Report No. 24855: "Bay 15 922. Generation Study on Rats," by Dr. E. Löser, Farbenfabriken Bayer AG Institut für Toxikologie, Wuppertal-Elberfeld (Report No. 1195, January 23, 1969). Acc. No. 244915.
2. Mobay Report No. 69298: "L13/59 (Trichlorfon). Studies of Embryotoxic and Teratogenic Effects on Rats Following Oral Administration," by Dr. L. Machemer, Bayer AG Institut für Toxikologie, Wuppertal-Elberfeld (Report No. 8400, May 29, 1979). Acc. No. 244915.
3. Mobay Report No. 69299: "L13/59 (Trichlorfon). Evaluation for Embryotoxic and Teratogenic Effects on Orally Dosed Rabbits," by Dr. L. Machemer, Bayer AG Institut für Toxikologie, (Report No. 8430, June 8, 1979). Acc. No. 244915.

4. Mobay Report No. 69367: "Trichlorfon. Mutagenicity Test on Bacterial Systems," by Y. Shirasu, M. Moriya and R. Koyashiki, Institute of Environmental Toxicology (Japan), October 30, 1979. Acc. No. 249535.

Individual DER's for these studies are attached.

Irving Mauer, Ph.D. -
Geneticist
Toxicology Branch/HED (TS-769c)

Irving Mauer
00-15-83
16/11/83

cc: Geraldine Werdig, RD (TS-791)
William Grosse, PSD (TS-757c)
TB Reading File + IM (2)
DCR-17356:Mauer:CM#2:HED-13:4/14/83:efs
REVISED-4/15/83:DCR-17356:Mauer:CM-2:HED-13:efs

TOX:MAUER:DCR-17262:04/07/83:pad:TOX-14
REVISED-4/8/83:DCR-26152:TOX-14:efs

Trichlorfon (TCF)

Caswell No. 385
(EPA Reg. No., 3125-9)DATA EVALUATION RECORD

TEST CHEMICAL, or FORMULATION: Technical TCF (chemically: dimethyl-2,2,2-trichloro-1-hydroxyethylphosphonate) >99% purity.

CITATION: "Trichlorfon: Mutagenicity Test on Bacterial Systems," by Yasuhiko Shirasu, Ritsuko Koyashiki, and Masaaki Moriya, Department of Toxicology, Institute of Environmental Toxicology (Report No. 69367, October 30, 1979, Mobay Chemical Corporation, Kansas City, MO.) Accession No. 249535

TRADE SECRET CLAIM: CBI

REASON FOR REVIEW: RS - response to data call-in (received 2/23/83).

REVIEWED BY: Irving Mauer, Ph.D., Geneticist
TB/HED

Irving Mauer
04-15-83

DATE OF REVIEW: April 6, 1983

TEST TYPES: Bacterial Mutagenicity: (1) Rec-assay (DNA damage/repair) in Bacillus subtilis; (2) Reversion assays (reverse point mutation) in Escherichia coli WP-2 and Salmonella typhimurium (5 TA strains).

STUDY-1. Rec-assay: Cultures of the DNA-repair competent strain H-17 (rec +) and repair-deficient sister strain M-45 (rec-) of B. subtilis were exposed concurrently to filter paper discs soaked with 6 concentrations (20 to 2000 μ g) of test chemical (TCF) dissolved in 0.02 ml DMSO, and the length of zones of inhibition measured after 24 hr incubation (37°C). Kanamycin (10 μ g/disc) served as negative control (expect equal zones of inhibition in both strains), and 0.1 μ g discs of mitomycin-C (MC) as positive control (greater inhibition of M-45). A solvent control (DMSO, no inhibition) was also run. [Metabolic activation is not appropriate in assay of this type.]

As shown in a tabular summary, only the two highest concentrations of RCB (1,000 and 2,000 μ g) caused zones of growth inhibition (1 and 3 mm) in the M-45 strain, but no inhibition at any TCF dosage in H-17 cultures. All controls performed as expected: MC causing 5 times greater inhibition (7.5 mm) in M-45 cultures than in H-17 growth (1.5 mm);

whereas kanamycin inhibited both strains to the same degree (4 mm), and DMSO produced none.

Hence the authors concluded that TCF was ("weakly") positive in the rec-assay with B. subtilis.

EVALUATION: The study is Acceptable, and the conclusion validly generated from the protocol.

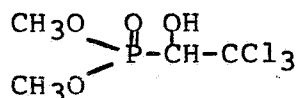
STUDY-2. Reversion assays: Plate cultures of the standard set of auxotrophic indicator strains (S. typhimurium his-: TA 5135, TA 1537, TA 1538, TA 98, TA 100; E. coli WP-2 hcr-/tryp-) were exposed to seven TCF concentrations (in DMSO) ranging from 50 to 20,000 ug/plate in replicate experiments, both in the absence and presence of a mammalian metabolic activation system consisting of Aroclor 1254-stimulated hepatic mixed-function oxygenases prepared from male S-D rats (S-9) plus appropriate co-factors (S-9 Mix), and revertents (his+ colonies) counted after 2 day's incubation. Positive (mutagens appropriate for each strain and mode of activation), solvent and S-9 controls were run concurrently. The highest dose (20,000 ug) was toxic (inhibited growth). As recorded in two tabular summaries, TCF induced significant increases in revertent colonies at concentrations of 5,000, 10,000 and 20,000 ug, in a roughly dose-related fashion for both the WP2 hcr- and TA 100 strains (3 to 4X DMSO control), equally both with and without S-9 activation. None of the other strains responded, even at the inhibitory dose (20,000 ug). Positive control cultures responded as expected (50 to >1,000 X DMSO controls).

The authors concluded that TCF was (weakly) mutagenic at high concentrations, probably by a base-substitution mechanism.

EVALUATION: The study is ACCEPTABLE, and the conclusion (positive mutagenicity) validly generated from the procedures employed.

Trichlorfon (TCF)Caswell No. 385
(EPA Registration 3125-9)

DATA EVALUATION RECORD

STUDY TYPE: (Oral) Rat Teratology.ACCESSION NUMBER: 244915MRID NUMBER: (Not assigned)CITATION: "L 13/59 (Trichlorfon)--Studies of Embryonic and Teratogenic Effects on Rats Following Oral Administration,"
By Dr. L. Machemer.SPONSOR: Mobay Chemical Corporation, Report # 69298, submitted
March 24, 1981.CONTRACTING LAB: Bayer AG Institut Für Toxikologie, Report
No. 8400.DATE: May 29, 1979TEST MATERIAL: Technical [0,0-dimethyl-2,2,2-(trichloro-
hydroxyethyl)-phosphonate], 98.4% purity.REVIEWED BY: Irving Mauer, Ph.D., Geneticist (TB/HED)DATE OF REVIEW: April 7, 1983PROTOCOL: TCF has the following chemical structure:

Three groups of 25 inseminated female Long-Evans (FB-30) rats, each received TCF in 0.5% aqueous Chromophor EL emulsion by oral intubation (constant volume of 10 ml/kg) at daily doses of 10, 30 and 100 mg/kg from gestation day-6 to -15 (total of 10 doses). Control females received the carrier during the same time period. Fetuses were removed by cesarean section on gestation day-20, examined externally (all fetuses), viscerally (one-third of all fetuses in a litter (by a modified Wilson technique, or necropsy), as well as skeletally (the remainder, by the alizarin-red technique).

Dams were observed daily for appearance and behavior, at which times they were weighed, and (any) mortality recorded.

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In addition to inspection for malformations, the following fetal data were also recorded: Numbers of implantations, live, stunted (<3 g), and dead fetuses; sex and weight (reported as the average weight per litter); and average placental weight per litter.

Ponderal and numerical fetal data were statistically analyzed by non-parametric ranking (Wilcoxon-Mann-Whitney "U" Test), except for: Skeletal alterations and malformations, which were analyzed by chi-square; and dam fertility, treated by chi-square or Fisher's Exact Test (depending upon frequency anticipated). Unless otherwise indicated, the level of significance for all statistical treatments was taken as $P < 0.05$.

RESULTS: Preliminary oral toxicity testing, performed at 150 mg/kg/day to 5 rats for 10 days, resulted in 100% survival, and "...good... weight gains..." but tremors were observed in all treated animals, and "...some of them had diarrhea as well."

Whereas dams tolerated the 10 and 30 mg/kg dose throughout treatment without apparent or behavioral impairment, those on 100 mg/kg/day manifested increased diarrhea (12 of 25 females), but no lethal consequences and no decreases in weight gain throughout either the treatment or the entire gestation period compared to controls.

Fertility indices were comparable in all treated and control groups and no differences were recorded for the following fetal parameters: Implantations; average numbers of fetuses; sex ratio; resorptions, or live and dead fetuses; average placental weight; skeletal retardation or stunting; type or number of malformations (all isolated cases which were reported occur spontaneously in this strain).

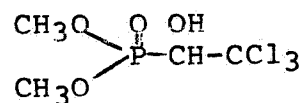
The author concluded that: "...L 13/59 [trichlorfon] administered at oral doses of up to and including 100 mg/kg/day produced neither embryotoxic nor teratogenic effects on rats....;" and thus: "...The no-effect level for the embryonic/fetal development was found to be 100 mg/kg/day p.o."

REVIEWER'S EVALUATION:

This study was conducted according to recognized protocols and is graded CORE Minimum. However, due to the lack of maternal, fetal or teratogenic effects at the highest level tested (100 mg/kg/day), additional teratogenic testing in the rat may be required to satisfy EPA regulatory data requirements.

Trichlorfon (TCF)Caswell No. 385
(EPA Registration 3125-9)

DATA EVALUATION RECORD

STUDY TYPE: (Oral) Rabbit Teratology.ACCESSION NUMBER: 244915MRID NUMBER: (Not assigned)SPONSOR: Mobay Chemical Corporation, Report #69299, submitted March 24, 1981.CITATION: "L 13/59 (Trichlorfon). Evaluation for Embryo-toxic and Teratogenic Effects on Orally Dosed Rabbits," by Dr. L. Machemer.CONTRACTING LAB: Bayer AG Institut für Toxikologie, Report No. 8430.DATE: June 8, 1979TEST MATERIAL: Technical, 98.4% TCF.REVIEWED BY: Irving Mauer, Ph.D., Geneticist (TB/HED)DATE OF REVIEW: April 6, 1983PROTOCOL: Chemically, trichlorfon is O,O-dimethyl-2,2,2-(trichlorohydroxyethyl)-phosphonate, with the following structural formula:

Fifteen inseminated female Himalayan rabbits per group were given daily oral doses (by gavage) of TCF (in 5 ml/kg 0.5% Cremopher Emulsion) from day-6 through day-18 of gestation (total of 13 doses) at 5, 15 and 45 mg/kg. Control animals received 5 ml/kg of the carrier. Does were examined and weighed daily. On gestation day-29, fetuses were resected (by cesarean), and the following recorded:

- a. The number of implantations.
- b. The number of viable and dead fetuses and embryos.
- c. The sex of each fetus.

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- d. Litter weight and average fetus weight per litter.
- e. The number of stunted fetuses (weighing less than "25 grams"). [*stated, but presumably 2.5 was meant.*]
- f. The average placental weight per litter.
- g. Thorough inspection of all fetuses for external anomalies and alterations.

All fetuses were autopsied, and the following regions examined:

- (i) All abdominal and thoracic organs;
- (ii) The brain, for malformations after removal of the head on a plane from angle of mouth to point of ear attachment, fixation in 70% alcohol:formol:glacial acetic acid (80:20:5 parts by volume), and preparation of cross-sections with a razor blade;
- (iii) After clearing in dilute potassium hydroxide solution, the skeleton stained with Alizarin Red S, and entire bone system assessed.

The following numbers of fetuses examined by these standardized methods were as follows:

<u>Test group</u>	<u>Number of fetuses</u>
Control	81
5 mg/kg	92
15 mg/kg	78
45 mg/kg	72

Statistical significance was assessed by the following methods:

1. Non-parametric ranking, by the "U" test of Wilcoxin, Mann and Whitney for weight gains, number of implantations, number of fetuses, number of resorptions, fetal weight and placental weight;
2. The chi-square test (with Yates correction) for the numbers of fetuses with skeletal alterations, anomalies, and stunting;
3. Either the chi-square test (with Yates correction), or Fisher's Exact Test, for incidences of fertilized and pregnant does, depending upon expected frequency.

Significance of differences between treated and control groups was set at the 5% level ($p < 0.05$).

RESULTS: Except for reduced food intake by 2 does of the 5 mg/kg group and 3 of the 15 mg/kg group, accompanied by loss of hair in 2 does of the 5 mg/kg group (which occur occasionally in these rabbits and thus cannot be attributed to administration of the test compound), treatment with TCF at dose levels up to and including 15 mg/kg/day per os did not appear to have any detrimental effects on the physical appearance or behavior of the does.

At 45 mg/kg/day, however, 2 of the 15 does aborted, one each on gestation days -20 and -24. These two rabbits showed signs associated with abortion, e.g., reduced food intake, intestinal disorders (manifested in one animal by failure to defecate, and in the other by diarrhea), and a "sickly" appearance.

One female treated at 15 mg/kg/day died of acute pneumonitis during the test, but all the other test animals survived until cesarian section. Therefore, doses up to and including 45 mg/kg/day were not considered lethal.

The following table summarizes the average weight gains reported (expressed in grams) made by the does of the different test groups during the treatment period from gestation day -6 to -18 as well as throughout gestation. Only does with viable fetuses at cesarian section were recorded.

Test group	Average weight gain (in g) during:	
	Treatment period	Entire gestation period
Control	130.7	155.4
5 mg/kg	74.0	179.7
15 mg/kg	70.4	125.0
45 mg/kg	67.7	125.8

Thus, it appears that although the does of each treated group made less weight gain on the average than the controls during the treatment period, the difference was not statistically significant. The average weight gains made by the does of the TCF-treated groups throughout gestation varied greatly, but the authors observed no indication of any systematic treatment-related influence on this parameter. (The individual results of doe body weights are presented in Tables 1-4 attached to the report.)

Of the does which copulated twice, the following incidences of fertility and pregnancy at Cæsarian section were recorded:

Dose (mg/kg)	No. of inseminated females	Fertilized females:		Pregnant females:	
		Total	% of inseminated	Total	% of fertilized
0	15	14	93.3	14	100.0
5	15	15	100.0	15	100.0
15	15	13	86.6	13	100.0
45	15	15	100.0	13	86.6

Hence, group fertility incidences (percentage of fertilized does in relation to those inseminated), which would not have been influenced since treatment commenced on gestation day-6, did not vary appreciably in any of the test groups, and were within the normal range (as also compared to historical records) for the rabbit strain used in this study.

It was also evident from the pregnancy rate (the above tabulation) that treatment with TCF at doses up to and including 15 mg/kg did not have any embryo-lethal effect. However, since the pregnancy rate in the 45 mg/kg group was decreased due to two abortions (compared to none in the control group), a treatment-related effect could not be excluded by the authors.

Data from the examination of cesarean-resected fetuses, presented for individual test animals in Tables 1 through 4 of the report (with group averages summarized as Table 5), revealed no statistical significant differences between treated groups (any dose) and the control in average numbers of implantations, live fetuses (although reduced due to the two abortions), or resorptions (insignificantly increased due to the same 2 abortions); and, no appreciable changes in sex ratio, fetal or placental weights, or the occurrence of stunted fetuses. Skeletal retardation was not observed in any group.

The following malformations, considered by the authors to be spontaneous, were seen in the control group and in the 5 mg/kg group (only) as follows:

Dose (mg/kg, p.o.)	Doe No.	Number of malformed fetuses	Malformation
0	1182	1	Kinky tail
	1183	1	Arthrogryposis of left forepaw
	1189	1	Arthrogryposis of both forepaws
5	1201	1	Rib fusion (4th and 5th, right)
15	-	-	None
45	-	-	None

The authors concluded that the administration of TCF at doses up to 45 mg/kg/day caused decreased weight gain in treated does, but was not lethal; had no evident untoward effects on appearance and behavior, but 2 of the 15 does aborted, manifesting adverse signs (thus contributed to embryonic toxicity, but only as a consequence of maternal effects).

No maternal or fetal effects were recorded in the 5 and 15 mg/kg groups.

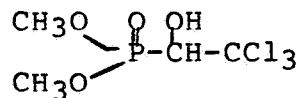
Hence, the authors considered the maternal (and fetal) NOEL of TCF in these rabbits to be 15 mg/kg p.o.

Finally, TCF apparently has no propensity to produce teratogenic effects at doses up to 45 mg/kg.

REVIEWER'S EVALUATION: The study is considered Core-Minimum Data.

Trichlorfon (TCF)Caswell No. 385
(EPA Registration 3125-9)

DATA EVALUATION RECORD

STUDY TYPE: Three-generation Reproduction Assay - Rats (Feed)ACCESSION NUMBER: 244915MRID 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)DATE OF REVIEW: April 11, 1983PROTOCOL: Bay 15 922 (trichlorfon) is an insecticidal compound, with the following structural formula:Trichlorfon

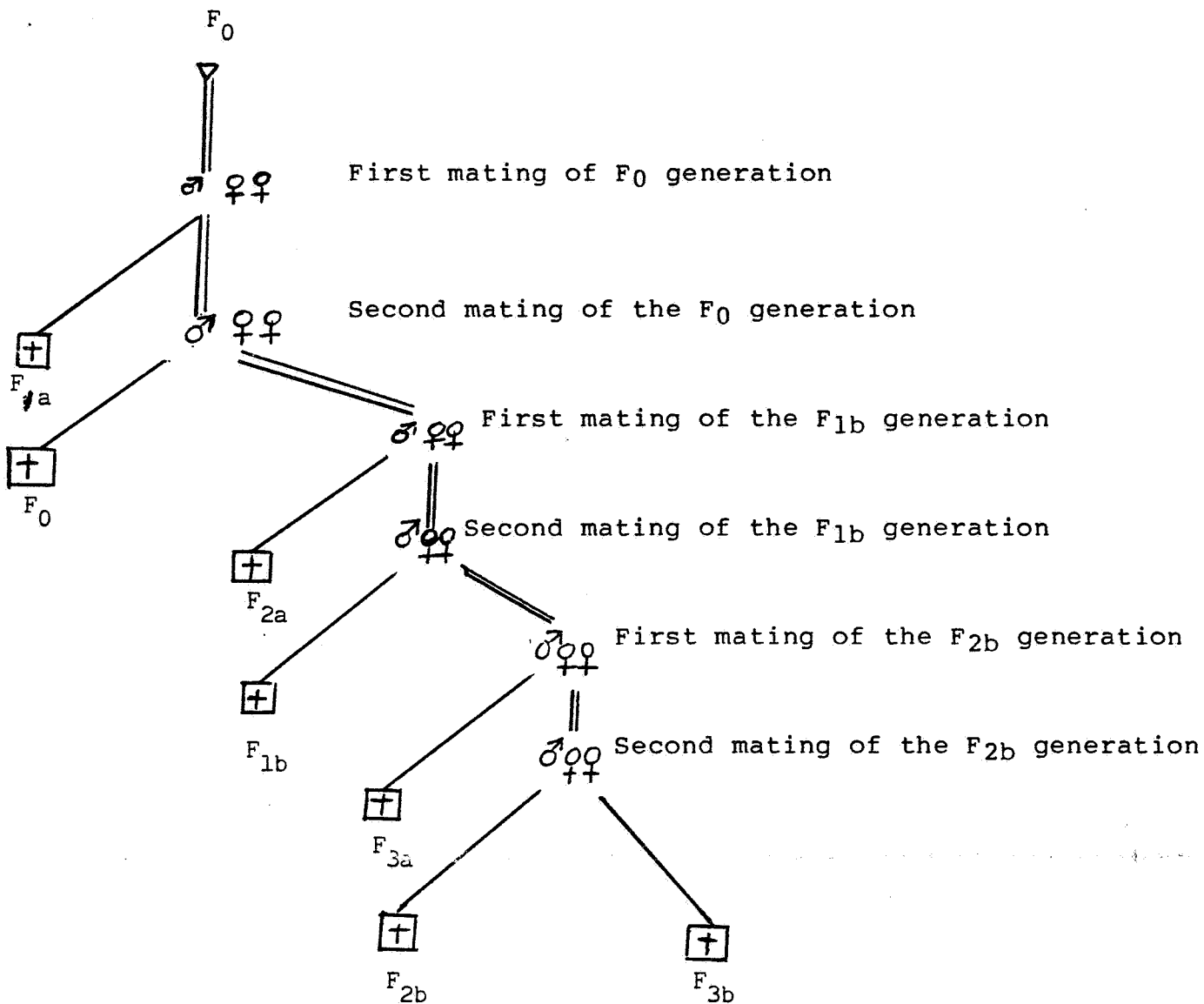
(0,0-dimethyl-(2,2,2-trichlorohydroxyethyl)-phosphonate)

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 F₀, 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:

F₀ (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 eliminated 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 F₂ 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 F₃ 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 F₀, 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 F₀ matings), and 3000 ppm had a significantly adverse effect (no F₁ 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).

TOX:MAUER:DCR-17262:04/07/83:pad:TOX-14
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REVISED:4/14/83:DCR-26151
NEW INPUT:4/14/83:DCR-17261:pad
REVISED:4/15/83:DCR-17363:pad