UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004501

6/4/85

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: FMC 54800 TECHNICAL
TALSTAR™ 2 EC Insecticide/Miticide
TALSTAR™ 10 WP Insecticide/Miticide

TO: Mr. Tim Gardner, PM 17
Registration Division (TS-767)

FROM: Byron T. Backus
Toxicologist
Toxicology Branch

THROUGH: Clint Skinner, Ph.D.
Head, Section III
and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Registration numbers: 279-GNLL (3055)
279-GNLA (3056)
279-GNLT (3057)

Registrant: FMC Corporation

Tox. Chem. 463F

Action Requested:

The Registration Division has requested a Toxicology review of data pertaining to the acute toxicity of Talstar™ 10 WP and Talstar™ 2 EC, and subchronic toxicity of the technical material.

Background:

Studies on the acute toxicity of the technical material and 2 EC formulation were previously reviewed (February 8, 1984), and were classified as acceptable.

These applications for registration involve non-food uses. It is noted that since this material was received, a number of EUP applications involving food crop usages (and issuance of temporary tolerances) have been made.

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Comments and Conclusions: 004501

1. The following is a listing of the studies reviewed, and their classifications:

   Acute oral LD_{50} (FMC 54800 10 WP): Guideline (Tox. Cat. II)
   Acute dermal LD_{50} (FMC 54800 10 WP): Guideline (Tox. Cat. III)
   Primary eye irritation (FMC 54800 10 WP): Guideline (Cat. III)
   Primary skin irritation (FMC 54800 10 WP): Guideline (Cat. IV)
   Dermal sensitization (FMC 54800 10 WP): Guideline

   Acute inhalation LC_{50} (FMC 54800 2EC): Guideline (Cat. II)

   Acute oral LD_{50} - hen (technical): Minimum
   Delayed neurotoxicity - hen (technical): Supplementary
   21-day repeated dermal (technical): Supplementary
   90-day feeding - rat (technical): Minimum
   13-week feeding - dog (technical): Supplementary
   Teratology - rat (technical): Supplementary
   Teratology - rabbit (technical): Minimum

2. The delayed neurotoxicity study has been classified as supplementary. While no histological evidence was found for delayed neurotoxicity, the hens showed a more severe response after the second dose than after the first. Another concern is that no nervous tissues were examined from hens which died a few days after the second dose. Since the test material is not an organophosphate, and "classic" delayed neurotoxicity involving phosphorylation of neurotoxic target esterase is not expected, a repeat of this study is not necessary. There was no evidence of neurological changes in the 90-day rat feeding study, and the tremors observed at 200 ppm were shown to stop shortly after rats were switched to a diet not containing the test material.

3. In the 21-day repeated dermal application study (classified as supplementary) the major problem is that little confidence can be placed in the organ weight determinations (the weights of two livers were reported as 7.1 and 14.7 g). Of somewhat minor concern is the fact that nerve tissue was not microscopically examined.

4. In the rat teratology study the only evidence of maternal toxicity was "intermittent" (otherwise undefined as to intensity or duration) tremors occurring in most females receiving 2 mg/kg/day of the test material. In the absence of other symptoms there is a question as to whether this dose level was reasonably close to the maternal MTD (maximally tolerated dose). It is possible that if a suitable rationale for the dose levels used is given, or if results of a range-finding or pilot study are made available, that the classification of this study can be upgraded.

   Also, there was an increased incidence (double that occurring in controls or any lower exposure group) of hydroureter in fetuses

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from female rats which had received 2 mg/kg/day. Five fetuses at this dose level had hydroureter without hydronephrosis, a finding not present in controls or any of the other exposure groups. Although this finding is equivocal (and the increased incidence of hydroureter in this group is not statistically significant), the fetotoxic NOEL is tentatively set at 1 mg/kg/day, with an LEL of 2 mg/kg/day. The teratogenic NOEL = 2 mg/kg/day (HDT).

Although the rat teratology study has been classified as supplementary, the results define the NOEL (1 mg/kg/day) and LEL (2 mg/kg/day) for the technical material.

5. In the 13-week dog study, classified as supplementary (as it is not certain a NOEL was defined), slight tremors were noted in one male of the (nominal) 2.5 mg/kg/day group during week 11. While "this was not considered to be compound related since slight spontaneous trembling is noted occasionally in some laboratory dogs at Hazleton Laboratories in response to handling" no further information is given. The immediate question is whether this animal was being (or had recently been) handled, or what other circumstances were present that might be relevant. A decision as to whether or not 2.21 mg/kg/day (= 2.5 mg/kg/day x purity of 0.8835) of the active is a NOEL is being deferred pending a response. Also, the Data Evaluation Report includes a number of requests for clarifications. Considering a number of factors (the low level of a possible response at 2.21 mg/kg/day; also, since temporary tolerances have been requested for this active, it is likely that a chronic feeding study with dogs will eventually be conducted) the 13-week study should not be repeated.

6. There is a question as to how adequately the signal word "WARNING" defines the acute oral toxicity of the technical product. An oral LD_{50} study (reviewed February 8, 1984) on a formulation with 91.4% active gave LD_{50} (+ S.E.) values of 70.1 (+ 13.04) and 53.8 (+ 4.92) mg/kg for male and female rats respectively. It is possible likely that the 95% confidence limits from this study are such that the oral LD_{50} of the technical product "straddles" toxicity categories I and II. Also, the acute oral LD_{50} (+ S.E.) values for the 10 WP (10% active) formulation were 395 (+ 50) and 355 (+ 40) mg/kg for males and females respectively. Dividing these values by 9 for a 90% product would give 43.9 and 39.4 mg/kg respectively.

7. Copies of the attached Data Evaluation Reports should be made available to the registrant.

8. Several mutagenicity studies on this material have been contracted out for review. This reviewer is of the opinion that a decision as to the registration of these products can be made without these reviews being completed.

WHO

Data Evaluation Reports (attached):

Freeman, C., DeProspo, J. R., Geiger, L. E. Acute Oral Toxicity of FMC 54800 10 WP in Rats. FMC Toxicology Laboratory. Study no. A84-1268, August 7, 1984.

Freeman, C., DeProspo, J. R., Geiger, L. E. Acute Dermal Toxicity of FMC 54800 10 WP in Rabbits. FMC Toxicology Laboratory. Study no. A84-1266, July 13, 1984.

Freeman, C., DeProspo, J. R., Geiger, L. E. Primary Eye irritation of FMC 54800 10 WP in Rabbits. FMC Toxicology Laboratory. Study no. A84-1265; July 13, 1984.

Freeman, C., DeProspo, J. R., Geiger, L. E. Primary Skin irritation of FMC 54800 10 WP in Rabbits. FMC Toxicology Laboratory. Study no. A84-1267; July 13, 1984.

Freeman, C., DeProspo, J. R., Geiger, L. E. Skin Sensitization of FMC 54800 10 WP in Guinea Pigs. FMC Toxicology Laboratory. Study no. A84-1264; August 7, 1984.

Seaman, L. R., DeProspo, J. R., Ballester, E. J., Geiger, L. E., Norvell, M. J., Fletcher, M. J. Twenty-one Day Repeated Dose Dermal Toxicity Study in Rabbits with FMC 54800. FMC Toxicology Laboratory. Study no. A83-1041; February 24, 1984.

Maedgen, J. L. Acute Inhalation Toxicity Study of FMC 54800 2EC in Rats. Stillmeadow, Inc. Study no. A83-1044; October 19, 1983.

Serota, D. G. 13-Week Subchronic Oral Toxicity Study in Dogs. Hazleton Laboratories, Inc. Project no. 104-217; February 7, 1984.

Rand, G. M., Seaman, L. R., Ballester, E. J., Kikta, E. J., Norvell, M. J., Fletcher, M. J. Ninety Day Feeding Study in Rats with FMC 54800 Technical. FMC Study no. A83-818; January 31, 1984.

Freeman, C., DeProspo, J. R., Nadasky, N., Fletcher, M. J., Barta, W. D., Bullock, W. L. Teratology study in rats with FMC 54800 technical. FMC Toxicology Laboratory. Study no. A83-1091; February 24, 1984.

Freeman, C., DeProspo, J. R., Nadasky, N., McConnell, R. F., Fletcher, M. J., Malloy, A. V., Bullock, W. L. Teratology study in rabbits with FMC 54800 technical. FMC Toxicology Laboratory. Study no. A83-1092; February 24, 1984.

Roberts, N. L., Hakin, B., Chirukandath, G., and Rao, R. S. The acute oral toxicity (LD50) and neurotoxic effects of FMC 54800 technical to the domestic hen. Huntingdon Research

Center, Huntingdon, England. FMC study no. A83-1081; 17 February 1984 with re-issue dates of 14 May 1984 and 10 July 1984.

Data Evaluation Report

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Compound FMC 54800 10 WP

Citation Acute Oral Toxicity of FMC 54800 10 WP in Rats. C. Freeman, J.R. DeProspo, L.E. Geiger. FMC Toxicology Laboratory, Study No. A84-1268, August 7, 1984.

Reviewed by Roy D. Sjoblad Ph.D. Microbiologist R.D. Sjoblad 5/30/85

Core classification Guideline

Tox category II

Conclusion The LD_{50} values for rats dosed orally with FMC 54800 10 WP were 395±50 mg/kg for males and 355±40 mg/kg for females.

Materials FMC 54800 10 WP; FMC-T #243, Ref. No. PL84-0113

Young adult Sprague-Dawley [Tac:N(SD)fBR] rats; Taconic Farms, Germantown, N.Y.

Methods Rats were fasted overnight before dosing. Rats were dosed by oral intubation with test material as a 10% (w/v) solution in corn oil. There were 10 male and 10 female rats in each dosage group. Animals were observed for clinical signs of toxicity at 0.5, 1, 2, 3, 4, and 6 hours after dosing, and then twice daily for 14 days. Rats were weighed on days 0,7, and 14 after dosing. Gross necropsy was performed on all animals that died on study and on all survivors after sacrifice on day 14.

Results The mortality data for each dose level were as follows:

Dose level (mg/kg)	Deaths/dosed Males	Females
550	10/10	10/10
480	8/10	8/10
400	4/10	9/10
350	--	2/10
300	2/10	1/9
200	--	0/10
LD_{50} (±S.E.):	395±50 mg/kg	355±40 mg/kg

All deaths occurred within 24 hours after dosing. Clinical signs of toxicity during the 6 hours after dosing were clonic convulsions, tremors, chromorhinorrhea, diarrhea, abdominogenital staining, oral discharge, chromodacryorrhea, and exophthalmia. Toxicity signs usually persisted for 1 to 3 days after dosing, except for exophthalmia, which was observed

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during the middle to latter part of the test period. All rats gained weight by the end of the study. Gross internal necropsy revealed no lesions.

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Compound FMC 54800 10 WP

Citation Acute Dermal Toxicity of FMC 54800 10 WP in Rabbits. C. Freeman, J.R. DeProspo, L.E. Geiger. FMC Toxicology Laboratories, Study No. A84-1266; July 13 1984.

Reviewed by Roy D. Sjoblad Ph.D. Microbiologist R.D. Sjoblad 5/30/85

Core classification Guideline

Tox category III

Conclusion The test substance at 2000 mg/kg caused no mortality when applied to the skin of rabbits. Erythema and desquamation were observed at the site of application.

Materials FMC 54800 10 WP; FMC-T #243, Reference No. PL84-0113

Young adult New Zealand white rabbits; Davidson's Mill Farm; Jamesburg, N.J.

Methods At least 10% of the trunk areas of 5 male and 5 female rabbits were shaven with an electric clipper. On the following day, the test substance, at 2000 mg/kg was applied to the exposed skin areas.Dose sites then were covered with gauze pads moistened with physiological saline. Each animal was fitted with an everted plastic Elizabethan collar. At 24 hours after dosing, wrappings were removed and excess test material was washed off with water. Rabbits were observed for clinical signs of toxicity at 0.5, 1, 2, 3, 4, and 6 hours after dosing and then twice daily for 14 days. Irritation of skin by the test compound was evaluated on days 1, 3, 7, and 14 after dosing. The collars were left on the rabbits during the observation period. Animals were weighed on days 0, 7, and 14. Gross necropsy was performed on all animals at 14 days after dosing.

Results None of the animals died as a result of dermal application of the test material at 2000 mg/kg. At 1 day after dosing, 5/5 female and 2/7 male rabbits exhibited erythema. At 14 days after dosing, 3/10 females and 1/10 males had desquamation over the test site. There was a slight mean body weight decrease (0.14 kg) in male rabbits during the test period, and a slight increase (0.07 kg) in mean body weight among the females. No gross internal lesions were observed upon necropsy in any of the test rabbits.

Discussion The weight loss among males, and slight weight gain among females was attributed to wearing of the Elizabethan collars.

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Compound FMC 54800 10 WP

Citation Primary Eye irritation of FMC 54800 10 WP in Rabbits. C. Freeman, J.R. DeProspo, L.E. Geiger. FMC Toxicology Laboratory; Study No. A 84-1265; July 13, 1984.

Reviewed by Roy D. Sjoblad Ph.D. Microbiologist R.D. Sjoblad 5/30/85

Core classification Guideline

Tox category III

Conclusion Dosing with FMC 54800 10 WP at 0.1 g produced a mild irritation in unwashed eyes that persisted for at least 4, but not 7 days. After 1 hour, the test substance was not irritating to washed eyes.

Materials FMC 54800 10 WP; FMC-T # 243, Ref No. PL84-0113

Young adult New Zealand white rabbits Davidson's Mill Farm, Jamesburg, N.J.

Methods Test material at 0.10 g was introduced into the lower conjunctival sac of the right eye of each test animal. Loss of material was minimized by briefly holding together the upper and lower eyelids. At 20-30 seconds after dosing, the treated and contralateral (control) eyes of three male rabbits were washed for 1 minute with 100 ml of lukewarm water. The treated and control eyes of 6 other male rabbits were not washed after dosing. Eyes were examined and scored according to the method of Draize at 1, 24, 48, and 72 hours after dosing, and also at 4 and 7 days. After the 24 hour observation period, the retention of fluorescein dye was followed to detect possible corneal ulceration in treated eyes.

Results Mild conjunctival redness, mild chemosis, and mild to severe discharge were observed, respectively, at 1 hour in 5/6, 6/6, and 6/6 unwashed eyes. By 48 hours after dosing these signs of irritation each were observed in 2/6 unwashed eyes, and at 4 days each in 1/6 eyes. At 7 days after dosing, no signs of irritation were observed. The only signs of irritation in washed eyes were slight conjunctival redness and slight chemosis at 1 hour after dosing.

Corneal opacity, iritis, and fluorescein dye retention were not observed in treated eyes.

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Data Evaluation Report

Compound FMC 54800 10 WP

Citation Primary Skin Irritation of FMC 54800 10 WP in Rabbits. C. Freeman, J.R. DeProspo, L.E. Geiger. FMC Toxicology Laboratory; Study No. A 84-1267; July 13, 1984.

Reviewed by Roy D. Sjoblad Ph.D. Microbiologist R.D. Sjoblad 5/30/85

Core classification Guideline

Tox category IV

Conclusion FMC 54800 is not a dermal irritant.

Materials FMC 54800 10 WP; FMC-T # 243, Ref. No. PL 84-0113

Young adult New Zealand white rabbits; Davidson's Mill Farm, Jamesburg, N.J.

Methods On the day prior to dosing, the trunks of 3 male and 3 female rabbits were clipped free of hair. One-half gram of the test material was applied to each test site under a gauze pad moistened with physiological saline. Trunks of the animals then were wrapped with a gauze bandage and necks were fitted with an Elizabethan collar. Gauze bandages and pads were removed after 4 hours and excess test material was wiped off. Test sites were evaluated according to the method of Draize at 4.5, 24, 48, and 72 hours after dosing.

Results The test material did not cause dermal irritation in rabbits when applied at 0.5 g to bare skin for 4 hours.

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Data Evaluation Report

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Compound FMC 54800 10 WP

Citation Skin Sensitization of FMC 54800 10 WP in Guinea Pigs. C. Freeman, J.R. DeProspo, L.E. Geiger. FMC Toxicology Laboratory; Study No. A84-1264; August 7, 1984.

Reviewed by Roy D. Sjoblad Ph.D. R.D. Sjoblad 5/30/85
Microbiologist

Core classification Guideline

Tox category Not applicable

Conclusion FMC 54800 10 WP is not a dermal sensitizer in guinea pigs

Materials FMC 54800 10 WP; FMC-T #243, Ref No. PL84-0113

DNCB; 1-chloro-2,4-dinitrobenzene, Eastman, Lot #D9E

Young adult male Hartley guinea pigs; Hill Top Lab Animals, Scottdale, PA

Hill Top Chamber™; Hill Top Research, Inc. Cincinnati, OH

Methods On the day prior to induction, the left shoulder regions of male guinea pigs were clipped free of hair with an electric clipper. There were 20 animals used for the test group, 10 for the positive control group, and 10 for the challenge control group. For induction of sensitization, the test material (unmoistened) at 0.40 g or DCNB [0.4 ml of a 0.15% (w/v) solution in methanol] were applied to Hill Top Chambers™. Each chamber was applied to the clipped shoulder area of a test animal, and the trunk then was wrapped with an occlusive elastic bandage. At 6 hours, wrappings and chambers were removed, and excess material was wiped off. Further applications of the test and positive control materials were made at 7 and 14 days after the first application. Test sites were evaluated at 24 and 48 hours after each application, and were scored according to the method of Draize. At 14 days after the final induction application, test animals were challenged by application of FMC 54800 10 WP at 0.40 g. The test material was applied to a clipped area of the right shoulder of each animal. Dosing was done as described for the induction applications. At 6 hours after the challenge dose, patches were removed and residual hair was removed by a depilatory (Neet® hair remover). Test sites were evaluated at 24 and 48 hours and were scored according to the method of Draize. In the same manner, a positive control group was challenged with DNCB (0.4 ml of a 0.15% solution in acetone) and a challenge control group was dosed with FMC 54800 10 WP at 0.4 g. All dosings in the challenge phase of the study were by topical application as described for the induction phase.

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Body weights of all guinea pigs were recorded at the initiation and termination of the study.

Results No response to induction or challenge was observed in the test animals. Positive controls gave the expected results. All test animals gained weight throughout the study.

One animal dosed with FMC 54800 10 WP died at day 12 after induction. Mortality was not considered to be related to administration of the test substance. Necropsy showed clear fluid in the peritoneal cavity.

Discussion The test material was not moistened with physiological saline because it "repelled the saline".

Data Evaluation Report

Compound FMC 54800

Citation Twenty-one Day Repeated Dose Dermal Toxicity Study in Rabbits with FMC 54800. L.R. Seaman, J.R. DeProspo, E.J. Ballester, L.E. Geiger, M.J. Norvell, M.J. Fletcher. FMC Toxicology Laboratory; Study No. A 83-1041; February 24, 1984.

Reviewed by Roy D. Sjoblad Ph.D. Roy D. Sjoblad 5/24/85
Microbiologist

Core classification Supplementary

Tox category Not applicable

Conclusion The most consistently observed signs of toxicity included loss of muscle control and tremors. The NOEL is 50 mg/kg/day because tremors were observed at 100 mg/kg/day. The study is considered as supplementary because nerve tissue was not microscopically evaluated and little confidence can be placed in the organ weight determinations.

Materials FMC 54800, Technical: 88.35% pure, [redacted] Lot No. E2392-105

Adult (2.0-3.0 kg) New Zealand White rabbits; from Hazleton-Dutchland, Inc., Denver PA

Methods At 24 hours before initial application of the test substance, approximately 10% of the dorsal trunk area of each test rabbit was shaved with an electric clipper. The test material was melted by heating at 70-80C for 1 hour and, after cooling, was applied under a gauze pad to each test site. The trunks of test animals then were wrapped in plastic sheeting, and necks were fitted with an everted plastic collar. The test material was applied at 0, 25, 50, 100 and 500 mg/kg and remained in contact with the skin for at least 6 hours per day for 21 consecutive days. After each daily exposure period, the plastic wrapping and gauze pads were removed and excess material was removed first with an acetone-wetted gauze pad and then with a water-wetted pad. Test sites were shaved as necessary during the study. Food consumption and body weights were determined at weekly intervals. Dose levels were based on the weekly body weights. There were 6 animals/sex/dosage group. Animals were observed twice daily for mortality and for clinical signs of toxicity. The following other examinations were performed on the test animals:

Hematology and clinical chemistry. Blood was taken from survivors at the end of the test period for hematology and clinical chemistry determinations.

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Hematology

hematocrit	platelet count
hemoglobin	mean corpuscular hemoglobin, hemoglobin concentration, and volume
erythrocyte count	
leucocyte count (total and differential)	

Clinical chemistry

Ca^{2+}, Na^{+}, P, Cl^{-}, K^{+}	albumin
fasting glucose	creatinine
SGPT	total bilirubin
SGOT	total protein
BUN	

Postmortem pathology. Examinations included gross necropsy, organ (liver, kidneys, testes) weights, body weights, and an histopathological examination of the following preserved tissues from rabbits in the control and high dose groups:

normal and treated skin	other target organs
liver	gross lesions and/or abnormally appearing tissues
kidney	

Results.

Mortality and clinical signs of toxicity. One female rabbit in the high dose group died on day 19. Death was attributed to ingestion of the test substance, since this animal was found on the day of death without its everted plastic collar on. Toxicity signs observed in this animal were chromorhinorrhea at day 3 after dosing and tremors on the day of death. No gross internal lesions were observed in this rabbit upon necropsy. Organs from this animal were not weighed.

In survivors, clinical signs of toxicity included erythema in both sexes at all dose levels. Lacrimation was observed in 1 male rabbit dosed at 500 mg/kg, and in 1 female rabbit each from the 50 and 100 mg/kg dose levels. Loss of muscle coordination was observed in all male and female animals in the high dose group. This toxicity sign appeared as early as 2 days after dosing, and often persisted to the end of the study period. Tremors were observed at day 17 in 1/6 females in the 100 mg/kg dosage group, and in 2/6 females in the high dose group at day 19. Tremors were observed in 3/6 of the male rabbits dosed at 500 mg/kg.

Body weight and food consumption. The mean body weights of animals from the control and from all test groups decreased by the end of the test period. The mean weight decreases (0.15 to 0.43 kg) were comparable in all groups, and probably were due to wearing of the collars. There were no differences in food consumption by treated versus control groups that could be attributed to repeated dermal application of the test substance.

Hematology. The mean values of erythrocyte count, hemoglobin, and hematocrit, were from approximately 2 to 6.5% higher for male rabbits in every dose group than for males in the control group. The mean values for white blood cell counts in males from the 25 and 50 mg/kg dosage group were, respectively, 9.3 and 10.8% higher than the control value. At the 100 and 500 mg/kg dosage levels, the mean values for the white blood cell count were, respectively, 19 and 7% lower than the control value. The only statistically significant differences were reported for the mean platelet count in male rabbits dosed at 25 mg/kg [$5.03(\pm 0.90)\times 10^{11}$/l; $p<0.05$] and at 500 mg/kg [$5.48(\pm 1.67\times 10^{11}$/l; $p<0.01$) versus $3.45(\pm 1.09)\times 10^{11}$/l as the mean control value.

The range of mean values for the white blood cell count, erythrocyte count, hemoglobin, and hematocrit for female rabbits at every dose level were, respectively, 9.2-24.2%, 1.8-6.5%, 2.2-9.5%, and 1.8-7.8% lower than the mean control values. The only statistically significant differences were reported for the mean hemoglobin value (12.52±0.845 g/dl) and the mean hematocrit value (37.92±2.855%) in females dosed at 100 mg/kg. Respective control group values for these two parameters were 13.83±0.662 g/dl and 41.12±1.604%. Mean platelet count values in females dosed at 25 and 500 mg/kg were, respectively, 15.1 and 18.2% higher than the mean control value. The mean values for segmented leucocytes (per 100 white blood cells) for female rabbits dosed at 0, 25, 50, 100, and 500 mg/kg were, respectively, 35.2±11.82, 55.7±7.61, 53.8±23.61, 45.2±16.07, and 47.4±20.14.

Clinical chemistry. There were no dose-dependent responses in clinical chemistry parameters attributable to repeated dermal application of the test substance. The only statistically significant difference ($p<0.05$) was noticed in the mean value for fasting glucose in females dosed at 50 mg/kg, which was 135.17±27.564 mg/dl versus 105.83±24.028 mg/dl for the mean control value. The mean values for fasting glucose in female rabbits dosed at 25, 100, and 500 mg/kg were, respectively, 15.8, 18.3, and 8.1% higher than the mean control value. The mean values for fasting glucose in male rabbits dosed at 25, 50, 100, and 500 mg/kg were, respectively, 4.6, 8.5, 1.3, and 12.3% lower than the mean control value. Mean values for SGPT activity in dosed male rabbits ranged from 14.4 to 23.1% less than the mean control value. In dosed females, the mean values for SGPT activity ranged from 17.6 to 26.8% less than the mean control value. The mean activity of SGOT in dosed male rabbits ranged from 20.6 to 30.6% less than the mean control activity.

Postmortem pathology. There were no statistically significant differences in the mean terminal organ weights from males and females at any dose level. The test substance had no effect on mean organ:total body weight ratios in males. Following are the data for for the mean organ and organ:body weight ratios for female rabbits dosed at 0, 50, and 500 mg/kg. Those values

considered statistically significant ($p<0.05$) are marked with an (*).

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Organ	Dose level (mg/kg) 0	50	500
Brain	8.02±2.10	9.03±0.56	9.18±0.65
Brain:total body	0.36±0.10	0.46±0.06*	0.43±0.05
Kidney	14.1±1.28	12.9±2.04	15.4±1.70
Kidney:total body	0.62±0.06	0.65±0.05	0.71±0.08*
Liver	60.5±26.6[a]	66.3±12.4	79.9±11.2
Liver:total body	2.63±1.12	3.32±0.30	3.70±0.60*

[a]The weight of one liver from this group was 7.1g; without this value the mean weight for this group is 71.12±5.62g.

Liver weight values of 108.4 and 105.0 were reported respectively for one female dosed at 100mg/kg, and one male dosed at 500mg/kg. The increases in mean liver and kidney:body weight ratios were attributed to repeated dermal application of the test substance. The increased brain:body weight ratio was considered due to the lower terminal body weights of this group.

No gross internal lesions attributable to administration of the test substance were noticed upon necropsy of the rabbits at the end of the study. Histopathological examination of preserved liver and kidney tissues from the control and high dose animals showed no signs of toxicity due to FMC 54800. Untreated skin from rabbits dosed at 500 mg/kg appeared normal, while treated skin showed epithelial thickening (1 to 2 cell layers) and hyperkeratosis. These changes were not attributed to administration of the test substance, but were considered the result of frequent wetting of the skin as described in the Methods section. Several control and dosed rabbits had liver and kidney lesions that were attributed to infection by the protozoan Encephalitozoon cuniculi. The frequency and severity of these lesions (e.g. lymphocytic infiltrates, lymphocytotic interstitial nephritis) generally were more pronounced in the control versus high dose group.

Discussion. The use of everted plastic collars on rabbits appeared to affect eating habits which in turn influenced weight gains. Thus, results relating food consumption, body weights, and organ:body weight ratios may be obscured. Organ weights were reported as unusually low values (e.g. liver weights of 7.2 and 14.7 g; brain weights of 3.9 and 5.3 g; and a kidney weight of 7.8 g) for several animals in control and test groups. Nevertheless, no gross internal or histomorphological lesions were reported for these organs in the post-mortem pathology report.

The statistically significant findings that platelet counts were elevated in male rabbits dosed at 25 and 500 mg/kg, hemoglobin and hematocrit values were decreased in females dosed at 100 mg/kg, and glucose levels were elevated in females dosed at 50 mg/kg, all were considered unrelated to administration of the test substance. No explanation for the occurrence of these abnormalities was forwarded. Under the conditions of the study it was reported that the NOEL for FMC 54800 was 100 mg/kg/day. However, a more appropriate NOEL is 50 mg/kg/day, since tremors were observed at 100 mg/kg/day. Nerve tissue was not histopathologically evaluated as a target of the test chemical. Testes weights from three females were recorded and subsequently corrected.

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Data Evaluation Report

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Compound FMC 54800, 2EC

Citation Acute Inhalation Toxicity Study of FMC 54800 2EC in Rats. J.L. Maedgen. Stillwater, Inc.; Study No. A 83-1044; October 19, 1983.

Reviewed by Roy D. Sjoblad Ph.D. R.D. Sjoblad 5/30/85
Microbiologist

Core classification Guideline

Tox category II

Conclusion The LC_{50} median values of FMC 54800 for rats were 1.943 mg/l for males and 1.861 mg/l for females. Major toxicity signs were tremors; polyuria, salivation, chromodaccryorrhea, loss of hindlimb motor control, discolored lungs, and difficulty in breathing.

Materials FMC 54800 2EC; Batch No. PL83-24

Young adult Sprague-Dawley rats;
Texas Animal Specialties, Humble TX

Methods Rats were housed individually in stainless steel cages within a 200 liter stainless steel dynamic flow inhalation chamber (Rochester type) and were exposed for 4 hours to an aerosol of the test chemical at 1.82, 1.86, 1.87, 1.92, 1.98, 2.14, and 4.98 mg/l.Portions of the test atmosphere were analyzed for FMC 54800 2EC at each half-hour of exposure by using GC. Nominal concentrations of the test chemical were determined at the end of each exposure. Ninety-five percent of the particulates at 1 and 3 hours at each dose level were <15 um. Animals were observed for mortality and clinical signs of toxicity frequently during exposure and at least once daily for the next 14 days. Rats were weighed prior to exposure and on days 7 and 14 after exposure, or at the time of discovery after death. Gross necropsy was performed on all animals that died on study and on all survivors sacrificed at 14 days after exposure. The number of animals at each dose level are presented in the mortality table below.

Results

Dose level[a]		Deaths/dosed	
Mean analytical (mg/l)	Nominal (mg/l)	Males	Females
1.82	4.29	0/5	0/5
1.86[a]	2.40	0/5	2/5
1.86[a]	5.63	0/5	4/5
1.87	5.07	8/10	--
1.92	5.73	5/10	--
1.98	5.33	5/5	5/5
2.14	5.04	5/5	5/5
2.23	6.24	2/5	5/5
4.98	13.40	5/5	5/5

[a] Independent tests done at the same concentration

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The LC_{50} values were 1.943 mg/l with 95% confidence limits of 1.592 to 2.294 mg/l for males, and 1.861 mg/l with 95% confidence limits of 1.824 to 1.899 mg/l for females. Of the 90 rats included in the study, 24 died within 1 day after exposure, 7 died from 2-3 days after exposure, and 25 died from 4-6 days after exposure. All the animals that died on study exhibited body weight losses. At the lowest dose level (1.82 mg/l), male rats showed weight gains of 60-80 g, while females gained little or no weight. At dose levels from 1.86 to 4.98 mg/l male and female rats generally either lost weight, did not gain weight, or gained less weight than rats at the lowest dose level.

Clinical signs of toxicity that were commonly observed during the first 24 hours after dosing were polyuria, epistaxis, salivation, lacrimation, chromodaccryorrhea, nasal discharge, piloerection, ptosis, constricted pupils, tremors (body, head, fore- and hindlimb), convulsions, loss of hindlimb motor control, unusual hindlimb extension, blinking, and difficulty in breathing. Less frequently observed signs of toxicity during the first 24 hours after dosing were respiratory gurgle, wheeze or chirp, distended penis, swollen neck, and sensitivity to touch. Toxicity signs that arose after the first day of dosing were corneal opacity, emaciation, and swollen face. Signs that persisted after 1 day post-treatment were body, hindlimb, and head and forelimb tremors, ptosis, polyuria, and piloerection.

Gross internal necropsy showed discolored lungs (usually pink or red) in almost 100% of the dosed rats. Also observed frequently were gastrointestinal tracts distended with gas, discolored (yellow, brown, or black) fluids or pastes in the stomach and small intestine, edematous and consolidated lungs, and adhered (to the rib cage) lungs. Less frequently observed were melanuria, red oral discharge, discolored penis, and cartilaginous material in the urinary bladder.

Data Evaluation Report (I) 004501

Compound:

TALSTAR™, FMC 54800 Technical

Study type:

13-week feeding - dog

Citation:

Serota, D. G., 13-Week Subchronic Oral Toxicity Study in Dogs. Study conducted at Hazleton Laboratories America, Inc., under project no. 104-217. Report dated February 7, 1984. Received at EPA 8-15-84; in Acc. 254408.

Reviewed by:

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Clint Skinner 6-4-85

Core Classification:

Supplementary (tentative)

Conclusions:

1. Since the purity of the technical compound was 88.35%, the nominal dosage levels of 2.5, 5, 10 and 20 mg/kg/day have been respectively recalculated to 2.21, 4.42, 8.84 and 17.7 mg/kg/day in terms of the active.

2. The most sensitive indicator of exposure in this study was the occurrence of tremors. Unequivocally dose-related tremors were present at and above dosage levels of 4.42 mg/kg/day, and were more frequent (or only occurred) towards the termination of the study. However, "slight tremors" were also noted in one male at 2.21 mg/kg/day during the 11th week. While this was "not considered to be compound related since slight spontaneous trembling is noted occasionally in some laboratory dogs at Hazleton Laboratories in response to handling" no further information is given. The immediate question is whether this animal was being (or had recently been) handled, or what other circumstances were present that might be relevant. A decision as to whether or not the 2.21 mg/kg/day of the active is a NOEL is being deferred pending a response.

3. Other dose-related symptoms included languidness and ataxia occurring at 8.84 and 17.7 mg/kg/day (ataxia was also observed on one occasion in a female of the 4.42 mg/kg/day group). Polypnea (increased rate of respiration) was occasionally observed in both males and females of the two

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highest dosage level groups.

4. Females at the highest dose level (17.7 mg/kg/day) showed a reduced mean weight gain (0.6 kg) with respect to controls (1.3 kg) and females of the other dose levels during the 13 weeks of the study. While the difference between highest-dose females and controls is not statistically significant, it is strongly suggestive of an effect.

5. It is reported (p. 18) that normal cyclic activity was present in two control females, two females at 4.42 and one at 8.84 mg/kg/day. Evidence of estrus was also observed in females of these 3 groups (p. 91). No estrus or evidence of cyclic activity was observed or detected in females of the two highest dosage levels. Again, this is suggestive of an effect.

6. There is no page 31 in the report, although it is uncertain whether there would be anything on it (p. 30 has Table 3; p. 32 contains Table 4). There should be some clarification on this point. Page 33 was, in the copy of the report received by this reviewer, between p. 105 and 106.

Materials:

Healthy purebred beagles, 22-26 weeks of age at the initiation of the study. Forty (20 males, 20 females) were selected from a total of 46 (23 of each sex). The dogs were received from Hazleton Research Animals, Inc., Cumberland, VA.

Test material, identified as FMC 54800, lot no. E-2392-105. The test material was assumed to be 100% active for dose calculation purposes, but it was subsequently found to consist of 88.35% active ingredient.

Procedure:

Dogs were "stratified by weight" and randomly assigned, 4 of each sex, to 5 groups. The individual dogs within a group were dosed once a day with 0, 2.5, 5, 10 or 20 mg/kg of the test material, administered by gelatin capsule. Dogs were observed at least twice daily for mortality, moribundity and clinical signs. Individual body weights were recorded one week before dosage began, and weekly thereafter. Individual food consumption was measured on a weekly basis.

The following hematology and serum chemistry values were obtained on all dogs prior to treatment, and at weeks 4, 8 and 13.

Hematology:

Total WBC and differential leucocyte counts
Erythrocyte (RBC) count
Hemoglobin
Hematoctrit (HCT)
Platelet count (PLATELET)
Erythrocyte and leucocyte morphology

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Serum chemistry:

Sodium (Na)
Potassium (K)
Chloride (Cl)
Total protein (T PROT)
Albumin (ALB)
Globulin (GLOB)
Calcium (Ca)
Total bilirubin (T BILI)
Blood urea nitrogen (BUN)
Glucose (GLUC)
Aspartate aminotransferase
Alanine aminotransferase
Phosphorus (IN PHOS)
Creatinine (CREAT)

Ophthalmologic examinations were performed on all dogs before dosage began and at week 13 using an indirect ophthalmoscope and slit lamp. Tropicamide ophthalmic solution (1% Mydriacyl) was used to dilate the pupil.

At 13 weeks all dogs were fasted overnight, then were weighed, anesthetized and sacrificed by exsanguination. The following tissues from each dog were preserved in 10% neutral buffered formalin. All of the preserved tissues from each dog were embedded in Paraplast®, sectioned, stained with hematoxylin and eosin, and examined microscopically. The asterisks indicate those which had been weighed when removed; from these weighings organ/body and organ/brain weight ratios were subsequently calculated:

*Brain (fore-, mid-, hind)
(weighed with brainstem
Pituitary
Spinal cord (thoracic and
lumbar)
Eyes
Salivary glands (mandibular)
*Thyroid with parathyroids
Thymus
Trachea
Esophagus
Lung (2 sections)
*Heart
Aorta
*Liver (2 lobes)
Gallbladder
Spleen
*Kidneys
Stomach
Duodenum
Jejunum
Ileum
Cecum
Colon
Rectum
Urinary bladder
*Testes with epididymides
or *Ovaries
Prostate or Uterus
Skin
Mammary gland
Bone marrow (sternum)
Muscle
Sciatic nerve
Mesenteric lymph node
Tissue masses or lesions
Adrenals
Pancreas

Statistics:

"Mean body weight changes for weeks 0-4, 0-8 and 0-13; total food consumption for weeks 1-13; clinical pathology data (excluding differential leukocyte counts and erythrocyte and leukocyte morphology); and organ weight data of the compound-treated groups were compared statistically to the data of the control group of the same sex."

A variety of statistical procedures were employed.

Results:

There were no mortalities.

Clinical symptoms included tremors and ataxia. The following dose-related incidences were observed:

Incidence of tremors in males (from p. 66)

Nominal dosage level	Total number of dogs involved	Total number of times observed
0	0	0
2.5	1	2
5	3	16
10	4	99
20	4	251

Incidence of tremors in females (from p. 79)

0	0	0
2.5	0	0
5	3	12
10	4	75
20	4	206

The following incidences of ataxia were observed:

Incidence of ataxia in males (from p. 68)

0	0	0
2.5	0	0
5	0	0
10	4	10
20	4	144

Incidence of ataxia in females (from p. 81)

0	0	0
2.5	0	0
5	1	1
10	4	8
20	4	93

Languidness occurred primarily at 20 mg/kg/day in both males and females, but this symptom also occasionally occurred in 10 mg/kg/day animals.

All of these symptoms tended to occur more frequently towards the end of the study, particularly in dogs at the highest dose level:

	Mean weekly incidence of tremors		
	week 2-5	week 6-9	week 10-13
10 mg/kg/day males	19.75	23.00	41.00
20 mg/kg/day males	52.75	64.25	99.00
(calculated from the data presented on p. 66)			
5 mg/kg/day females	0	0	10.75
10 mg/kg/day females	8.00	12.50	44.75
20 mg/kg/day females	41.00	45.50	89.25
(calculated from the data presented on p. 79)			

Mean weekly incidence of ataxia

10 mg/kg/day males	4.50	1.75	1.75
20 mg/kg/day males	33.25	26.00	65.25
(calculated from the data presented on p. 68)			
5 mg/kg/day females	0	0	1.00
10 mg/kg/day females	3.50	1.00	1.75
20 mg/kg/day females	15.25	12.50	48.25
(calculated from the data presented on p. 81)			

Mean weekly incidence of languidness

20 mg/kg/day males	20.50	10.75	50.00
(calculated from the data presented on p. 67)			
20 mg/kg/day females	28.50	13.50	49.00
(calculated from the data presented on p. 80)			

In one female (dog #22039) of the 20 mg/kg/day group tremors, ataxia and languidness (as well as lacrimation and salivation) were more frequent at the beginning of the study than in the other females of this group.

Other symptoms which occurred in a dose-related fashion included blinking, mydriasis, nystagmus, lacrimation, and polypnea. One female in the high-dose group appeared thin and/or dehydrated during the final weeks of the study.

None of the females at 10 or 20 mg/kg/day went into estrus. The following incidences of estrus are reported from observation (p. 91) and histopathology (p. 18):

Group	Number with signs of estrus (p. 91)	Showing evidence of cyclic activity (see p. 18)
Control	1	2
2.5 mg/kg/day	2	2
5 mg/kg/day	1	1
10 mg/kg/day	0	0
20 mg/kg/day	0	0

The total incidence of evidence of estrus activity (from p. 18) was 5/20 dogs. An approximation of the probability that there would be no

evidence of estrus in the 8 females of the two highest dose level groups would then be $(3/4)^8$, or about 10%. While this is not statistically significant, it is suggestive.

Estrus activity occurred only during weeks 12-13, as these were fairly young dogs at the initiation of the study.

Body weights:

The following group mean body weight gains (in kg) are reported (p. 30) for weeks 0-13:

Group	Males	Females
Control	2.0	1.3
2.5 mg/kg/day	1.6	2.8*
5 mg/kg/day	2.6	2.0
10 mg/kg/day	2.3	1.4
20 mg/kg/day	1.6	0.6

*statistically significant relative to control value

Females at 20 mg/kg/day had less than half the mean weight gain that their controls had, but this was not statistically significant (possibly at least in part because of the low number of animals). However, it is reported (p. 1) as a compound-related effect. The statement is also made (p. 1) that a "borderline effect" was observed in highest-dose males.

Males and females of all exposure groups had food consumptions that were similar to those of their respective controls.

Hematology and clinical chemistry:

No dose-related changes and/or trends and no significant differences between groups were observed for WBC and RBC counts, or in levels or activities for HGB, Cl^-, globulin, calcium, total bilirubin, BUN, and alanine aminotransferase. The report states (p. 2) that a slight decrease in the red cell mass (HCT) was observed at the 2 highest dose levels, and a dose-related trend (but with no significant differences) does seem to present (refer to p. 33).

Highest dose males consistently had lower mean serum potassium levels than those of controls, and the difference was statistically significant at week 4 (in part because of a low standard deviation on that date for values from high-dose males). However, the highest-dose males had an initial mean potassium serum level that was lower than those of any of the other groups. There were no dose-related trends or significant differences among the female groups with respect to this parameter.

At 13 weeks mean serum sodium levels were slightly (1.36-2.04%) but significantly ($p < 0.05$) depressed relative to the control value for female dogs at 5, 10 and 20 mg/kg/day. Females at 5 mg/kg/day had a lower mean serum sodium level than females at 10 or 20 mg/kg/day. The 20 mg/kg/day female (#22039) in which tremors etc. had been most frequent at the start

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of the study had the lowest serum sodium level (143 mmol/liter) of the dogs at that dosage level at 13 weeks; 2 females in the 5 mg/kg/day group (#22021 and #22024 - refer to p. 180) also had sodium levels that were this low at 13 weeks. Most of the tremors in this group that were observed during weeks 12-13 were in animal #22021, but none were observed in #22024. Although males at these 3 levels also showed slightly lower (1.36%) sodium serum concentrations relative to their control value, differences were not statistically significant.

Slight (6.3-9.7%) but statistically significant elevations in mean serum albumin were observed for females at 2.5 mg/kg/day (weeks 8 and 13) and 5 mg/kg/day (week 8). However, no dose-related trends were evident, and highest-dose females consistently had a mean serum albumin value that was within about 3.5% of that for controls. No significant differences were seen between the mean values for the different male groups.

Highest-dose males consistently showed lower mean aspartate transferase (AST) activity than did controls and the three lower dosage groups, and differences were statistically significant at weeks 4 and 8. However, this group also had the lowest mean AST activity at the initial reading. There was no evidence for a dose-related response among the female groups.

Males at the highest dose level consistently had higher glucose levels than did controls, and the difference was statistically significant at week 8. In both males and females the control group had the lowest glucose levels at week 13, but at this time there were no statistically significant differences between controls and any of the dosage level groups.

Males at 10 and 20 mg/kg/day consistently (including the initial reading) had lower mean creatinine levels than controls, but the only statistically significant difference was at week 8 for highest-dose males. Differences between the mean creatinine levels for the female groups were consistently minor, showing no evidence of a dose-related pattern.

On p. 15 it is noted: "The electrolyte changes (decreased sodium and potassium) were subtle and were felt to be of uncertain relationship to treatment. The remaining clinical chemistry changes were considered to be of little biological importance, based on the low magnitude of the response, unusual control group values, and/or similarity to initial results, where appropriate."

Opthalmoscopic observations:

According to information on p. 200 one high-dose male (#22035) had bilateral epiphora (overflow of tears) at week 13. This same male is reported (p. 69) as having lacrimation from the first week of the study. This was the only possible dose-related finding from the opthalmoscopic examination, other findings having been present in the subjects at the pretreatment examination.

Organ weights:

Mean absolute thyroid weights in females of the 10 and 20 mg/kg/day dose groups were lower (by 11.1 and 23.1% respectively) than their controls,

but the difference was not statistically significant. Mean absolute weights for ovaries in females of the 10 and 20 mg/kg/day dose groups were lower (by 41.1 and 58.8% respectively) than their controls, presumably because estrus had not occurred.

Both males and females of the 20 mg/kg/day group had liver to body weight ratios that were slightly higher than those of their controls or the other dosage groups. The female (#22039) in the 20 mg/kg/day group which had the most tremors and other symptoms also had the highest liver to body weight ratio of all the females. This prompted the following examination of the data (from p. 241-279):

Female #	Dosage Level	Body weight at termination (g)	Absolute liver wt (g) at termination	Liver to body weight ratio (%)
22005	0	8100	212	2.6
22006	0	7200	192	2.7
22007	0	8400	217	2.6
22008	0	9800	235	2.4
Control group means		8375	214	2.6
22013	2.5	10000	253	2.5
22014	2.5	9800	222	2.3
22015	2.5	10500	254	2.4
22016	2.5	9100	196	2.2
2.5 mg/kg/day group means		9850	231	2.35
22021	5	10200	245	2.4
22022	5	9500	238	2.5
22023	5	8000	216	2.7
22024	5	7600	171	2.3
5 mg/kg/day group means		8825	217.5	2.48
22029	10	9300	218	2.3
22030	10	7500	174	2.3
22031	10	8400	203	2.4
22032	10	8400	169	2.0
10 mg/kg/day group means		8400	191	2.25
22037	20	7700	211	2.7
22038	20	6700	177	2.6
22039	20	7400	211	2.9
22040	20	8100	208	2.6
20 mg/kg/day group means		7475	201.8	2.7

Although dog #22039 had the highest liver-to-body weight ratio of any of the 20 females, this was due to the animal's relatively low body weight as its liver weight was not exceptional. The only histology finding for the liver of dog #22039 (p. 276) is focal mononuclear infiltration, which was a common finding in all dogs, including the controls.

Pathology and histopathology:

Pituitary cysts are reported (p. 50) in 2/4 highest-dose males and 2/4 highest-dose females, but did not occur in controls or any of the dogs at lower dosage levels. However, according to the histopathology summary on p. 58 only 1/4 highest-dose males had a pituitary cyst, and this finding was present in a number of the lower dose dogs, as well as in 1/4 male and 1/4

female controls.

One male at 10 mg/kg/day and 2 at 20 mg/kg/day are reported (p. 51) as having thickened atrioventricular valves, a finding which did not occur in any of the other male groups, although present in one female at 5 mg/kg/day. One female at 20 mg/kg/day had areas of "dark focus" in the cecum (p. 53), a finding not observed in any other dog. These were the only possible dose-related findings.

Discussion:

As the purity of the test material was 88.35%, the nominal dosages of 2.5, 5, 10 and 20 mg/kg/day have been respectively recalculated as 2.21, 4.42, 8.84 and 17.7 mg/kg/day of active ingredient.

The tremors, languidness and ataxia, occurring at 4.42 mg/kg/day and/or higher dosage levels, must be considered dosage-related symptoms, with tremors apparently being the most sensitive indicator of exposure to this test material. Slight tremors did occur in a 2.21 mg/kg/day male (see p. 12, 66) during week 11. It is stated (p. 12) that "this finding was not considered to be compound related since slight spontaneous trembling is noted occasionally in some laboratory dogs at Hazleton Laboratories in response to handling." While this seems to be a reasonable explanation, no further information is The immediate question then is whether in fact this animal was being or had been recently handled (or what other circumstances were present) on the two occasions when the slight trembling occurred. Until this information is given, a decision as to whether the 2.21 mg/kg/day level is a NOEL must be deferred.

There was a definite increase in the incidence of tremors as the study continued, suggesting some sort of "cumulative" effect.

While it is tempting to relate the occasional blinking, mydriasis and nystagmus which occurred in some males and females of the 20 mg/kg/day dosage group to the tremors which also occurred in these animals, the eye symptoms tended to occur during the first few weeks of the study, while the tremors became more frequent towards termination.

The tremors were not due to changes in serum sodium levels, as the dog (#22039) in which tremors were fairly pronounced during the earlier weeks of the study had a serum sodium level value (147 mmol/liter) at week 4 which was the same as the mean control level on that date. However, serum sodium levels may have been slightly affected by exposure to 4.42 mg/kg/day or more of the test material.

This reviewer agrees with the statement made in the report (p. 2) that the hematology and clinical chemistry findings were such that they could be considered, in this study at least, as "of little biological significance."

The reduced weight gains for highest-dose females, as well as the lack of estrus in any of the females of the two highest dose level groups, while

not statistically significant, are suggestive of additional effects of exposure to the test material.

There is no page 31 in the report, although it is uncertain whether it would contain anything (page 30 has Table 3; page 32 contains Table 4). There should be a clarification on this point. Page 33 was (at least in the copy received by this reviewer) between pages 105 and 106.

Data Evaluation Report II

Compound:

TALSTAR™, FMC 54800 Technical

Study type:

90-day feeding - rat

Citation:

Rand, G. M., Seaman, L. R., Ballester, E. J., Kikta, E. J., Norvell, M. J., Fletcher, M. J. Ninety Day Feeding Study in Rats with FMC 54800 Technical. FMC Study no. A83-818; dated January 31, 1984. Study received at EPA 8-15-84; in Acc. 254407.

Reviewed by:

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Toxicologist
Toxicology Branch

Approved by:

Clint Skinner, Ph.D.
Section Head
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Core Classification:

Minimum

Conclusions:

1. Under the conditions of this study, the NOEL was 50 ppm. At 100 ppm tremors occurred in some males and females during the first 16 days of the study. Levels tested (dietary exposure) were 0, 12, 50, 100 and 200 ppm.

2. Effects at 200 ppm included tremors (seen in some animals throughout the 91-day period) and decreased mean body weight gains for both males and females relative to controls. Possible effects included a slight reduction in mean BUN for both males and females, and slight changes in mean serum calcium and potassium levels.

3. The tremors which occurred at 200 ppm were reversible, as a group of 10 rats/sex stopped having tremors within 3 days of being placed on a recovery diet not containing the test material.

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Materials:

Male and female Sprague-Dawley derived rats, received as weanlings (3-4 weeks of age) from Taconic Farms, Hover Ave., Germantown, NY 12526.

Test material: identified as FMC 54800 Technical, 2-methyl ((1,1' -biphenyl)-3-yl) methyl cis-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2 ,2-dimethyl- cyclopropane-carboxylate, sample E2425-145. 91.4% pure; approximately [redacted]

Procedure:

Individual rats, approximately 5 weeks of age, were weighed and randomly assigned to groups consisting of 15 males and 15 females. Groups were fed diets containing 0, 12, 50, 100 or 200 ppm of the test material. All rats were observed daily for mortality or possible signs of toxicity. Rats were individually weighed every week. Individual food consumptions were calculated from the amounts of feed remaining uneaten at the end of every week.

All rats received an ophthalmological examination before being exposed to the test material, and during the last week of the study.

Prior to terminal sacrifice, blood samples were taken from 10 rats/ sex/dosage level. The following hematology and clinical chemistry determinations were made:

Hematology:

Hematocrit
Hemoglobin
Erythrocyte (RBC) count
Platelet count
Total and differential leucocyte count
Mean corpuscular hemoglobin concentration (MCHC)
Mean cell volume (MCV)
Mean corpuscular hemoglobin (MCH)

Clinical chemistry:

Calcium
Phosphorus
Chloride
Sodium
Potassium
Fasting glucose
Serum Glutamic-Pyruvic Transaminase (SGPT)
Serum Glutamic-Oxaloacetic Transaminase (SGOT)
Urea Nitrogen
Gamma Glutamyl-Transpeptidase
Serum Alkaline Phosphatase (SAP)
Albumin
Blood Creatinine
Total Bilirubin
Total Serum Protein
Globulin

At the end of 90 days, all rats were weighed, sacrificed, and necropsied. The following organs and tissues from all rats were preserved in 10% buffered neutral formalin. Those marked with an asterisk were also weighed:

All gross lesions
*Brain, including sections of medulla/pons, cerebral cortex, and cerebellar cortex
Spinal cord (thoracic and lumbar)
Pituitary
Thyroid
Thymus
Lungs
*Heart
Sternum and femur with bone marrow
Salivary gland (mandibular)
*Liver (2 sections)
Spleen
*Kidneys (both)
*Adrenals (both)
Pancreas
*Gonads (both)
Uterus
Aorta
Esophagus
Stomach
Duodenum
Jejunum
Ileum
Cecum
Colon
Rectum
Urinary bladder
Lymph node (2 nodes): including mediastinal & mesenteric
Peripheral nerve (sciatic)
"Any tissue(s) if indicated by signs of toxicity or target organ involvement (e.g., trachea, parathyroid, mammary gland, thigh musculature, eyes).

At termination, bone marrow smears were prepared from 10 rats/sex in the control and high concentration groups. However, the smears were not subsequently evaluated "since anemia was not evident from blood analysis."

Histopathology was done on the following:

1. All preserved tissues:	All animals in the control and highest dose groups.
2. Lungs, livers, kidneys:	Animals in the low and intermediate concentration groups.
3. Gross lesions:	All animals

In addition to the 15 rats/sex/group that were in the part of the study indicated above, there were an additional 10 rats/sex/group that received a diet containing 200 ppm cf test material, and a group (10 animals/sex) which served as their controls. After 91 days these rats were fed a recovery diet (not containing any test material) for an additional 28 days. These rats were weighed weekly, their food consumption was determined on a weekly basis, and clinical signs were observed, but the data so obtained was kept separate from that obtained from the other rats (including the ones at 200 ppm) in the study. These rats were sacrificed after receiving the "recovery" diet for 28 days; no blood measurements were made and no gross necropsies were performed on these animals.

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A number of statistical procedures were used to compare group means for body weights, food consumptions, organ weights, and blood parameters.

The concentration of FMC 54800 Technical in all batches of test diet was "analytically validated."

Results:

There was no mortality.

Tremors occurred in a dose-related pattern. The following is calculated from Table 4 in the Appendix:

Dose level (ppm)	No. of animals affected (out of a total of 15)	No. of days on which tremors were observed*
0	0	0
12	0	0
50	0	0
100 (M)	3	8
100 (F)	3	17
200 (M)	15	700
200 (F)	15	953

*As there were 15 rats/sex/group the total number of observation-days per group/sex was about 15 x 90 = 1350.

The tremors noted at 100 ppm occurred only during the early part of the study. In males at this dosage level no tremors were noted after day 6, and in the females no tremors were observed after day 17.

In the "recovery group" (rats that were held for an additional 28 days during which they were fed a diet not containing the test material) tremors were observed at various times in all the rats while they were being fed 200 ppm. However, they were not observed in males after day 92 nor in females after day 94 (p. 16: "Tremors subsided in all animals of the 200 ppm group within 3 days of initiation of the 28-day post-treatment period.").

Males and females in the 200 ppm dosage group consistently had lower mean body weights than their respective controls. For males, the difference between mean body weights for the 200 ppm group and controls was statistically significant ($P \leq 0.05$) at weeks 1 and 2; for females it was statistically significant only for week 1.

Overall mean weight gains for 200 ppm males and females were lower than those of their respective controls or any of the other dosage level groups. However, weight differences between the controls and 200 ppm dosage level groups were not statistically significant at the end of the study.

WHO

Mean body weight gains (grams) at termination:

	Controls	12 ppm	50 ppm	100 ppm	200 ppm
Males	341.4	351.2	345.4	350.8	339.8
Females	162.9	166.4	164.8	175.8	153.4

A similar pattern in mean body weight gains was observed with the 200 ppm "recovery period" rats and their controls. From p. 20-21:

	Controls (13 weeks)	200 ppm (13 weeks)	Controls (17 weeks)	200 ppm (17 weeks)
Males	359.0	323.9	376.2	354.6
Females	172.3	156.1	188.8	173.0

Despite the consistent and well-defined trend, there were no statistically significant differences between mean body weights for males and females of the 200 ppm "recovery" group and their respective controls.

There were no statistically significant differences between mean food consumptions of the 200 ppm group males and their controls. Males of the 100 ppm group showed significantly greater mean food consumption in the period from weeks 1 to 3. Females at 200 ppm had less mean food consumption than their controls after week 4, but this was statistically significant only during week 9.

Ophthamology: All rats were ophthalmoscopically normal except for one male in each of following groups: control, 12 ppm, 50 ppm and 100 ppm, and one female in the 12 ppm group. One control male and the female at 12 ppm had multiple bands of focal retinal degeneration in one eye; the males at 50 and 100 ppm had focal retinal degeneration in one eye. The male at 12 ppm had "paracentral superficial corneal opacity," which, it is suggested, probably resulted from trauma.

Hematology: There were no statistically significant differences in hematology measurements between highest dietary level (200 ppm) males or females and their respective controls. There were no dose-related trends.

Clinical chemistry: The mean BUN's in 200 ppm males and females were lower than those of their respective controls (or any other dosage group). However, there were no statistically significant differences (from p. 34 and 35):

	0 ppm	12 ppm	50 ppm	100 ppm	200 ppm
BUN (mg/dl) males	14.50	17.30	14.70	14.70	13.80
" females	17.30	17.90	16.60	17.70	15.80

In the male groups there was a possible dose-related trend with respect to potassium levels, with serum potassium levels in the 3 highest dosage level groups being significantly "different" (lower) than the control value. However, females at 200 ppm had a significantly higher mean potassium level than did their control group (from p. 34-35):

	0 ppm	12 ppm	50 ppm	100 ppm	200 ppm
Potassium levels-males	5.28	5.06	4.98*	4.97*	4.94*
Potassium levels-females	4.62	4.70	4.49	4.43	4.91*

*Significantly different from controls at $p \leq 0.05$.

In the 200 ppm rats there was no correlation between serum calcium levels, serum potassium levels and the last day on which tremors were observed:

Animal # (females)	Last day tremors were observed and rank		Serum Ca++ MG/DL and rank		Serum K+ MEQ	
A6327	79	(8)	10.6	(1)	5.1	(3)
A6326	91	(2)	10.5	(2.5)	4.7	(8.5)
A6333	90	(4)	10.5	(2.5)	5.2	(2)
A6328	87	(5)	10.3	(4.5)	5.0	(4)
A6334	78	(9)	10.3	(4.5)	4.8	(7)
A6329	80	(7)	10.2	(6)	5.3	(1)
A6330	84	(6)	10.0	(7.5)	4.5	(10)
A6331	91	(2)	10.0	(7.5)	4.9	(5.5)
A6332	66	(10)	9.9	(9.5)	4.9	(5.5)
A6335	91	(2)	9.9	(9.5)	4.7	(8.5)
(males)						
A6239	58	(8)	11.3	(1)	4.9	(5.5)
A6237	66	(6.5)	10.7	(2)	5.4	(1)
A6238	91	(1)	10.6	(3)	4.8	(8)
A6236	73	(3)	10.5	(4)	4.8	(8)
A6232	71	(4.5)	10.4	(5)	4.9	(5.5)
A6233	90	(2)	10.2	(6.5)	4.8	(8)
A6235	66	(6.5)	10.2	(6.5)	5.1	(3)
A6231	55	(10)	10.1	(8.5)	4.5	(10)
A6240	71	(4.5)	10.1	(8.5)	5.2	(2)
A6234	56	(9)	9.8	(10)	5.0	(4)

Organ weights: there were no significant differences between groups with respect to organ weights.

Microscopic findings: the report states (page D-3) that there was "no histomorphological evidence of a treatment induced or related effect." However, some notable differences did exist between the control and 200 ppm rats with respect to incidences for certain findings (refer to p. D-7):

TISSUE AND FINDINGS	INCIDENCE/15 ANIMALS CONTROLS M	CONTROLS F	200 PPM M	200 PPM F
LUNGS				
Parabronchiolar lymphocytic infiltrates	14	4	3	3
Parabronchiolar lymphoid hyperplasia	8	5	2	0
MEDIASTINAL LYMPH NODE				
Lymphoid hypoplasia	1	0	1	5
Lymphoid hyperplasia	9	6	0	0
SPLEEN				
Increased hemosiderin pigment	7	15	0	13

Discussion:

The occurrence of tremors was the most sensitive indicator of exposure to the test material. As tremors occurred in both sexes of the 100 ppm group during the first two weeks of dietary exposure, this level must be considered the LEL under the conditions of this study, with the next lowest level (50 ppm) the NOEL. This conclusion differs from that of the abstract which states (p. 4): "...it may be concluded that the lowest observed effect concentration is 200 ppm and the no observed effect concentration is 100 ppm for FMC 54800."

Since no tremors were observed after day 94 in the rats of the 200 ppm "recovery" group, it can be stated that under the conditions of the 13-week study the tremors which occurred as a result of 200 ppm dietary exposure are reversible.

The statistically non-significant decreases in mean body weight gains at 200 ppm for males and females relative to their respective controls, both in the animals that were sacrificed at 13 weeks and those that were maintained an additional 4 weeks on a recovery diet, must be considered as treatment (and dose) related. Mean body weights of the 200 ppm recovery males and females were still below those of their respective controls at 17 weeks.

As mean BUN concentrations were lower both in 200 ppm males and females (by about 4.1 and 8.6% respectively) relative to controls, and were also below values for any of the lower-dose groups, this must also be considered an effect of exposure to the test material.

Although there appears to be a dose-related downward trend with respect to mean serum potassium levels in males (with levels for the 50, 100 and 200 ppm male rats being significantly different from the control value), the control value (5.28 meq/l) appears somewhat high. Also, there is less difference between the mean serum potassium levels for the 12 ppm and 200 ppm males (0.12 meq/l) than between the control and 12 ppm males (0.22 meq/l), indicating that an actual dose-relationship, at least at 12, 50 and 100 ppm exposure levels, is somewhat tenuous. In contrast to the downward trend in the males, females at 200 ppm show a significantly elevated (about 4.9%) mean serum potassium level relative

to their controls. The tentative conclusion is that it is possible that dietary exposure to the test material at 200 ppm causes changes in mean serum potassium levels, but that there is no evidence of effects on this parameter from dietary exposure to less than 200 ppm of the test material.

The apparent dose-related increase in mean serum calcium levels in females is statistically significant only in the 200 ppm group with respect to the control value. It is possible that dietary exposure to the test material at 200 ppm had an effect on serum calcium level.

There is no evidence for any correlation between the last date on which tremors were observed in any one animal at the 200 ppm level and that animal's mean serum calcium or potassium level at termination.

This reviewer agrees with the statement made (p. 16) regarding the serum calcium and potassium levels: "The significance of these findings cannot be determined at this time."

The differences that existed between 200 ppm rats and their controls with respect to microscopic findings seem to suggest that the former were actually healthier than the latter, particularly with regard to lung infections.

There is no evidence for any other effects relating to ophthalmology, hematology, clinical chemistry, behavior, gross necropsy, or histopathology.

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Data Evaluation Report (III)

Compound:

TALSTAR™, FMC 54800 Technical

Study type:

Teratology - rat

Citation:

Freeman, C., DeProspo, J. R., Nadasky, N., Fletcher, M. J., Barta, W. D., and Bullock, W. L. Teratology study in rats with FMC 54800 technical. Study conducted at the FMC Toxicology Laboratory (Somerville, NJ 08876) under study number A83-1091. Report dated February 24, 1984. Received at EPA 8-15-84; in Acc. 254409.

Reviewed by:

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Core Classification:

Supplementary

Conclusions:

1. The only evidence of maternal toxicity was "intermittent" tremors (otherwise undefined as to intensity or duration) occurring in most females receiving 2 mg/kg/day (HDT) of the test material. The NOEL for maternal toxicity is then 1 mg/kg/day. However, the study has been classified as supplementary partly because no rationale is given for the dose levels used, and, in the absence of such indicators of toxicity as reduced mean weight gains, changes in mean food consumption, or similar effects, there is concern as to whether the highest dose tested was reasonably close to the maternal MTD (Maximal Tolerated Dose).

2. There was an increased incidence of hydroureter in fetuses from female rats which had received 2 mg/kg/day (HDT) of the test material from days 6-15 of gestation. Although the incidence of this finding was more than double (in terms of percentages of both fetuses and number of litters affected) that which occurred in controls or any lower exposure group, it was not statistically significant. Also, 5 fetuses from dams at 2 mg/kg/day had hydroureter without hydronephrosis, a finding which was not present in controls or any of the other exposure groups (including

positive controls). Although the significance of the finding is equivocal, it adds to the uncertainties in interpreting this study. Therefore the fetotoxic NOEL is set at 1 mg/kg/day, with a possible fetotoxic LEL at 2 mg/kg/day.

3. The teratogenic NOEL is 2 mg/kg/day (HDT).

4. It is possible that, if a preliminary range-finding or pilot study was conducted, then the results would give some rationale for the dosage levels subsequently used, and might (assuming enough data had been obtained) provide some information regarding the increased incidence of hydroureter indicating above. If such a study was conducted, then the results should be reported.

Materials:

Sprague-Dawley rats, from Taconic Farms, Germantown, N.Y.

Test material: FMC 54800 Technical, lot no. E2392-105; FMC-T# 170; purity 88.35%. Composition [redacted]

Positive control: Aspirin, powder, U.S.P., from J. T. Baker, Lot no. 244343; FMC-T# 211.

Procedure:

After an acclimation period of two weeks, virgin female rats were placed with male rats. The presence of sperm in vaginal smears the following morning was considered indicative of mating, and these females were considered to be at day 0 of gestation. Pregnant females were ranked according to body weight and placed into 5 groups in consecutive order until each contained 25 animals. On days 6-15 of gestation each member of these groups was dosed with either 5 ml/kg corn oil (negative control), 0.5, 1.0 or 2.0 mg/kg of the test material administered as a 5 ml/kg corn oil suspension, or with 250 mg/kg of U.S.P. aspirin (positive control) administered in a 5 ml/kg 2% carboxymethylcellulose solution. These doses were administered between 11 A.M. and 1 P.M.

The rats were observed twice daily for mortality and signs of toxicity. Individual body weights were taken on days 0, daily from day 6 through 15, and then on day 20. Individual food consumption was calculated on a weekly basis. On day 20 the rats were asphyxiated with CO_2, their abdomens were opened, and their uteri were exposed. After a gross necropsy of the dams, the number and distribution of implantation sites, early and late resorptions, live and dead fetuses and corpora lutea were recorded.

Each fetus was weighed, sexed and examined for gross external malformations. Approximately half of each litter was preserved in Bouin's fixative, sectioned and examined microscopically using a variation of the Wilson technique. All findings out of the ordinary were recorded and classified as major or minor malformations or normal variants.

sternebrae, ribs, carpals, metacarpals, tarsals and metatarsals. Fetuses were classified as having delayed skeletal ossification if there were signs of delayed development in at least 2 ossification sites from different anatomical regions.

Statistical analysis (mostly ANOVA and Dunnett's test, along with Kruskal Wallis test) was performed on a number of parameters (maternal body weights, food consumption, number of implantations, number of corpora lutea, litter size, number of total resorptions, mean live fetal body weights, mean male fetal body weights, mean female fetal body weights, number of live males per litter/number of live fetuses per litter, number of fetuses with major malformations, number of minor malformations, and the Arc Sine transformation on proportion of number of fetuses having delayed ossification from each litter).

Results:

There was no mortality among the dams.

Tremors were observed in 18/25 dams receiving 2.0 mg/kg/day of the test material. The earliest tremors were observed on day 10 (4 days after the first dose of test material was administered). Tremors were observed through day 19 (4 days after the last dose was received).

There were no significant differences or dose-related trends between groups with respect to mean maternal body weight gains. Mean weight gains in grams for the different groups are given below (pregnant animals only - from pages 16 and A-1 through A-4):

Group	Wt. change 6-15 days	Range	Wt. Change 0-20 days	Range
Controls	31.7	7 - 49	115.6	48 - 182
0.5 mg/kg/day	29.5	18 - 41	111.3	70 - 140
1.0 mg/kg/day	29.7	13 - 41	113.1	81 - 140
2.0 mg/kg/day	32.9	23 - 42	116.9	87 - 150
Aspirin				

With respect to mean food consumption, there were no significant differences between the groups, nor were there any possible dose-related trends. From table 2 (p. 17) and the individual data on pages A-5 through A-8 (pregnant females only):

Group	Food Consumption (grams)		
	Day 0-6	Day 6-13	Day 13-20
Controls	119.1	127.3	160.2
0.5 mg/kg/day	119.9	127.9	155.2
1.0 mg/kg/day	115.8	119.3	155.6
2.0 mg/kg/day	119.8*	127.3*	158.5*
Aspirin			

*Food consumption was not measured for one pregnant female in the 2.0 mg/kg/day group on day 0. As a result, data from this one animal were not used in the computations for food consumption during subsequent

periods.

There were no statistically significant differences between the groups with respect to pregnancy rates; from p. 13:

Group	No pregnant/total number	Percentage
Vehicle control	24/25	96.0
0.5 mg/kg/day	24/25	96.0
1.0 mg/kg/day	25/25	100.0
2.0 mg/kg/day	23/25	92.0
Positive control	23/25	92.0

There were no possible dose-related trends or statistically significant differences between the vehicle control group and those receiving FMC 54800 with respect to numbers of corpora lutea, implantation sites and resorptions, litter sizes, sex ratios, fetal body weights or viability.

There were a considerable number (certainly statistically significant with respect to the vehicle control group) of early resorptions in the positive control group. There were 7 litters which were completely resorbed, a finding not present in any of the other 4 groups. Fetal body weights were markedly depressed.

No external anomalies were observed in any of the fetuses from the vehicle control group or any of those receiving FMC 54800. There were many in the positive control litters.

There were no major skeletal malformations in any of fetuses examined of the 3 groups receiving FMC 54800. The interparietal was absent in 1/144 fetuses of the control group. There were a few minor malformations (abnormal sternebrae, abnormal thoracic vertebrae, abnormal cervical vertebrae) in the controls and FMC 54800 groups, but there were no dose-related patterns or significant differences. As expected, the incidences of both major and minor skeletal malformations was increased in the positive control litters.

Among visceral anomalies, the incidence of hydroureter in the 2.0 mg/kg/day group was more than double that observed in the vehicle control and lower FMC 54800 dose level groups. The increased (but not at a statistically significant level) incidence was due to the occurrence of 5 cases (in 5 different litters) of hydroureter without hydronephrosis, a combination finding not present in vehicle controls, any of the lower-dose FMC 54800 groups, or in the positive controls. From table 6, p. 23; table 8, p. A-32 through A-35; table 7, p. B-9; and table 15, p. B-22:

Incidences and Percentages of Hydroureter

Dosage group	Hydroureter with Hydronephrosis	Hydronephrosis without hydroureter	Hydroureter without hydronephrosis
vehicle control	3/146 (2.05)	0/146 (0.00)	0/146 (0.00)
0.5 mg/kg/day	2/142 (1.41)	0/142 (0.00)	0/142 (0.00)
1.0 mg/kg/day	3/148 (2.03)	2/148 (1.35)	0/148 (0.00)
2.0 mg/kg/day	2/141 (1.42)	0/141 (0.00)	5/141 (3.55)
Positive control	5/52 (9.61)	2/52 (3.85)	0/52 (0.00)

Discussion:

There are a number of concerns that this reviewer has regarding this study.

There is no justification or rationale given for the specific dosage levels used, which are in a fairly narrow range (0.5 - 2.0 mg/kg/day). The immediate inference is that a pilot or range-finding study was used to determine these dosage levels, but there is no summary or anything within the text of the report referring to the findings of such a study. A possible indication that a pilot study took place is found on page C-1 of appendix C where it is noted that the study number was A83-1091 "Changed from A83-975 (pilot study number) to ensure unique identification of the study notebooks, protocols and reports for both the pilot and the definitive studies."

The highest dose level (2.0 mg/kg/day) produced "intermittent" (otherwise undefined as to frequency or severity) tremors. There were no effects on mean weight gains or any other parameter. As the oral LD_{50} of the test material is 54.5 mg/kg, there is a question as to whether the highest dose level administered in this teratology study was in fact the MTD (maximal tolerated dose) or was reasonably close to it. If a pilot study was conducted, it is possible that its results would shed some light on this question.

The increased incidence of hydroureter in the fetuses of females receiving 2 mg/kg/day, although not statistically significant, is somewhat disturbing, particularly as there were 5 cases (in 5 separate litters) of hydroureter without hydronephrosis, a finding which did not occur in negative controls, the two lower-dose FMC 54800 groups or even in the positive controls. This adds to the uncertainties associated with interpreting this study.

From the information appearing in the report, a NOEL for maternal toxicity can be set at 1 mg/kg/day (LEL = 2 mg/kg/day). The increased incidence of hydroureter without associated hydronephrosis is equivocal, but without further information it is being interpreted as indicating a slight fetotoxic effect at this dosage level, with no teratogenic effect present. The fetotoxic NOEL is then 1 mg/kg/day (LEL = 2 mg/kg/day) and the teratogenic NOEL is 2 mg/kg/day (HDT).

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Data Evaluation Report (IV) 004501

Compound:

TALSTAR™, FMC 54800 Technical

Study type:

Teratology - rabbit

Citation:

Freeman, C., DeProspo, J. R., Nadasky, N., McConnell, R. F., Fletcher, M. J., Malloy, A. V., and Bullock, W. L. Teratology study in rabbits with FMC 54800 technical. Study conducted at the FMC Toxicology Laboratory (Somerville, NJ 08876) under study number A83-1092. Report dated February 24, 1984. Received at EPA 8-15-84; in Acc. 254410.

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Core Classification:

Minimum

Conclusions:

1. At 4.0 mg/kg/day there was head and forelimb twitching in several animals. At 8 mg/kg/day there was head and forelimb twitching and/or tremors in almost all animals; also, two rabbits aborted under circumstances (occurrence of tremors in one, occurrence of tremors and clonic convulsions in the other) indicating treatment-related maternal toxicity. The LEL for maternal toxicity then is 4.0 mg/kg/day, and the NOEL for maternal toxicity is 2.67 mg/kg/day (Doses tested: 0, 2.67, 4, and 8 mg/kg/day).

2. There was no evidence for fetotoxicity and/or teratogenicity at 8.0 mg/kg/day (HDT).

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Materials:

Male and virgin female New Zealand white rabbits, from Davidson's Mill Farm, Jamesburg, NJ. The females were approximately 5 months old.

Test material: FMC 54800 Technical, lot no. E2392-105; FMC-T# 170; purity 88.35%. Composition [redacted]

Positive control: 6-Aminonicotinamide, from Sigma Chemical Co., lot no. 102F-0380.

Procedure:

After one week acclimation, females were placed with males. They were observed until copulation occurred, and this event was considered as defining day 0 of gestation. Mated does were ranked by body weight and placed in 5 groups until each group contained 20 rabbits. On days 7-19 of gestation each member of four of these groups received, via stomach tube, either 1 ml/kg of corn oil alone (negative or vehicle control), or FMC 54800 at 2.67, 4.0 or 8.0 mg/kg in corn oil at a constant dosage volume of 1 ml/kg. The fifth group served as positive control; each doe received 3.0 mg/kg/day of 6-Aminonicotinamide in 2% carboxymethylcellulose solution, administered via IP injection. Doses were administered between 9 A.M. and 12 P.M.

Rabbits were observed for mortality and symptoms twice daily, except for days 0 and 29 when they were observed only once. Individual body weights were recorded on days 0, days 7 through 19, 21, 28 and 29. Body weights were also recorded at necropsy for all animals which died or were sacrificed prior to study termination. Individual food consumption was not recorded on a quantitative basis; however, the animals were observed, and when anorexia occurred it was noted.

Necropsies were performed immediately upon discovery of death or at sacrifice for animals which did not survive to final sacrifice. "Uterine contents and any abnormalities recorded." Selected tissues were preserved when it seemed appropriate.

On day 29 of gestation does were sacrificed by CO_2 asphyxiation, the abdomen was opened, and the uterus was exposed. After examination of the females for gross lesions, the numbers and distribution of implantation sites, early and late resorptions, live and dead fetuses and corpora lutea were recorded. The heart, lungs, liver and kidneys were saved from all the does.

"Each fetus was weighed, numbered, tagged and examined for gross external malformations." The brain, thoracic and abdominal viscera of each fetus were subsequently examined on the same day using a variation of the method of Staples. During this examination, the sex of each fetus was determined.

All fetuses were stained with Alizarin Red-S, cleared and observed for skeletal variations. Abnormalities were classified as major malformations, minor malformations, variations or indicators of delayed ossification. A fetus was considered as having delayed ossification if delayed development was present at ossification sites from 2 or more different anatomical regions.

All skeletal specimens were stored in glycerin/alcohol and saved.

A number of statistical tests (principally ANOVA & Dunnett's Test, and Kruskal-Wallis Test) were performed on the data.

Results:

Ten rabbits died during the study, of which 9 deaths were considered to be due to Pasteurella multocida. One rabbit receiving 4 mg/kg/day FMC 54800 died on day 10 from unknown causes. The following (from p. 13, A-5 through A-18, and B-7 through B-8) gives the number and dates of mortalities which occurred in each group:

Dosage	Incidence of Death	Dates Death(s) Occurred
0 mg/kg/day	3/20	13, 14, 19
2.67 mg/kg/day FMC 54800	2/20	14, 22
4.0 mg/kg/day FMC 54800	1/20	23
8.0 mg/kg/day FMC 54800	4/20	10, 19, 22, 22
3.0 mg/kg/day 6-Aminonicotinamide	4/20	21, 23, 26, 27

Some of the rabbits which were sacrificed on day 29 had varying degrees of lung damage "indicative of" (suggesting?) Pasteurella multocida infection. Animals showing no signs of infection (at termination) were distributed as follows (from p. 14):

Dosage level	Showing no signs of Pasteurella multocida
0 mg/kg/day	15
2.67 mg/kg/day FMC 54800	13
4.0 mg/kg/day FMC 54800	15
8.0 mg/kg/day FMC 54800	14

The identification numbers of the individual animals with lung damage are given in Table 5 (individual necropsy results) of Appendix A, p. A-24 through A-26. There were no necropsy findings that be attributed to exposure to the test material.

Symptoms - the only symptoms which occurred in a dose-related pattern were head and forelimb twitching, and tremors. The following incidences are derived from Appendix A, Table 2 (p. A-5 through A-18):

Dosage level	Number of rabbits with tremors	Number of rabbits with head and forelimb twitching
0 mg/kg/day	0/20	0/20
2.67 mg/kg/day FMC 54800	0/20	0/20
4.0 mg/kg/day FMC 54800	0/20	4/20
8.0 mg/kg/day FMC 54800	17/20	14/20

19/20 of the rabbits in the 8 mg/kg/day FMC 54800 group showed either tremors or head and forelimb twitching during the study; the only animal in this group that showed neither of these symptoms was B1962F, which was dead on day 10, before these symptoms had occurred in many of the other animals in this group.

Body weights - the mean maternal body weights and body weight changes, as reported (Table 1, p. 17) for any one date, are derived from data from all animals which were pregnant, including those which died later during the study and those which were found to have possible P. multocida infection after terminal sacrifice. The mean body weights (in kg), as presented, are given below (from p. 17) with body weight changes (in kg) as given on p. A-1 through A-4:

Dosage level	Day 0	Day 7	Day 19	Day 29	Change Days 7-19	Change Days 0-29
0	3.66	3.86	3.91	4.02	0.05	0.36
2.67 mg/kg/day FMC 54800	3.70	3.82	3.78	3.95	-0.04	0.25
4.0 mg/kg/day FMC 54800	3.65	3.80	3.90	3.94	0.10	0.29
8.0 mg/kg/day FMC 54800	3.67	3.87	3.83	4.14	-0.04	0.47

It is reported (p. 13) that animals in the 2.67 mg/kg/day group exhibited a significant decrease in body weight gain in the interval from day 0 to day 7; the test material was not administered until day 9. Rabbits in the 4 mg/kg/day group had a significantly decreased body weight gain between days 21 and 28. "Body weight means for the four groups differed significantly ($p<0.05$) for the interval day 21-28 and for day 0-29 using the Kruskal-Wallis Test."

Recalculating the means from individual weight data (from pages A-1 through A-4) to exclude animals which died during the course of the study and those found to symptoms of P. multocida infection at necropsy following terminal sacrifice gives the following (in kg):

Dosage level	Day 0	Day 7	Day 19	Day 29	Change Days 7-19	Change Days 0-29
0	3.61	3.82	3.94	4.07	0.12	0.46
2.67 mg/kg/day FMC 54800	3.71	3.83	3.83	4.02	0.00	0.31
4.0 mg/kg/day FMC 54800	3.67	3.81	3.92	4.00	0.11	0.33
8.0 mg/kg/day FMC 54800	3.60	3.83	3.92	4.14	0.09	0.54

The recalculated values for mean body weights appear fairly similar for all groups.

The following group pregnancy rates were recorded (see p. 14 and p. B-1):

Dosage level	Total no. animals	Number Pregnant	Percentage Pregnancy
0	20	20	100%
2.67 mg/kg/day FMC 54800	20	19	95%
4.0 mg/kg/day FMC 54800	20	19	95%
8.0 mg/kg/day FMC 54800	20	20	100%
3.0 mg/kg/day 6-Aminonicotinamide	20	19	95%

The following summary is from Table 3, p. 19:

Dosage level	Litters Examined	Total Live Fetuses	Mean Live fetal body weight	% Males
0	17	149	35.8	54.4
2.67 mg/kg/day FMC 54800	16	116	36.8	59.5
4.0 mg/kg/day FMC 54800	17	130	36.4	53.1*
8.0 mg/kg/day FMC 54800	14	131	38.8	50.4
3.0 mg/kg/day 6-Aminonicotinamide	15	90	35.9	60.0

*sex not recorded for one fetus in the 4 mg/kg/day group; % males for this group assumes this fetus was a female.

The number of dead and resorbed fetuses in each group was as follows (from p. A-19 through A-22 and p. B-9):

Dosage level	Total no. implantations	No. of dead fetuses	No. resorbed fetuses
0	165	0	16
2.67 mg/kg/day FMC 54800	130	0	14
4.0 mg/kg/day FMC 54800	149	11*	7
8.0 mg/kg/day FMC 54800	134	0	3
3.0 mg/kg/day 6-Aminonicotinamide	130	9	31

*Stated (p. 15) that 11 fetuses were dead at cesarean section, probably due to an overdose of CO_2 at maternal sacrifice.

Skeletal anomalies: there were no major skeletal malformations in the negative control group or those receiving FMC 54800. There was no indication of any dose-related response in either the minor malformations (refer to p. 20) or indicators of delayed skeletal ossification (p. 21). Among variations (p. 22) there appeared to be a negative correlation for absence of or partial ossification of sternebrae 5 and dosage level of FMC 54800:

	Sternebrae 5 absent or partially ossified	
Dosage level	Litter incidence and %	Fetal incidence and %
0	15/17 (88.2)	66/148†(44.6)
2.67 mg/kg/day FMC 54800	10/15 (66.7)	40/116 (34.5)
4.0 mg/kg/day FMC 54800	13/16 (81.3)	40/141 (28.4)
8.0 mg/kg/day FMC 54800	10/14 (71.4)	22/131 (16.8)
3.0 mg/kg/day 6-Aminonicotinamide	15/15 (100.0)	76/99 (76.8)

† not explained why this number is 148, when supposedly 149 were evaluated.

There were no major or minor external or visceral fetal abnormalities observed in either the vehicle control or any of the FMC 54800 groups (refer to p. 15). Among the positive controls 11/99 fetuses had cleft palate, 2/99 had forelimb rotation, 5/99 had hindlimb rotation, 1/99 had micrognathia, and 1/99 had hydrocephalus (refer to Table 4, p. B-4).

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For the total number of minor malformations (including external, visceral and skeletal) the groups receiving FMC 54800 showed a lower incidence of these findings than controls (refer to p. 23):

	Minor malformations	
Dosage level	Litter incidence and %	Fetal incidence and %
0	10/17 (58.8)	20/149 (13.4)
2.67 mg/kg/day FMC 54800	5/15 (33.3)	5/116 (4.3)
4.0 mg/kg/day FMC 54800	4/16 (25.0)	4/141 (2.8)*
8.0 mg/kg/day FMC 54800	3/14 (21.4)	7/131 (5.3)

*significantly different from the control value.

The listing above is essentially for minor skeletal malformations, as there were no external or visceral malformations in any of these groups.

Discussion:

There is no evidence in this study for any teratogenic or fetotoxic effects related to administration of the test material at maternal dosage levels of up to 8 mg/kg/day (HDT).

Although it is not certain that the highest dose tested (8 mg/kg/day) was a maximal tolerated dose, the occurrence of clonic convulsions and abortion in one of the rabbits at this dosage level suggests this value is sufficiently close to the MTD for this type of study. The occurrence of head and forelimb twitching in some animals at 4.0 mg/kg/day indicates that this level is the LEL for maternal toxicity, which then means that 2.67 mg/kg/day is the NOEL.

Overall, the study is acceptable as core minimum data.

Data Evaluation Report (V)

Compound:

TALSTAR™, FMC 54800 Technical

Study types:

Oral LD_{50} - chicken
Neurotoxicity - chicken

Citation:

Roberts, N. L., Hakin, B., Chirukandath, G., and Rao, R. S. The acute oral toxicity (LD50) and neurotoxic effects of FMC 54800 technical to the domestic hen. Study conducted at the Huntingdon Research Center, Huntingdon, Cambridgeshire, England. FMC study number A83-1081. Report dated 17 February 1984, with re-issue dates of 14 May 1984 and 10 July 1984. Received at EPA 8-15-84; in Acc. 254405.

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6-4-85

Core Classification:

Acute oral LD_{50} (chicken): Minimum
Neurotoxicity (chicken): Supplementary

Conclusions:

1. The oral LD_{50} study is acceptable. The high oral LD_{50} value (above 5000 mg/kg) is remarkable, as the same material was found previously to have a rat oral LD_{50} value of about 55 mg/kg.

2. While no histological evidence was found for delayed neurotoxicity, the hens showed a considerably more severe response following the second dosage of test material. Also, no nervous tissue was examined from the hens which died in the days immediately following the second dosage. For these reasons, the neurotoxicity study is considered as inconclusive.

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Acute oral LD_{50} - hen:

Materials:

Adult female domestic hens (Gallus gallus domesticus) from Graygable Poultry Service, Bury St. Edmunds, Suffolk.

Test material: FMC 54800 Technical, lot no. E2392-105; purity 88.3%. [redacted]

Procedure:

Groups of 10 birds were orally dosed with vehicle (corn oil) only, 1250, 2500 or 5000 mg/kg FMC 54800 in a constant dose volume of 12.5 ml/kg. There was a subsequent 14-day observation period. There were no gross necropsies.

Results:

The following mortality table is derived from the information on p. 20-21:

Dosage Level	Mortalities (all causes)
0 (vehicle control)	0/10
1250 mg/kg FMC 54800	2/10
2500 mg/kg FMC 54800	1/10
5000 mg/kg FMC 54800	0/10

No signs of toxicity were evident within 5 hrs of dosage. After 21 hrs one bird in the 1250 mg/kg group, 2 at 2500 mg/kg, and 3 at 5000 mg/kg displayed symptoms, which included unsteadiness or inability to walk, "wing-dropping" and twitching of the head and neck. An additional hen in the 5000 mg/kg group showed symptoms a few hours later. Severity of symptoms was correlated with dosage level. Several of the birds with symptoms were "bullied" by their cagemates. One bird in the 1250 mg/kg group was sacrificed as a result because it was in poor condition, while one in the 2500 mg/kg group died. Symptoms were diminishing by 48 hrs after dosage, and by the end of day 3 the birds were quiet and "appeared to have recovered."

An additional hen in the 1250 mg/kg which had been pecked and bullied was found dead on day 12.

The acute oral LD_{50} of the test material in hens is greater than 5000 mg/kg.

Discussion:

The study adequately defines the acute oral toxicity (>5000 mg/kg) of the test material in hens. It is remarkable that this material is much more toxic in the mammalian species in which it has been tested (the rat oral LD_{50} is about 55 mg/kg).

Neurotoxicity - hen:

Adult female domestic hens (Gallus gallus domesticus), approximately one year old, from Graygable Poultry Service, Bury St. Edmunds, Suffolk.

Test material: FMC 54800 Technical, lot no. E2392-105; purity 88.3%.

[redacted]

Positive control: tri-ortho-cresyl phosphate (TOCP), supplied by the Coalite Group Ltd.; labeled Ref. no. S16848.

Procedure:

Following an acclimation period of several weeks, groups of 10 birds were treated either with corn oil only (vehicle control group), 500 mg/kg of TOCP, or (2 groups) 5000 mg/kg of FMC 54800. Corn oil was the vehicle for TOCP and FMC 54800, and all birds were dosed at constant volumes of 12.5 ml/kg.

The birds were examined daily for signs of ataxia, which, when it occurred, was supposedly scored using a point system with a scale ranging from 0 to 8 (see p. 19 and 41). However, scores are given only for TOCP-treated hens (p. 12).

Individual body weights and food consumption were recorded twice weekly during the study.

Since only one hen in the positive control group showed ataxia on day 21, this bird was sacrificed, and it was decided to redose the remaining 9 birds in this group, and to dose an additional 10 hens with TOCP at 500 mg/kg, but at a reduced volume (20% w/v) in corn oil. These animals were observed for 22 days. As the TOCP re-dosed birds developed classical delayed neurotoxicity symptoms, the second group of TOCP-treated hens was discarded. The surviving hens which had been previously treated with FMC 54800 at 5000 mg/kg received another 5000 mg/kg dose of this material.

"Macroscopic post mortem examinations were carried out on all birds that died sporadically during the study and on all birds surviving until termination on Day 43. Because of the number of birds involved, the terminal sacrifice took place over three days following termination."

Tissues were taken from 6 birds of the vehicle control group, 10 birds of the (first) TOCP-treated group, 5 birds of the first FMC 54800 group receiving 5000 mg/kg, and 5 birds of the second 5000 mg/kg FMC 54800 group. The processing involved fixative perfusion through the heart, after which the head, spinal column and sciatic nerves of each of these birds was stored in 10% neutral formalin.-

"The following samples were taken for histological examination:"

Brain	- medulla/pons, cerebellar cortex and cerebral cortex.
Spinal cord	- multiple longitudinal and cross sections of the cervical, thoracic and lumbar-sacral regions.
Peripheral nerve	- proximal and distal sciatic nerve and tibial nerve (distal branch)

Samples were processed and embedded in wax. Histological sections were cut at 8 um thickness and stained with hemotoxylin and eosin. Additional sections were stained for axons and myelin.

Results:

Mortality (all causes):

	Number of hens dying:			
Treatment group	Between days 0-3	Between days 3-21	Between days 21-24	Between days 24-43
Corn oil	0	2	1	0
500 mg/kg TOCP	0	2	0	0
5000 mg/kg FMC 54800	0	0	1	0
5000 mg/kg FMC 54800	0	1	0	3

Some of the mortalities, particularly those occurring before day 21, are reported as due to "bullying."

For the hens receiving FMC 54800, clinical symptoms (unsteadiness) were observed in some within 20 hrs of receiving the first dose, and subsequently all were making jerking head movements. By the end of day 3 most had recovered.

Symptoms in the hens receiving the FMC 54800 were more severe following the second dose at 21 days. There were "violent movements of the head and legs" and 11/18 hens were unable to stand. However, by day 28 those hens which had survived appeared to have recovered.

Although ataxia was supposedly scored (and the scoring system is given on p. 19 and 41) there is no reporting of either mean or individual scores for hens treated with FMC 54800.

There was a considerable drop in mean body weight in the period following the second dosage, greater than that which had occurred following the first dose:

	Mean body weight (g)					
Treatment group	Day 0	Day 3	Change	Day 21	Day 24	Change
Corn oil	2143	2309	+166	2183	2196	+ 13
500 mg/kg TOCP	2189	2292	+103	2221	2209	- 12
5000 mg/kg FMC 54800	2330	2321	- 9	2274	2064	-210
5000 mg/kg FMC 54800	2139	2116	- 23	2276	1976	-300

In the two groups receiving FMC 54800 there was a considerable drop in mean food consumption in the periods from day 22 to 24 and from day 25 to 28, with subsequent recovery. From Table 6, p. 17:

	Mean food consumption (g/bird/day)					
Treatment group	Day -4 to -1	Day 1 to 3	Day 18 to 21	Day 22 to 24	Day 25 to 28	Day 29 to 31
Corn oil	173	177	103	86	143	152
500 mg/kg TOCP	118	120	89	67	109	117
5000 mg/kg FMC 54800	145	87	108	26	67	107
5000 mg/kg FMC 54800	140	83	153	22	53	139

There were no findings on gross necropsy, either in animals which died during the study or which were sacrificed at termination, that could be ascribed to FMC 54800.

In the examination of the nervous tissues, small numbers of degenerating axons in both the spinal cords and sciatic nerves were observed in vehicle control hens and those treated with FMC 54800, with a maximum neuropathology grade of II (From p. 27: "Disruption or fragmentation of occasional axons. Myelin abnormalities are rare. In general, on any slide of the spinal cord (two longitudinal and one transverse sections), the numbers of altered/degenerate fibres detected varied from one to approximately four. On a slide of peripheral nerve, one or two degenerate fibres were included in this grade). By contrast, positive controls showed "significant axonal degeneration related to treatment with TOCP." These symptoms "correlate with clinical observations of ataxia." In positive control hens grades of III and IV were common, the latter involving "disruption, fragmentation and distortion of many axons." The maximum score on the neuropathology grading system used is V.

Discussion:

It is disturbing that the response following the second dose of FMC 54800 was considerably more severe than that following the first. This greater severity was evident in several respects (symptoms were more pronounced, there was a greater mean weight loss, and there was a more drastic drop in mean food consumption). It is uncertain whether this might have been due to cumulative toxicity (which includes the possibility of some sort of delayed neurotoxicity, although not the classical form involving phosphorylation of neurotoxic target esterase) or whether other factors (such as more rapid absorption of the test material in the intestine) might have been involved.

While no histological evidence for delayed neurotoxicity was found as a result of oral administration of FMC 54800, there was no examination of nervous tissues from the three hens in which symptoms had been most pronounced (and which had died) following the second dose.

Because of these uncertainties, the test is classified as supplementary. However, it is noted that the test compound is not an organophosphate, and classic delayed neurotoxicity (involving phosphorylation of neurotoxic target esterase) is not expected.