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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: December 22, 1982

TO: Robert Taylor, PM 25
Registration Division (TS-767)

THRU: Christine F. Chaisson, Ph.D.
Head Section IV, Toxicology Branch (TS-769)

Charles Lansdown for CFC 3/1/83

SUBJECT: Review of 28 Day Feeding Studies of FMC 57020 in the Dog, the Rat, and the Mouse. Interim Reports on 90-Day Mouse and Rat Studies. CAS# 463b

Request for Waiver of the 90-day Dog Subchronic Study

Introduction

FMC has previously submitted an EUP on soybeans (crop destruct).

Preliminary dose-range finding studies have been submitted by the registrant FMC and are reviewed herein.

Dr. John Lauber of FMC has sent a request on November 16, 1982 for a waiver for a separate 90-day subchronic dog study. On Decmeber 17, 1982, Drs. John Lauber and Michael Norvell of FMC met with Drs. Holder and Chaisson of Toxicology Branch and yourself from RD. The possibility of the waiver was discussed. It was explained to FMC representatives that Tox necessarily has to review such data that allow establishment of a provisional NOEL when consideration of an EUP involving finite residues in food are possible.

Conclusions

1. In the 28-day study on dogs there was no demonstrable effect of toxicological consequence at doses as high as 125 mg. a.i./kg (5000 ppm in the feed).

   Doses higher than 5000 ppm of FMC 57020 proved to be not palatable to Beagle dogs.

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2. In the 28-day study in the Sprague Dawley Rat, increased absolute and relative liver weights were noted at 400 mg/kg in females and 800 mg/kg in males, or higher. Gross pathologic discolorations were noted in livers at 400 mg/kg, or higher, as well as liver enlargement.

3. The 28-day mouse study apparently showed an increased liver weight which apparently became significant at 1200 mg/kg.

   This preliminary study was remiss in a number of experimental points, e.g., no gross pathology or clinical chemistries reported.

4. The interim 90-day studies that were reported were quite preliminary in nature and in reporting. The mouse 90-day was classified as INVALID because liver data did not agree with tabulated summary data. No experimental detail was given in the 90-day rat study. A suggestion of a NOEL of 100 mg/kg (2000 ppm) was made in this experiment, but the report was so preliminary that it was classified as Supplemental.

5. The reporting and nature of the data of the 28-day and interim 90-day studies reported here were such that little regulatory use can be made of these studies at this time.

Recommendation

TOX recommends the request for waiver of the 90-day subchronic dog feeding study be denied.

This recommendation is based on conclusion 5. The reduction of statistical certainty down to the FMC-proposed 2 dogs/sex/dose group* and the present data base on FMC 57020 indicate to TOX Branch that FMC 57020 should not be considered for a reduction in registration requirements at this time.

TOX reiterates the point that favorable action for a food EUP would require that both a rodent and a non-rodent 90-day study be submitted and that a provisional NOEL and LEL from the studies could, in fact, be established from these studies.

More data from FMC is necessary before any abbreviation of data requirements can be considered.

*OECD guidelines proposed four and 1978 EPA Guidelines proposed six non-rodent animals.

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28-Day Oral Range-Finding Study in Dogs
(FMC Study No. A82-758)

Beagle dogs (4-6 months old at start of study September, 1982) were evaluated by Hazelton-Raltech for toxicity in a 28-day study. Oral ingestion in dog chow was at 0, 100, 1000, 5000, and 10,000 ppm. The high dose was dropped after one week to 2,500 ppm becasue of palatability. Body weights at 10,000 ppm were down 10% and the dogs vomited what food they did ingest. Two of four-dogs (2M and 2F/dose group) would not eat and lost weight in the 5000 ppm group. At week two, 2% corn oil was placed in the feed/FMC 57020 mixture to enhance acceptability of FMC 57020. Weight gains and food consumption were normal and comparable for the remainder of experiment. Thus, the dose groups were ("lowered" dose group was time-weighted to get effective dose):

Group:	1	2	3	4	5
mg a.i./kg. b.w.	0	2.5	25	109.4	125

Liver organ to body weights showed an "apparent" increase in males:

1	2	3	4	5
3.1615	3.3131	3.8670	4.0185	4.3541

However, statistical analysis of covariance showed the F-value equal to 0.5726 where significance at the 0.05 level the F-value would have to be 6.34 (communication with biostatistician, B. Litt). The registrant (FMC) submitted a "t" test which said the high dose was not equal to control at p 0.07. This "apparent" increase was not significant at the 0.05 level. Although the apparent increase in relative liver weights is not statistically significant at 28 days, the effects on liver could be more pronounced (and therefore statistically significant) at longer times such as subchronic (90 days) or chronic (2 yrs.) feeding of FMC 57020 to dogs.

The only other organ weight alteration was a relative decrease in the heart/b.w. at 25 mg/kg in the bitches. All other dose groups (male or female) showed no heart weight changes.

Clinical chemistry: no electrolyte changes other than male BUN values:

Grp.	1	2	3	4	5
BUN	64	55	51	49	40

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Since these values show as apparent BUN decrease with dose, the effect is not considered biologically significant. There were no liver enzyme increases, e.g., SGOT and SGPT, that might correlate with increased liver weight (see above discussion).

Other clinical chemistry values were normal. Cell count data were normal and not affected by FMC 57020.

No histopathology was done in this 28-day dose-range finding dog study.

No significant toxicological effect was manifest in this 28-day study and no provisional NOEL was established.

Study Classification: Core Mimimum

28-Day Range-Finding Study in the Rat
(Toxigenetics Study 410-0743; FMC Study A81-611

In the Sprague Dawley rat, 87.9% a.i. FMC 57020 was tested orally at levels of 0, 100, 200, 400, 800, 1200, and 2500 mg/kg b.w. with 10 of each sex per dose group. In males at 800 mg/kg food consumption was decreased as were weight gains and body weights. In females at the same level food consumption and weight gains were decreased. At the next level down at 400 mg/kg none of these effects were noted. Mortality was not affected in either sex until 2500 mg/kg where male mortality was 3/10 and female mortality was 3/10 also.

The liver weights (absolute and relative) seemed to show a dose-related increase, moreover liver weights at doses of 800 mg/kg (or higher) were significantly increased ($p < .05$) compared to untreated controls. Females showed increased liver weights at $\geq$ 400 mg/kg. Increased brain weights (absolute and relative) were seen in both sexes at the high dose, 2500 mg/kg. Also, at the high dose increased weights of gonads, kidneys, and adrenals were observed ($p \leq .05$).

Clinical chemistry results in males show a significant ($p < .05$) increase at the high dose in BUN and SGPT values along with an apparent increase in SGOT. Females also show these liver enzymes increases, but did not show the BUN elevation. These results could correlate with increased liver weights.

Gross pathology at the high dose group showed discolorations, depressions in the glandular stomach. The urinary bladder of one rat had bloody urine. Hepatic changes such as discoloration and enlargement were observed in 17 rats from the 4 highest dose groups:

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Dose	Occurrence in liver
400 mg/kg	2M
800 mg/kg	4M
1200 mg/kg	6M, 2F
2500 mg/kg	3M

Toxigenics relates these liver gross pathologic findings to compound administration of FMC 57020. Tox Branch agrees and concludes the liver stress should be looked at further in 90-day and 2-year chronic feeding studies on FMC 57020.

Study Classification: Core Minimum.

28-Day Mouse Oral Range-Finding Study in Mice
(Report number not given)

The analytical purity of FMC 57020 was not reported. FMC does not report who did this mouse study, how many mice/group, or any conditions of the animal husbandry. Summary Tables are submitted by FMC showing doses to have been:

mg/kg:	0	300	600	1,200	2,400	3,600	7,500
ppm:	0	2,000	4,000	8,000	16,000	24,000	50,000

Body weights and weight gains in this 28-day feeding study were depressed in both male and female mice.

Liver weights were increased in what appears to be dose-response manners in both males and females. The difference between control and treated groups became significant (at $p < .05$) at 1200 mg/kg for males and females. Brain weights were decreased ($p < .05$) in the high dose group. No other organ weights showed significant changes.

Unlike with the rat study, no clinical chemistry on mice was given.

No gross pathology results were presented on mice.

Classification of Study: Invalid.

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Interim Reports of Mouse and Rat
Subchronic 90-Day Feeding Studies

Mouse - 90-Day - Interim Report

No experimental detail was given in this feeding study reported.

No gross pathology was submitted nor was any clinical chemistry reported.

Summary organ weights (absolute and relative) for brain, testes, ovaries, heart, kidney, and liver were submitted.

It would "appear" that doses equal to or higher than 400 ppm (600 mg. a.i./kg) in the mouse produced increased liver weights. However, the data in the Summary Table on liver do not agree with liver data in the following table for males or for females. Tox is unable to resolve this discrepency.

Classification of Study: Invalid

Rat - 90-Day - Interim Report

No experimental detail was given in this 90-day rat feeding study.

Doses of 400 ppm (200 mg/kg) or higher appeared to cause increased absolute and relative liver weight increases (both M and F).

No gross pathology was reported.

Clinical Chemistries were reported.

Notable changes were seen in the following:

Test	Males	Females
Platlet Count	+ 500 ppm	NC
	+ 4000 ppm	NC
	+ 8000 ppm	NC
Gamma-glutamyl Transpeptidase (GGT)	+ 8000 ppm	NC
Total Cholestrol	+ 8000 ppm	+ 1000 ppm
		+ 4000 ppm
		+ 8000 ppm
All Other Cell and Blood Chemistry Tests	NC	NC

NC - No change.

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The GGT is a liver enzyme which indicates stress or injury to the liver when released into the blood. The increase in GGT at 8000 ppm correlates with increased liver weights at this high dose level. The 4000 ppm did not produce increased GGT, but may do so at dosage times longer than 90-days. These preliminary results suggest that the subchronic NOEL could be 100 mg/kg (2000 ppm) and LEL could be 200 mg/kg (4000 ppm). However, these levels should set from the complete 90-day rat report.

Study Classification: Supplementary.

J. W. Holder 1/7/83

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