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BIFENTHRIN

RESPONSE TO U.S. EPA TOXICOLOGY BRANCH

REVIEWS OF RAT CHRONIC/ONCOGENICITY AND MOUSE ONCOGENICITY STUDIES

CONDUCTED WITH BIFENTHRIN

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I. Introduction

FMC Corporation's Toxicology Department has received and reviewed a copy of a letter from G. T. LaRocca (EPA) to E. M. Cuirle (FMC) concerning U.S. EPA Toxicology Branch reviews of long term rodent feeding studies conducted with bifenthrin (FMC 54800).

We have studied these reviews and have comments to make on statements made in the reviews of the mouse oncogenicity study (FMC Study Number A83-974; EPA Accession Numbers 261948 through 261955) and the rat chronic toxicity/oncogenicity study (FMC Study Number A83-952; EPA Accession Numbers 261940 through 261942, and 261944 through 261947). We have no comments on the review of the reproduction study (FMC Study Number A83-977; EPA Accession Numbers 261933 through 261935, and 261937 through 261939).

It should be noted that the bifenthrin studies represent the first chronic program which was conducted at the FMC Toxicology Laboratory in Somerville, NJ. Final report preparation is now in progress on a second set of chronic rodent studies (including a rat chronic toxicity/oncogenicity study and a mouse oncogenicity study) conducted at the same laboratory and with animals from the same supplier. A draft of the histopathology report for the second rat chronic/oncogenicity study has recently become available (FMC Study Number A84-1287) and relevant results are cited in this document. Histopathology on the second rat study was conducted at Hazleton Laboratories America, Inc. by Richard W. Voelker, D.V.M., Ph.D. We anticipate that the pathology report for the mouse oncogenicity study will become available about January of 1987. The attached discussion represents FMC's position based on the currently available data but this may be subject to revision when additional historical control data become available. FMC notes that EPA has requested historical control data for both the mouse and rat oncogenicity studies and we will provide additional historical control data from our laboratory to the Agency when it becomes available (anticipated in January, 1987). FMC believes that final assignments as to which tumors are compound-related, and the categorization of the oncogenic potential of bifenthrin to man, should await the availability of these additional historical control data.

Some confusion arose in both the rat and mouse oncogenicity study reviews pertaining to "sentinel animals" which were used for microbial and viral screening. Terminology used in the FMC reports indicated that these screens were performed at each study quarter. Since these were two year studies, a study quarter represents 6 months rather than 3 months, and a total of 12 animals per sex were used for this purpose.

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II. Product Information

Bifenthrin (FMC 54800) insecticide/miticide represents substantial progress in providing agricultural producers with new pyrethroid chemistry. Bifenthrin controls a broader spectrum of insect pests when compared to currently registered pyrethroids, as well as difficult to control mite species at rates of 0.02 to 0.1 lb ai/acre. These rates are far below (generally one-tenth) those of established miticides and will dramatically reduce the quantity of pesticide introduced into the environment. Due to the broad spectrum control capabilities of bifenthrin many tank-mix combinations of miticides and insecticides will become unnecessary, further reducing pesticide levels available to the environment. In addition to the excellent efficacious properties of bifenthrin, commercial use under existing temporary tolerance programs and through the Federal registered use on greenhouse grown ornamentals, bifenthrin has shown longer residual control when compared to existing products. Longer residual control on particularly difficult to control aphid and whitefly pests affords growers the opportunity to apply fewer applications over the course of their production season. These features provide a realistic approach to improved overall pest control and allow us to accomplish a basic goal of reducing the quantity of pesticide exposure.

Environmental safety represents a significant concern of the public and bifenthrin has shown exceptional safety to avian and terrestrial animal species. Bifenthrin is not dermally toxic to animals and is considered virtually non-toxic to birds. Under field studies and residual cage studies bifenthrin has also been found to represent a nil to low hazard to honeybees when applied at recommended use rates. Although bifenthrin is toxic to aquatic organisms as are other pyrethroids, the extremely low water solubility and high affinity to soil and suspended organic matter contribute to the reduced availability in aquatic systems. These properties also ensure bifenthrin will not leach through soil and pose a threat to groundwater.

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The EPA Review of this study arrived at conclusions which differed from FMC's conclusions concerning the interpretation of liver tumors in male mice and lung tumors in female mice. The following comments discuss these areas of disagreement.

1. EPA Position: "It is tentatively concluded that the increased incidences (38-52%) of pulmonary tumors in females receiving FMC 54800 (as compared to 28% in controls) were compound-related." (Page DER I-2)

FMC Position: "The incidence of combined bronchiolar-alveolar adenocarcinomas and adenomas in the lungs of female mice (Table A) demonstrated that Groups II, III and V were significantly higher than the control group ($p=0.012$, $p=0.048$, and $p=0.041$ for Groups II, III and V respectively) as judged by pairwise comparisons using Fisher's exact test. However, time-to-tumor tests for positive trend and heterogeneity indicated that there was no significant trend and that the incidence rates are not significantly different between groups. This reinforces the pathologist's conclusion that the observed incidence pattern was not compound related." (Page 21 of FMC Study Number A83-974)

Time-to-tumor tests for positive trend and heterogeneity indicated no significant positive dose-related trend in the incidence of lung tumors in female mice and no statistically significant differences in incidence rates between groups. Pairwise comparisons by Fisher's Exact test revealed differences between the control group and Groups II, III, and V, but not Group IV.

Despite results of these statistical analyses, and based on a comparison with permethrin, the Reviewer suggests the possibility of a treatment-related effect. Firstly, FMC believes that comparison with permethrin is inappropriate (see point 3 below). Secondly, as the Reviewer points out, the data demonstrate "lack of a pronounced dose-trend ..." (page DER I-17). The lack of a trend (and no trend is evident from this data) may simply reflect the absence of a treatment-related effect. Very likely is the possibility of a low value in the control group for this study. An initial EPA review of the FMC 54800 female mouse lung tumor incidence data opined that "the 'statistically significant' increased incidence of combined adenomas/carcinomas

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of the lungs of female mice is probably the result of a lower than normal number of occurrences in controls, particularly as no dose-related trend is evident, and incidences in exposed females are essentially the same as those in males." (GT LaRocca, 1986). This previous review also indicates the need for historical control data. Lung tumor incidences of up to 57% have been reported in the open literature for female Swiss Webster mice (refer to FMC submission of historical control data to EPA, 5/86). The most relevant historical control data are for Swiss-Webster mice from our laboratory; as previously mentioned, these data may aid greatly with regard to elucidating the significance of the tumor incidences observed in this study.

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2. EPA Position: "It is tentatively concluded that the dose-related trend (with p=0.025) of increased incidence of combined adenocarcinomas and adenomas in the liver of male mice (2/49, 2/50, 4/50, 4/50, and 7/49 at 0, 50, 200, 500 and 600 ppm respectively) is directly related to exposure to FMC 54800, even in the absence of apparent preneoplastic changes." (Page DER I-2)

FMC Position: "The combined incidence of adenomas and adenocarcinomas in male livers (Table A) shows that none of the treatment groups are significantly different than the control group as judged by pairwise comparisons to the control group using Fisher's exact test. Time-to-tumor tests show a significant positive trend (p=0.022) in conjunction with a non-significant (p=0.354) test for heterogeneity. The statistical tests recognize the trend in the data which is evident upon inspection, but do not identify any group as being significantly different than the control. The study pathologist has concluded for biological reasons that hepatocellular neoplasms were unlikely to have been treatment induced." (Page 22 of FMC Study Number A83-974)

Time-to-tumor analyses of liver tumor incidence data in male mice in the FMC 54800 study demonstrated a statistically significant positive trend in conjunction with a non-significant test for heterogeneity (thus indicating no significant difference between groups). Likewise, analysis of the liver tumor incidence data using the Cochran-Armitage trend test (as employed by NTP) yields a similar probability for a positive linear trend ($0.025 < p < 0.05$), though inclusion for continuity correction yields a non-significant test for trend ($0.05 < p < 0.10$). Pairwise comparison of treatment groups with the control using Fisher's Exact test indicated no significant differences. Importantly, no pre-neoplastic lesions were observed in treated animals. The Reviewer (tentatively) concludes that these data may represent an effect primarily because "There were some possible indications, although nothing conclusive, of a similar effect in at least one oncogenicity study with permethrin" (DER I-18). FMC considers that 1) the incidence data of the FMC 54800 study do not demonstrate convincing evidence of a neoplastic effect on the liver (non-significant differences between treated groups and control), and 2) comparison with the permethrin data base is neither appropriate (see point 3 below) nor convincing (liver tumors were found in one of three studies only, and were found in female mice, not male mice).

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3. EPA Position: Regarding interpretation of the liver and lung tumor incidence data of the FMC 54800 mouse study, the Reviewer relies heavily on comparison with studies conducted with permethrin. (Conclusions 2,4 DER I-1,2)

FMC Position: FMC does not believe a comparison between FMC 54800 and permethrin is appropriate. The following differences between FMC 54800 and permethrin argue against the validity of this comparison and thus, argue for treating the FMC 54800 data independently:

- FMC 54800 is a structurally unique compound in that both the acid and alcohol moieties are new. Although it bears some structural resemblance to other pyrethroids such as permethrin, the dissimilarities result in differences in mode and spectrum of biologic action. A prime example of small differences in chemical structure leading to large biologic differences is found with benzo[a]pyrene versus benzo[e]pyrene.

- The mode of action of FMC 54800 is dissimilar to other pyrethroids in that it cannot be classified as evoking either a Type I or Type II pyrethroid syndrome (Gammon and Sander, 1985). Permethrin elicits the typical Type I pyrethroid syndrome.

- Differences in potency between FMC 54800 and permethrin are evident on inspection of the dose levels used in the chronic studies: FMC 54800 treatment groups ranged from 50 to 600 ppm and permethrin dose levels ranged up to 5000 ppm.

- Compared with permethrin, FMC 54800 is much more lipophilic due to a combination of three factors: 1) [redacted] In mammalian systems, due to its increased lipophilicity, FMC 54800 is more extensively excreted in the feces (up to 83% radiolabel in the feces) as compared to permethrin (ca. 50% in the feces).

- Oncogenicity studies in mice with permethrin revealed liver tumors in female mice only, whereas the purported effect of FMC 54800 on liver tumor incidence was observed in males.

- Finally, to restate the obvious, the FMC 54800-induced urinary bladder leiomyosarcomas observed in male mice were not observed in any of the three mouse oncogenicity studies with permethrin.

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4. EPA Position: "An oncogenic NOEL was not established." (Conclusion 5, DER I-2)

   FMC Position: FMC Corporation is uncertain as to the significance of this statement. Linearized multi-stage models used by the Agency to perform carcinogenic risk assessments assume that there is no threshold for oncogenic effects and the concept of an "oncogenic NOEL" is not relevant to the use of such a model. On the other hand, for classical (non-oncogenic) toxic effects, statistical tests such as Fisher's Exact Test are among the criteria used to differentiate between significant and non-significant effects. By this criterion (i.e., Fisher's Exact Test) 500 ppm would be the NOEL for urinary bladder tumors in male mice. As always, the use of statistical tests must be tempered by dose-response considerations and the scientific judgement of the reviewer. Would the Agency please define what mechanisms are used to define an "oncogenic NOEL"? In addition, would the Agency elaborate on the regulatory use of an "oncogenic NOEL" once it has been established? Lastly, concerning conclusion number 5, FMC Corporation does not agree at this time that the observed pattern of female lung tumors is indicative of a compound-related effect as noted elsewhere in this document.

5. EPA Position: " '... The [urinary bladder] tumors were slow growing, did not metastasize, and were not responsible for the death of any of the affected mice' [page 20 of FMC Study Number A83-974]. This reviewer does not consider this statement to be entirely accurate." (DER I-15)

   FMC Position: The above statement from the report is correct in that the two tumors to which the Reviewer refers were not directly a cause of death. Rather, these tumors were considered to have caused restricted urinary flow which subsequently lead to the demise of the two mice. This situation occurred in only two of the 14 urinary bladder leiomyosarcomas in male mice of the high dose group.

6. On page DER I-6 of the Review, the quality assurance statement is signed by Alice V. Malloy, ASQC-CQE, Quality Assurance Supervisor. The statement of compliance was signed by Lee E. Geiger.

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III. Oncogenicity Study of FMC 54800: Lifetime Feeding Study in Albino Mice (FMC Study A83-974)

Summary

FMC Corporation does not consider the lung tumor incidence of female mice and the liver tumor incidence of male mice to be related to ingestion of FMC 54800. Forthcoming historical control data from our laboratory should be compared with that of the FMC 54800 oncogenicity study. Comparison of data of the FMC 54800 mouse oncogenicity study with data from oncogenicity studies with permethrin is neither appropriate nor convincing.

References

(1) Gammon, D.W. and Sander, G. (1985) "Two Mechanisms of Pyrethroid Action: Electrophysiological and Pharmacological Evidence" in Neurotoxicology 6(2), 63-86.

(2) LaRocca, G.T. (1986) Letter of March 21, 1986 to J. Lauber, FMC Corporation (see attached)

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IV. Oncogenicity Study of FMC 54800: 2 Year (734 day) Feeding Study in Albino Rats (FMC Study A83-952)

In general, the EPA reviewer was in agreement with FMC concerning the results and interpretation of the study. The areas in which further discussion is needed include the following items listed by conclusion number.

1. The interpretation of the incidences of pancreatic islet cell adenomas in males and combined sexes.

1. Incidences of fibrosarcoma in male rats.

5. Retinal atrophy as a possible effect in females.

8. Significance of increases in the mean liver and kidney weights, and liver and kidney organ to body weight ratios.

These items are discussed below.

1. EPA Position: "While there was no conclusive evidence of dose-related oncogenicity, there were presumably statistically non-significant increases of pancreatic islet cell adenomas in 200 ppm rats of both sexes... The registrant should supply some historical control data..." (DER II-16 and Conclusion 1, DER II-1).

FMC Position: FMC agrees that there is no conclusive evidence of neoplastic effects in this study. The data referred to in the Reviewer's conclusion number 1 are presented in a summary table of the incidence of pancreatic islet cell adenomas below. Analysis of the incidence of pancreatic islet cell adenomas for combined sexes (males and females) results in a probability value for the Fisher's Exact Test of $p = 0.191$ when the control and high dose groups are compared. "In the analyses of oncogenic activity by the Agency, it is considered more appropriate to separate males and females..."(1). They are two separate and independent studies that should not be combined. When the males are examined alone, the probability value for the Fisher's Exact Test is $p = 0.332$ when the control and high dose groups are compared.

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	Pancreatic Islet Cell Adenoma Incidence				
Dietary 54800 Concentration (ppm)	0	12	50	100	200
Males and Females					
All animals	1/97	0/46	0/40	0/49	4/99
Terminal Sacrifice	1/51	0/4	0/3	0/4	2/51
Died/Sacrificed	0/46	0/44	0/37	0/43	2/48
Males					
All animals	1/47	0/25	0/27	0/31	3/50
Terminal Sacrifice	1/22	0/2	0/3	0/2	2/23
Died/Sacrificed	0/25	0/23	0/24	0/29	1/27
Females					
All animals	0/50	0/23	0/13	0/16	1/49
Terminal Sacrifice	0/29	0/2	0/0	0/2	0/28
Died/Sacrificed	0/21	0/21	0/13	0/14	1/21

An important point that should be taken into consideration when comparisons are made using all animals in all groups is that the study design did not include histopathology of all the tissues of the intermediate dose group animals that survived to termination. The pancreas was evaluated histopathologically in the mid-dose animals that died or were sacrificed prior to termination of the study, but not in those animals who were sacrificed at termination unless there was a gross lesion identified at necropsy. Therefore trend tests based on all animals regardless of their fate, including the intermediate dose groups are not valid ways to analyze the data since the groups were not all sampled the same way. Trend tests are also not appropriate due to the low numbers of findings (less than five in each group). Examination of the incidence of islet cell adenomas in animals that died or were sacrificed prior to study termination shows two animals with the tumor in the high dose group, one male and one female, and none in any of the other groups.

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This study is the first chronic bioassay in rats conducted in the FMC laboratory. The histopathology data from the second chronic bioassay in rats have recently become available in draft form. Data from this recently completed study (FMC Study Number A84-1287) conducted in the same laboratory with Sprague-Dawley rats from the same supplier showed no pancreatic islet cell adenomas among the control animals (0/51 males and 0/50 females).

Reference to historical control data in Sprague-Dawley rats from Hazleton Laboratories (2) shows an incidence of pancreatic islet cell adenomas in combined sexes of 20/564 or 3.5% with a range of percentages of 2.4-5.9%. It appears that in study A83-952, the control incidence of 1/97 (1%) for the combined sexes is low compared to the Hazleton studies, while the high dose group incidence of 4/99 or 4% is typical of Sprague-Dawley rats at 104 weeks. The Hazleton historical control data for the males had an incidence of 17/291 or 5.8% and a range of percentages of 5-13. The 6% incidence of pancreatic islet cell adenomas in males is well within this range while the control incidence of 1/47 or 2% is well below the Hazleton historical control incidence.

In summary, analysis of the tumor incidence for male pancreatic islet cell adenomas show no conclusive evidence of dose-related oncogenicity based on a comparison of the high dose and control groups. Also the incidence of this tumor type is not considered to be "rare" and the incidence in the high dose group is similar to that found in historical control data from the Hazleton Laboratories.

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2. EPA Position: "While there was no conclusive evidence of dose related oncogenicity, there were presumably statistically non-significant increased incidences ... of fibrosarcoma in male rats at 200 ppm". (DER II-16, Conclusion 1, DER II-1)

FMC Position: The incidences of fibrosarcoma in male rats were 0/50, 1/50, 0/50, 0/50 and 3/50 for the 0, 12, 50, 100, and 200 ppm groups respectively. A comparison of the high dose group and the controls using a Fisher's Exact Test showed that there is no significant difference between the groups (p= 0.121). It is FMC's belief that the slight increase in the incidence of fibrosarcomas in the male rats is not a dose-related trend, and that it is not biologically significant. The historical control data provided from a recently completed study (Study Number (A84-1287) with Sprague-Dawley rats in the same laboratory had 0/51 males and 1/50 females with fibrosarcomas. This information does not change our conclusions concerning the lack of significance of the incidence of fibrosarcomas in the male rats.

3. EPA Position: "Three of 28 group 5 (200 ppm) females (and none of 40 control females) had retinal atrophy, a distribution pattern which approaches statistical significance at $p \leq 0.05$. This must be considered, given the reporting of the study (with comparatively little data from females of 12, 50 and 100 ppm) as a possible effect." (Conclusion 5, DER II-2)

FMC Position: It was suggested in conclusion number 5 that the incidence of retinal atrophy (3/28 in the high dose group and 0/40 in the control females) may be a possible compound related effect. Fisher's Exact Test comparing these two groups shows that they are not significantly different from each other (p = 0.06). The eye examination conducted on all surviving animals just prior to termination of the study only found one instance of retinal atrophy in a male that received 12 ppm of the test material in the diet. None of the terminal females examined had evidence of retinal degeneration. Although there was an increased finding of retinal atrophy in the high dose group identified histopathologically, the in-life eye examination did not confirm this finding (3).

Historical histopathological data from a recently completed study (Study Number A84-1287) with Sprague-Dawley rats in the same laboratory had an incidence of retinal degeneration of 0/51 males and 1/50 females in the control groups.

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This information does not change the conclusion regarding the lack of a relationship between dose and retinal atrophy in the female rats.

FMC also notes that the other chronic toxicity study conducted with FMC 54800 (one year dog study; FMC Study Number A83-821) showed no such effect on the retina and takes this as further evidence that the observed pattern in the rats does not indicate a treatment related effect.

4. EPA Position: "While not statistically significant, 200 ppm males had increases in mean liver (10.9%) and kidney (28%) weights at 24 months with respect to control values. Males and females at 200 ppm, as well as males at 100 ppm, showed higher (but not statistically significantly so) liver and kidney organ-to-body weight ratio relative to controls, and these should be considered as possible effects." (Conclusion 8, DER II-2)

FMC Position: In conclusion item number 8, the reviewer suggests that there may be an effect at the high dose on male liver and kidney absolute organ weights and male and female organ to body weight ratios for kidneys and liver. A summary of the data is presented below:

Mean Absolute Organ Weights (grams)

Concentration (ppm)	0	12	50	100	200
Males					
Kidneys	4.271	5.284	4.451	4.984	5.477
Liver	15.717	17.424	15.877	17.182	17.442
Females					
Kidneys	2.952	2.890	3.117	2.793	2.764
Liver	11.520	11.941	11.527	10.700	10.957

Mean Organ to Body Weight Ratio (Percent)

Males					
Kidneys*	0.807	1.010	0.870	0.973	1.032
Liver*	2.927	3.422	3.094	3.342	3.275
Females					
Kidneys*	0.846	0.800	0.837	0.789	0.872
Liver*	3.255	3.176	3.094	3.000	3.369

* An error in the preparation of the summary tables on pages 67 and 68 of the final report assigned the wrong organ to the kidney and liver organ to body weight ratios. They should be the reverse of what was originally presented. The correct values are shown above.

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Statistical analysis of these data according to the plan described in the text of the report using the attached flow diagram found there to be no significant differences between any of the treated groups and the control using a predetermined $p = 0.05$ as the significance level. The male absolute liver weights were not significantly different from each other, with an analysis of variance test $p = 0.6386$. The test for unusual variability was negative. The female liver weights showed a decrease in the mean weight with increasing dose levels which is the opposite of what was found in the males. The male absolute kidney weights were analyzed using the non-parametric Kruskal-Wallis test because of an outlier. The resulting $p = 0.0585$ is close to, but greater than, the predetermined value of $p = 0.05$. However there were no dose related-histopathological findings for either the kidneys or the liver.

The statistical analyses of the organ/body weight ratios for the liver and kidney for both the males and the females did not have any results that were close to the cutoff point of $p = 0.05$. The results of the Kruskal-Wallis test were as follows: male liver/body weight, $p = 0.2248$; male kidney/body weight $p = 0.1630$; female liver/body weight $p = 0.2967$. The female kidney/body weight data did not have any outliers. The analysis of variance for this parameter had a $p = 0.8197$. The statistical analyses show that there is clearly no dose-related effect on the organ/body weight ratios for the kidneys or livers in the animals on this study.

The Reviewer raised a question as to whether the organ weights taken from ten animals per sex per group were representative of each of the individual groups. An expanded table of the type prepared by the Reviewer comparing the body weights of the animals whose organs were weighed and the body weights of the group as a whole is presented below.

	Mean terminal body weight (gm) (Group)	Standard Deviation	Mean terminal body weight (gm) 10/sex/group	Percent of whole Group
Male controls	510.9	83.34	537.8	105%
Group 5 males	528.5	66.88	534.8	101%
Female controls	378.4	54.27	357.1	94%
Group 5 females	335.0	49.65	323.3	96%

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The guidelines for conducting this type of test specify that ten animals per sex per dose should have their organ weights taken as was done in this study. The animals that were selected for weighing organs were the first ten animals alive in each group at termination. Since the animals were randomly assigned to the study, the first ten also represent a random selection from each group. The mean terminal body weight of each group of ten animals selected for organ weights is within 6% of the mean for the group as a whole.

FMC believes that there is no dose related effect on the organ weights or the organ/body weight ratios in this study for the following reasons:

- The male and female kidney weights show different patterns of response: the males show an increase in the kidney weights with increasing dose levels while the females show decreasing kidney weights with increasing dose level.

- The statistical analyses show there to be no conclusive dose-related effect.

- There were no significant dose-related histopathological findings associated with the either the kidneys or the liver.

IV. Oncogenicity Study of FMC 54800: 2 Year (734 day) Feeding Study in Albino Rats (FMC Study A83-952)

Summary

FMC Corporation does not consider the pancreatic islet cell adenoma incidence in male rats, the incidence of fibrosarcomas in male rats or the incidence of retinal atrophy in female rats to be related to ingestion of FMC 54800. FMC also believes that there is no compound related effect on the organ weights or the organ/body weight ratios in this study.

References

(1) EPA. FR 51 (Number 210), October 30, 1986, page 39660. Pesticide Tolerance for Fenarimol. Final Rule.

(2) Representative Historical Control Data (1984) Hazleton Laboratories America, Inc., Vienna, Virginia.

(3) Clinton, J.M., Letter of October 3, 1986 to JD McCarty, FMC Corporation (see attached).

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