CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
SUMMARY OF TOXICOLOGICAL DATA
MEDICAL TOXICOLOGY BRANCH

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FLUCYTHRINATE

SB 950-310, Tolerance #400

July 18, 1986
Revised August 12, 1987

I. DATA GAP STATUS

Combined rat: (chronic + onco)	Data gap, inadequate study on file, possible adverse effect indicated
Chronic dog:	No data gap, possible adverse effect
Onco mouse:	No data gap, no adverse effect
Repro rat:	Data gap, inadequate study on file, possible adverse effect
Terato rat:	Data gap, inadequate study on file, no adverse effect indicated
Terato rabbit:	Data gap, inadequate study on file, no adverse effect

indicated

Gene mutation: Data gap, inadequate study on file, no adverse effect indicated (new study to be conducted)

Chromosome: Data gap, inadequate study on file, no adverse effect indicated (new study to be conducted)

DNA damage: No study on file (study to be conducted)

Neurotox: No data gap, not required at this time,inadequate study on file, no adverse effect indicated.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name SB310FLU.JG2
Toxicology Summary prepared by J. Gee based on reviews by A. Apostolou, J. Parker and J. Remsen (Gee)

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

RAT

022 037407, 037409, 037410 "24-Month Feeding Study in Rats." (IRDC, 7/22/81, 144-005). Flucythrinate (80%) fed in the diet at 0, 30, 60, or 120 ppm for 24 months; 50/sex/group; dose-related skin lesions, dose-related weight retardation; apparent onco NOEL greater than 120 ppm, chronic NOEL = 60 ppm (body weight). Initially reviewed as unacceptable (no eye exam, no individual clinical observations). Rereview by Gee, 7/18/86, found that, although 6 shipments of material were made on different dates (see pages 4 & 5), the lot number-batch number is the same. The description varies slightly for some shipments but this could be technician variability. The number of animals and the clinical parameters are adequate for a rat ONCO study. Hematology, clinical chemistry and urinalysis done with 5/sex/group at 3, 6, 12 and 24 months - not in the same animals at each interval. The points in the initial review were made in view of the classification of the study as a combined chronic/onco test type. At week 104, the body weights were reduced in a dose-related manner with that of high-dose males being lower by 12% and females, 17%. In addition, g/rat/day food intake was slightly decreased at the high dose for males. Thus, an adequate high dose was used. Rereview agrees that no oncogenic effect is reported. The incidence of benign mammary tumors is at the high end of the lab’s range for controls and the mid dose incidence was higher than that of the high dose for females. The initial review did not indicate that diet was analyzed for stability, homogeniety and content over the span of the study. The data at the end of the report do address these and this not a deficiency. With regard to the skin lesions, these are described as scabbed areas, hair loss or ulcerated areas. The incidence is given for two weeks (3 and 104) as follows:

	Control		30		60		120 ppm	
	M	F	M	F	M	F	M	F
Week 3	2/50	0/50	1/50	0/50	5/50	2/50	19/50	20/50
Week 104	0/32	3/27	4/36	6/32	5/34	4/34	4/35	12/39

The incidence at week 3 is significant but not at week 103, (by Fisher's exact, p = 0.068 in males and 0.055 in females). In the absence of findings in the esophagus, the biological significance is not clear. The study is evaluated as unacceptable but possibly upgradeable with the submission of individual clinical observations so that the skin lesions can be evaluated. UNACCEPTABLE. AA, 12/10/85 and JG, 7/18/86.

005 994549 Summary of 037407.

CHRONIC

DOG

****027 43870** "Chronic Dietary Toxicity Study in Dogs." (IRDC, 1/5/84.) Flucythrinate (85.4%) fed in the diet at 0, 30, 100 and 300 ppm of 24 months; eye exam included; 6/sex/group; NOEL stated in report = 100 ppm (emesis); reviewer's NOEL = 30 ppm (emesis, others); adverse "pharmacological" effect on heart (arrythmia, slower rate); ACCEPTABLE, Possible adverse effect. JG, 7/14/86.

ONCOGENICITY

MOUSE

** 021 037404, 037405, 037406 "18-Month Feeding Study of AC 222,705 to Mice." (IRDC, 4/30/81.) Flucythrinate(80%) given in the diet at 0, 30, 60 or 120 ppm for 18 months; 50/sex/group; dose-related skin lesions, hepatocellular adenomas in males at high dose; neither the onco nor the chronic NOEL established; initially reviewed as unacceptable but upgradable with justification of dose selection, absence of blood smears and serum chemistry and urinalysis.) Rereview by Gee, 7/21/86, found this study should have been categorized initially as an oncogenicity study. Although four shipments were recieved by IRDC, the lot numbers are the same as is the purity. Therefore, this is not a deficiency. While no justification of dose selection is included, based on body weight and food consumption, an m.t.d. was approached. For example, in females, the mean body weight at week 26 was 6.7% lower than control and at week 78 (end of study), 8.8% lower than control. Food consumption was reduced throughout the study in females. By considering this as an oncogenicity study, some of the objections in the initial review are mitigated (clinical chemistry, hematology, urinalysis). Skin lesions (abrasions, ulcerations and scabs) were seen in treated animals, especially females, at higher incidences at weeks 50 and 60 with less of a difference at weeks 70 and 78. There are no findings reported for the esophagus and no mention of the mouth. [Compare this finding with that in the rat, 037407, above.] The initial review pointed out hepatocellular neoplasms in males. The overall incidence is:

	Control	30	60	120 ppm
Adenoma	8/49	12/50	7/50	18/50
adenocarcinoma/ carcinoma	4	6	2	2

Combined	12	18	9	20*

* p = 0.075 for the combined hepatocellular adenoma/carcinomas in males and p = 0.022 for adenomas only in males. If the Bonferroni correction is applied, this is not statistically significant at the 95% confidence level. In response to a rebuttal dated 1/7/87 (no volume, pages only), the study was again considered for acceptability and possible adverse effects. Based on the above discussion, the study was upgraded to ACCEPTABLE status with no adverse oncogenic effect. AA, 12/9/85 and JG, 7/21/86 and 8/11/87.

005 994548 Summary of 037404.

005 994547 Summary of 037404.

REPRODUCTION

RAT

023 037411, 037412, 037413 "Three Generation Reproduction Study of AC 222,705 to Rats." (IRDC, 4/20/81). AA, 12/11/85. Flucythrinate (80%) fed in the diet at 0, 30, 60 or 120 ppm for a 3 generation, two litters/generation study; 12 males/group, 24 females/group; pup weights consistently reduced at mid- and high dose and at 30 ppm in F1b, F2a and F3b; initially reviewed as unacceptable based on no justification of dose levels, necropsy and histopathology limited to F3b generation, no justification for use of several batches of test article and probably not upgradeable. Rereview by Gee, 7/21/86, found that the four shipments had the same purity and lot number so that is not a deficiency. In terms of justification of dose selection, the reduction in litter weight at days 4 and individual pup weight at day 21 suggests that the high dose was adequate. No litter weight at day 0 or 1 is included (major deficiency). It should be noted that the control weights for

the F1 week 10 and F2, week 10, are considerably higher than the F0, week 10 mean weights, therefore making the weights of the treated groups appear even lower in comparison. The net weight gain over the ten weeks (from 1 to 10) are about the same for all groups and the food consumption is either the same or slightly higher in the high dose group so that palatability was not a factor. There was no effect on the fertility index or pup survival at birth. At day 4, survival was lower in all litters at the high dose and at day 21, the lactation index was decreased in the F1 litters, marginally decreased in the F2a, F3a and F3b litters. The F2b index was comparable with control. Skin lesions were again seen in the treated groups in a dose-related incidence especially in the younger animals of the F1 and F2 generations that were used as parents. Deficiencies include no litter weights for days 0 (or day 1) and 14, no necropsy and histopathology on F0 and F1 parents' reproductive organs. No individual body weights and food consumption are included. No individual clinical observations. NOEL: 30 ppm (litter weight). No parental toxicity other than decreased weight. Study remains UNACCEPTABLE with a possible adverse effect on pup survival. AA, 12/11/85 and JG, 7/21/86 and 8/10/87.

SUMMARY: The occurrence of skin lesions in several studies in rats should be evaluated in terms of the exposure and label instructions for possible adverse effect.

005 994553 Summary of 037411.

005 994552 Summary of 037411.

TERATOGENICITY

RAT

024 037414 "Teratology Study of AC 222,705 in Rats." (IRDC, 4/11/79.) Flucythrinate ((80%) given by gavage at 0, 2, 4 or 8 mg/Kg on days 6-15 of gestation; 30 females/group; Maternal NOEL = 4 mg/kg/day (decreased weight gain during dosing period and mortality, 19/30). (Prior review had stated that high dose level not justified.) Developmental NOEL = 8 mg/kg/day, no evidence of developmental toxicity. (Prior review had stated 4 mg/kg/day since the number of fetuses available for examination was reduced.) UNACCEPTABLE, UPGRADABLE (Prior review said not upgradeable). NO adverse effect Need necropsy observations, pilot study, individual fetal observations, clinical observations, revised and original pages of report. AA, 12/13/85 and JAP, 7/23/86.

005 994550 Summary of 037414.

TERATOGENICITY

RABBIT

24 037415 "Teratology Study with AC 222,705 in Rabbits." (IRDC, 4/7/80.) Flucythrinate (80%) given by gavage at 0, 10, 30, or 60 mg/Kg on days 6-19 of gestation; 19-20 females/group; no evidence of developmental toxicity; maternal NOEL = 30 mg/Kg, developmental NOEL = 60 mg/Kg; UNACCEPTABLE (need justification of dose levels, need clinical and necropsy observations), UPGRADABLE. JAP, 1/10/86.

005 994551 Summary of 037415.

MUTAGENICITY

GNMU

025 037416 "Mutagenicity Testing of CL 222,705, (+) Butyric Acid, 2-[p-(difluoromethoxy)phenyl]-3-methyl-alpha-cyano-m-phenoxybenzyl ester, in the Ames Bacterial Test." (American Cyanamid, 3/23/79.) Flucythrinate (84.8%) tested at 0, 10, 100 or 1000 ug/plate on Salmonella typhimurium strains TA 98, 100, 1535 and 1537 +/- S9; no increase in mutation frequency reported; UNACCEPTABLE (no repeat trial, no description of S9, no comments on cytotoxicity, missing controls, no justification of dose levels, no indication of number of platings), NOT UPGRADABLE. JR(G), 12/16/85.

005 994554 Summary of 037416.

A new study will be conducted - see rebuttal letter dated 1/7/87.

MUTAGENICITY

CHROMOSOME

025 037417 "A Dominant Lethal Test in Male Rats Treated with CL 222,705 by Gavage for 5 Days." (American Cyanamide, 11/26/79.) Flucythrinate (88.6%) tested in a dominant-lethal assay at 0, 2, 5 or 10 mg/Kg on rats; daily adminsitration for 5 consecutive days by gavage; 10 males per group; mated 1:1 for 5 days/week for 8 weeks; no adverse effect reported other than on body weight gain during treatment; UNACCEPTABLE (inadequate number of males and females, copora lutea and/or preimplantation loss not reported), NOT UPGRADABLE. JR(G), 12/16/85.

005 994555 Summary of 037417.

A new study will be conducted - see rebuttal letter dated 1/7/87.

MUTAGENICITY

DNA

No study on file. A study will be conducted - see letter of 1/7/87.

NEUROTOXICITY

Not required at this time.

026 037418 "Delayed Neurotoxicity Study with CL 222,705 in Mature Laying Hens." (American Cyanamid, 4/15/80.) Flucythrinate, (80%) in single doses of 0, 500, 2500 or 5000 mg/Kg by gavage; 15 hens/group; TOCP positive controls; no adverse effects reported; UNACCEPTABLE (no repeat dosing on day 21, positive controls not adequate for histology, no forced activity testing, no histopathology of medulla oblongata), NOT UPGRADABLE. AA, 12/13/85.

005 994546 Summary of 037418.