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Toxicological evaluation of formetanate hydrochloride

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Division of Regulations and Petitions Control (WH-569)

PESTICIDE PETITION No. 0F0961 [illegible] Agricultural Products, Inc.
Woodstock, Illinois 60098
(EF 0-767)

This petition proposes to establish tolerances for the acaricide and insecticide formetanate hydrochloride of 4 ppm on oranges, lemons and limes of which no more than 0.4 ppm shall be present on the fruit after removing the peel.

This compound was evaluated previously in connection with PP No. 9G0764, a proposal for the establishment of a temporary tolerance on citrus which was subsequently established at 4 ppm as of March 21, 1969 for 1 year and extended to March 21, 1971.

Review of additional toxicological data furnished follows:

Chronic Studies

1. RAT - 2 year feeding

Groups of 45 male and 45 female Charles River rats were placed on diets containing formetanate hydrochloride at levels of 0, 10 (increased to 200 at 42 weeks), 30, and 100 ppm. Animals were checked daily for mortality and abnormal behavior. Food consumption was determined on alternate weeks during the first 13 weeks and periodically thereafter. Animal weights were determined weekly during the first 13 weeks and monthly thereafter. Hematology (Hb, hematocrit, rbc, wbc & differential) chemistry (BUN, glucose, SAP, SGPT) urinalysis (glucose, albumin, microscopic, pH, sp.gr.) were performed on 5 rats of each sex from the control and high dose level groups. At 13 weeks 10 animals per group and at termination all survivors were sacrificed for autopsy. Weights of liver, kidney, spleen, gonad, heart, adrenal, pituitary thyroid and brain were determined for each animal. These tissues as well as trachea, lung, pancreas, esophagus, stomach, small and large intestines, lymph node, urinary bladder, prostate, uterus, salivary gland, skeletal muscle, sternum, optic nerve, eye and tongue were examined microscopically for all animals sacrificed at 13 weeks and for 10 males and 10 females of the control and 200 ppm groups sacrificed

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at termination. Animals which died during the course of the study were autopsied and where autolysis did not preclude, tissues were preserved. Incidence of tumors for the various groups were reported.

RESULTS: In terms of the parameters studied there were no effects produced which were attributable to the compound studied. Dietary levels of 100 ppm fed for 2 years and 200 ppm fed for about 24 months are then without apparent effect.

2. 200 - 2 year feeding

Groups of 5 male and 5 female beagle dogs were placed on diets containing formetanate hydrochloride on the following schedule (levels in ppm):

	Test Level		
Group	0-200	200-1	100-120
Control	0	0	0
I	10	10	100
II	20	40	20
III	100	200	200

Dogs were examined daily for evidence of systemic toxicity. Animal weights and food consumption were determined weekly. Hematology (rbc, wbc, Hb, hematocrit, differential), chemistry (BUN, glucose, SGP, SGOT, ALKT), and urinalysis (albumin, glucose, pH, microscopic) were performed at 0, 1, 3, 6, 9, 12, 18 and 24 months. At 90 days 2 males and 2 females from each group were sacrificed. At first estrus following 1 year of feeding each female was bred to a male from the same diet group. Resulting offspring were held for four weeks after weaning (Note - for reproduction results see below). After 2 years all remaining dogs were sacrificed for gross autopsy and organ weights were determined for liver, kidney, heart, brain, spleen, gonad, adrenal, thyroid and pituitary. These organs as well as eyes, large and small intestine, esophagus, eye, gall bladder, lung, lymph node, skeletal muscle, optic nerve, pancreas, sciatic nerve, prostate, salivary gland, skin, spinal cord, sternum, stomach, trachea, tongue, uterus, urinary bladder were examined histologically.

REVIEW: In terms of the parameters studied there were no effects produced which were attributable to the test compound. A dietary level of 100 ppm fed for 2 years would thus appear to be without apparent effect. An additional 100 ppm fed for approximately 14 months was also without apparent effect under the conditions of this study.

Reproduction Studies

1. RAT - 3 generation

Groups of 8 male and 16 female Charles River rats, used for this study, were fed diets containing formetanate hydrochloride at dosage levels of 0, 10, 30 and 100 ppm, these dietary levels being employed throughout the study. The design of the experiment was as follows:

F_0 Parents

F_{1a} litter F_{1b} litter

F_{1b} Parents

F_{2a} litter F_{2b} litter

F_{2b} Parents

F_{3a} litter F_{3b} litter

"a" litters were discarded following weaning. Body weights of parental animals were determined weekly until mating and then at sacrifice. All surviving male parents and 8 female parents from each group in each generation were sacrificed for gross examination. Weights of liver, kidney, spleen, gonad, heart and brain were determined at that time. Microscopic examination was made of these organs as well as trachea, lung, pancreas, stomach, small and large intestine, lymph node, urinary bladder, prostate, uterus, pituitary, adrenal, submaxillary, thyroid, parathyroid, skeletal muscle, bone marrow, sciatic nerve, seminal vesicles, esophagus, spinal cord for 5 male and five females of the control and high level groups. Mating was initiated for each parental generation when the animals were 100 days old. Ten days following weaning of the "a" litters mating was instituted for production of the "b" litters. All matings were within the respective feeding groups. Eight males and 16 females from the "b" litters were used in each successive parental group. All pups were examined for abnormalities at birth. All litters were reduced to a maximum of 10 pups at lactation day 5. Data taken permitted determination of indices as follows: fertility, mating, lactation, live birth, [illegible]

RESULTS: No effects upon reproduction were apparent as judged by fertility, mating and lactation indices. The data with respect to the mean litter size suggests the possibility of an effect at the 100 ppm level, data submitted in this regard being:

Parent Group	Litter No.	Dosage Group: Control	10 ppm	30 ppm	100 ppm
F_0	F_{1a}	11.0	11.3	11.7	9.5
	1b	11.6	11.3	12.2	11.0
F_{1b}	F_{2a}	9.1	11.2	9.2	9.5
	2b	9.9	10.6	10.9	10.9
F_{2b}	F_{3a}	10.7	9.4	10.2	8.8
	3b	10.7	11.1	8.5	7.6

With respect to survival of the young the 5-day survival indices reported were as follows:

Parent Group	Litter No.	Dosage Group: Control	10 ppm	30 ppm	100 ppm
F_0	F_{1a}	96.9	83.0	86.8	87.7
	1b	96.3	69.0	71.6	85.6
F_{1b}	F_{2a}	90.8	87.5	79.8	61.5
	2b	75.4	68.0	72.5	63.9
F_{2b}	F_{3a}	80.7	62.2	67.9	60.7
	3b	80.3	58.4	74.2	87.3

These data indicate that survival to 5 days was affected at all three dosage levels - this effect appearing somewhat progressive.

2. DOG - 1 generation

This study was carried out in the course of a 2-year feeding study which was described previously. Groups of 3 male and 3 female beagle dogs which had been receiving diets at levels previously described (up to 200 ppm) were used. During the first estrus after 1 year each female was bred to a male from the same group. For

each litter there was recorded the total number of pups by sex, number of stillborn pup by sex and number of pups alive at four weeks by sex.

RESULTS: Data are not indicative of any compound related effects.

DISCUSSION:

Results of feeding studies in both rats and dogs are without evidence of effect upon the parameters studied when fed for about 6 months at 100 ppm and 14 additional months at 200 ppm.

In dogs receiving dietary levels up to 200 ppm no effects were seen upon single litters in terms of litter size and viability. However a 3-generation study in rats receiving dietary levels of 10, 30 and 100 ppm of formetanate hydrochloride gave evidence of an increase in neo-natal mortality during days 1-5 post-partum. This was seen at all three levels, there being some indication of a progressive effect. While one can only speculate as to the basis for this increased mortality, one possibility may be the anticholinesterase action of this carbamate. No reliable data has been furnished as to the effects of the chronic ingestion of this compound upon rat blood and brain cholinesterase activity. That significant depression can occur however is evident from data previously furnished. Thus rats given 5 mg/kg of formetanate hydrochloride acutely, showed, at one hour following dosing, pertinent cholinesterase depressions as follows:

Sex	Plasma	RBC	Brain
Male	36		73
Female	46	39	75

It would also appear appropriate to call attention here to the observation previously made (PP No. 9G0561, memo 10/2/68 T.I. Chiba) of the increased numbers of resorption sites seen in the rabbit teratology study.

These were reported as follows:

	Treatment Group			
	Control	Positive control	10 mg/kg	25 mg/kg
Total no. of resorption sites	2	10	13	17
No. of fetus	1	4	13	7

While these increases may be due to the direct toxic effect of the compound itself, the possibility of mutagenic effect is not ruled out and must be looked into.

CONCLUSIONS:

1. The toxicological safety of formetanate hydrochloride has not been established.

2. Data with respect to the effect of chronic ingestion of formetanate hydrochloride upon rat blood and brain cholinesterase activity are required.

3. The reduced 5-day survival seen in all dosage groups of the 3-generation rat study must be explained.

4. The question of possible mutagenicity raised by the increased numbers of resorptions seen in the teratogenicity study must be resolved by suitable investigation.

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INIT:HBSilverthal

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PF-210
PF-216
PF-143
PF-140
VM-100
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