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

007302

JUN 30 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PYRINEX (Chlorpyrifos): Makhteshim-Agan (America) Inc. Response to EPA's Request Regarding a Thirteen-Week Rat Study and a Rabbit Teratology Study [Toxicology Document No. 006851; Caswell No. 219AA; MRID Nos. 404364-06 for 13-week rat and 404364-08 for rabbit teratology] HED Project No. 9-0446.

FROM: Alan C. Levy, Ph. D. Alan C. Levy 6-19-89
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Health Effects Division (HED), H7509C

TO: Dennis Edwards PM 12
Registration Division (H7505C)

THROUGH: Yiannakis M. Ioannou, Ph. D. J.M. Ioannou 6-20-89
Section Head, Review Section I
HFAS Toxicology Branch (II), HED (H7509C)

and

Marcia van Gemert, Ph. D. M. van Gemert 6/20/89
Branch Chief, HFAS Toxicology Branch (II)
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Registrant: Makhteshim-Agan (America) Inc.

Action Requested: Review the Registrant's responses to the Agency's requests for clarification regarding the above mentioned studies with the possibility of upgrading the classification from "supplementary" to "minimum". [Memorandum from A. C. Levy to D. Edwards, 9/2/88.]

Recommendation:

1. Thirteen-Week Rat Study - Upgrade from "Supplementary" to "Core Minimum".

2. Rabbit Teratology Study - Upgrade from "Supplementary" to "Core Minimum".

NOTE: See Agency's Reply, determination of "non-pregnancy", on page 3 of this memorandum. Even though the study is recommended to be upgraded to "Core Minimum", the Agency would like a response from the Registrant.

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A. Thirteen-Week Rat Study (MRID 404364-06)

Agency's Request:

Regarding cholinesterase values, female group means were 3300, 3639, 295 and 1427 IU (0, 0.5, 10 and 200 ppm, respectively). The registrant is requested to comment on/ explain the 295 value.

Registrant's Response:

[See full response in attachment to this memorandum.]

"Raw data were retrieved from archives, labels were compared for proper dose level and dates were compared for consistency to the final report. The final report accurately reflects the raw data."

"Nonetheless, the inconsistency remains, particularly since the data reflect a linear relationship if dose levels 2 and 3 are reversed. We are, therefore, unable to explain satisfactorily the data, but suspect that an error might have occurred in processing the sample which was undetected upon in-depth audit."

Agency's Reply:

There is agreement with the Registrant that an error was probably made in labeling samples for cholinesterase determination and that possibly the results from groups 2 and 3 should be reversed.

Toxicology recommends that this study be upgraded from "supplementary" to "minimum" for the following reasons:

1. This 13-week study is not considered pivotal. Evaluation of a chronic rat study would be considered to yield more data.

2. In the 13-week study, the male cholinesterase values appeared to be as anticipated and only the values in females were in question.

3. The test article (PYRINEX, Chlorpyrifos) is an organophosphate chemical with known cholinesterase inhibiting properties.

4. The purposes of the 13-week study were to observe signs of toxicity at the concentrations administered (cholinesterase as well as other parameters) and to use the results in choosing doses for the chronic study.

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B. Rabbit Teratology (MRID 404364-08)

1. Determination of "Non-Pregnancy"

Agency's Request:

There are rabbits in each group which were said to be "non-pregnant". Please indicate how "non-pregnancy" was determined. Necropsy sheets for "non-pregnant" animals should be submitted.

Registrant's Response:

"Animals reported as "not pregnant" were described at necropsy as having "no implantation sites" in either horn. "Implantation site" includes visible early or late resorptions (i.e., respectively, with or without a discernable fetus), empty implantation sites (i.e., implantation scars without discernable fetal or placental remains), or swellings, visable on the intact uterus, indicating very early resorptions. Any animal described at necropsy with "no implantation sites" showed NONE of the above."

"Necropsy sheets for the following animals are enclosed:

Group 1 (Control):	Dam No. 836
Group 2 (1 mg/kg/day):	None
Group 3 (9 mg/kg/day):	Dam No. 820
Group 4 (81 mg/kg/day):	Dam No. 819
	Dam No. 824
	Dam No. 841
	Dam No. 891"

Agency's Reply:

The explanation for "non-pregnant" is acceptable.

There still appears to be some inconsistencies regarding the necropsy sheets. The Registrant's list above does not include a necropsy sheet for Dam No. 809, Group 5 (140 mg/kg/day), and yet a sheet for this animal was included in the Registrant's response.

Group	Dose mg/kg/day	No. of rabbits dosed	No. of rabbits pregnant†	
1	0	14	13	
2	1	14	13	--
3	9	14	13	
4	81	21*	15	
5	140	14	11	--

*=7 extra animals added
†=from Table 5, page 9 of Agency memo (Table 6, page 40 of the report)

Should there be a "non-pregnant" necropsy sheet for one animal in group 2 and a total of 3 for group 5? The Registrant is requested to respond. It is not considered that this current lack of clarification should prevent upgrading the study to "Core Minimum".

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2. The value of N

Agency's Request:

Explain the value of N on Table 5 of this review, Group 4, mean fetal weight and SD where the value is 14 and for all other parameters N = 15 (Table 6, page 40 of the report).

Registrant's Response:

"Fetuses from Dam 4F873 were not weighed. They were necropsied, in error, before these weights were obtained. Tables 10 and 11 of the report indicate that these weights were not recorded, in error. Accordingly, the N value for this parameter, on Table 6, page C-9, is reduced from 15 to 14."

Agency's Reply:

The explanation for the difference in N value of 14 vs 15 is acceptable.

3. Fetal Data for Litter No. 880

Agency's Request:

Individual fetal data for litter No. 880 (Group 4, 81 mg/kg/day) as this is missing from the report (Appendix 11, typed page No. D-80 is missing).

Registrant's Response:

"A photocopy of page D-80 is enclosed. This page is certified as an exact copy of the original by the Study Director and the Head of Quality Assurance. These data will hopefully resolve the issue described above."

Agency's Reply:

The previously missing page has been received and therefore, the Agency's request has been fulfilled.

Maternal Systemic Toxicity NOEL = 81 mg/kg/day
Maternal Systemic Toxicity LOEL = 140 mg/kg/day (decreased food consumption gestation days 15-19; body weight loss during the dosing period followed by a compensatory weight gain; suggestion of post-implantation loss)

Developmental Toxicity NOEL = 81 mg/kg/day
Developmental Toxicity LOEL = 140 mg/kg/day (slight reduction in fetal weights and crown-rump lengths; increased incidence of unossified 5th sternebra and/or xiphisternum)

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Feeding-3 month Species: dog	Chlorpyrifos Tech.		Data requirement waived when used as an inert in plastic insecticide ear tags for domestic animals.		006539
Feeding-3 month Species: rat	Chlorpyrifos Tech		Data requirement waived when used as an inert in plastic insecticide ear tags for domestic animals.		006539
Inhalation-21 day Species: rat Dow Biochem Res. Lab. 35.12-44793-6; 12/8/66	Dursban	256040	ChE NOEL > 0.007 ug/L (no Che inhibition & no deaths; analytical, ODT) Only females studied, no necropsy of animals, no data for body weights or clinical, % a.i. not given.		Supplementary 000191
Feeding-13 week Species: rat Life Science Research AK/058/PYRA; 10/25/85 Amendment 6-1-89	Chlorpyrifos tech 45.5%	404364-06	Doses (diet) : 0.05, 10 , and 200 ppm (S.D.) ; ChE (M) = 0.5 ppm Sys. Toxicity NOEL = 10 ppm ; Sys Toxicity LEL = 200 ppm (decrease in body weight gain and possible anemia)		~~Supplementary~~ 006851 MINIMUM
0 day oral Species: rat Dow Chem; Lake Jackson Res. (T:K-044793-071	Dursban 95.7%-98.5% batch MM820905-610	409528-01	Levels tested by gavage: 0, 0.1, 1.0, 5.0 & 15 mg/kg/day. ChE NOEL = 0.1 mg/kg/day. ChE LEL = 1.0 mg/kg/day. (Decreased plasma and RBC cholinesterase activity). Systemic NOEL = 0.1 mg/kg. Systemic LEL = 1.0 mg/kg (incr. brain wt. (M); incr. heart wt. (F)). At 50 mg/kg - increased brain wt. in males and vacuolation of afrenals. At 15 mg/kg/day - increased brain and heart wt. in males, decr. body wt. gain in males; vacuolation of adrenal; perineal soiling; incr female kidney wt.		Minimum 007102
olinesterase- 12 weeks ecies: cat l Research Lab L-52013; 4/12/88	Chlorpyrifos 3% cat collar	406031-03	Exposure levels: 0 (placebo), 1 and 5 collars with 4 cats/sex/level. Method of Ellman et al. used to measure ChE activities. Substantial (>80%) plasma ChE depression occurs in cats wearing a single 3% collar; no indication of RBC ChE depression or symptoms of ChE inhibition were noted, even in cats wearing five collars. Substantial (to 60 - 80% normal activity) plasma ChE recovery occured in cats which had worn one collar in the two week period after collar removal at week 13.		Minimum 007150
olinesterase- 21 days ecies: cat l Research Lab -52012; 12/9/87	Chlorpyrifos 3% cat collar	406031-02	Preliminary study with 1 cat/sex/exposure level. Substantial plasma ChE depression (> 70%) associated with exposure to one collar, and even greater plasma ChE depression (> 80%) from exposure to five collars. No indication of RBC ChE depression or symptoms of ChE inhibition even in cats wearing five collars. Considerable (to 60 - 65% normal activity) recovery of plasma ChE occured in the period from week 3 (when collars were removed) to week 4.		Supplementary 007150

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Teratology Species: mice Tox Res Lab Health & Environ 7/24/74	Chlorpyrifos Tech.	098912	Terata NOEL > 25 mg/kg/day (HDT). Fetotoxic NOEL = 10 mg/kg Fetotoxic LEL = 25 mg/kg (HDT). (decr. fetal length; incr. skeletal variants). Plasma & RBC cholinesterase NOEL = 0.1 mg/kg/day.		Minimum 000181
Teratology Species: rat Tox Res Lab Health & Environ 7/5/83	Chlorpyrifos Tech.	071866	Teratogenic NOEL > 15 mg/kg (HDT)' Fetotoxic NOEL > 15 mg/kg (HDT). Maternal NOEL = 0.1 mg/kg; Mat LEL = 3.0 mg/kg (AChE inhibition). Levels tested: 0.1, 3.0 & 15 mg/kg.		Minimum 003822
Reproduction-3 generation Species: rat Dow Chemical Co. 8/20/71	Chlorpyrifos	112116	Reprod. NOEL > 1.0 mg/kg/day (HDT). Teratogenic NOEL = inconclusive. ChE NOEL = 0.1 mg/kg. Levels tested: 0, 0.1, 0.3 & 1 mg/kg		000179 000181 Minimum 003822
Reproduction-2 generation Species: rat Dow Chemical Co. 7/83	Chlorpyrifos Tech.	071867	Reprod. NOEL > 1.2 mg/kg (HDT). Sys NOEL = 0.8 mg/kg. Sys LEL = 1.2 mg/kg (decr wt. gain). Doses: 0.5, 0.8, 1.2 mg/kg in SD str.		Supplementary 03822
Teratology Species: rabbit	Tech		Data requirement waived when used as an inert in plastic insecticide ear tags for domestic animals.		006539
Teratology Species: rat Life Sciences Res. Israel, Ltd NAK/101/PYR; 7/15/87	Chlorpyrifos tech 96.1%	404364-07	Doses (gavage): 0, 0.5, 2.5, and 15 mg/kg/day (CR,CD); CHE Maternal NOEL < 0.5 mg/kg/day (LDT); Maternal Sys Toxicity NOEL = 15 mg/kg/day; Maternal Sys Toxicity LEL = 15 mg/kg/day (decrease in food consumption [only first few days of dosing] and decrease in body wgt. gain during dosing [15 mg/kg]). Developmental Toxicity NOEL = 2.5 mg/kg ; Developmental Toxicity LEL = 15 mg/kg/day (post implantation loss) .		Minimum 006851
Teratology Species: rabbit Life Sciences Res. Israel, Ltd NAK/103/PYR; 7/15/87 Amendment 6/19/89	Chlorpyrifos tech 96.1%	404364-08	Doses (gavage) : 0, 1, 9, 81, and 140 mg/kg day (N.Z.); ChE Maternal NOEL < 1 mg/kg (LDT). ~~Maternal Sys Toxicity NOEL and LOEL as well as Developmental Toxicity NOEL and LOEL will be determined after Registrants response to agency's request for information.~~		~~Minimum~~ ~~Supplementary~~ 006851 Minimum
Feeding-2 year Species: dog Dow Chemical Co. 12/10/71	Chlorpyrifos		Sys NOEL = 1.0 mg/kg/day. Sys LEL = 3.0 mg/kg/day. (incr. liver wt.) Plasma ChE NOEL = 0.01 mg/kg/day. Plasma LEL = 0.1 mg/kg. RBC AChE NOEL = 0.10 mg/kg/day. RBC ChE LEL = 1.0 mg/kg/day. Brain ChE NOEL = 1.0 mg/kg/d. Brain ChE LEL = 3 mg/kg/day. Levels tested: 0, 0.01, 0.03, 0.1, 1.0 & 3 mg/kg.		000179 000195 000191 Supplementary 003822 Minimum 004712

Maternal Systemic Toxicity NOEL = 81 mg/kg/day
Maternal Systemic Toxicity LOEL = 140 mg/kg/day (decreased food consumption gestation days 15-19; body weight loss during the dosing period followed by a compensatory weight gain; suggestion of post-implantation loss)

Developmental Toxicity NOEL = 81 mg/kg/day
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