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

JUN 30 1989

007302

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*  
Toxicologist, Review Section I  
Herbicide/Fungicide/Antimicrobial Support Branch (II)  
Health Effects Division (HED), H7509C

TO: Dennis Edwards PM 12  
Registration Division (H7505C)

THROUGH: Yiannakis M. Ioannou, Ph. D. *Y. 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)  
HED (H7509C)

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, visible 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  
 Feeding-3 month  
 Species: dog

Feeding-3 month  
 Species: rat

Inhalation-21 day  
 Species: rat  
 Blochem Res. Lab.  
 35.12-44793-6; 12/8/66

Feeding-13 week  
 Species: rat  
 Life Science Research  
 AK/058/PYRA; 10/25/85  
 Amendment 6-19-89

0 day oral  
 Species: rat  
 Dow Chem; Lake Jackson Res.  
 (T:K-044793-071)

Cholinesterase- 12 weeks  
 Species: cat  
 Research Lab  
 L-52013; 4/12/88

Cholinesterase- 21 days  
 Species: cat  
 Research Lab  
 L-52012; 12/9/87

ACCESSION/ NRID NO.	MATERIAL	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
	Chlorpyrifos Tech.	Data requirement waived when used as an inert in plastic insecticide ear tags for domestic animals.		006539
	Chlorpyrifos Tech	Data requirement waived when used as an inert in plastic insecticide ear tags for domestic animals.		006539
256040	Dursban	ChE MOEL > 0.007 ug/L (no ChE inhibition & no deaths; analytical, OOT) Only females studied, no necropsy of animals, n.o. data for body weights or clinical, % a.i. not given.	Supplementary 000191	
404364-06	Chlorpyrifos tech 45.5%	Doses (diet) : 0.05, 10, and 200 ppm (S.D.) ; ChE (M) = 0.5 ppm Sys. Toxicity MOEL = 10 ppm ; Sys Toxicity LEL = 200 ppm ( decrease in body weight gain and possible anemia)	Supplementary 006851 M/M/M L/M	
409528-01	Dursban 95.7%-98.5% batch M4620905-610	Levels tested by gavage: 0, 0.1, 1.0, 5.0 & 15 mg/kg/day. ChE MOEL = 0.1 mg/kg/day. ChE LEL = 1.0 mg/kg/day. (Decreased plasma and RBC cholinesterase activity). Systemic MOEL = 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 adrenals. 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	
406031-03	Chlorpyrifos 3% cat colla	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 occurred in cats which had worn one collar in the two week period after collar removal at week 13.	Minimum 007150	
406031-02	Chlorpyrifos 3% cat colla	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 occurred in the period from week 3 (when collars were removed) to week 4.	Supplementary 007150	

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CITATION ..... MATERIAL ..... ACCESSION/ NRID NO. .... RESULTS ..... COREGRADE/ DOCUMENT#

<p>Teratology Species: mice Tox Res Lab Health &amp; Environ 7/24/74</p>	<p>Chlorpyrifos Tech.</p>	<p>098912</p>	<p>Terata NOEL &gt; 25 mg/kg/day (MDT). Fetotoxic MOEL = 10 mg/kg Fetotoxic LEL = 25 mg/kg (MDT). (decr. fetal length; incr. skeletal variants). Plasma &amp; RBC cholinesterase NOEL = 0.1 mg/kg/day.</p>	<p>Minimum 000181</p>
<p>Teratology Species: rat Tox Res Lab Health &amp; Environ 7/5/83</p>	<p>Chlorpyrifos Tech.</p>	<p>071866</p>	<p>Teratogenic NOEL &gt; 15 mg/kg (MDT). Fetotoxic NOEL &gt; 15 mg/kg (MDT). Maternal NOEL = 0.1 mg/kg; Mat LEL = 3.0 mg/kg (ACHE inhibition). Levels tested: 0.1, 3.0 &amp; 15 mg/kg.</p>	<p>Minimum 003822</p>
<p>Reproduction: 3 generation Species: rat Dow Chemical Co. 8/20/71</p>	<p>Chlorpyrifos</p>	<p>112116</p>	<p>Reprod. NOEL &gt; 1.0 mg/kg/day (MD). Teratogenic MOEL = inconclusive. CHE NOEL = 0.1 mg/kg. Lev-1s tested: 0, 0.1, 0.3 &amp; 1 mg/kg</p>	<p>000179 000181 Minimum 003822</p>
<p>Reproduction: 2 generation Species: rat Dow Chemical Co. 7/83</p>	<p>Chlorpyrifos Tech.</p>	<p>071867</p>	<p>Reprod. NOEL &gt; 1.2 mg/kg (MDT). 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.</p>	<p>Supplementary 03822</p>
<p>Teratology Species: rabbit</p>	<p>Tech</p>		<p>Date requirement waived when used as an inert in plastic insecticide ear tags for domestic animals.</p>	<p>006539</p>
<p>Teratology Species: rat Life Sciences Res. Israel, Ltd MAK/101/PIR; 7/15/87</p>	<p>Chlorpyrifos tech 96.1%</p>	<p>404364-07</p>	<p>Doses (gavage): 0, 0.5, 2.5, and 15 mg/kg/day (CR, CD); CHE Maternal NOEL &lt; 0.5 mg/kg/day (LDT); Maternal Sys Toxicity MOEL = 15 mg/kg/ day; Maternal Sys Toxicity LEL = 15 mg/kg/day (decrease in food co- nsumption [only first few days of dosing] and decrease in body wt. gain during dosing [15 mg/kg]). Developmental Toxicity NOEL = 2.5 mg /kg; Developmental Toxicity LEL = 15 mg/kg/day (post implantation loss).</p>	<p>Minimum 006851</p>
<p>Teratology Species: rabbit Life Sciences Res. Israel, Ltd MAK/103/PVR; 7/15/87 <i>Amel Amery 6/19/89</i></p>	<p>Chlorpyrifos tech 96.1%</p>	<p>404364-08</p>	<p>Doses (gavage): 0, 1, 9, 81, and 140 mg/kg/day (M.Z.); CHE Maternal NOEL &lt; 1 mg/kg (LDT). Maternal Sys Toxicity NOEL and LOEL as well as Developmental Toxicity NOEL and LOEL will be determined after single- sexable response to agency request for information.</p>	<p>Supplementary 006851 Minimum</p>
<p>Feeding: 2 year Species: dog Dow Chemical Co. 12/10/71</p>	<p>Chlorpyrifos</p>		<p>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 &amp; 3 mg/kg.</p>	<p>000179 000195 000191 Supplementary 003822 Minimum 004712</p>

Maternal Systemic Toxicity NOEL = 81 mg/kg/day  
Maternal Systemic Toxicity LOEL = 140 mg/kg/day (decreased food con-  
sumption 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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