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

007349

JUL 13 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PYRINEX (CHLORPYRIFOS) - Thirteen Week Inhalation Study in Rats - Identification No. 11678-UL; MRID No. 409084-01; Record No. 235611; Caswell No. 219AA; HED Project No. 9-0466.

FROM: Alan C. Levy, Ph. D. Alan C. Levy 7/10/89
Toxicologist, Review Section I
Herbicide/Fungicide/Antimicrobial Support Branch (II)
Health Effects Division (HED), H7509C

TO: Dennis Edwards PM # 12
Registration Division (H7505)

THROUGH: Yiannakis M. Ioannou, Ph. D. Y.M. Ioannou 7-10-89
Section Head, Review Section I
HFAS Toxicology Branch (II), HED (H7509C)

and

Marcia van Gemert, Ph. D.
Branch Chief, HFAS Toxicology Branch (II)
HED (H7509C)

Registrant: Makhteshim-Agan (America) Inc.

Action Requested: Review a thirteen week inhalation study in rats administered PYRINEX (chlorpyrifos).

RECOMMENDATION:

This study is classified Core Supplementary.

PYRINEX (Chlorpyrifos) is a crystalline material which is applied as an aerosol. This study appears to be an exposure to a vapor. An inhalation study with the test article administered as an aerosol (dust or spray) is required.

The No Observed Effect Level (NOEL) = 20 ppb (HDT)
The Lowest Observed Effect Level (LOEL) = Not attained. (The study author stated that the saturation or near saturation level was 20 ppb (the highest dose tested).

REQUEST: The Registrant is requested to respond to the Reviewer's comment on the top of page 12 of this DER concerning apparent inconsistencies in the number of rats which died accidently or were killed in extremis or died spontaneously.

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Primary Reviewer: Alan C. Levy, Ph. D. Alan C. Levy 7/10/89
Review Section I/HED (H7509C)

Secondary Reviewer: Yiannakis M. Ioannou, Ph. D.
Section Head, Review Section I 7-10-89

I. Study Type: Subchronic Inhalation Toxicity (rat)
(Guideline § 82-4)

EPA Identification Numbers:

EPA Identification: 11678-UL
EPA MRID: 409084-01
EPA Record: 235611
Caswell: 219AA
HED: 9-0466

Sponsor: Makhteshim-Agan (America) Inc.

Testing Laboratory: Bio/dynamics, Inc.
Mettlers Road
East Millstone, NJ 08875

Study Number: 88-8058

Study Date: November 14, 1988

Study Author: Paul E. Newton

Test Material:

Name: Chlorpyrifos Technical (PYRINEX)
Lot No.: 489205
Purity: 95% active ingredient
Description: Off-white crystals

II. Materials and Methods - Results - Discussion

A. Animals

Five week old male and female Fischer 344 rats were received from Charles River Breeding Laboratories, Inc., Raleigh, NC. Animals were acclimated for about 12 days. At inhalation exposure, the body weight means and ranges were 106/90-120 g for males and 78/73-82 g for females. Acclimation to the nose-only tubes and chamber was for 5 days (progressively longer periods/day up to 7.5 hours/day). [The report author stated that the protocol indicated acclimation was to be 6 hours/day for 2 weeks and felt that the deviation from the protocol did not affect the quality or integrity of the study. This reviewer agrees.]

Rats were selected to be placed on study based upon pretest physical exams, ophthalmic exams and body weights. Animals were placed 15/sex/group (4 groups) by a computerized random sort program (body

weight means were comparable for all groups). Animals were housed 2/stainless steel wire mesh cage for the first 6 days of acclimation and then individually during the remainder of acclimation as well as other nonexposure periods; food and water were available ad libitum with temperature, humidity and light/dark cycle controlled. During exposure periods, rats were individually housed in polycarbonate nose-only tubes attached to a cast aluminum and alloy 40 liter exposure chamber (no food or water). Temperature (specified range 68-75°F, actual range 67-78°F) and humidity (specified range 30-70%, actual range 2-69%; adjustments could not be made while chamber was operating) were monitored throughout the study.

B. Test Substance Administration and Chamber Operation

METHODS AND MATERIALS

The test material was administered by nose-only inhalation to rats 6 hours/day, 5 days/week for 13 weeks at target exposure levels of 0, 5, 10 and 20 ppb. Airflow rates, air changes and equilibrium time were as follows:

Table 1

AIRFLOW RATES, AIR CHANGES AND EQUILIBRIUM TIME FOR RATS ADMINISTERED PYRINEX BY INHALATION FOR 13 WEEKS

Group (ppb)	Airflow Rate (lpm)	Air Change (min)	99% Equilibrium Time (min)
I (0)	10-24	4.0-1.7	18.4- 7.7
II (5)	12-24	3.3-1.7	15.3- 7.7
III (10)	10-16	4.0-2.5	18.4-11.5
IV (20)	10-12	4.0-3.3	18.4-15.3

Table from page 13 of the report.

Diagrams of the nose-only chamber and generation system were included (Figures F 1-1 and F 1-2, report pages 28 and 29).

About 15 g of test substance were melted and resolidified onto glass beads which were placed in a 400 or 600 ml glass fritted-bottom fluidizing bed. Air was delivered to the bed. Dilution air entered the chamber through a metering valve and flowmeter. The vapor-laden airstream was directed into the chamber housing the rats. The animals remained in the chamber for 30 minutes post exposure to allow the chamber to clear (using clear air). Controls were subjected to the same procedures except that they were exposed to air only.

Samples for the determination of test article concentrations were collected 4 times during each exposure (from the breathing zone). To check the uniformity of PYRINEX distribution within the chamber, an additional sample was taken from a different area prior to the start of exposures.

Samples were obtained once/week/group to measure particulates in the chamber. Particle size distributions were calculated based on the amount of material collected. Temperature, humidity and airflow rates were continuously monitored (12 recordings/exposure).

RESULTS

The analytical concentration of the test article was measured in the chamber daily (when animals were exposed). Of the 65 exposure days, the concentration in the control group (0 ppb) measured "0.00" with the exceptions of 0.25 on day 2 of exposure, 0.35 on day 34 of exposure and 0.64 on day 51 of exposure (Appendix B, pages 51-59 of the report). This reviewer feels that the three instances of "measurable test article" are either attributable to analytical methodology or to a very small degree of contamination. It is not felt that these results influence the overall evaluation or integrity of the study.

Although the mean concentrations for the three PYRINEX groups, measured analytically, were similar to the target concentrations over the 13-week period (4.9 vs 5.0 ppb, measured vs target; 10 vs 10; and 20 vs 20), the amount of variation was great. Table 2 and Figure 1 (a composite of Figure 2: F2-1, F2-2 & F2-3, report pages 30-32) indicate the extent of these variations.

Table 2

CHAMBER MONITORING RESULTS IN A THIRTEEN WEEK NOSE-ONLY INHALATION STUDY OF PYRINEX (CHLORPYRIFOS) IN THE RAT

Target Concentration (ppb)	Mean±S.D. of 65 Exposure Days (ppb)	Range during weeks:*				
		1	4	7	10	13
5	4.9 ± 4.5	4.1-9.4	0.2-2.8	1.8-13	1.1-4.5	3.3-24
10	10.0 ± 4.0	11-17	5.8-11	5.2-13	5.4-11	8.4-25
20	20.0 ± 6.9	21-30	14-18	6.6-21	12-23	14-33

* = Weeks chosen at constant intervals to show examples of variations during the entire 13 weeks.

Data extracted from Appendix B, pages 51-59 of the report.

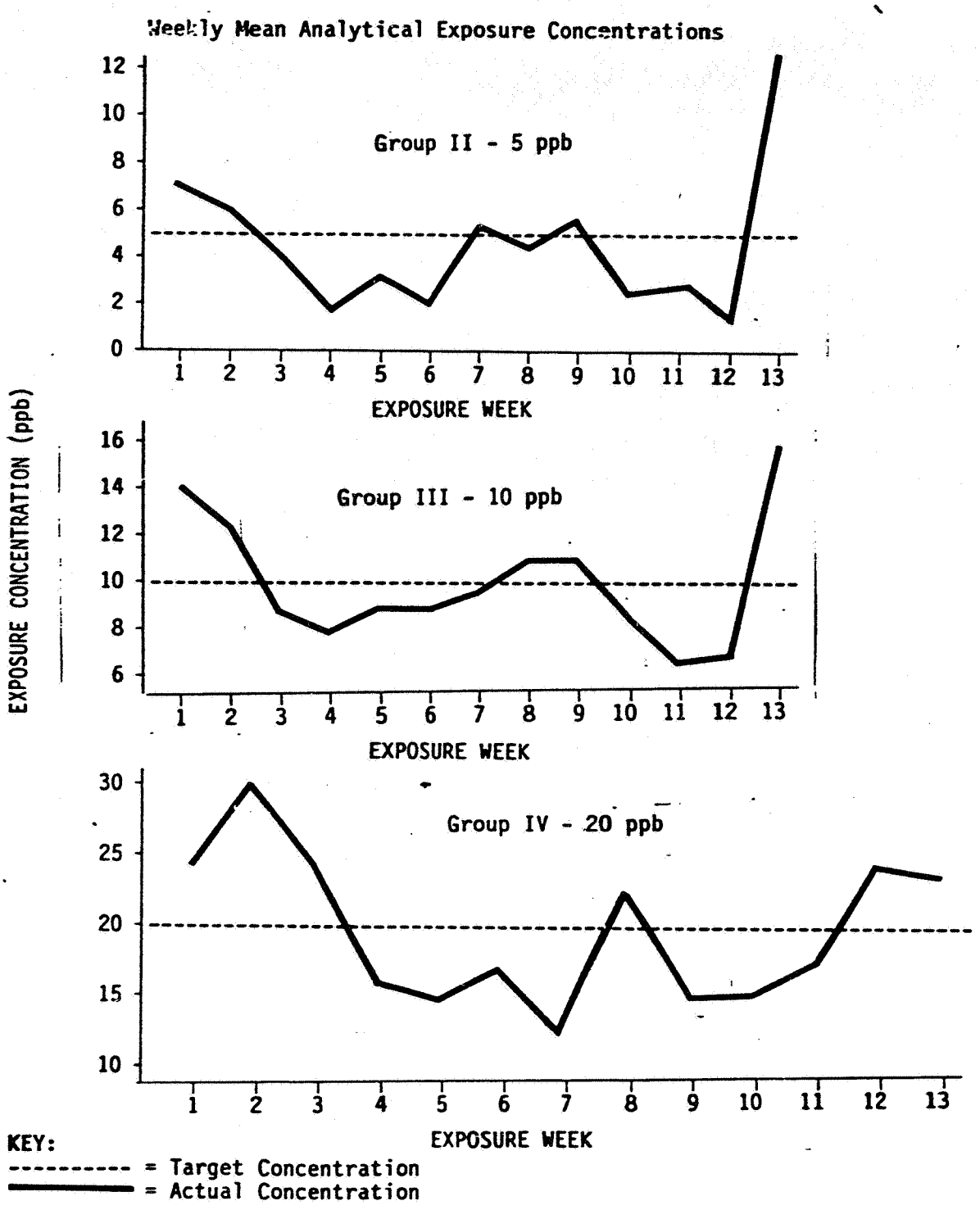
Determinations of particle sizes (Appendix B, pages 51-59 of the report) indicated that 100% of the particles were 10 um or less in diameter during each week at each concentration with the following exceptions: 0 ppb = 11%, week 11; 5 ppb = 70%, week 12; 10 ppb = 72%, week 12; and 20 ppb = 23%, week 12 and 60%, week 13.

DISCUSSION

The individual values of analytical concentration reported in the

Figure 1

A Thirteen Week Nose-Only Inhalation Toxicity Study of Chlorpyrifos Technical (Pyrinex) in the Rat



5 ppb group are considered to be too great (4.9 ± 4.5 ppb with N = 65) in order to make the statement that this group of rats received approximately 5 ppb throughout the duration of the study. However, as no toxic effects were observed at this target concentration or at the two higher concentrations (10 and 20 ppb), the Toxicology Branch will not request that the 5 ppb level be repeated. Although the amount of variation at 10 and 20 ppb is greater than would be desired, the range of analytical values is considered to be acceptable for this study.

C. Mortality, Clinical Signs, Ophthalmoscopy, Body Weight and Food Consumption

Mortality and Clinical Signs

Animals were observed once in the A.M. and once in the P.M. for mortality as well as once daily during each exposure for pharmacologic/toxicologic effects.

The following rats died during the 13-week study.

0 ppb = one male - died during or immediately following blood collection at the interim bleeding interval

5 ppb = none

10 ppb = female (3808) - euthanized in moribund condition test day 37; excessive lacrimation, ano-genital staining, mucoid nasal discharge and dried material on fur. [The study author considered these signs to be the result of nose-only tubes and not the test substance.]
four females - died during or immediately following blood collection at the interim bleeding interval

20 ppb = one male and one female - died during or immediately following blood collection at interim bleeding interval

The only clinical signs observed (in control as well as PYRINEX treated groups) were mucoid and/or red nasal discharge, matted fur, dried material on the facial area and ano-genital staining. All of these were considered by the study author to be the result of the use of nose-only exposure tubes.

Ophthalmoscopy

All rats were examined by Lionel F. Rubin, V.M.D. (Veterinary Ophthalmologist) prior to the start of treatment and at study termination (indirect ophthalmoscopy).

Rats with positive ophthalmic findings pretest were excluded from the study. At termination, it was determined that there was no indication that any of the ocular abnormalities were attributable to test article administration. [Letters from Dr. Rubin were included in the report.]

Body Weight and Food Consumption

Animals were weighed twice pretest, weekly during exposure and terminally (after fasting). Food consumption was measured weekly, starting one week before exposure and was presented (Appendix F, report pages 141-146 and 153-158) as g/kg/day, g/int (week interval) and % difference from control).

As shown in Table 3, at most intervals there were greater mean body weights in male groups treated with PYRINEX than in the control group. Statistical significance was primarily noted only at the high dose of 20 ppb. There were little or no differences between treated and control female groups.

Even though there is an apparent increase in mean body weights of treated males over the control value, it is questionable as to whether this can be definately attributable to PYRINEX administration. At any rate, this possible increase is not considered to be of toxicological significance.

Food consumption values in males were comparable among all four groups. In females, throughout most of the study in all three test article groups, there appeared to be a lower amount of food/kg/day consumed than in the respective control group (most differences were statistically significant). During week 10, the 5 and 10 ppb group means were greater (statistically significant) than the control mean (20 ppb mean about equal to control). Though statistical significance was noted, there were relatively small decreases in food consumed (g/kg/day), and as there was an equal or only slight body weight decrease in females, it is considered that treatment did not have any severe toxicological affect on this sex.

D. Hematology and Clinical Chemistry

Blood was obtained by orbital sinus venipuncture under light ether anesthesia (overnight fasting). Samples were taken from 14 males and 10 females pretest (control group) as well as from 10/sex/group at week 8 and at termination. In order to allow for comparison between bleeding intervals, an additional 4 males (control) and 4 females (10 ppb) were bled at the pretest and week 8 intervals, respectively, to replace those which died during blood drawing. Also, a 10 ppb male was mistakenly bled at termination rather than a 10 ppb female.

Hematology

The following parameters were evaluated (includes all Guideline determinations): hemoglobin, hematocrit, erythrocyte, platelet, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, prothrombin time, activated partial thromboplastin time and total as well as differential leukocyte counts.

Table 4 presents group mean values for all bleeding intervals. Although there are numerous instances of statistically significant differences between treated and control groups regarding hemoglobin,

Table 3

MEAN BODY WEIGHTS, CHANGES IN BODY WEIGHTS AND PERCENT DIFFERENCES IN BODY WEIGHTS IN RATS ADMINISTERED PYRINEX (CHLORPYRIFOS) BY INHALATION FOR THIRTEEN WEEKS

	Body Weights (g)				Change in Body Weight (g)				Difference in Body Wt. (%)			
ppb=	0	5	10	20	0	5	10	20	0	5	10	20
Week												
						MALES						
- 1	107	106	105	108	--	--	--	--	0	0	-1	1
0	138	142	143	143	31	35*	38†	36*	0	3	4	4
1	157	161	160	163	19	20	17	20	0	3	2	4
2	165	173	167	177*	8	11*	8	14†	0	5	2	8
3	170	186†	179	186†	6	13†	12†	9	0	9	5	9
4	175	197†	191	199†	4	11†	12†	13†	0	13	9	14
5	185	201	198	206*	11	4†	8	8	0	8	7	11
6	194	207	206	217†	8	6	7	11	0	7	6	12
7	199	211	211	224†	5	4	6	7	0	6	6	13
8a	-	205	206	213	-	-7	-5	-10	-	0	0	0
9	208	222	219	231†	-	17	14	19	0	7	6	11
10	218	230	230	239*	10	8	11	8	0	5	6	10
11	229	240	237	254†	12	11	7†	15*	0	5	3	11
12	236	245	233	257*	7	5	-4†	3	0	4	-1	9
						FEMALES						
- 1	78	78	77	77	--	--	--	--	0	0	0	0
0	96	99	98	99	19	21	21	22*	0	3	2	3
1	105	112†	110*	108	9	13†	11	9	0	7	4	3
2	113	116	113	116	8	4†	3†	8	0	2	-1	2
3	114	122†	119	120*	1	6†	6†	5*	0	6	4	5
4	121	125	123	125	7	4	5	5	0	4	2	4
5	126	129	126	129	5	4	3	4	0	3	0	3
6	131	133	129	133	5	4	4	4	0	2	-1	2
7	131	135	133	132	1	2	4†	-1	0	3	2	1
8a	-	132	132	129	-	-3	-2	-3	0	-	-	-
9	136	141	142	143	-	9	10	14	0	4	5	5
10	144	145	149	149	8	4†	7	6	0	0	4	3
11	149	150	151	157*	4	5	2	8†	0	1	2	5
12	153	153	152	158	5	3	0†	1†	0	0	-1	3

Statistical Significance (p <): * = 0.05; † = 0.01
- = No data available.
-- = No calculation applicable for this interval.
a = Interim bleeding; rats fasted.

NOTES: 1. Data in report stated to one decimal place; in this table, these data were rounded off to a whole number (therefore, change in body weight may be different by one).

2. Values are means of 14 or 15 rats.

Data extracted from Tables F-2 to F-7 (report pages 135-140) and Tables F-14 to F-19 (report pages 147-152).

Table 4

MEAN HEMATOLOGY VALUES FOR RATS ADMINISTERED PYRINEX (CHLORPYRIFOS) BY INHALATION FOR THIRTEEN WEEKS

Concentration (ppb)		Parameter									
		HGB	HCT	RBC	PLAT	MCV	MCH	MCHC	PT	APTT	WBC
MALES											
Pretest (13)a	-	14	38	6	10	61	22	36	-	-	5.4
Interim Bleed (week 8)	0 (11)a	13	37	7	6	55	20	36	12f	37e	3.3
	5 (9)	18†	48†	9†	7*	55	21	37	12	32	8.0†
	10 (10)	18†	49†	9†	7*	55	20	37	13	43	5.8†
	20 (10)	14	38	7	7	55	20	36	13	30	3.5
Terminal Sac. (after week 13)	0 (10)	18	50	9	7	59	20	35	12	31	6.2
	5 (10)	19†	53†	9†	6†	57*	21	36†	13f	30	6.3
	10 (11)	19†	52†	9†	7*	57†	20	36†	13*	29	6.6
	20 (10)	20†	51	9†	7*	57†	22†	38†	13*	31	7.0
FEMALES											
Pretest (10)a	-	14	38	6	9	62	22	36	-	-	5.0
Interim Bleed (week 8)	0 (10)	16	45	8	7	58	20	35	10f	28e	4.2
	5 (10)	17†	49†	8	8	60†	21†	35	10c	28b	6.4†
	10 (14)	17†	48*	8	8†	60	21†	36	10f	29d	5.2
	20 (7)	16	47	8	8	60*	21	35	11g	28g	2.9*
Terminal Sac. (after week 13)	0 (10)	18	51	8	8	61	21	34	11f	24f	4.8
	5 (10)	19†	52	9*	7	59†	21	36†	10*	24	5.6*
	10 (8)	19†	53*	9	7	61	22	35†	11f	23f	5.7*
	20 (10)	19†	51	8	8	61	23†	38†	11	25	5.2

HGB = Hemoglobin Concentration ..... g/dl
HCT = Hematocrit ..... percent
RBC = Erythrocyte Count ..... 10^6/microliter (mil/ul)
PLAT = Platelet Count ..... 10^5/microliter (100T/ul)
MCV = Mean Corpuscular Volume (calculated)..... cubic u
MCH = Mean Corpuscular Hemoglobin (calculated)..... uug
MCHC = Mean Corpuscular Hemoglobin Concentration ... g/dl (calculated)
PT = Prothrombin Time ..... seconds
APTT = Activated Partial Thromboplastin Time ..... seconds
WBC = Total Leukocyte Count ..... 10^3/microliter (thous/ul)

Statistical Analyses (p <) : * = 0.05; † = 0.01
a = Number of values in group mean unless otherwise designated.
"-" = Not determined.
Number of values in mean: b = 2; c = 5; d = 6; e = 8; f = 9; g = 10

Data extracted from report Tables G-2 to G-6 (report pages 280-284).

hematocrit and RBC parameters (including calculated MCV, MCH and MCHC), these do not appear to be attributable to test article administration as there is not only a lack of dose response, but all mean values appear to be within expected limits. Statistical significances were also noted regarding leukocyte counts in both sexes; but, these differences were not dose dependent, were in some instances higher or lower, were all considered within or near expected ranges and were not observed at the terminal interval in males. It is therefore concluded that there was no apparent influence of PYRINEX administration on this parameter. Other hematological parameters showed similar mean values for all four groups.

Clinical Chemistry

The following parameters were evaluated (includes all Guideline determinations): serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, lactic acid dehydrogenase, cholinesterase (brain at termination, erythrocyte calculated at 8 weeks and termination and plasma at 8 weeks and at termination), blood urea nitrogen, fasting glucose, cholesterol, triglycerides, total protein, albumin, globulin (calculated), A/G ratio (calculated), creatinine, uric acid, total bilirubin, sodium, potassium, chloride, calcium, inorganic phosphorus, creatine phosphokinase and gamma glutamyl transpeptidase.

Terminal plasma cholinesterase levels were statistically significantly lower than comparative controls in high-dose (20 ppb) males and in all three treatment female groups. Interim (8 week) test article values were similar or slightly greater than controls with the possible exception of the 20 ppb males which had a group mean value of 0.42 uM/ml/min versus 0.48 uM/ml/min in controls. There appeared to be little or no differences in the group mean values of red blood cell (interim or terminal) or brain (terminal) cholinesterase levels in either males or females. It therefore seems that the administered concentrations of PYRINEX by inhalation (5, 10 and 20 ppb) had no severe effect on group mean cholinesterase levels (plasma, red blood cell or brain).

Regarding other clinical chemistry parameters, although there were some sporadic differences between treated and control values, there did not appear to be any definitive effect of test article administration (not dose related and/or no consistency between the 8 week and terminal intervals).

Postmortem Examinations

Gross examinations were made on all rats that died accidently, were killed *in extremis* or were sacrificed at study termination. Animals were fasted prior to sacrifice. The following tissues (includes all Guideline tissues) were examined histopathologically (lungs were examined for all animals; other tissues examined only in 0 and 20 ppb groups; organs weighed = *): adrenals*, aorta, bone and bone marrow (sternum), brain*, esophagus, eyes, heart*, intestine

(cecum, colon, duodenum, ileum, jejunum, rectum), kidneys*, larynx, liver*, lungs*, lymph nodes, nasopharyngeal tissues, ovaries*, pancreas, pharynx, pituitary, prostate, salivary gland, skin with mammary gland, spinal cord, spleen*, stomach, testes* with epididymides, thymic region, thyroid/parathyroid, trachea, urinary bladder, uterus, gross lesions (including normal tissue) and tissue masses. In addition, the exorbital lacrimal gland and nerve (sciatic, with biceps femoris) were preserved but not examined histopathologically.

Group mean fasted terminal body weights, absolute organ weights, organ-to-body weight ratios and organ-to-brain weight ratios are presented in Table 5.

Terminal Body Weights

The 20 ppb males had a terminal group mean body weight statistically ($p < 0.01$) greater than controls (231 g vs 207 g).

Organ Weights

A number of sporadic statistically significant differences were observed between one or two treated group mean organ weights and the respective control. The majority of these appeared in the 5 or 20 ppb male groups and were considered to be due, at least in part, to mean body weights being greater in the treated groups (especially at 20 ppb). There does not appear to be any pattern and the administration of the test article is not thought to have caused a change in any organ weights examined.

Gross Pathology

Table 6 indicates the disposition of all animals in this study.

Table 6

DISPOSITION OF ANIMALS IN A 13-WEEK INHALATION STUDY IN RATS WITH PYRINEX (CHLORPYRIFOS)

Target Conc. (ppb)	Exposed	Number of Animals* Clinical Lab Studies Pre.	Interim	Term.	Nec[a]	Histo[b]	Term Sac.	Ext[c]	Spon Death	Acc. Death
0	15/15	14/10[d]	11/10	10/10	15/15	11/10	14/15	0/0	1/0	0/0
5	15/15	-	10/10	10/10	15/15	10/10	15/15	0/0	0/0	0/0
10	15/15	-	10/14[d]	11/9[e]	15/15	10/15	15/9	0/2	0/1	0/3
20	15/15	-	10/10	10/10	15/15	11/11	14/14	0/0	0/0	1/1

*=Male/Female a=Necropsy b=Histopathology c=Killed in extremis
Pre.=Pretest Term.=Terminal Spon=Spontaneous Acc.=Accidental
d=Four additional rats bled to replace those that died during bleeding.
e=Blood obtained inadvertently for one male rather than one female.

Data extracted from report pages 403 and 407.

Table 5

GROUP MEAN ABSOLUTE, RELATIVE-TO-BODY WEIGHT AND RELATIVE-TO-BRAIN WEIGHT ORGAN WEIGHTS OF RATS ADMINISTERED PYRINEX (CHLORPYRIFOS) BY INHALATION FOR THIRTEEN WEEKS

	Males				Females			
ppb =	0	5	10	20	0	5	10	20
Terminal Body Wt. (g)	207a	216	204	231**	134	133	132	145
BRAIN								
Absolute (g)	1.77	1.82	1.76	1.78	1.69	1.65	1.66	1.70
Rel. to B.W. x 1000	8.67	8.42	8.67	7.74**	12.71	12.45	12.58	12.02
Rel. to brain x 1	-	-	-	-	-	-	-	-
ADRENALS								
Absolute (g)	.0486	.0501	.0474	.0493	.0572	.0579	.0568	.0557
Rel. to B.W. x 10000	2.41	2.32	2.32	2.13	4.30	4.50	4.31	4.06
Rel. to brain x 100	2.75	2.76	2.69	2.77	3.39	3.61	3.44	3.28
HEART								
Absolute (g)	.785	.774	.805	.796	.578	.550	.585	.560
Rel. to B.W. x 1000	3.81	3.58*	3.95	3.45**	4.35	4.14	4.44	3.97
Rel. to brain x 10	4.43	4.25	4.57	4.46	3.42	3.33	3.54	3.29
KIDNEYS								
Absolute (g)	1.72	1.63	1.68	1.78	1.23	1.16	1.27	1.27
Rel. to B.W. x 1000	8.34	7.51**	8.23	7.70	9.24	8.75	9.61	8.95
Rel. to brain x 10	9.70	8.94**	9.52	9.98	7.27	7.03	7.65	7.45
LIVER								
Absolute (g)	6.16	6.31	5.80	7.00**	4.08	4.08	4.00	4.39*
Rel. to B.W. x 100	2.97	2.91	2.84	3.03	3.07	3.07	3.04	3.10
Rel. to brain x 1	3.47	3.47	3.29	3.93**	2.41	2.47	2.42	2.58
LUNGS								
Absolute (g)	.973	.902	.987*	.966	.730	.703	.763	.733
Rel. to B.W. x 1000	4.69	4.17	4.85	4.19	5.48	5.29	5.80	5.18
Rel. to brain x 10	5.48	4.97	5.60*	5.42	4.32	4.25	4.61*	4.31
SPLEEN								
Absolute (g)	.373	.348	.362	.413*	.307	.241**	.271	.307
Rel. to B.W. x 1000	1.80	1.61**	1.78	1.79	2.30	1.82**	2.06	2.17
Rel. to brain x 10	2.10	1.92	2.05	2.31*	1.82	1.46**	1.63	1.81
GONADS								
Absolute (g)	1.52	1.58	1.63	1.55	.0542	.0515	.0565	.0574
Rel. to B.W. x 1000	7.51	7.33	7.96	6.68	4.03	3.87	4.30	4.03
Rel. to brain x 10	8.60	8.73	9.23	8.66	3.19	3.11	3.41	3.38

Statistical Significance (p<): * = 0.05; ** = 0.01
a = Fasted body weight.

Data extracted from Appendix J, J-1 to J-9, report pages 360-368.

REVIEWER'S COMMENT: In Group III (10 ppb), the table on report page 407 indicates that two females were killed in extremis and three females died an accidental death. On report page 22 (B. Mortality), it is stated that one mid-exposure female (3809) was euthanized in a moribund condition and four mid-exposure females died during or immediately following blood collection at the interim bleeding interval. Appendix C, C-2, report page 61, indicates 4 females at 10 ppb died during blood collection (accidental death) and one died moribund sacrifice. Also, there were 10 indicated at the terminal sacrifice, whereas page 407 of the report indicates 9. Appendix K, Table 1, report page 412, indicates that in the mid-exposure (10 ppb) female group three rats died accidentally (A), two were killed in extremis (S) and one died spontaneously (D).

It is requested that the Registrant comment on the apparent inconsistencies noted above.

There were no apparent grossly observable changes in any of the tissues that were considered to have been caused by PYRINEX administration.

Histopathology

Unilateral degeneration of testicular germinal epithelium was observed in 10/11 control and 10/11 high-dose (20 ppb) groups (the 5 and 10 ppb animals were not examined). It is not considered that this finding was test article related.

The only tissue which appeared to show an effect of the inhalation procedure was the lung. Most of these changes appeared in the control as well as in all treated groups. There does not seem to be an effect of PYRINEX administration. Table 7 presents the histopathological lung findings.

Table 7

HISTOPATHOLOGICAL LUNG FINDINGS IN RATS EXPOSED TO PYRINEX (CHLORPYRIFOS) BY INHALATION FOR THIRTEEN WEEKS

	Males				Females			
Finding ppb =	0	5	10	20	0	5	10	20
No. of Rats Examined.....	11	10	10	11	10	10	15	11
Chronic Interstitial Pneumonia....	6	10	10	7	6	10	10	6
Pulmonary Arteries: Mineralization	3	3	0	1	0	0	9	1
Congestion.....	0	0	0	1	0	0	4	1
Hemorrhage.....	0	0	0	0	0	0	1	1

Data extracted from Appendix K, Table IV, report page 54).

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Detailed statistical methodology was described.

A Quality Assurance statement was included.

A copy of the Materials and Methods Section from the report is appended.

The reviewer has no comments regarding the Materials and Methods section.

III. Conclusions

The study author stated that the saturation or near saturation level was 20 ppb (the highest concentration tested).

There were no negative effects of toxicological significance which were felt to be attributed to the administration of PYRINEX (CHLORPYRIFOS) at the concentrations tested. There was the suggestion that a small degree of cholinesterase inhibition was observed, but the data were not considered to be definitive.

IV. Recommendation

This study is classified Supplementary.

PYRINEX (Chlorpyrifos) is a crystalline material which is applied as an aerosol. This study appears to be an exposure to a vapor. An inhalation study with the test article administered as an aerosol (dust or spray) is required.

The No Observed Effect Level (NOEL) = 20 ppb (HDT)
The Lowest Observed Effect Level (LOEL) = Not attained.

Chlorpyrifos toxicology review

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