

August 18, 1967

Mr. Morgan H. Hoover
Food, Drug and Cosmetic Chemicals
Committee
Manufacturing Chemists Association, Inc.
1825 Connecticut Avenue, N.W.
Washington, D.C. 20009

Dear Mr. Hoover:

Pursuant to your letter of August 1 on reproduction studies, attached herewith are unpublished data on an organic phosphate which showed progressing effects with succeeding generations such that lowest feeding level ultimately showed some effect.

While most of these data are in the hands of the Food and Drug Administration, they should remain confidential until our toxicologist (outside laboratory) has had opportunity to publish. They are submitted here as an unfortunate demonstration that single generation reproduction studies may not be adequate to demonstrate reproductive effects.

Very truly yours,

Original Signed
W. A. Knapp

W. A. Knapp
Consultant-Toxicology

WAK:dmk
Encls.

ASI 00002112

QUESTIONNAIRE FOR DATA ON
REPRODUCTION STUDIES

Material: (chemical or common
name optional)

Use, or Anticipated Use:

(e.g.)

A
Food Additive
or Insecticide

REPEATED DOSES TO RATS

Longest period fed	2 years
Lowest dosage level with measurable effect	2 gm/kg
Criteria affected at this level	body weight
Highest non-measurable effect level	1 gm/kg

REPRODUCTION STUDY

Maximum no. of generations to rats	3
1st or 2nd litter used to establish next generation?	1st
Highest level fed with no effect	1 gm/kg
Any effect at any level?	no
If yes, describe.	_____
Generation(s) in which seen	_____

TERATOLOGY STUDY

To rats, rabbits, or both?	Rats
Did some receive it throughout gestation?	Yes
Did some receive it during a portion of gestation period?	Yes
What portion?	Middle 1/3
Highest level with no effect	5gm/kg
Any effect at any level?	no
If so, describe.	_____

REGULATORY STATUS

Does material have tolerance or limitation under Food Additive or Miller Pesticide Amendments?	no
If yes, at what levels and for what foods or crops?	_____

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Food, Drug, and Cosmetic Chemicals Committee

See attached sheet to

No studies

Not yet

DATA ON REPRODUCTION STUDY

Compound - An organic phosphate

Anticipated Use - Pesticide

Chronic Feeding Study - Rats

Two-year feeding study at 10, 30, 100 and 300 ppm in the diet produced no clear-cut effect, excepting that on red-blood cell and plasma cholinesterase which were depressed at 10 ppm in females and at 30 ppm in males. There was some growth depression in females during study but final weights were not significantly different from controls. Also, liver to body weight ratio was shown in males at 100 ppm but not at 300 ppm.

Reproduction Study

Basis above study, a 3-generation reproduction study was run using feeding levels of 30, 100 and 300 ppm. All feeding levels showed deleterious effect which might be roughly summarized as follows. Complete table of results is attached.

<u>Criteria</u>	<u>Effect</u>
Weanling Survival	-- Depressed in all litters at 100 and 300 ppm.
Fertility Index	-- Depressed in 2nd. generation at 30, 100 and 300 ppm.
Gestation Index	-- Unaffected at any feeding level.
Viability Index	-- Depressed in 2nd. litter of each generation at 100 and 300 ppm.
Birth Weight Index	-- Questionably depressed in 2nd., litter of each generation at 100 and 300 ppm.

Note: - A repeat of this study has been made using feeding levels of 1 and 3 ppm. Results are not yet available.

WAK
8/18/67

ASI 00002114

Table 6

Summary of Reproduction Data for Control Rats and Rats on Various Dietary Levels of [REDACTED]

for Two Matings Through Three Generations

Generation	Diet level (ppm)	Number of rats			Total number of pups					Weanlings		Indices (%)			
		Mated	Preg-nant	Whelped	Born alive	Born dead	Alive day 5	Discard ^a	Weaned	Mean Wt. (g)	Survival (%)	F.I. ^d	G.I. ^e	V.I. ^f	L.I. ^g
F ₀	0	20	17 ^b	16	157	1	152	15	137	34	97	85	94	97	100
	30	20	18	18	193	5	188	23	160	32	94	90	100	95	97
	100	20	20	20	174	13	140	12	102	29	63	100	100	80	80
	300	20	17	17	149	8	96	0	63	28	42	85	100	64	66
	0	19	15	15	133	8	130	17	103	34	89	79	100	98	91
	30	20	20	20	193	17	185	25	114	32	68	100	100	96	71
	100	19	19	19	165	12	55	0	27	34	16	100	100	33	49
	300	20	17	17	119	18	39	2	19	29	16	85	100	33	51
F _{1b}	0	20	14	14	116	4	93	5	87	31	78	70	100	80	99
	30	20	12	12	71	17	66	2	62	33	90	60	100	93	97
	100	11	4 ^c	3	22	1	17	0	15	34	68	36	75	77	88
	300	7	2	2	13	1	10	0	0	0	0	29	100	77	0
	0	20	16	16	137	14	129	14	112	35	91	80	100	94	97
	30	19	15	15	139	3	129	11	111	31	86	79	100	93	94
	100	10	5	5	32	4	13	0	10	34	31	50	100	41	77
	300	6	2	2	8	7	0	0	0	0	0	33	100	0	0
F _{2b}	0	20	18	18	161	7	149	19	101	36	71	90	100	93	78
	30	20	9	9	94	1	91	12	69	35	84	45	100	97	87
	100	7	1	1	10	2	10	0	9	27	90	14	100	100	90
	0	20	14	14	125	19	118	13	84	41	75	70	100	94	80
	30	20	6	6	74	0	67	8	40	34	61	30	100	91	68
	100	7	1	1	3	0	0	0	0	0	0	14	100	0	0

a. Number of pups discarded on fifth day to reduce litter size to 10.

b. One rat died with 14 fetuses in utero.

c. One rat died with 5 fetuses in utero.

d. Fertility index = (pregnancies/matings) 100.

e. Gestation index = (litters cast/pregnancies) 100.

f. Viability index = (pups surviving 5 days/pups born alive) 100.

g. Lactation index = (pups weaned/live pups on day 5 less discards) 100.

Manufacturing Chemists' Association, Inc.

(FOUNDED 1872)

1825 CONNECTICUT AVENUE, N. W.
WASHINGTON, D. C. 20009

August 1, 1967

TO: Members of the Food, Drug, and Cosmetic Chemicals Committee and
All Others Receiving This Memo Including Drs. Oser (Food and
Drug Laboratories), Treon (Atlas), and Zapp (DuPont)

SUBJECT: Request for Data on Three-Generation Rat Studies

Gentlemen:

To assist in preparing MCA recommendations to be presented to the Panel on Reproduction Studies of the FDA Advisory Committee (ref. minutes of the June 13, 1967 FDCC Committee meeting), you are requested by Dr. C. P. Carpenter (Chairman of the Reproduction Studies Group within the FDCC Committee) to send in to me the enclosed questionnaire on three-generation rat studies in the event your toxicologists have carried out or contracted out such studies.

Hopefully, these data will enable the FDCC Committee to decide whether or not to support the requirement for three-generation studies in addition to the usual two-year feeding tests on rats and dogs which are partial requirements to obtain clearances for direct food additives. If your data have been used by the National Agricultural Chemicals Association Toxicology Committee, please so state and do not resubmit. Data are needed by August 22, 1967.

Sincerely yours,



Morgan M. Hoover

MMH:sjg

Enclosure

QUESTIONNAIRE FOR DATA ON
REPRODUCTION STUDIES

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name optional)

(e.g.)

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or Insecticide

B

C

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REGULATORY STATUS

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If yes, at what levels and for what foods or crops?	_____

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Food, Drug, and Cosmetic Chemicals Committee

ASI 00002117