1/25/1993

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DATA EVALUATION RECORD

STUDY TYPE: Subchronic feeding - rodent; Guideline §82-1a

EPA PESTICIDE CHEMICAL CODE: 064103 (OPP); 064104 (SOPP)
TOXICOLOGY CHEMICAL NO: 623AA (OPP); 787 (SOPP)
MRID NO.: 407602-06
TEST MATERIAL: o-phenylphenol
SYNONYMS: OPP, Dowcide 1

SPONSOR: The Dow Chemical Company

TITLE OF REPORT: Subchronic Toxicity of o-Phenylphenol (OPP) by Food Administration to Rats

TESTING FACILITY: Tokyo Metropolitan Research Laboratory of Public Health, 24-1 Hyakunincho 3 chome, Shinjuku-ku, Tokyo 160 Japan

STUDY NUMBER: Annual Report of Tokyo Metropolitan Research Laboratory P.H., Vol. 35, pgs. 407-415, 1984

AUTHOR(S): S. Iguchi, K. Takahasi, T. Fujii, N. Fukumori, H. Mikuriya, Y. Tada, K. Yuzawa, K. Hiraga

REPORT ISSUED: 1984

CONCLUSIONS: Dose levels of 0, 0.156, 0.313, 0.625, 1.250 and 2.500 % of OPP were given to F344/DuCrj albino rats in the diet for 13 weeks. From the limited data provided, it was noted that OPP at 1.25% and above in the diet produced reduced body weights (females only at that dose, taken from graphically depicted data) with food consumption affected at study initiation but not at study termination in males and females at 1.25 % and above. The reduced food consumption was probably related to a palatability problem with the test compound mixed in with the feed noted in other studies. Other effects included an increase in absolute and relative kidney weights in male rats treated with 0.313% OPP and above and in females at 1.25% OPP and above. The absolute and relative bladder weights were increased in male rats at 1.25% OPP and above; females did not show a similar effect. The investigators also noted gross and histopathological effects in the kidneys, but did not provide any data to support it., No definitive conclusions can be drawn from these data; however, tentatively the **NOEL for systemic toxicity is 0.156 % (182/202 mg/kg/day male/female) OPP with a LOEL of 0.313 % (391/411 mg/kg/day male/female) OPP** based on the above mentioned observations.

This study was apparently used as a range-finding study for a chronic toxicity/carcinogenicity study.

Core Classification: Core-Supplementary Data; this study does not satisfy the Guideline requirement (§82-1a) for a subchronic feeding study in rodents.

A. **MATERIALS AND METHODS:** A copy of the material and methods section from the investigators report is appended.

1. **Test compound:** o-phenylphenol
   Description - not provided
   Lot # - MM01040
   Purity - > 98%

2. **Test animals:** Species: Albino rats
   Strain: F344/DuCrj
   Age: 4 weeks
   Weight:
   Source: Nippon Charles River Co.

3. **Animal assignment**

Animals were assigned to the following test groups:

Test Group	Dose in diet	# Animals/sex
1 Control	0%	10
2 Low (LDT)	0.156%	10
3 Low Mid (LMDT)	0.313%	10
4 Mid (MDT)	0.625%	10
5 High Mid (HMDT)	1.250%	10
6 High (HDT)	2.500%	10

A "Satellite" group of 1 to 2 animals were added to each of the above groups and given different dosages of OPP than those animals they were housed near to.

4. **Diet Preparation**

Test compound was added to Nippon Kurea's CE-2 solid diet. Diet preparation periods were not provided. No data was provided for analysis of diet mixtures in this document; a separate document entitled "Quantitative Analysis of Sodium o-Phenylphenol Added Into the Standard Animals Foods and Effect of Preservation" (MRID# 921540-34) was provided to support the subchronic study. No storage information was provided.

5. Animal Husbandry

Animals were kept under standard animal care conditions, acclimated for about 1 week and received food (CE-2 solid diet, Nippon Kurea, Co., Ltd.) and water *ad libitum*.

6. Clinical Observations:

Animals were inspected once daily for "general condition" and twice daily to "see if they were alive."

7. Body Weight

Animals were weighed weekly for the experimental duration.

8. Food and Water Consumption and Compound Intake

Food and water consumption were determined every week by group. Compound intake was calculated; however food efficiency was mentioned but apparently not calculated.

9. Ophthalmological Examinations

Ophthalmological examinations were not performed.

10. Hematology and Clinical Analysis

Blood was collected at the end of treatment (EDTA-2K treated). The following parameters (X) were examined.

a. Hematology

X Hematocrit (HCT)*	X Leukocyte differential count*
X Hemoglobin (HGB)*	X Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*	X Mean corpusc. HGB conc.(MCHC)
X Erythrocyte count (RBC)*	X Mean corpusc. volume (MCV)
Platelet count*	Reticulocyte count
Blood clotting measurements	
(Thromboplastin time)	
(Clotting time)	
(Prothrombin time)	

* Required for subchronic and chronic studies

b. Clinical Chemistry

Electrolytes:
- Calcium*
- Chloride*
- Magnesium
- Phosphorous*
- Potassium*
- Sodium*

Enzymes
- X Alkaline phosphatase (ALK)
- Cholinesterase (ChE)#
- Creatinine phosphokinase*^
- Lactic acid dehydrogenase (LAD)
- X Serum alanine aminotransferase (also SGPT)*
- X Serum aspartate aminotransferase (also SGOT)*
- Gamma glutamyl transferase (GGT)
- Glutamate dehydrogenase

Other:
- Albumin*
- Blood creatinine*
- X Blood urea nitrogen*
- X Cholesterol*
- Globulins
- X Glucose*
- Total bilirubin
- X Total serum Protein (TP)*
- Triglycerides
- Serum protein electrophoresis
- Calculated Alb/Glob coeff.

* Required for subchronic and chronic studies
^ Not required for subchronic studies

11. Urinalysis

Urine was collected on week 9 and 13. The following parameters (X) were examined.

- Appearance*
- Volume*
- Specific gravity*
- X pH
- Sediment (microscopic)*
- X Protein*
- X Glucose*
- X Ketones*
- Bilirubin*
- X Blood*
- Nitrate
- Urobilinogen

The above not required for subchronic studies
* Required for chronic studies

12. Sacrifice and Pathology

All surviving animals were sacrificed at 13 weeks. A gross pathological examination was conducted. No histological examinations were conducted; however, apparently the tissues were used in another "publication" according to the study authors. The bladder was fixed in 10% neutral buffered formalin and weighed after one week. The following organs also were weighed.

Digestive system	**Cardiovas/Hemat.**	**Neurologic**
Tongue	Aorta*	X Brain*+
Salivary glands*	X Heart*	Periph. nerve*#
Esophagus*	Bone marrow*	Spinal cord (3levels)*#
Stomach*	Lymph nodes*	Pituitary*
Duodenum*	X Spleen	Eyes (optic n.)*#
Jejunum*	X Thymus*	**Glandular**
Ileum*	**Urogenital**	X Adrenal gland*
Cecum*	X Kidneys*+	Lacrimal gland#
Colon*	X Urinary bladder*	Mammary gland*#
Rectum*	X Testes*+	Parathyroids*++
X Liver *+	Epididymides	Thyroids*++
~~Gall bladder~~*	X Prostate	**Other**
Pancreas*	Seminal vesicles	Bone*#
Respiratory	X Ovaries*+	Skeletal muscle*#
Trachea*	X Uterus*	Skin*#
Lung*		All gross lesions and masses*
Nose		
Pharynx		
Larynx		

* Required for subchronic and chronic studies.
\# Subchronic studies, only if indicated by signs of toxicity or target organ involvement.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

13. Statistics

The following statistical procedures were utilized:

The difference in the average values of the results was tested (t-test) and the significant level was 5% (P=0.05).

14. Compliance

A signed "Statement of NO Data Confidentiality Claims" was provided.

A signed "Compliance with Good Laboratory Practice Standards" document was provided.

A signed "Flagging Statement Per 40 CFR 158.34" was **not** provided.

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B. RESULTS:

1.Clinical Observations:

According to the investigators: "Although no special change in behavior was observed, the rats of both sex in the 2.5% group treated with 2.5% OPP spilled an excessive amount of feed in the initial stage of the study, and they tended to be thin through the study period." Further, "Two male rats in the group treated with 2.5% OPP dies {died} four days into the study and one female rat in the same group died eight days into the study." No data were provided to support these statements.

2. Body Weight

The following attached figures present the body weight data as growth curves and changes in body weight gain. According to the investigators: "Both female and male groups treated with 2.5% OPP and female{s} in the group treated with 2.5% {1.25%} OPP exhibited significantly less weight gain through the entire study." This is somewhat supported by the supplied data; however, no group mean or individual animal data were provided.

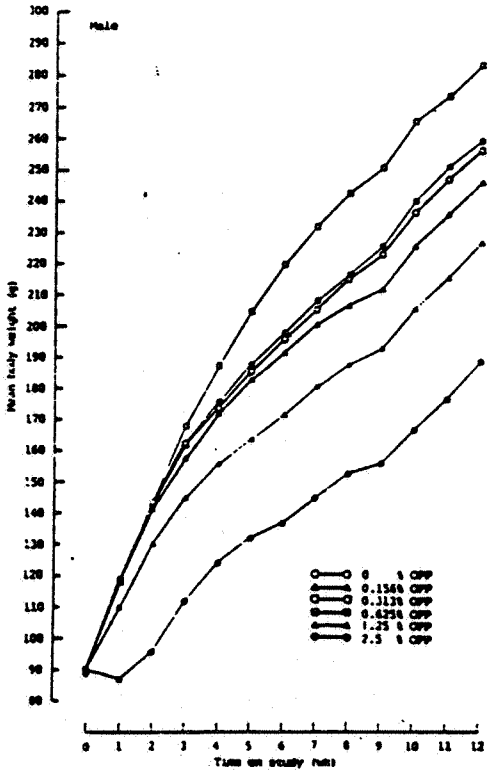

Fig. 1 Growth Curve

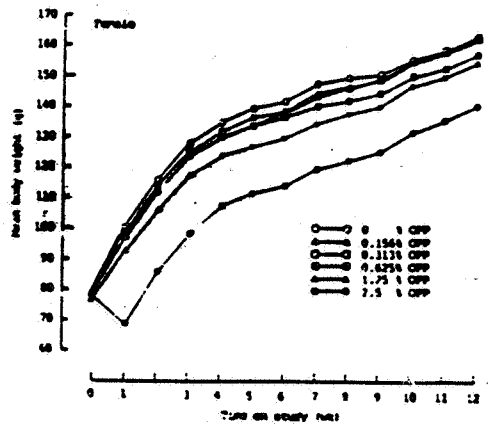

Fig. 2 Growth Curve

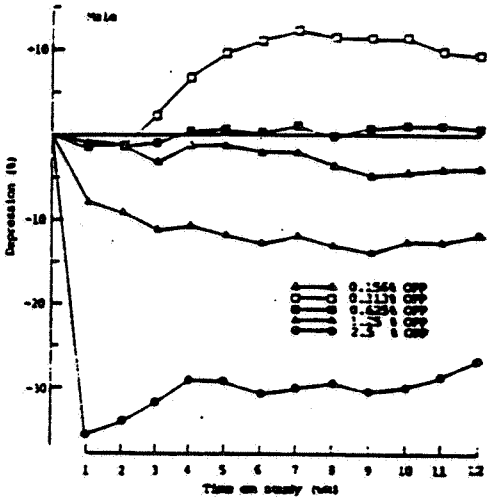

Fig. 3 Changes of Degree for Depression in Body Weight Gain of Dosed Groups

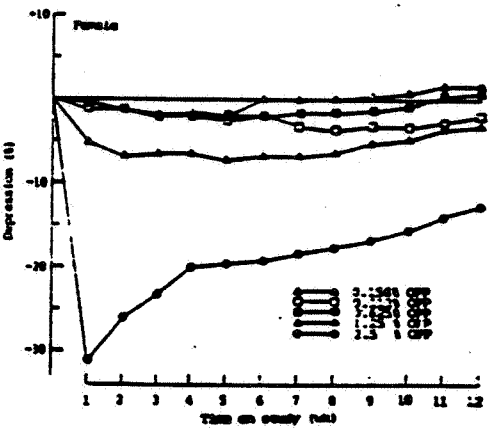

Fig. 4 Changes of Degree for Depression in Body Weight Gain of Dosed Groups

3. Food and Water Consumption and Compound Intake

The following tables provide food and water consumption. No compound intake was calculated. No individual animal data were provided.

Food Consumption (g/kg/day)

Week	Control	0.125%	0.313%	0.625%	1.25%	2.5%
			Males			
0	96.6	101.4	111.6	103.2	88.6*	16.4*
1	99.8	98.4	105.5*	104.1*	106.6*	113.2*
7	50.5	47.9	56.4	52.2	51.0	49.9
12	49.4	45.3*	47.0	47.0	47.8	48.8
			Females			
0	95.8	101.2	111.5*	97.3	91.7	20.2*
1	106.1	97.4	104.2	105.6	105.3	117.4*
7	54.1	56.3	53.7	53.7	57.0	54.0
12	49.9	52.0	51.1	52.2	55.0	52.3

p < 0.05 compared to control

Data extracted from Table 1 of the investigators report.

Water Consumption (g/kg/day)

Week	Control	0.125%	0.313%	0.625%	1.25%	2.5%
			Males			
0	185.4	184.5	182.3	189.7	166.0*	196.7*
1	136.8	140.1	142.3	152.1*	154.2*	211.1*
7	77.3	72.0	75.6	76.4	80.2	104.3*
12	73.6	65.5*	70.8	73.1	77.6	119.6*
			Females			
0	201.1	198.2	202.3	202.5	177.3*	93.0*
1	160.4	156.3	156.3	158.7	154.5	216.6*
7	73.4	85.0	89.6	92.5	95.5	112.3*
12	86.2	94.6	91.5	96.1	101.6*	132.3*

p < 0.05 compared to control

Data extracted from Table 1 of the investigators report.

At the 1.25 % dose level and above males and females consumed less food initially and then rebounded. At the end of the study no major differences were noted in food consumption. According to the investigators, there was decreased food efficiency, but no data were provided. At the 1.25 % dose level and above animals consumed less water initially than controls and then rebounded and were consuming more water at the end of the study; however, the biological relevance of this observation is unclear. The compound intake was 182/202, 391/411, 761/603, 1669/1650, and 2798/3014 mg/kg/day for the 0.156, 0.313, 0.625, 1.25, and 2.5 % OPP males/females, respectively.

4. Hematology and Clinical Analysis

a. Hematology

The following table presents the results of the hematological tests (no individual animal data were provided):

Table 4. Hematology

Dietary level of OPP(%)	No. of rats	RBC (×10⁶/mm³)	Hgb (g/dl)	Hct (%)	MCV (μ³)	MCH (μμg)	MCHC (%)	WBC (×10³/mm³)	Differential count of leucocytes (%)			
									Neutro	Lympho	Mono	Eosino
Male		0										
0	12	8.78±0.37*	17.7±0.4	44.4±1.0	51.2±1.1	20.2±0.8	39.9±1.4	8.31±1.27	14.7±5.5	83.4±5.6	1.1±1.2	0.6±1.2
0.156	11	8.81±0.51	17.3±0.5	43.1±1.1	51.5±1.2	20.2±0.9	39.4±1.5	8.03±0.37	16.2±5.9	82.1±5.6	0.9±0.9	0.5±0.5
0.313	11	8.54±0.51	17.7±0.8	43.2±1.9	50.8±0.9	19.9±0.5	39.1±0.9	8.22±1.59	14.5±4.5	84.5±4.6	0.1±0.4	0.7±1.0
0.625	11	8.63±0.46	17.5±0.6	43.6±1.4	51.2±1.1	20.3±0.7	39.9±0.8	8.42±1.55	15.0±4.4	83.0±5.1	0.7±1.0	1.1±1.0
1.25	12	8.50±0.42	17.1±0.9	43.5±2.2	51.3±1.0	20.1±0.7	39.4±1.3	7.39±1.93	12.7±4.5	85.4±4.9	0.6±0.7	1.1±1.2
2.5	8	8.22±0.47*	16.5±0.9*	43.4±3.0	52.4±2.5	19.9±0.5	38.1±1.1*	7.53±1.65	12.5±5.2	86.0±5.2	0.5±0.5	1.0±1.2
Female												
0	11	8.72±0.45	17.7±0.9	46.6±1.0	54.1±1.3	20.4±0.2	38.1±1.2	7.23±1.31	14.1±4.0	84.8±4.6	0.1±0.4	0.5±0.9
0.156	11	8.87±0.50	17.5±0.8	46.9±1.4	54.0±1.3	20.2±0.5	38.2±1.3	8.47±0.50	14.2±5.8	84.3±5.5	0.5±0.8*	0.3±0.5
0.313	12	8.73±0.53	17.7±0.9	46.3±2.9	54.2±1.2	20.2±0.6	38.2±1.6	8.73±0.53	13.5±5.6	85.0±6.9	0.7±1.0	0.6±0.8
0.625	11	8.73±0.50	17.5±0.5	46.4±1.5	53.3±1.2	20.1±0.7	37.7±1.3	8.73±0.50	11.3±3.8	88.0±4.2	0.0±0.2	0.8±1.2
1.25	12	8.56±0.46	17.0±0.8*	45.5±2.5	53.4±1.3	19.9±0.4*	37.4±1.2	8.56±0.46	11.8±5.8	87.0±5.9	0.5±0.6	0.5±0.5
2.5	12	8.53±0.37	16.7±0.9*	44.6±3.0	52.3±1.0*	19.7±0.6*	37.6±1.6	8.53±0.37	11.5±7.1	86.4±7.7	1.1±1.9	0.5±0.5

1) Mean±SD
* Significantly different from control group at $P<0.05$

The investigators felt that there was a decrease in RBC, Hgb and MCHC in 2.5% males and in Hgb and MCH for females treated with 1.25% and above; however, the differences were within experimental error for the parameters although they were statistically different from the control..

b. Clinical Chemistry

The following attached table presents the results of the clinical analysis of the blood, no individual animal data were provided. No treatment related or biologically relevant effects were noted.

Table 5. Blood Chemistry

Dietary level of OPP(%)	No. of rats	GOT (KU/ml)	GPT (KU/ml)	Alp (KAU/dl)	TP (g/dl)	Glu (mg/dl)	UN (mg/dl)	Cho (mg/dl)
Male								
0	10	113.7±14.6*	45.4± 6.9	13.4±1.0	6.6±0.3	145.0± 4.2	22.2±0.9	66.4±2.3
0.125	10	124.1±21.2	53.0±12.3	15.6±4.4	7.2±1.1	145.0±16.3	22.5±3.6	70.8±4.7
0.313	10	118.8±18.0	50.4±12.2	15.1±3.4	7.3±1.4	140.5±22.1	22.5±4.1	68.8±4.5
0.625	10	120.5±21.5	45.1±10.4	14.8±3.6	7.1±1.3	130.3±22.3	21.1±4.0	67.7±3.3
1.25	10	118.0±19.9	43.3± 7.2	15.0±3.3	6.8±0.9	144.2±11.9	20.7±2.7	67.6±3.1
2.5	8	128.0±12.9	49.4±20.4	19.2±7.0	7.3±1.5	151.0±18.2	24.0±8.3	70.1±7.2
Female								
0	10	138.2±21.9	46.6±13.2	14.2±4.6	6.9±0.9	148.5±13.4	22.2±3.6	72.3±4.2
0.125	10	121.8±15.6	41.8± 7.7	14.7±3.3	6.7±1.2	151.5±17.6	20.3±3.2	71.2±4.5
0.313	10	132.2±17.9	44.3±10.9	15.4±3.1	6.7±1.2	146.5±15.1	20.6±3.9	67.7±5.2*
0.625	10	136.7±23.8	43.9± 9.6	16.7±3.8	7.0±1.0	132.3±18.7	22.4±3.8	71.7±6.3
1.25	10	121.2±23.0	39.5±10.1	14.7±4.2	7.1±1.0	141.2± 6.2	20.7±2.6	71.6±3.7
2.5	9	120.2±22.9	35.0± 6.3	15.5±3.3	7.0±1.3	136.7± 6.7	22.3±4.3	73.8±4.4

1) Mean±SD
* Significantly different from control group at $P<0.05$

5. Urinalysis

No individual animal data were provided for the urinalysis measurements. Occult blood was detected in the urine of 1 male rat each of the 1.25 % and 2.5 % groups; however too few animals were involved to say this was treatment related. But it must be noted that the urinary system is the target organ for this chemical. No other effects were noted.

6. Organ Weights

The following table presents selected organ weight data, no individual animal data were provided.

Absolute (A) and Relative (R) Organ Weights

Organ	Control	0.125%	0.313%	0.625%	1.25%	2.5%
Males						
Kidney Right (A = Absolute in mg, R = Relative in mg/100 g bw)						
A	891	881	989	967	893	829
R	351	350	347	366*	371*	408*
Kidney Left						
A	887	874	1010*	965	903	778
R	349	347	354	366*	376*	409*
Bladder (A = Absolute in mg, R = Relative in mg/100 g bw)						
A	95.2	92.5	95.1	103.6	103.1*	97.6
R	37.1	37.2	33.4	39.5	55.4*	59.3*
Females						
Kidney Right						
A	629	603	608	604	601	632
R	379	370	380	370	385	436*
Kidney Left						
A	626	616	610	615	607	620
R	377	377	381	376	389	423*
Bladder						
A	85.5	78.9	76.9	79.6	85.5	86.0
R	52.2	48.0	47.4	48.8	54.8	58.9

p < 0.05 compared to control

Data extracted from Table 1 of the investigators report.

There was an increase in absolute and relative kidney weights in male rats treated with 0.313% OPP and above and in females at 1.25% OPP and above. The absolute and relative bladder weights were increased in male rats at 1.25% OPP and above; females did not show a similar effect.

7. Pathology

According to the investigators, the autopsy of the animals that died "showed nothing in the stomach and only a small amount of material ... in the intestine. Histologically, no pronounced change was observed in stomach, intestine and other organs."

The investigators "visually observed" organs in animals sacrificed at the end of the study. They found that: "The surface of the kidneys exhibited rising water bubbles in one male rat in the group treated with 0.156% OPP and twelve male rats in the group treated with 2.5% OPP. No other recognizable change was observed. After the organs were fixed, small bums were observed on the mucous membrane of the bladder from the males of a group treated with 1.25% OPP."

They further stated that: "In a pathological and histological observation of the organs, the only changes related to OPP administration consisted of an inflammation of the kidneys and the abnormal growth in the mucous membrane of the bladder. The change in the kidneys was most pronounced in the group of female and male rats treated with 2.5% OPP and the change in the bladder was most pronounced in the group of male rats treated with 1.25% OPP. No special change was observed in any other organs and tissues."

They apparently published a separate report on these observations; however, no data were provided to support any of the above statements.

C. DISCUSSION/CONCLUSIONS:

Dose levels of 0, 0.156, 0.313, 0.625, 1.250 and 2.500 % of OPP were given to F344/DuCrj albino rats from Nippon Charles River Co. in the diet for 13 weeks. From the limited data provided, it was noted that OPP at 1.25% and above in the diet produced reduced body weights (females only at that dose, taken from graphically depicted data) with food consumption affected at study initiation but not at study termination in males and females at 1.25 % and above. The reduced food consumption was probably related to a palatability problem with the test compound mixed in with the feed (also noted in other studies). Other effects included an increase in absolute and relative kidney weights in male rats treated with 0.313% OPP and above and in females at 1.25% OPP and above. The absolute and relative bladder weights were increased in male rats at 1.25% OPP and above; females did not show a similar effect. The investigators also noted gross and histopathological effects in the kidneys, but did not provide any data to support it. No definitive conclusions can be drawn from this data; however, tentatively the **NOEL for systemic toxicity is 0.156 % (182/202 mg/kg/day male/female) OPP with a LOEL of 0.313 % (391/411 mg/kg/day male/female) OPP** based on the above mentioned observations.

This study was apparently used as a range-finding study for a chronic toxicity/carcinogenicity study.

Core Classification: Core-Supplementary Data; this study does not satisfy the Guideline requirement (§82-1a) for a subchronic feeding study in rodents.

ORTHOPHENYLPHENOL (064103)

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