1/19/1993

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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.: 921540-35 reformat of 407602-07

TEST MATERIAL: Orthophenylphenol

SYNONYMS: OPP, Dowcide 1

SPONSOR: The Dow Chemical Company

TITLE OF REPORT: Subacute Toxicity of o-Phenylphenol by Food Administration to Male Rats.

STUDY NUMBER: *Annual Report of Tokyo Metropolitan Research Laboratory* P.H. 32 (2), 33-39, 1981.

TESTING FACILITY: Tokyo Metropolitan Research Laboratory of Public Health, 3-24-1 Hyakunin-cho, Shinjuku-ku, Tokyo-to 160

AUTHOR(S): K. Nakamura, S. Iguchi, T. Ikeda, K. Hiraga

REPORT ISSUED: 1981, reformatted January 18, 1990

CONCLUSIONS: Dose levels of 0, 0.625, 1.250 and 2.500 % OPP in the diet were administered to only male Fischer (F344/DuCrij) albino rats from Nippon Charles River Co. Ltd. for 90 days. From the limited data provided, it was noted that OPP at 1.25 and 2.5 % in the diet produced reduced body weights (with a slight effect in the low dose group), ~~increased~~ decreased food and ~~decreased~~ increased water consumption. The reduced food and increased water consumption may be related to a palatability problem with the test compound mixed in with the feed (also noted in other studies). Other effects were an increase in relative organ weights for the brain, lung, liver, spleen, kidney, adrenal, testis, and bladder from 0.625 % and above. No definitive conclusions can be drawn from these data; however, tentatively the **NOEL for systemic toxicity is less than 0.625 % (377 mg/kg/day) OPP (LDT).** It must be noted that the percent active ingredient in the test compound was not provided.
Core Classification: Core-Supplementary Data; this study does not satisfy the Guideline requirement (§82-1a) for a subchronic feeding study in rodents.

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

1. **Test compound:** orthophenylphenol
Description - not provided
Lot # - MM01040
Purity - not provided

2. **Test animals:** Species: Albino rats - males only
Strain: Fischer (F344/DuCrij)
Age: 4 weeks
Weight: approx. 100 g at start of study
Source: Nippon Charles River Co. Ltd.

3. **Animal assignment**

Animals were assigned to the following test groups:

Test Group	Dose in diet	Animals
1 Control	0%	10
2 Low (LDT)	0.625%	10
3 Mid (MDT)	1.250%	10
4 High (HDT)	2.500%	10

4. **Diet Preparation**

Diet was added to CE-2 powder feed and made into pellets. Diet preparation periods were not provided. The investigators stated that the diet mixtures were stable for at least 8 weeks, no data were provided in this document to support this claim; 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 (pelleted CE-2) and water *ad libitum*.

6. **Clinical Observations:**

Animals were inspected daily for "condition".

7. **Body Weight**

Animals were weighed weekly for the experimental duration.

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8. Food and Water Consumption and Compound Intake

Food and water consumption was determined at the beginning of each experimental week. Compound intake was calculated. Food Efficiency was not determined.

9. Ophthalmological Examinations

Ophthalmological examinations were not performed.

10. Hematology and Clinical Analysis

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

a. Hematology

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

* 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:
X Albumin*
Blood creatinine*
X Blood urea nitrogen*
Cholesterol*
Globulins
X Glucose*
Total bilirubin
X Total serum Protein (TP)*
Triglycerides
Serum protein electrophoresis

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

11. Urinalysis

Urine was collected during the eighth and twelfth week. The following parameters (X) were examined.

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

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

12. Sacrifice and Pathology

All surviving animals were sacrificed at 13 weeks. The following organs were weighed. No gross pathological or histological examinations were conducted.

Digestive system	**Cardiovas/Hemat.**	**Neurologic**
Tongue	Aorta*	X Brain*+
Salivary glands*	X Heart*	Periph. nerve*#
Esophagus*	Bone marrow*	Spinal cord (3levels)*#
Stomach*	Lymph nodes*	X 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	Ovaries*+	Skeletal muscle*#
Trachea*	Uterus*	Skin*#
X 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 procedures were utilized in analyzing the numerical data (from the investigators report):

All of the experimental results were statistically checked for the risk ratio of 5% by student's t-test. (The results of the autopsy and pathological examination are presented in a separate report.)

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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 provided.

B. RESULTS:

1.Clinical Observations:

According to the investigators: "One animal in a group of ten administered 2.5% of OPP was near death, and he was slaughtered after ten weeks. All the rest of the animals exhibited no change in appearance regardless of the dosage of OPP administration." No data were provided to support this statement.

2. Body Weight

The following table and figure (ratio of weight gain) present the body weight data:

	Body Weights (Body Weight Gains) (g)		
Week/Control	**0.625%**	**1.250%**	**2.500%**
0 101.5	99.5	99.2	101.0
1 125.8 (24.3)	121.4 (21.9)	116.3* (17.1)	101.6* (0.6)
7 232.2 (130.7)	222.5 (123.0)	199.1* (99.9)	172.2* (71.2)
13 293.8 (192.3)	285.0 (185.5)	259.0* (159.8)	227.7* (126.7)

p < 0.05 compared to control

Data extracted from Table 1 of the investigators report.

The mid and high dose groups gained less weight as compared to the control.

3. Food and Water Consumption and Compound Intake

	Food Consumption (g/kg/day)		
Week/Control	**0.625%**	**1.250%**	**2.500%00%**
1 97.9	101.1	102.0	101.9
7 50.8	52.7	53.5	51.2
13 47.1	49.5	48.6	52.5*

p < 0.05 compared to control

Data extracted from Table 2 of the investigators report.

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Week/Control		Water Consumption (g/kg/day) 0.625%	1.250%	2.500%
1	131.4	136.3	144.0*	164.9*
7	78.3	79.5	?	98.3*
13	62.5	66.4	70.6*	117.8*

p < 0.05 compared to control

Data extracted from Table 4 of the investigators report.

The high dose group consumed less food and the mid and high dose group consumed more water than that of control. The compound intake was 377, 763 and 1554 mg/kg/day for the 0.625, 1.25 and 2.5 % OPP, respectively.

4. Hematology and Clinical Analysis

a. Hematology

The following table presents the results of the hematological tests:

Table 6. Hematological Tests

	0 %(Control)	0.625%	1.250%	2.500%
WBC (10^3/mm^3)	6.91±1.99	6.49±1.93	6.52±2.09	7.11±2.07 (9)
RBC (10^6/mm^3)	8.44±0.33	8.24±0.29	8.25±0.42	8.03±0.32*(9)
Hgb (g/dl)	16.2±0.6	16.0±0.5	16.0±0.5	15.7±0.6* (9)
Hct (%)	43.6±2.8	42.6±2.5	43.4±3.4	42.6±2.3 (9)
MCV (μ^3)	51.8±2.9	51.7±2.8	52.5±2.7	53.2±3.3 (9)
MCH (ng)	19.3±0.6	19.4±0.4	19.5±0.7	19.6±0.5 (9)
MCHC (%)	37.4±2.2	37.4±1.8	37.2±2.4	36.9±2.1 (9)

The figures represent an average±S.D. for ten animals unless otherwise noted. The number of examples in parentheses. *P<0.05 compared to the control group.

As shown on the above Table 6 (from the investigators report), the RBC and Hgb values in the high dose group were statistically significantly lower than that observed in the control group. The differences noted have very little biological relevance since they are within experimental error for the groups.

b. Clinical Chemistry

The following table presents the results of the clinical analysis of the blood, no differences were noted in measured parameters.:

Table 7. Serum Biochemical Tests

	0 %(Control)	0.625%	1.250%	2.500%
TP (g/dl)	8.27±1.43	8.15±1.63	8.12±1.52	8.62±1.59 (9)
Alb (g/dl)[a]	6.35±1.72	5.86±0.34	6.81±2.49	6.13±0.89 (9)
Glu (mg/dl)	190.6±44.2	190.0±52.0	176.1±14.7	172.4±28.7 (9)
UN (mg/dl)	22.6±1.6	22.3±2.7	23.2±3.3	24.1±2.1 (9)
Alp (KA-U/dl)	38.7±9.7	38.7±12.5	41.0±14.3	43.1±7.4 (9)
GOT (K.U/ml)	141.6±16.8	139.8±21.9	135.9±19.2	146.0±29.0 (9)
GPT (K.U/ml)	69.9±27.5	53.6±8.8	60.0±23.1	52.2±9.0 (9)

The figures represent an average±S.D. for ten animals unless otherwise noted. The number of examples in parentheses. a) Measured according to the bromocresol green method.

5. Urinalysis

The following table presents the results of the urinalysis:

Table 8. Urinalysis

	PROTEIN 蛋白量 (mg/dl) (−)	(±)	30	100	300	>1000	FOFUKINE 検出例数[a]
0 %	0	1	0	9	0	0	10
0.625%	0	0	2	4	1	0	7
1.250%	0	0	2	7	0	0	9
2.500%	0	3	2	1	0	0	6

	pH 5.5	6	6.5	7	7.5	8	8.5	検出例数[a]
0 %	0	1	1	4	3	1	0	10
0.625%	0	0	1	4	1	1	0	7
1.250%	0	3	2	4	0	0	0	9
2.500%	0	3	1	1	0	1	0	6

a) Omitted the samples in which sperm was detected.

The investigators reported that no positive results were obtained for glucose or ketones; however, no data were provided. They also stated that only one sample contained blood and that no pathological signs such as "renal cylinder" were noted; however, again no data were provided. The provided information stated that "A tendency for the pH and protein to decrease was observed in the groups fed 2.5% OPP and 1.25% OPP feed." However, any biological relevance is unclear.

6. Organ Weights

The following table presents the organ weight data:

表 5. Organ Weights of Rats Fed by OPP at 13 Week

		0 %(Control)	0.625%	1.250%	2.500%
No. of Rats		10	10	10	9
Brain	(mg)	1935± 36 a) (657± 50) b)	1893± 53 (662± 50)	1894± 59 (730± 56)*	1860± 51*(8) c) (811± 56)*
Heart	(mg)	819± 46 (277± 17)	814± 51 (284± 17)	732± 70* (280± 12)	668± 57* (287± 7)
Lung	(mg)	838± 74 (284± 28)	823± 70 (287± 22)	761± 93 (290± 14)	718± 50* (310± 16)*
Liver	(g)	10.36±1.22 (3.49±0.18)	10.82±0.99 (3.76±0.19)*	9.83±1.33 (3.75±0.27)*	10.28±1.27 (4.41±0.24)*
Spleen	(mg)	549± 42 (186± 12)	544± 48 (190± 12)	512± 49 (196± 9)	496± 37* 214± 15)*
Thymus	(mg)	179.3±21.0 (60.9± 7.5)	175.6±25.7 (61.1±6.9)	163.4±23.4 (62.8±8.9)	148.4±23.3* (64.3±11.4)
Kidney	R (mg)	863± 75 (292± 13)	919± 78 (320± 14)*	861±103 (329± 16)*	885±113 (381± 36)*
	L	888± 57 (301± 13)	948±101 (330± 20)*	868± 90 (332± 11)*	929±112 (400± 33)*
Pituitary G.	(mg)	8.0±0.5 (2.7±0.2)	8.2±0.9 (2.9±0.2)	7.6±1.6 (2.9±0.8)	6.7±0.8* (2.9±0.3)
Adrenal G.	R (mg)	19.7±2.0 (6.7±0.7)	20.1±3.1 (7.0±0.9)	19.2±2.6 (7.4±0.8)	18.7±2.5 (8.0±0.6)*
	L	21.7±3.1 (7.4±1.2)	22.2±2.4 (7.7±0.9)	20.2±4.0 (7.7±1.1)	21.7±2.3 (9.4±0.9)*
Testis	R (mg)	1353± 34 (460± 42)	1368± 79 (477± 37)	1338± 97 (512± 29)*	1298± 83 (560± 21)*
	L	1401± 45 (476± 41)	1407± 95 (490± 33)	1376± 95 (527± 31)*	1348± 71 (582± 23)*
Prostate	(mg)	277± 51 (93± 12)	301± 60 (105± 21)	218± 61* (83± 18)	214± 52*(8) (90± 19)
Bladder**	(mg)	111.4±24.0 (38.0±8.4)	120.2±13.8 (41.9± 5.7)	139.0±19.5* (53.7±10.6)*	128.7±10.0 (55.8±6.7)*
Body Weight	(g)	296± 27	287± 23	262± 29*	232± 18*

1) absolute wet weight ± S.D. 2) relative weight (/100g body weight) ± S.D.
3) No. of the organs 4) weighed after fixation * $P<0.05$

There was a dose related change in relative (but not absolute) weight of the brain, lung, liver, spleen, kidney, adrenal, testis, and bladder (after formalin treatment) with statistical significance achieved in the low dose group for kidney and liver weights, the mid dose group for kidney. liver, brain, testis, bladder and high dose groups for the previous organs and lung, adrenal, and spleen. The utility of organ weights after formalin fixation is unclear, although several organs are easier to handle after this treatment, it is not known if the bladder is one of these. However, it is known that the bladder (and the urinary system as a whole) is a target organ for this chemical and the effect may be real.

C. DISCUSSION/CONCLUSIONS:

Dose levels of 0, 0.625, 1.250 and 2.500 % OPP in the diet were administered to only male Fischer (F344/DuCrij) albino rats from Nippon Charles River Co. Ltd. for 90 days. From the limited data provided, it was noted that OPP at 1.25 and 2.5 % in the diet produced reduced body weights (with a slight effect in the low dose group), increased food and decreased water consumption. The reduced food and increased water consumption may be related to a palatability problem with the test compound mixed in with the feed (also noted in other studies). Other effects were an increase in relative organ weights for the brain, lung, liver, spleen, kidney, adrenal, testis, and bladder from 0.625 % and above. No definitive conclusions can be drawn from these data; however, tentatively the **NOEL for systemic toxicity is less than 0.625 % (377 mg/kg/day) OPP (LDT).** It must be noted that the percent active ingredient in the test compound was not provided.

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

ORTHOPHENYLPHENOL (064103)

Page_____ is not included in this copy.

Pages 10 through 13 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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