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DATA EVALUATION RECORD

STUDY TYPE: Chronic feeding/carcinogenicity in the rodent
Guideline §83-1a, §83-2a

EPA PESTICIDE CHEMICAL NO.: 064104 (SOPP); 064103 (OPP)
TOXICOLOGY CHEMICAL NO: 787 (SOPP); 623AA (OPP)
MRID NO.: 407602-03

TEST MATERIAL: Sodium Orthophenylphenate

SYNONYMS: OPP-Na, Dowcide A, SOPP

TITLE OF REPORT: Carcinogenicity Testing of Sodium Orthophenylphenate in F-344/DuCrj rats.

STUDY NUMBER: Published in *J.Saitama Med.School*. 12:277-287, 1985

SPONSOR: The Dow Chemical Company

TESTING FACILITY: Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, 1983

AUTHOR(S): Kogo Hiraga

REPORT ISSUED: 1983 or 1985 (published)

CONCLUSIONS: Sodium orthophenylphenate was administered to male and female F344/DuCrj albino rats from Charles River Japan, Inc. at dose levels of 0, 0.7 and 2 % in the diet to males and 0, 0.5 and 1 % in the diet to females for 106 weeks (104 weeks with treated diet, 2 weeks with basal) and for a "lifespan" study at dose levels of 0, 0.25, 0.7, and 2 % in the diet to males and 0, 0.25, 0.5, and 1 % in the diet to females. There were not sufficient data (measured parameters) to establish chronic toxicity LOEL and NOEL in this study.

No treatment related non-neoplastic lesions were observed in the 104(6) week study (however, no individual animal data were provided). Some increase in interstitial nephritis and pyelonephritis was observed in the high dose group females (slightly increased in males). Neoplastic lesions (no individual animal data were provided) were found in the urinary tract, particularly the urinary bladder, in both 106-week and lifespan studies. In the 106-week study, urinary bladder tumors occurred in 47/50 (94%) high-dose males, 2/50 (4%) low-dose males, 4/50

(8%) high-dose females, 1/50 (2%) low-dose females and 0/50 (0%) controls in both sexes. In the lifespan study, urinary bladder tumors occurred in 23/25 (92%) high-dose males, 3/25 (12%) mid-dose males, 2/25 (8%) high-dose females, 0/24 (0%) mid-dose females and 0/25 (0%) the other groups including controls of each sex. There was an increase in endometrial stromal polyp of the uterus in the high dose group of the 104(6) week study but not in the lifespan study.

Based on the available data, Na-OPP appears to be carcinogenic in male and female rats. This chemical will be recommended to the HED Carcinogenicity Peer Review Committee for evaluation of the carcinogenic potential.

Core Classification: Core-Supplementary Data; this study does not satisfy the chronic toxicity requirement (§83-1a) and the carcinogenicity (oncogenicity) requirement (§83-2a) in rodents due to severe study design and reporting deficiencies.

A. MATERIALS AND METHODS:

A copy of the materials and methods sections from the investigators report is appended.

1. Test compound: Sodium orthophenylphenate (OPP-Na)
Dowcide A
Description - reddish brown or white flakes
Lot # - MM01044
Purity - 95.5 %
Contaminants - list was provided

2. Test animals: Species: Male and Female rats
Strain: F344/DuCrj
Age: 37-40 days of age
Weight: 83-105 g (males), 70-89 g (females)
Source: Charles River Japan, Inc.
Kanagawa Japan

3. Animal assignment and husbandry

Animals were assigned by stratification to the following test groups (from the investigators report):

Treatment group	Initial number of rats	OPP-Na in diet (%)	Observation period	
			Treated (Weeks)	Untreated (Weeks)
106-week study				
Male				
Matched-control	50	0	0	106
Low-dose	50	0.7	104	2
High-dose	50	2	104	2
Female				
Matched-control	50	0	0	106
Low-dose	50	0.5	104	2
High-dose	50	1	104	2
Lifespan study				
Male				
Matched-control	25	0	0	*
Low-dose	25	0.25	104	*
Mid-dose	25	0.7	104	*
High-dose	25	2	104	*
Female				
Matched-control	25	0	0	*
Low-dose	25	0.25	104	*
Mid-dose	25	0.5	104	*
High-dose	25	1	104	*

* Rats fed basal diet to the death or moribundity.

Doses were based on a 13-week toxicity test in the same strain of rats as that used in the primary study. The following table presents the results of the 13-week study:

Feeding Study of OPP-Na for 13 Weeks in F344/DuCrj Rats

Dietary level of OPP-Na (%)	Male		Female	
	Survival[1)]	Relative body weight[2)] (%)	Survival[1)]	Relative body weight[2)] (%)
0	10/10	100	10/10	100
0.125	10/10	102	10/10	101
0.25	10/10	100	10/10	94
0.5	10/10	94	10/10	88
1.0	10/10	99	10/10	95
2.0	10/10	98	10/10	84
4.0	10/10	83	10/10	93

1) Number of rats surviving / initial number of rats in group.
2) Mean body weight of dosed group at week 13 x 100 / mean body weight of control group at week 13.

The investigator used a 10% depression of body weight gain as an estimation of the "MTD". A 2% concentration in feed was determined for males and a 1% concentration in feed for females. Additional information is presented in the attached materials and methods.

Animals were kept under standard animal care conditions and received pelleted CE-2 (Clea Japan, Inc.) and water *ad libitum*.

4. Diet preparation

Diet was prepared into pellets prior to study initiation and apparently stored at room temperature. Samples of treated food were analyzed for stability and concentration as reported in a separate document entitled "Quantitative Analysis of Sodium o-Phenylphenol Added Into the Standard Animals Foods and Effect of Preservation" (MRID# 921540-34).

5. Observations:

Animals were inspected twice daily for signs of toxicity and mortality.

6. Body weight

Animals were weighed once biweekly for the first 18 weeks, then once every four weeks.

7. Food consumption and compound intake

Consumption was determined once weekly for the first 2 weeks, once biweekly for the second 4 weeks and then once every 4 weeks until week 104.

8. Ophthalmological examination

Ophthalmological examination were not performed.

9. Hematology and Clinical Analysis

No blood was collected and therefore no hematology or clinical analysis were conducted.

10. Urinalysis

Although urine was removed from the bladders by cannulation, no urinalysis was conducted.

11. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological and microscopic examination (for neoplasitc and non-neoplastic observations). No organs were weighed. The following tissues (X) were collected for histological examination.

Digestive system
- Tongue
- X Salivary glands*
- X Esophagus*
- X Stomach*
- X Duodenum*
- X Jejunum*
- X Ileum*
- X Cecum*
- X Colon*
- X Rectum*
- X Liver *+
- ~~Gall bladder*~~
- X Pancreas*

Respiratory
- X Trachea*
- X Lung*
- X Bronchi

Cardiovas/Hemat.
- Aorta*
- X Heart*
- X Bone marrow*
- X Lymph nodes*
- X Spleen
- X Thymus*

Urogenital
- X Kidneys*+
- X Urinary bladder*
- X Testes*+
- X Epididymides
- X Prostate
- Seminal vesicle
- X Ovaries*+
- X Uterus*

Neurologic
- X Brain*+
- Periph. nerve*#
- X Spinal cord(3 levels)*#
- X Pituitary*
- Eyes (optic n.)*#

Glandular
- X Adrenal gland*
- Lacrimal gland#
- Mammary gland*#
- X Parathyroids*
- X Thyroids*++
- X Preputial gland
- X Clitoral glands

Other
- X Bone (femur)*#
- Skeletal muscle*#
- X Skin*#
- X All gross lesions and masses*
- X Blood smear

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

Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin and sectioned. The urinary bladders were evacuated of urine and then distended with 10% neutral buffered formalin, removed from the animal and stored in formalin. Following a 7 day fixation, the bladders were bisected longitudinally and examined for any gross leasions, vesical calculi and parasites using a microscope.

12. Statistics - The following procedures were utilized in analyzing the numerical data:

Pertinent data on the studies were analyzed using the following statistical techniques. Student's t-test was used to compare both body weight gains and survival times of matched-control with those of dosed groups ($P<0.05$).

The Fisher exact test was used to compare survival rates, tumor incidence and incidence of nonneoplastic lesions of matched-control with those of dosed groups. And the Fisher exact P values showed in the tables when P was less than 0.05.

The Cochran-Armitage test for linear trend in proportions, with continuity correction was also used (Armitage, 1971)[7].

13. Compliance

A signed Statement of NO Data Confidentiality Claims was provided.

A signed statement of Compliance with Good Laboratory Practices was provided.

A signed quality assurance statement was **not** provided.

A signed Flagging Statement was **not** provided.

B. RESULTS

1. Observations:

Toxicity/Mortality (survival)

According to the investigators: "Dark red, blood-like vicidity (suspicious hematuria) was observed in floors of cages for high-dose males from week 40, and increased in number of rats showing the sign with the times"; however, no data were provided to confirm this statement. No other clinical signs related to treatment were provided.

Survival curves were provided for male and female rats. According to the investigators: "Survival curves for high-dose males in both 106-weeks and lifespan studies were markedly similar {to} each other. In high-dose males, survival times in each study were significantly shorter ($p<0.05$) than those of matched-controls, and survivals at week 104 were 20% for 106-week study and 24% for lifespan study." Further, "In female rats of each study, both percents of survival and survival times were not shown dose-related differences. Survivals of dosed and control rats of each sex except high-dose males were more than 50% at week 104, in the two studies." This seems to be supported by the graphical and tabular data; however, no other data were provided.

The following tables from the investigators report presents the survival in both segments of the study:

Survival in 106-Week Study

Male			Female		
Dietary level of OPP-Na (%)	Survival at wk 104 (%)	Range (Weeks)	Dietary level of OPP-Na (%)	Survival at wk 104 (%)	Range (Weeks)
0	70	25 - 106	0	84	70 - 106
0.7	88	58 - 106	0.5	82	59 - 106
2	20[1] (P<0.001 ,[2]	39 - 106	1	86	66 - 106

1) Fifty percent of 2% OPP-Na group died until week 83, and survivals of other groups were more than fifty percent at the end of the study.
2) Figures in parentheses shows the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05.

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Survival in Lifespan Study

Male				Female			
Dietary level of CPP-Na (%)	Mean survival time[1] (Weeks)	Range (Weeks)	Weeks on study for 50% survival[2]	Dietary level of CPP-Na (%)	Mean survival time[1] (Weeks)	Range (Weeks)	Weeks on study for 50% survival[2]
0	111 ± 22	49 - 141	113	0	108 ± 32	42 - 158	104
0.25	121 ± 18	79 - 157	124	0.25	111 ± 26	40 - 144	117
0.7	114 ± 29	50 - 156	119	0.5	117 ± 32	22 - 156	128
2	82 ± 23*	43 - 126	77	1	123 ± 22	82 - 160	130

1) Mean ± SD (experimental weeks)
2) It shows weeks on study that the survival of each group decreased to 50 %.
* Siginificantly different from control group at P < 0.001.

2. Body weight

According to the investigators: "In 106-week study, mean body weights of low-dose rats each sex were comparable to those of matched-controls throughout the study. Mean body weights of high-dose rats each sex were lower than those of matched-controls throughout the study. High-dose males was (were) significantly lower ($p<0.05$) than those of matched-control, at weeks 65 in the depression of 6%. High-dose females was (were) significantly lower ($p<0.05$) than that of matched-control throughout the study, in the maximum depression of 9%." Further, "In lifespan study, mean body weights of dosed rats of each sex except high-dose males were comparable to those of matched-controls throughout the study. Mean body weights of high-dose males was (were) significantly lower ($p<0.05$) than that of matched-control throughout the study, in the maximum depression of 15% at week 69." The graphed data provided are attached and the depicted data seem to support the above conclusions; however, no numerical data were provided to support the graphed data.

3. Food consumption and compound intake

The investigators provided the following table with mean food intake and compound intake for the "lifespan study."

Mean Intakes of Food and OPP-Na in Lifespan Study

Male				Female			
Dietary level of OPP-Na (%)	Food intake[1]	OPP-Na intake[2]	CPP intake[3]	Dietary level of OPP-Na (%)	Food intake[1]	OPP-Na intake[2]	CPP intake[3]
0	39.5	0	0	0	47.9	0	0
0.25	39.7	95	61	0.25	47.4	113	73
0.7	40.3	270	174	0.5	46.9	224	144
2	40.3	770	496	1	48.8	466	300

1) Food intake (g/kg/day) = { weight of initial diets − weight of remainder after 3 days (diets remained in the hopper and dropped to a filter paper under the cage) } /3/B.W. kg.
2) OPP-Na intake (mg/kg/day) = food intake x concentration of OPP-Na x purity of OPP-Na used the study (0.955).
3) CPP intake (mg/kg/day) = OPP-Na intake x molecular weight of CPP (170.21) / molecular weight of OPP-Na (264.25).

No apparent effects of treatment were noted; however, this was the only data provided and food efficiency could not be calculated.

4. Pathology

a. Gross pathology

The only gross pathology observation reported was for the urinary bladder tumors that appeared as "papillary or polypoid, having a cauliflower-like appearance. Many of these tumors were multiple and arosed in the ventral wall of the bottom growing into the lumen." They also observed vesical calculi measuring 0.1 to 6 mm in dimeter with a dark or greenish brown color and a rough spiny or smooth surface. These calculi were observed in dosed

rats only in 27/50 (54%) of the high dose males and 2/50 (4%) of the low dose males in the 106 week study, and in 8/25 (32%) of high dose males and 1/25 (4%) high dose females in the lifespan study. According to the investigators "All rats with vesical calculi had urinary bladder tumors in the two studies."

b. Microscopic pathology

1) Non-neoplastic

The investigators provided a summary of non-neoplastic lesions observed in the 104 week study. No treatment related effects were noted; however, no individual animal data were provided. Since the urinary system is the target organ of the test compound, the investigators focused their discussion on that area. Chronic nephropathy was noted in both treated and control rats, but a few cases of interstitial nephritis (2/50 (4%) high-dose males, 1/50 (2%) low-dose males, 11/50 (22%) high-dose females, 3/50 (6%) low-dose females and 0/50 (0%) matched-controls both sexes) and pyelonephritis (3/50 (6%) high-dose males and 9/50 (18%) high-dose females) was observed in treated rats. Also, hyperplasia of transitional cells in the urinary bladder or the renal pelvis was observed (1/50 (2%) high-dose males, 4/50 (8%) high-dose females and 1/50 (2%) low-dose females in 106-week study, but not in the lifespan study).

2) Neoplastic

The investigators provided a summary of neoplastic lesions observed in the 104 week study; however no individual animal data were provided. The investigators paid particular attention to the urinary system. Tumors were found in the urinary tract, particularly the urinary bladder, in both 106-week and lifespan studies. In 106-week study, urinary bladder tumors occurred in 47/50 (94%) high-dose males, 2/50 (4%) low-dose males, 4/50 (8%) high-dose females, 1/50 (2%) low-dose females and 0/50 (0%) controls in both sexes. The following table presents these findings:

Urinary Bladder Lesions - Transitional Cell (50 animals examined M/F)

	Control	Low	High
Hyperplasia	0/0	0/1	1/4
Papilloma	0/0	0/1	1/3
Carcinoma			
Non-invasive	0/0	2/0	18/1
Invasive	0/0	0/0	21/0
Metastasized	0/0	0/0	7/0
TOTAL	**0/0**	**2/1**	**47**/4***

** * = p < 0.025 (Fishers); ** = p < 0.001 (Cochran-Armitage)**

Data extracted from Table 6 of the investigators report.

The lifespan study, urinary bladder tumors occurred in 23/25 (92%) high-dose males, 3/25 (12%) mid-dose males, 2/25 (8%) high-dose females, 0/24 (0%) mid-dose females and 0/25 (0%) the other groups including controls of each sex. The following table presents these findings:

Urinary Bladder Lesions - Transitional Cell
(25 animals examined M/F)

	Control	Low	Mid	High
Hyperplasia	0/0	0/0	0/0	0/0
Papilloma	0/0	0/0	2/0	2/1
Carcinoma				
Non-invasive	0/0	0/0	0/0	11/0
Invasive	0/0	0/0	1/0	7/1
Metastasized	0/0	0/0	0/0	3/0
TOTAL	**0/0**	**0/0**	**3/0**	**23**/2**

** = p < 0.001 (Cochran-Armitage)

Data extracted from Table 7 of the investigators report.

Other tumor incidences were as follows:

Neoplastic Lesions 106 Week Study
(50 animals examined M/F)

	Control	Low	High
Uterus - Endometrial stromal polyp	-/3	-/7	-/13**

** = p < 0.006 (Fishers)

Data extracted from Table A7 of the investigators report.

Neoplastic Lesions Lifetime Study
(25 animals examined M/F)

	Control	Low	Mid	High
Uterus - Endometrial stromal polyp	-/2	-/1	-/9*	-/2

* = p < 0.015 (Fisher)

Data extracted from Table A6 of the investigators report.

Other tumors did not show an increase over control, while several were less than control: incidence of interstitial cell tumors of the testes in high-dose was 2/50 for the 106 week study and 11/25 for the lifespan study compared to controls of 42/50 for the 106 week study and 18/25 for the lifespan study; incidence of islet cell adenoma of the pancreas in the 106-week study for both the low- and high-dose males was 2/50 for both groups compared to controls of 8/50; incidence of adenomas of the pituitary in high-dose males in the lifespan study was 0/25 as compared to controls of 6/25; incidence of pheochromocytoma of the adrenal in high-dose males was 0/25 and for females was 1/25 as compared to controls of 6/25 for both sexes.

C. DISCUSSION/CONCLUSIONS:

Sodium orthophenylphenate was administered to male and female F344/DuCrj albino rats from Charles River Japan, Inc. at dose levels of 0, 0.7 and 2 % in the diet to males and 0, 0.5 and 1 % in the diet to females for 106 weeks (104 weeks with treated diet, 2 weeks with basal) and for a "lifespan" study at dose levels of 0, 0.25, 0.7, and 2 % in the diet to males and 0, 0.25, 0.5, and 1 % in the diet to females. There were not sufficient data (measured parameters) to establish chronic toxicity effect and no effect levels in this study.

No treatment related effects were noted in the non-neoplastic lesions observed in the 104(6) week study (however, no individual animal data were provided). Some increase in interstitial nephritis and pyelonephritis was observed in the high dose group females (slightly increased in males). Neoplastic lesions (no individual animal data were provided) were found in the urinary tract, particularly the urinary bladder, in both 106-week and lifespan studies. In the 106-week study, urinary bladder tumors occurred in 47/50 (94%) high-dose males, 2/50 (4%) low-dose males, 4/50 (8%) high-dose females, 1/50 (2%) low-dose females and 0/50 (0%) controls in both sexes. In the lifespan study, urinary bladder tumors occurred in 23/25 (92%) high-dose males, 3/25 (12%) mid-dose males, 2/25 (8%) high-dose females, 0/24 (0%) mid-dose females and 0/25 (0%) the other groups including controls of each sex. There was an increase in endometrial stromal polyp of the uterus in the high dose group of the 104(6) week study but not in the lifespan study.

Based on the available data, Na-OPP appears to be carcinogenic in male and female rats. This chemical will be recommended to the HED Carcinogenicity Peer Review Committee for evaluation of the carcinogenic potential.

Core Classification: Core-Supplementary Data; this study does not satisfy the chronic toxicity requirement (§83-1a) and the carcinogenicity (oncogenicity) requirement (§83-2a) in rodents due to severe study design and reporting deficiencies.

ORTHOPHENYLPHENOL (064103)

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