1/19/2001

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DATA EVALUATION RECORD

STUDY TYPE: 90-Day (Subchronic) Feeding-Rodent; Guideline§82-1(a)

EPA PESTICIDE CHEMICAL CODE: 064103 (OPP); 064104 (SOPP)
TOX. CHEM NO: 623AA (OPP); 787 (SOPP)
MRID NO.: 921540-32 - reformat of 00091022 and 00145962

TEST MATERIAL: Orthophenylphenol and Sodium Orthophenylphenol

SYNONYMS: OPP, Dowcide 1; SOPP, Dowcide A

TITLE OF REPORT: Molecular Mechanisms involved in the Toxicity and Carcinogenicity of Orthophenylphenol and its Sodium Salt

STUDY NUMBER: HET-K-1025-8

TESTING FACILITY: Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, Midland, MI 47674

AUTHOR(S): R.H. Reitz, T.R. Fox, J.F. Quast, E.A. Hermann, P.G. Watanabe

REPORT ISSUED: December 10, 1981. Reformatted January 16, 1990

SPONSOR: Dow Chemical Company

CONCLUSIONS: The study used only male F344 rats obtained from Charles River Laboratories receiving 2% OPP and 2% SOPP in the diet for 90 days and examined only on a limited number of parameters. From the limited data provided, it was noted that OPP at 2% in the diet produced decreases in body weights and food consumption. The reduced food consumption may be related to a palatability problem with the test compound mixed in with the feed. Other effects were generally related to effects on the liver and kidneys. No definitive conclusions can be drawn from the data provided as only one dose for OPP and SOPP was tested, no NOELs can be determined.

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:

1. Test compound: Orthophenylphenol (OPP, Dowcide 1)
Description - none provided
Lot # - MM09250
Purity - 99.8 %
Sodium Orthophenylphenol (SOPP, Dowcide A)
Description - none provided
Lot # - MM09220B
Purity - 72.0 %

2. Test animals: Species: Male rats
Strain: F344
Age: 7-10 weeks old
Weight: 125-175 g
Source: Charles River Laboratories
Wilmington, MA

Animals were kept under apparently standard animal care conditions and were acclimated for 7 days prior to use. They received Purina Certified Laboratory Chow and water *ad libitum*.

3. Animal assignment

Thirty animals were assigned randomly to a control and 2 test groups of 2% OPP and 2% SOPP.

4. Diet preparation

Diet preparation periods were not provided. The investigators stated that the diet mixtures were stable for at least 8 weeks, no data provided 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. Samples of treated food were analyzed for homogeneity, stability and concentration. Periods of measurement were not provided. Analytical methodology was provided. The investigators stated that "All diets were within plus/minus 20% of the targeted concentration, and were homogeneous within the same limits.

5. Observations:

Animals were inspected daily for signs of toxicity and mortality. Animals were weighed weekly. Food consumption was "monitored" weekly. No ophthalmological examinations were performed. Blood was collected at autopsy. No hematology parameters were examined. Clinical chemistry measurements included only blood urea nitrogen and serum creatinine levels. Urinalysis measured pH, specific gravity, protein, glucose, ketones, blood,

bilirubin, and urobilinogen. Histological examinations involved the liver, urinary system (bladder, urethra and kidneys), prostate and stomach. No organ weights or microscopic pathology were reported.

6. Statistics - Apparently no statistical analysis was performed.

7. Compliance:

A signed Statement of No Data Confidentiality Claims was provided.

A signed quality assurance and compliance with GLP's statement was provided.

A signed Flagging Statement per 40 CFR 158.34 was provided, the study neither meets nor exceeds the applicable criteria.

B. RESULTS:

1. Observations:

Toxicity/Mortality (survival)

Apparently some animals died on study, although this was not clear from the provided data. The investigators reported in the table below (from the report) that 7 animals in the 2% OPP group were found dead or moribund on day 14 and apparently died of starvation rather than an effect of the test compound. No clinical signs were reported.

Numbers of animals and dates of sacrifice for the 90 day feeding study. The indicated number of animals were randomly selected from treatment groups and fasted overnight before sacrifice. Samples of blood, liver, kidney, and urinary bladder were obtained at necropsy.

	Days on Test					
	3	7	14	30	65	90
Control	5	5	5	5	3	7
2% OPP	5	5	0*	3	3	7
2% SOPP	5	5	5	5	3	7

*No animals were sacrificed from the 2% OPP group at this time, but 7 animals were found dead or moribund during this period and submitted to necropsy. These animals apparently had died from starvation rather than chemical effects.

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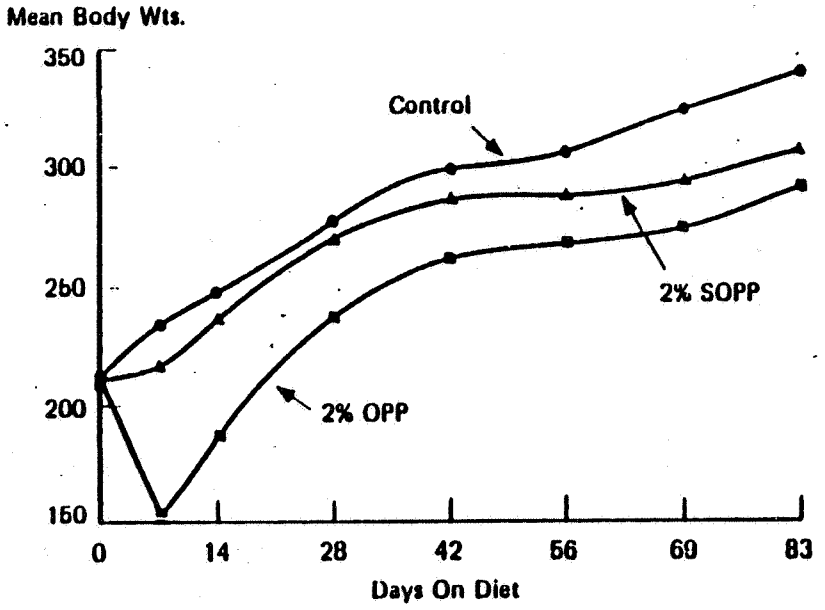
2. Body weight

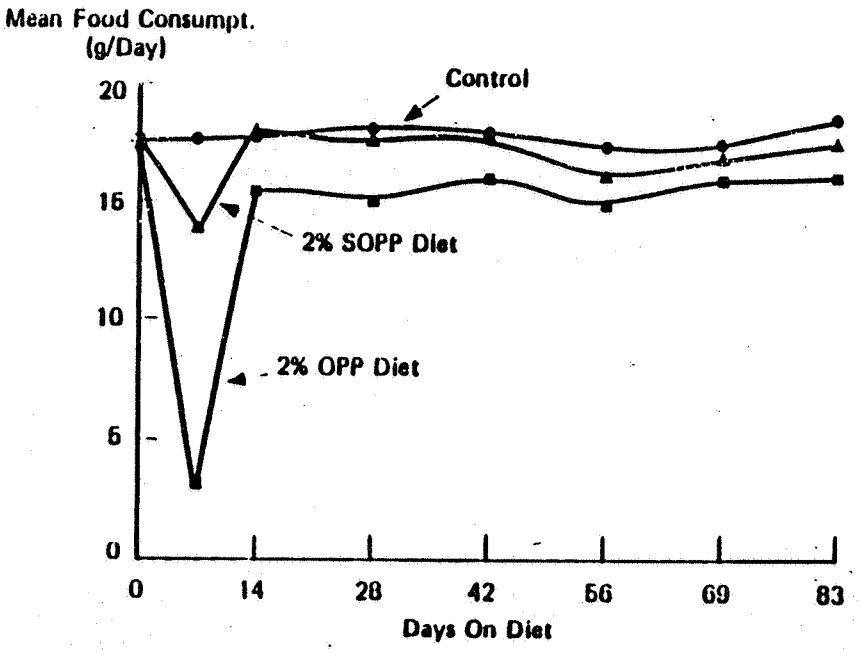
According to the investigators, the mean body weights of rats receiving test compound were less than the control. The following figure provides the only data available.



Mean body weights for the three test groups in the subchronic feeding study. Circles = control group triangles = 2% SOPP group; squares = 2% OPP group.

3. Food consumption

According to the investigators, the mean food consumption of rats receiving test compound was less than the control with the OPP treated animals being the most affected. The investigators reported that the animals had signs of severe malnutrition before they finally ate the treated diet. The following figure provides the only data available.



Mean food consumption (g/animal/day) for the three test groups in the subchronic feeding study. Circles = control group triangles = 2% SOPP group; squares = 2% OPP group.

4. Clinical Chemistry

BUN and serum creatinine were monitored throughout the study; however, only "a small transient increase in BUN" was noted in the OPP group at 7 days and was "considered prerenal in origin and probably related to the malnutrition." No data were provided.

5. Urinalysis

No effects were noted on urinary pH, protein, glucose, ketones, bilirubin, and urobilinogen; however, "specific gravities were significantly decreased in animals receiving 2% OPP for 65 or 90 days, and small amounts of blood were also detected." No data were provided.

6. Pathology

a. Gross pathology

Signs of malnutrition were noted early in the study and increased liver and kidney sizes were noted towards the end of the study. Also focal cortical cysts were noted in the kidneys of animals receiving OPP but not SOPP. Data are presented on the table below (some illegible):

GROSS PATHOLOGIC OBSERVATIONS IN RATS MAINTAINED ON OPP OR SOPP DIETS FOR VARYING LENGTHS OF TIME

	3 days			7 days			14 days			30 days			55 days			90 days		
	Control	OPP 2.5	SOPP 2.5	Control	OPP 2.5	SOPP 2.5	Control	OPP 2.5	SOPP 2.5	Control	OPP 2.5	SOPP 2.5	Control	OPP 2.5	SOPP 2.5	Control	OPP 2.5	SOPP 2.5
No visible lesions on external or internal examination	3/3	3/3	3/3	3/3	0/3	0/3	3/3	NA	2/3	4/3	3/3	1/3	3/3	3/3	0/3	3/7	3/7	3/7
Focal corneal cloudiness	0/3	0/3	0/3	0/3	0/3	0/3	0/3	NA	0/3	0/3	0/3	0/3	0/3	3/3	0/3	3/7	3/7	1/7
Small carcass upon external examination	0/3	0/3	0/3	0/3	3/3	3/3	0/3	NA	1/3	0/3	3/3	0/3	0/3	3/3	0/3	3/7	4/7	3/7
Decreased amount of intraabdominal fat	0/3	0/3	3/3	0/3	3/3	4/3	3/3	NA	1/3	0/3	3/3	0/3	0/3	3/3	0/3	3/7	4/7	3/7
Decreased amount of intestinal contents	3/3	3/3	3/3	0/3	3/3	0/3	0/3	NA	2/3	3/3	3/3	3/3	3/3	3/3	0/3	3/7	3/7	3/7
Gastric change with edema, erosions, and/or ulcers in the nonglandular portion	3/3	0/3	3/3	3/3	3/3	3/3	3/3	NA	2/3	3/3	3/3	3/3	3/3	3/3	3/3	3/7	3/7	3/7
Decreased size of internal organs	0/3	0/3	0/3	0/3	3/3	2/3	3/3	NA	3/3	3/3	3/3	0/3	3/3	3/3	3/3	3/7	3/7	3/7
Urinary Bladder																		
Mucosa thickened or discolored, slight	3/3	0/3	3/3	0/3	0/3	0/3	0/3	NA	2/3	3/3	0/3	0/3	3/3	3/3	0/3	3/7	0/7	1/7
Liver																		
Herniated portion attached to diaphragm	0/3	0/3	0/3	0/3	1/3	2/3	0/3	NA	2/3	1/3	0/3	0/3	0/3	3/3	0/3	3/7	0/7	3/7
Slightly increased in size	3/3	0/3	0/3	0/3	0/3	0/3	3/3	NA	2/3	0/3	2/3	4/3	0/3	2/3	3/3	3/7	7/7	1/7
Kidney																		
Slight increase in size	0/3	0/3	3/3	0/3	0/3	0/3	0/3	NA	2/3	0/3	3/3	0/3	3/3	3/3	2/3	3/7	4/7	1/7
Focal pale discoloration in the cortex, slim wedge-shaped pattern	0/3	0/3	3/3	0/3	0/3	0/3	0/3	NA	2/3	0/3	3/3	3/3	0/3	3/3	1/3	3/7	3/7	3/7
Focal cortical cyst(s)	3/3	0/3	0/3	0/3	0/3	0/3	0/3	NA	2/3	0/3	3/3	0/3	3/3	3/3	3/3	3/7	7/7	1/7

NA - Not applicable because no animals in this group were necropsied at this time.

Data listed as number of animals affected/number examined.

b. Microscopic pathology

According to the investigators "the livers from animals receiving either OPP or SOPP for periods exceeding two weeks revealed slightly swollen cells, but no other signs of toxicity were noted in this organ. The following description of histopathologic observations is from the investigators report:

Effects Produced by OPP

Treatment-related changes of the kidney were noted in the animals consuming the 2% OPP diet. Beginning at 30 days, focal areas of discoloration were noted upon gross necropsy. Microscopy revealed multiple areas of focal tubular collapse and atrophy in the cortex of the kidneys, suggestive of an obstructive phenomenon. Cystic degeneration was noted in the OPP group in subsequent sacrifices at 65 and 90 days. The lesions observed were not considered to be such as to seriously impair renal function, and no increase in the severity of the lesion was noted from 30 to 90 days. No treatment-related lesions were noted in the urinary bladders of the group receiving 2% OPP diets at any time (Table 9).

Effects Produced by SOPP

Beginning at 3 days, increased mitosis was evident in the bladder epithelial cells of rats consuming the 2% SOPP diet. The degree of mitosis appeared to decrease during subsequent sacrifices, but remained above normal throughout the study. Beginning at 14 days, a progressive thickening of the bladder epithelium was noted. This was accompanied by increased inflammatory cell infiltration. Thickening of the epithelium increased throughout the treatment period. This was characterized as a hyperplasia. None of the animals studied developed any lesion of the bladder which were characterized as a tumor, malignant or otherwise (Table 9).

No treatment-related effects were noted in the prostate. The stomachs of animals receiving OPP diet showed edema and erosions at 7 days but at no other time period. No consistent treatment-related effects were noted in the urethra (Table 9).

ORTHOPHENYLPHENOL (064103)

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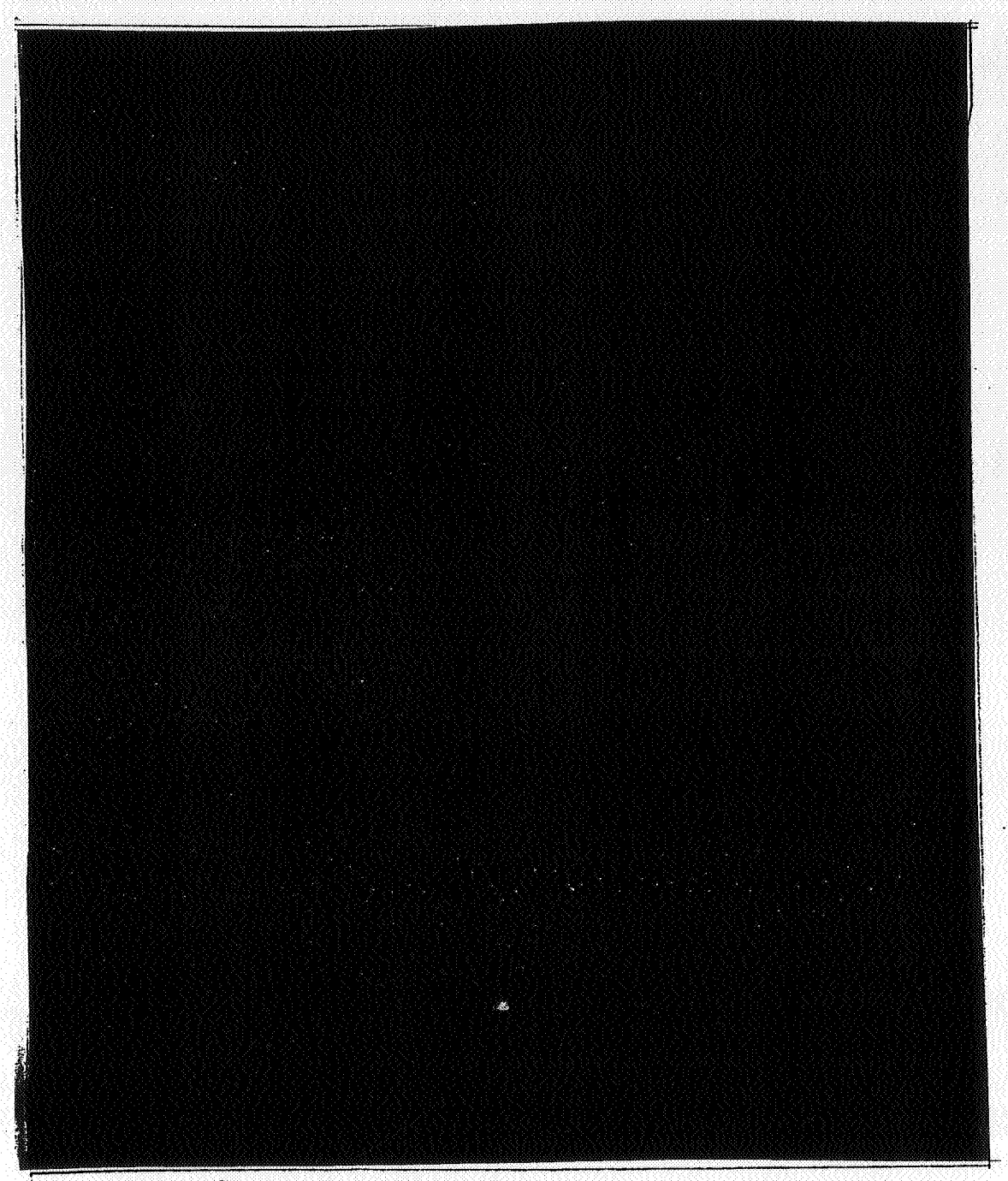
According to the investigators:



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D. DISCUSSION/CONCLUSIONS:

The study used only male F344 rats obtained from Charles River Laboratories receiving 2% OPP and 2% SOPP in the diet for 90 days and examined only on a limited number of parameters. From the limited data provided, it was noted that OPP at 2% in the diet produced decreases in body weights and food consumption; however, this is from graphical representation of the data. The reduced food consumption may be related to a palatability problem with the test compound mixed in with the feed and was indicated by the investigators that the animals became severely malnourished before they began to eat the treated diet. The investigators also noted an increase in liver and kidney size; however, no organ weights were provided. They further stated that the cells of the liver were slightly swollen. No definitive conclusions can be drawn from the data provided as only one dose for OPP and SOPP was tested, no NOELs can be determined.

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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