UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Orthophenylphenol and Sodium Orthophenylphenate - Review of subchronic and chronic toxicity feeding studies in rodents submitted in support of reregistration. EPA DP Barcode D181536; EPA Submission No. S423421; MRID #'s 91022, 407602-05, 407602-06, 407602-07, 407602-08, 161577, 164361, 407602-01, 407602-03, 149992, 141535, 921540-14 through -19, 921540-27 through -29, 921540-32, 921540-34 through -36, 921540-33; EPA Pesticide Chemical Code 038501, Caswell No. 398.

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Action Requested: Review of Orthophenylphenol and Sodium orthophenylphenate chronic and subchronic feeding studies in rodents.

Recommendations: Toxicology Branch II reviewed the several subchronic and chronic toxicity/carcinogenicity studies on OPP and Na-OPP.

These studies do not satisfy Guideline requirements §82-1a, subchronic feeding in rodents, §83-1a, chronic feeding in rodents, §83-2a Carcinogenicity (Oncogenicity) in rats, §83-2b Carcinogenicity (Oncogenicity) in mice. New studies are required; however, due to the evidence of carcinogenicity, although from limited data, this chemical will be recommended to the HED Peer Review Committee for Carcinogenicity for further evaluation and classification of the carcinogenic potential.

The following are the comments and or conclusions from the reviews of the studies:

Study MRID # 407602-06: Subacute Toxicity of o-Phenylphenol (OPP) by Food Administration to Rats, Tokyo Metropolitan Research Laboratory of Public Health, Annual Report of Tokyo Metropolitan Research Laboratory P.H., Vol. 35, pgs. 407-415, 1984. Guideline §82-1a.

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.

Study MRID # 161577: NTP Technical Report on the Toxicology and Carcinogenesis Studies of *Ortho*-Phenylphenol (CAS No. 90-43-7) Alone and with 7,12-Dimethylbenz(a)anthracene (CAS No. 57-97-6) in Swiss CD-1 Mice (Dermal Studies), National Toxicology Program, NTP TR 301, March 1986. Guideline §83-1a and 83-2b.

CONCLUSIONS:

Based on the available data from this NTP report, very little information can be obtained on the systemic and carcinogenic activity of OPP as only one dose was tested producing very little toxicity and only non-neoplastic lesions in the form of skin irritation.

Core Classification: Core-Supplementary Data; this study does not satisfy the Guideline requirements for chronic feeding study in rodents (§83-1a) or for a carcinogenicity study in the mouse (§83-2b).

Study MRID # 164361: Long-Term Toxicity and Carcinogenicity Study of Sodium *o*-Phenylphenate in B6C3F$_1$ Mice, First Department of Pathology, Nagoya City University Medical School, Fd.Chem. Toxic. Vol 22, No. 10, pgs. 809-814, 1984. Guideline §83-1a and 83-2b.

This study is an open literature report with no data other than the report to support it. The following is the abstract from the report:

> Sodium-*o*-phenylphenate (OPP-Na) was given at dietary levels of 0 (control), 0.5, 1.0 and 2.0% to groups of 50 male and female mice for 96 wk, and all the animals were maintained without OPP-Na for a further 8 wk. Both sexes given 2% OPP-Na and females given 0.5% and 1% OPP-Na showed growth retardation. Serum alkaline phosphatase activity in OPP-Na treated females was significantly increased in a dose-related manner. There were no treatment-related effects on clinical signs, mortality, urinalysis, haematology or organ weights. The incidences of several non-neoplastic and neoplastic lesions achieved statistical significance but none was considered to be related to treatment. There were increased incidences of haemangiosarcomas of the liver in males given 1% and of hepatocellular carcinomas in 1 and 2% males, and haemangiomas and leiomyomas of the uterus, present in the controls, were absent or decreased in all treated females. Therefore, this study did not demonstrate any clear carcinogenic effect of OPP-Na on mice at dietary levels of up to 2%.

Despite the investigators statements that there was no clear carcinogenic effect; there appears to be a dose related increase

in male hepatocellular carcinomas. However, without supporting information this study is of limited usefulness.

Study MRID # 407602-01: Quality and Determination of o-Phenylphenol-Na in Animal Feeds, Tokyo Metropolitan Research Laboratory of Public Health, Annual Report of Tokyo Metropolitan Research Laboratory P.H., Vol 32-2, pgs. 28-32, 1981. Guideline §83-1a and 83-2b.

This study was reformatted as MRID # 921540-33, and was used to support chronic/carcinogenicity study reviews.

Study MRID # 407602-03: Carcinogenicity Testing of Sodium Orthophenylphenate in F-344/DuCrj rats, Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, *J.Saitama Med.School*. 12:277-287, 1985. Guideline §83-1a and §83-2a.

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.

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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.

Study MRID # 149992: Induction of Tumours of the Urinary Bladder in F344 Rats by Dietary Administration of o-Phenylphenol, Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Fd.Chem.Toxic. Vol 22, No. 11, pgs. 865-870, 1984. Guideline §83-1a and 83-2b.

This study is an open literature report with no data other than the report to support it. The following is the abstract from the report:

> o-Phenylphenol (OPP), a fungicide approved as a food additive in Japan, was given in pelleted diets at dietary levels of 0.156, 0.313, 0.625, 1.25 or 2.5% to groups of 11 or 12 F344/DuCrj rats of each sex for 13 weeks, and at 0.625, 1.25 or 2.5% to groups of 20-24 male F344/DuCrj rats for 91 wk. In the 13-wk study, transitional cell papillomas of the urinary bladder occurred in 6/12 (50%) of the male 1.25% group. In the 91-wk study, urinary bladder tumours, transitional cell carcinomas were found in 20/23 (87%) of 1.25% and 2/4 (50%) of the 2.5% groups. A dose-related increase in the incidence of nephritic lesions was also observed in dosed rats in both the 13- and 91-wk study.

There was a clear carcinogenic effect with the formation of transitional cell papillomas and carcinomas in males. However, without supporting information this study is of limited usefulness.

Study MRID # 141535: Induction of Tumours of the Urinary System in F344 Rats by Dietary Administration of Sodium o-Phenylphenate, Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Food and Cosmetic Toxicology. Vol 19, No. 3. pgs. 303-310, 1981. Guideline §83-1a and 83-2b.

This study is an open literature report with no data other than the report to support it. The following is the abstract from the report:

> Sodium *o*-phenylphenate (OPP-Na), a fungicide approved as a food additive in Japan, was given in pellet diets at dietary levels of 0, 0.125, 0.25, 0.5, 1.0, 2.0 or 4.0% to groups of about 10 male and female F344/Du rats for 13 wk and to male F344/Du rats for 91 wk. In the 13-wk study, urinary bladder tumours developed in one out of ten male rats fed 1% OPP-Na, nine out of ten male rats fed 2% OPP-Na. Five transitional cell carcinomas were observed in male rats fed 2% OPP-Na and one such carcinoma was found in a male rat fed 4% OPP-Na. In the 91-wk study, tumours of the urinary bladder, renal pelvis and renal papilla developed in one out of 21 rats (5%) fed 0.5% OPP-Na, seven out of 21 rats (33%) fed 1% OPP-Na, 20 out of 21 rats (95%) fed 2% OPP-Na and 17 out of 21 rats (85%) fed 4% OPP-Na. These were all transitional cell carcinomas, except for one carcinosarcoma in the 2% group. A dose-related increase in the incidence of non-neoplastic lesions of the kidney were observed in treated rats. In the 13-wk study, slight to moderate pyelonephritis was observed in six out of ten male rats and one out of ten female rats fed 4% OPP-Na. In the 91-wk study, moderate to severe pyelonephritis was observed in four out of 21 rats (19%) fed 2% OPP-Na and in all of 20 rats fed 4% OPP-Na.

There was a clear carcinogenic effect with the transitional cell carcinomas in males. However, without supporting information this study is of limited usefulness.

MRID #'s 921540-14 through -19, 921540-27 through -29 were submitted as summaries of previously submitted studies and were considered using the acceptance criteria under Phase II of FIFRA 88. These documents do not contain enough information for separate reviews but have been covered by the DER's attached with this MEMO.

Reformat MRID # 921540-32 (reformat of MRID # 91022): Molecular Mechanisms involved in the Toxicity and Carcinogenicity of Orthophenylphenol and its Sodium Salt, Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, HET-K-1025-8, December 10, 1981. Reformatted January 16, 1990. Guideline §82-1a.

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.

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

Reformat MRID # 921540-34 (reformat of MRID # 407602-05): Quantitative Analysis of Sodium o-Phenylphenol Added Into Standard Animals Foods and Effects of Preservation, Tokyo Metropolitan Research Laboratory of Public Health, Annual Report of Tokyo Metropolitan Research Laboratory P.H. Vol 29-2, pgs 97-98, 1987. Guideline §82-1a.

This study was used to support subchronic study reviews.

Reformat MRID # 921540-35 (reformat of 407602-07): Subacute Toxicity of o-Phenylphenol by Food Administration to Male Rats, Tokyo Metropolitan Research Laboratory of Public Health, *Annual Report of Tokyo Metropolitan Research Laboratory* P.H. 32 (2), 33-39, 1981. Guideline §82-1a.

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.

Reformat MRID # 921540-36 (Reformat of MRID # 407602-08): Phase 3 Reformat of MRID 407602-08: Subacute Toxicity of Sodium o-Phenylphenate by Food Administration to Rats, Tokyo Metropolitan Research Laboratory of Public Health, Tokyo eiken Nenpo (Ann. Rep. Tokyo Metr. Res. Lab. P.H.), Vol. 30-2, pgs. 67-79, 1979. Guideline §82-1a.

CONCLUSIONS:

Dose levels of 0, 0.125, 0.250, 0.500, 1.000, 2.000, and 4.000% sodium orthophenylphenate in the diet were given to Kinko type Fischer (F344/DuCrj) albino rats from Nippon Charles River K. K. for a period of about 13 weeks. From the limited data provided, it was noted that Na-OPP at 0.5% and above in the diet produced reduced body weights with food consumption affected at the 4% dose level in males and females and also at the 2% dose level in females. The reduced food consumption was probably related to a palatability problem with the test compound mixed in with the feed (noted also in other studies). Other effects included an increase in absolute and relative liver and kidney weights. The effects on the liver also include decreases in enzyme activities (at 0.5% and above). No definitive conclusions can be drawn from these data; however, tentatively the NOEL for systemic toxicity is 0.5% Na-OPP with a LOEL of 1.0% Na-OPP. It must be noted that the percent active ingredient in the test compound was not provided.

The study is classified as Core-Supplementary Data and does not satisfy the Guideline requirement (§82-1a) for a subchronic feeding study in rodents.

Reformat MRID # 921540-33 (Reformat of MRID # 407602-01): Quality and Determination of o-Phenylphenol-Na in Animal Feeds, Tokyo Metropolitan Research Laboratory of Public Health, Annual Report of Tokyo Metropolitan Research Laboratory P.H., Vol 32-2, pgs. 28-32, 1981. Guideline §83-1a and 83-2b.

This study was used to support chronic/carcinogenicity study reviews.

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