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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA# 7969-58; Review of Rat Subchronic Studies on 5-OH-MSO_2
Tox. Chem. No. ~~72A~~ 427K

TO: Robert J. Taylor, PM Team #25
Registration Division (TS-767c)

FROM: John E. Whalan, Toxicologist
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THRU: Edwin R. Budd, Section Head
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The Toxicology Branch has reviewed the Rat Teratology and Subchronic Feeding studies of 5-OH-MSO_2, a hydroxylated plant metabolite of NP-55 (Poast).

Based on the results of these studies and the mutagenicity studies on 5-OH-MSO_2 (see review by M. Sochard, dated 2-18-85, on EPA Reg. No. 7969-58), Toxicology Branch has concluded that the toxicological potency of the plant hydroxymetabolites of Poast is likely to be equal to or less than that of the parent compound. It will no longer be necessary to continue the "provisional MPI" concept for the hydroxymetabolites of Poast as described in the review by M. Sochard and E. Budd, dated 3-9-83, on PP 2F2670 and EPA Reg. No. 7969-LI.

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TERATOLOGY STUDY of a Hydroxylated Plant Metabolite, 5-OH-MSO_2 in Rats

Nisso Institute for Life Science; Report No. 0091; October 28, 1983

Protocol: Forty-five male and 120 female Sprague Dawley (Crj;CD) rats (approximately 10 weeks old) were mated. Inseminated females were assigned to three dosed groups and a vehicle control group (24 female rats/group). The test article, 5-OH-MSO_2 (a major hydroxylated plant metabolite of NP-55), was suspended in 5% gum arabic aqueous solution and administered by gavage on gestation days 6-16 at doses of 40, 100, and 250 mg/kg/day. They were observed daily for clinical signs (gestation days 6-21) and body weight changes (gestation days 0-21).

The dams were sacrificed by chloroform anesthesia on gestation day 21. Their uteri and abdominal and thoracic organs were examined, and organ weights recorded for liver, kidneys, spleen, ovaries, and adrenals. All viable fetuses were weighed, sexed, and examined for external malformations and variations. Approximately half of each litter was preserved in Bouin's fixative, then examined for visceral malformations and variations. The method of Wilson was used for head and cervical examination, and the microdissection technique of Nishimura was used for thoracic, abdominal and pelvic examination. The remaining fetuses were stained with alizarin red S by the method of Dawson for skeletal examination.

Results: There were no toxic signs or deaths in any of the female rats. Body weight gain and organ weights were similar for all groups. The implantation rate, corpora lutea, litter sizes, number of resorptions (mostly early resorptions), sex distribution, and mean fetal placental weights were similar for all groups. One control animal each had gross findings of hydronephrosis and adrenal congenital aphasia. One of the low-dose fetuses had a kinked tail malformation. Subcutaneous hemorrhage was seen in one fetus from each of the dosed groups. Visceral malformations included dilatation of the renal pelvis and dilatation of the 4th ventricle and were similar in all groups. In addition, 2 control fetuses had hydranencephaly. Slight nondose-related increases in skeletal anomalies and malformations were observed in the dosed groups. Thus, there were no indications of maternal or fetal toxicity, or teratogenic effect at the doses tested:

Teratogenic NOEL = 250 mg/kg/day
Fetotoxic NOEL = 250 mg/kg/day
Maternal NOEL = 250 mg/kg/day

This study is CORE MINIMUM. The doses used were based on a teratology study of the parent compound, NP-55, which produced maternal toxicity at 250 mg/kg.

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SUBCHRONIC FEEDING STUDY of a Hydroxylated Plant Metabolite, 5-OH-MSO_2 in Rats

Nisso Institute for Life Science; Report No. 0090; October 31, 1983

Protocol: Sixty male and 60 female Wistar® rats (6 weeks old) were divided into 1 control and 3 dosed groups (15 rats/sex/group). The rats were dosed orally by mixing 5-OH-MSO_2 (a major hydroxylated plant metabolite of NP-55) into a powdered rat diet at concentrations of 0 (vehicle control), 120, 360, and 1080 ppm. The calculated mean dosage over the 13 week study was 0, 7.6, 23.2, and 70.2 mg/kg/day respectively for males, and 0, 8.1, 24.9, and 74.0 mg/kg/day respectively for females. The rats were observed daily for clinical signs, and weekly for body weight changes and food consumption. Clinical pathology measurements were made for 10 rats/sex/group after 1.5 and 3 months. They were bled from the orbital sinus and evaluated for the following parameters:

- RBC
- HCT
- HGB
- WBC (total and differential)
- thrombocytes
- MCV (Mean corpuscular volume)
- MCH (Mean corpuscular hemoglobin)
- MCHC (Mean corpuscular hemoglobin conc.)
- alkaline phosphatate
- SGOT
- SGPT
- total bilirubin
- total protein
- BUN
- total cholesterol
- albumin
- glucose
- lactic dehydrogenase
- Ca
- Na
- K
- Cl

The rats were also evaluated at the same time for the following urinalysis parameters:

- color
- urinary volume
- specific gravity
- pH
- protein
- glucose
- occult blood
- ketone bodies
- urobilinogen
- bilirubin

All surviving animals were sacrificed after 13 weeks and examined grossly. The brain, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads of these rats were weighed. The following organs were evaluated microscopically for the control and high dose groups:

- brain (3 levels)
- pituitary
- eyes
- harderian glands
- salivary gland
- thyroids and parathyroids
- thymus
- esophagus
- trachea
- lung
- heart
- liver (2 lobes)
- spleen
- kidneys
- adrenals
- stomach
- pancreas
- duodenum, jejunum, ileum
- colon
- lymph node (mesenteric)
- urinary bladder
- testes, epididymis, prostate
- seminal vesicle
- ovaries, uterus (horns and cervix)
- vagina
- sternum (bone and marrow)
- sciatic nerve with muscle
- skin, mammary gland
- unusual lesions

The liver, kidneys, adrenals, and spleens were examined for all groups.

Results: The only clinical signs observed were iatrogenic eye lesions. A low dose female died while being bled. Mean weight gain was similar for all males. The dosed females had slightly less weight gain than the controls, but this finding was not dose-related. Food consumption and food efficiency were similar for all groups, except for some minor nondose-related fluctuations among the females. Mean clinical pathology, urinalysis, and organ weight values were within normal ranges for all groups. No compound-related gross or microscopic lesions were seen. Thus, 5-OH-MSO_2 was not toxic to rats during this study, and the NOEL is 1080 ppm (70.2 mg/kg/day for males, 74.0 mg/kg/day for females).

This study is CORE MINIMUM. A toxic dose was not administered. Ophthalmologic examinations should have been performed.