PP-1166
TR-2000

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: R. Taylor, PM #25
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch/HED (TS-769)

ERB 6/18/82

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch/HED (TS-769)

SUBJECT: PP 0G2396. Six-Month Dog Feeding Study with NP-55 (BAS 9052H). Accession No. 099996.
TOX Chem. No.72A

Petitioner: BASF Wyandotte Corporation
Parsippany, New Jersey

Action Requested:

Review of study to support future requests..

Recommendation:

1. This is a Core Category Guideline study, with a NOEL of 20 mg/kg/day (males and females) and an LEL of 177 mg/kg/day for males and 223 mg/kg/day for females. It is an acceptable study to support future requests.

2. According to RCB (E. Zager, personal communication 5/25/82) there are no nitrosamine impurities in the technical chemical.

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DETAILED REVIEW OF STUDY

Six Month Dog Feeding Study with NP-55 (BAS 9052 H). International Research and Development Corporation, for Nippon Soda Co., Ltd. Study No. 449-004. March 9, 1981; Accession No. 099996.

Protocol:

Four groups of purebred beagle dogs aged 4 1/2 months, each group consisting of 6 males and 6 females were administered NP-55 technical (97.6% purity) admixed in certified Canine Diet No. 5007 ad lib. Dosages for the four groups were, respectively 0, 60 ppm, 600 ppm and 6000 ppm. Based on diet analyses and measurements of food consumption during the study, these are approximately equivalent to 0, 2, 20 and 200 mg/kg/day respectively. Diets were analytically checked for homogeneity and to insure target concentrations. Animals were examined twice daily for physical appearance and pharmacotoxic symptoms. Animal eyes were examined ophthalmoscopically prior to testing, at 3 months and 6 months. Body weights and food consumption were determined weekly. Hematology studies, performed monthly, included hemoglobin, hematocrit, erythrocyte count, total leucocyte count, platelet counts, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoblobin concentration (MCHC), reticulocyte counts and differential leucocyte counts. Urinalysis was done on fasted animals prior to study and at 2, 4 and 6 months, and included pH, glucose, occult blood, nitrites, urobilinogen, ketones, bilirubin, specific gravity, volume, color, appearance, protein and microscopic examination of sediment.

Biochemistry tests, performed pre-test and at monthly intervals included sodium, potassium, chloride, calcium, phosphorus, serum glutamic oxaloacetic and glutamic pyruvic transaminases, lactic dehydrogenase. alkaline phosphatase, gamma glutamyl transpeptidase, albumin, blood urea nitrogen, bilirubin, total protein, glucose, cholesterol, creatinine, uric acid and globulin. Retention of bromsulphalein was determined prior to and at 3 and 6 months of study. The phenol sulphonphthalein clearance test was done prior to testing and at 6 months. Gross pathology examinations were performed on all animals at the termination of the experiment following sacrifice by exsanguination. Weights of trimmed organs were determined; these included adrenals, heart, kidneys, liver, pituitary, testes or ovaries, thymus and thyroid/parathyroids. Sections of tissues examined histologically (in all animals) included adrenals, aorta, fore-, mid- and hindbrain, eye, gallbladder, heart, trachea, esophagus, stomach, duodenum, ileum, jejunum, cecum, colon, rectum, kidneys, liver, lung with mainstem bronchi,

mesenteric lymph node, skeletal muscle, skin, mammary gland, sciatic nerve, spleen, pancreas, pituitary, prostate/corpus and cervix uteri, rib junction (bone marrow), salivary gland (submaxillary), spinal cord (cervical and thoracic), testes/ovaries, thymus, thyroid/parathyroid, urinary bladder and any other tissue(s) with lesions. Administered diet was tested to assure homogeneity of dose as well as target concentrations.

Results:

No mortalities or compound-related pharmacotoxic symptoms were noted in any animals during the course of the study. Occasional random incidents of ocular symptoms associated with enlarged Harderian glands and diarrhea were found in controls as well as in experimental animals. No compound related effects were seen ophthalmoscopically at 3 or 6 months. Mid- and high dose males and all treated female groups showed a slightly higher percent gain in body weight throughout the study as compared with controls, which was not statistically significant. High dose males showed significant decreases in erythrocytes, hemoglobin and hematocrit from months 2-6, whereas high dose females showed significant decreases in erythrocytes at months 1-6, hemoglobin at months 1-5 and hematocrit at months 1-4. For high dose males, platelet levels increased at months 1-5; for high dose females platelets increased at months 1-3. Mean corpuscular hemoglobin and mean corpuscular volume in high dose females were respectively significantly different from controls at months 1-4 and 2-6. Hemosiderosis was seen in high dose males (5/6) and females (5/6) on examination of the spleen. This effect was considered due to non-specific anemia. Spleens were not weighed. A dose-related decrease in phenolsulfonthalein excretion was seen at 6 months in males and females at doses of 600 and 6000 ppm. High dose males showed a significant change in SGPT at six months, (elevation in levels). High dose males and females showed statistically significant changes in cholesterol, total protein, albumin, globulin and alkaline phosphatase suggesting an effect on liver function. This suggestion is further supported by findings of statistically significant elevations in absolute and relative weights of liver in both high dose males and females. Significant decreases in serum calcium levels were seen at 6000 ppm in males at 2-6 months and at 6000 ppm in females at 4 and 5 months; these values were considered related to changes in serum protein levels. The histopathology report of trace lymphocytic infiltration (5/6 males, 5/6 females) at 6000 ppm and trace Kupfer cell hyperplasia (4/6 males, 5/6 females) at 6000 ppm in liver further suggests liver stress. (See Table I for details.)

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Core Category - Guideline

NOEL = 600 ppm, males and females. Based on diet analyses and measurements of food consumption during the study this is equivalent to 20.0 mg/kg/day for males and females.

LEL = 6000 ppm, males and females (non-specific anemia; liver effects; possible kidney effects). Based on diet analyses and measurements of food consumption during the study, this is equivalent to 177 mg/kg/day for males and 223 mg/kg/day for females.

Minnie R. Sochard, Ph.D. MRS. 6/2/82
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachments:

OPP:HED:TOX: M.SOCHARD:sb X71511 6/2/82 Rm 824 #m2

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TABLE I
SUMMARY OF SIGNIFICANT CHANGES IN VARIOUS CHARACTERISTICS OF DOGS TREATED WITH BAS 9052H (NP-55)

CHARACTERISTIC	MALE/FEMALE	DOSE LEVEL - PPM OF NP-55 0	60	600	6000
HEMATOLOGY					
RBC	M	-	-	-	2-6 mos **
	F	-	-	-	2-6 mos **
Hb	M	-	-	-	2,4,5,6 mos **, and 3 mos *
	F	-	-	-	1-4,6 mos ** 5 mos *
Hematocrit	M	-	-	-	2,4,6 mos **, 3,5 mo*
	F	-	-	-	2 mos **, 1,4,5 mos *
Platelets	M	-	-	-	1-5 mos **
	F	-	-	-	1-3 mos **
MCH	M	-	5 mos **	5 mos **	5 mos **
	F	-	-	-	2,4 mos ** 1,3 mos **
MCV	M	-	-	-	-
	F	-	-	-	2,4,6 mos **
Hemosiderosis (in spleen)	M	-	-	-	5/6 animals **
	F	-	-	-	5/6 animals **
BIOCHEMISTRIES					
SGPT	M	-	-	-	6 mos *
	F	-	-	-	-
Cholesterol	M	-	-	-	1,2,4,6 mos **
	F	-	-	-	1,4 mos ** 2,6 mos *
Total Protein	M	-	-	-	1-4,6 mos ** 5 mos *
	F	-	-	-	1-5 mos ** 6 mos *
Albumin	M	-	-	-	1-6 mos ** 5 mos *
	F	-	-	-	1,4,5 mos **3 mos *
Globulin	M	-	-	-	3,4 mos **
	F	-	-	4 mos *	0,2 mos *
Alkaline Phosphatase	M	-	-	-	1-3,4,6 mos **5 mos *
	F	-	-	-	-
PSP Excretion	M	-	-	6 mos **	6 mos **
	F	-	-	6 mos **	6 mos **
Calcium	M	-	-	-	3-6 mos ** 2 mos *
	F	-	-	-	4 mos ** 5 mos *

** Significance at $P < 0.01$
* Significance at $P < 0.05$

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TABLE I
SUMMARY OF SIGNIFICANT CHANGES IN VARIOUS CHARACTERISTICS OF DOGS TREATED WITH BAS 9052H (NP-55)

(cont.)

CHARACTERISTIC	MALE/FEMALE	DOSE LEVEL - PPM OF NP-55 0	60	600	6000
PATHOLOGY LIVER					
Lymphocytic infiltration	M	-	-	-	5/6 animals
	F	-	-	-	5/6 animals
Kupfer cell hyperplasia	M	-	-	-	5/6 animals
	F	-	-	-	5/6 animals
Increase in weight					
a) Absolute	M	-	-	-	*
	F	-	-	-	*
b) Relative	M	-	-	-	*
	F	-	-	-	**

** Significance at P < 0.01
* Significance at P < 0.05

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