18 TDES DATA EVALUATION RECORD PAGE OF

CASE PM

CHEM Chlorsulfuron

002652

BRANCH TB DISC TOPIC 2-Year Feeding - Mouse

FORMULATION Technical

FICHE/MASTER ID CONTENT CAT

Long-Term Feeding Study With INW-4189 In Mice, Haskell Laboratory Report No. 836-81, Wood, C. K.

SUBST. CLASS =

OTHER SUBJECT DESCRIPTORS

DIRECT RVW TIME = 7 hours START-DATE END DATE

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Conclusion:

A. Core Guideline
B. A NOEL of 5000 ppm for oncogenic effects was established when technical chlorsulfuron was fed to mice for two years at dietary levels of 0, 100, 500, or 5000 ppm. No treatment effects were seen at up to 500 ppm with the exception of slight body weight effects which may be of no biological significance.
C. This study conforms to EPA Proposed Guidelines in Section 163.83.2 Oncogenicity Studies (43 Federal Register 37379, 8/22/78).

Methods:

Three hundred sixty male and three hundred sixty female CD®-1 mice were received from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Following a 14 day pretest, 320 mice of each sex, selected on the basis of weight gain and freedom from signs of disease or injury, were divided by randomization into four groups of 80 males and 80 females and housed individually. The 5000 ppm group was an exception with 79 males and 81 females due to a sex identification error. Groups were fed ground Purina® Laboratory Chow diets containing 0, 100, 500, or 5000 ppm chlorsulfuron for two years. Diets were prepared fresh weekly and stored under refrigeration until used. Mice received test diet and water ad libitum.

All mice were examined at least one daily for abnormal behavior, clinical signs of toxicity and mortality. Mice were individually examined for palpable tissue masses at least once every two weeks. Mice were weighed once a week during the first six months, once every other week during the second six months, and once a month during the last year. Diet consumed by mice was determined on a group basis at each weighing interval, and food efficiency and intake were calculated.

Approximately 1, 3, 6, 12, 18, and 24 months after the study's start, ten mice from each test group were subjected to hematological examinations. Parameters examined included erythrocyte and leukocyte counts; relative numbers of neutrophils, lymphocytes, eosinophils, monocytes, and basophils; hematocrits, hemoglobin, and total plasma protein concentrations. Mean corpuscular volumes, mean corpuscular hemoglobins and mean corpuscular hemoglobin concentrations were calculated.

At the end of two years all surviving mice were sacrificed and necropsied. Mice found dead or sacrificed in extremis during the study were also necropsied. The brain, heart, lungs, liver, spleen, kidneys (with adrenals attached), testes (with epididymides attached), and thymus were weighed. Mean final body weights, organ weights, and organ to body weight ratios were calculated. The tissues noted above and the following tissues were examined microscopical for all mice at all feeding levels for histopathologic changes: trachea, aorta, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, salivary glands, gall bladder, pancreas, thyroid, parathyroid, pituitary, urinary bladder, ovary, uterus, prostate, lymph nodes, bone, bone marrow, peripheral nerve, eye, skin, mammary gland, skeletal muscle, exorbital lacrimal gland, and all gross lesions and tissue masses.

Results:

Mice in the 5000 ppm groups had consistently lower mean body weights and body weight gains than the control mice during the first 72 weeks of the study. However, these statistically significant differences were no longer evident after 72 weeks. Mean body weights and weight gains of male mice in the 100 and 500 ppm groups were comparable to and generally paralleled those of the male control group. Mean body weights and weight gains of female mice in the 100 and 500 ppm groups were statistically significantly lower (7% or less)) during the first 72 weeks of the study. However, these differences were not statistically significant after 72 weeks. These body weight effects in the 100 and 500 ppm females paralleled lower food consumption than in the female control group and may be of no biological significance. Food efficiency values for both male and female mice in the test groups were generally comparable to those of the control groups. Except for the nutritional effects described above which may be of no biological significance, no treatment effects were seen at up to 500 ppm.

SURVIVAL

Treatment Group		Median Survival (Weeks on Test)	Number Alive On Test Week 104
Male:	Control	80.0	10
	100 ppm	78.5	24
	500 ppm	77.0	16
	5000 ppm	81.0	15
Female:	Control	101.0	30
	100 ppm	101.5	37
	500 ppm	97.5	33
	5000 ppm	103.5	37

Treatment Group		Incidence Of Palpable Tissue Masses	Number Mice Affected	Median Time to First Observation (Weeks on Test)
Male:	Control	4	4	76
	100 ppm	3	3	99
	500 ppm	4	3	86
	5000 ppm	1	1	56
Female:	Control	1	1	99
	100 ppm	3	3	88
	500 ppm	5	5	102
	5000 ppm	-	-	-

FEMALE BODY WEIGHTS

TIME WEEKS	0	100	500	5000
0	20.5	20.4	20.4	20.4
6	26.4	26.2	26.0	25.3
13	29.4	30.1	30.0	29.4
26	32.8	32.5	31.5*	31.2*
52	36.5	35.2*	35.1*	34.0*
76	37.2	36.1	35.9	35.8
104	35.8	35.2	35.5	34.7

* Different from control at .05 level of significance.

No behavioral, clinical, hematological, gross pathological, or histopathological abnormalities were observed that could be related to the dietary administration of chlorsulfuron. Survival, tumor incidence and first observation of palpable tissue masses were comparable among test and control groups. The pathologist concluded that the test material was not observed to be carcinogenic or toxic, under conditions of this study. A summary incidence of microscopic observations is attached at the end of this evaluation. A NOEL of 5000 ppm for oncogenic effects was established based on the absence of these effects.

Discussion:

The methods and materials, scientific principles, validity of conclusions, and adequacy of data for conclusions were adequate for the study. The reviewer agrees with the conclusion that chlorsulfuron was not oncogenic under conditions of this study.