Six Month Feeding Study In Dogs With 2-Chloro-N-[(4-Methoxy-6-Methyl-1,3,5-Triazin-2-Yl)Aminocarbonyl]Benzenesulfonamide (INW-4189), Haskell Laboratory Report No. 108-80, Schneider, P. W., Jr.
Conclusion:

A. Core Minimum (Number of animals tested; 4 vs. 6)
B. A NOEL of 2500 ppm based on no significant effects was found when technical chlorsulfuron was fed to beagle dogs at 0, 100, 500 or 2500 ppm (highest level) for 26 weeks. No mortality, body weight, clinical, hemato-
logical, gross or histopathologic evidence of toxicity was noted.
C. This study generally conforms to EPA proposed guidelines in section 163.82-1 Subchronic oral dosing studies (43 Federal Register 37363, 8/22/78) with some modifi-
cations.

Methods:

Four pure-bred beagle dogs/sex/level approximately 9-11 months old were fed 0, 100, 500 or 2500 ppm diets of chlorsulfuron for 6 months. Diets were prepared fresh weekly and stored under refrigeration until used. Dogs were weighed weekly and examined daily for abnormal behavior or clinical signs of toxicity. Individual diet consumption was measured weekly, and food efficiency and dose were calculated.

Hematological examinations were conducted on each dog two times before study initiation and after approximately one, two, three and six months of feeding. Analysis included erythrocyte count, hemoglobin, hematocrit, total leukocyte count and relative number of neutrophils, lymphocytes, eosinophils, monocytes and basophils. From this data, mean cellular volume, mean cellular hemoglobin, and mean cellular hemoglobin concentration indices were calculated. At the same time blood was examined for glucose, urea nitrogen, creatinine, cholesterol, uric acid, total protein, albumin, alkaline phosphatase, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase and lactic dehydrogenase activity, and albumin/globulin ratio. Urine (24 hour) was checked for volume, osmolality and pH, blood, sugar, protein, bilirubin, urobilinogen, ketones, color, appearance and a microscopic examination of sediments.

After approximately six-months of continuous feeding, all dogs were sacrificed for gross and microscopic pathological appraisal. The following organs were weighed at necropsy: thymus, spleen, heart, lung, stomach, liver with gall bladder, kidneys, testes with epididymides, prostate, thyroids with parathyroids, adrenals, pituitary gland, and brain. Group mean body and organ weights and relative organ weight-
body weight ratios were calculated. In addition to tissues removed from grossly observed lesions, the following organs and tissues were collected for histological examination: back and abdominal skin with underlying mammary tissue, skeletal muscle (posterior thigh muscle) bone (sternebrae), bone marrow (sternebrae and femur), thymus, spleen, lymph nodes (salivary, mediastinal and mesenteric) heart, aorta (thoracic) trachea, lung, salivary gland, tonsil, esophagus,
stomach, small intestines (duodenum, jejunum and ileum) large intestines (cecum, colon and rectum), liver with gall bladder, pancreas, kidneys, urinary bladder, testes with the epididymides, prostate, ovaries, fallopian tubes, uterine horns and body, vagina, thyroids with parathyroids, adrenals, pituitary gland, brain, spinal cord (cervical), peripheral (sciatic) nervere, eyes and lacrimal gland.

Results:

No significant compound-related mean body weight and weight gain, food consumption and efficiency, and clinical observation effects were found. No mortality occurred. The relative numbers of lymphocytes and eosinophils in male dogs fed 2500 and 500 ppm diets, respectively, were significantly elevated in comparison to control values. There were no abnormalities in urine analysis. Lower than average serum glutamic-pyruvic transaminase activities in control females during the test period caused an apparent increase in the activity of that enzyme in 2500 ppm diet female dogs. All dose groups of male dogs exhibited lower albumin concentrations than controls throughout the test period. These changes in clinical laboratory measurements were neither dose-related nor considered to be attributable to the feeding of chlorosulfuron.

No gross or microscopic abnormalities were considered compound-related. Males in the 2500 ppm group had decreased relative pituitary weights and males in all test groups had decreased relative thyroid/parathyroid weights. In the absence of any dose response relationships or any evidence of gross or histopathological effects, however, the changes in relative organ weights were not considered to be attributable to the feeding of chlorosulfuron. The NOEL was 2500 ppm based on no significant effects being attributed to chlorosulfuron.

Discussion:

The methods and materials, scientific principles, validity of conclusions, and adequacy of data for conclusions were adequate for the study. Some deviations from proposed guideline 163.82-1 such as 4 rather than 6 dogs/sex/level, dogs of 9-11 months of age rather than 4-6 months of age, and time variations in hematology evaluation do not affect the validity of the study, particularly since no compound-related histological effects were found at any test level.