

US EPA ARCHIVE DOCUMENT



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

6-10-80

JUN 10 1980

MEMORANDUM

OFFICE OF TOXIC SUBSTANCES

SUBJECT: EPA Reg.#100-607; Subacute Inhalation Toxicity Pilot Study in Rats with CGA-48988 - Spiked cigarettes. CASWELL#375AA

FROM: William Dykstra
Toxicology Branch, HED (TS-769) *WDD 6/3/80*

TO: Henry Jacoby (21)
Registration Division (TS-767) *WJB*

Recommendation:

- 1) The study is acceptable as core-minimum data. The NOEL is the high-dose group (13,000 ppm of CGA-48988).

Review:

- 1) Final Report. Subacute Pilot Inhalation Toxicity Study in Rats with CGA-48988 - Spiked cigarettes (Hazelton Project No. 483-187, March 31, 1980)

The study was initiated on November 21, 1979 and the final exposure was on December 19, 1979. The study consisted of four groups of 10 male and 10 female rats each with each animal being exposed to the smoke from 16 cigarettes per day, puffed by A.D. Little, Mark II smoking machines at the rate of one 35-ml puff per minute and delivered into 38-liter cylindrical glass and stainless steel static chambers for 20 seconds per puff. Three groups (group 2, 3 and 4) received exposures to smoke from cigarettes made from tobacco sprayed with CGA-48988 technical in weight proportions of 130, 3900 and 13,000 ppm, respectively. Group I was exposed to smoke from untreated tobacco. The males in each group were exposed 3 1/2 hours in the morning, five days per week, for four weeks. The females were similarly exposed during the afternoons. The rats were weighed weekly at the same time of day (+ 1 hour) each week.

Prior to initiation and at termination, blood from the clipped tail of each rat was analyzed for RBC, WBC, differential WBC, hematocrit and hemoglobin concentration. At termination, blood was drawn from the abdominal aorta for serum chemistry analyses of calcium, potassium, BUN, glucose, SAP, SGOT, SGPT, bilirubin, and total cholesterol.

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At termination, a complete necropsy was performed on each rat (none died during the study) and tissue samples from the following organs were taken and prepared for histopathological evaluation:

brain	spleen
thyroids	adrenals*
trachea	stomach
lungs*	small intestine
heart*	large intestine
liver*	gonads
kidneys*	peripheral nerve
nasal turbinates	skeletal muscle
larynx	

The asterisked organs were weighed at necropsy, after being dissected free of fat, for use in calculating organ/terminal body weight ratios.

Results:

There were no differences in pharmacotoxic signs observed (all groups had a few animals which salivated, all animals appeared to squint and become inactive during each exposure, and all animals preened actively between cigarettes). All animals gained weight at comparable rates during the study and no effects due to compound exposure were indicated. Analysis of covariance indicated that the group mean value for the Group 4 male rats for WBC was slightly but significantly higher than the Group 1 mean value with both means adjusted for pre-exposure differences. No other statistically significant hematologic differences were indicated.

The mean value for Group 3 males for SGOT was slightly but significantly higher than the Group 1 male mean value.

The mean female values for group 2, 3, and 4 for calcium were slightly but significantly lower than the Group 1 female mean value. The magnitude of the change in calcium does not reflect the wide range of doses used in the *Study*: control, 10; 130 ppm, 9.6; 3900 ppm, 9.2; 13,000 ppm, 9.1. These changes in calcium are of uncertain biological significance.

The mean female value for groups 2 and 3 for SGOT were significantly higher than the group 1 female mean value. The mean female value for group 2 for SGPT was significantly higher than the group 1 female mean value.

No other statistically significant differences in clinical chemistry values were indicated.

No consistent gross pathological between the three CGA-48988 - exposed groups and group 1 were seen. The mean value for absolute (but not relative) liver weight for the group 3 male rats was significantly higher than the group 1 mean value. Compound-related histomorphological alterations were not observed in the tissues examined.

Conclusion: The NOEL for the study is considered to be the high-dose (13,000 ppm).

Classification: Core-Minimum Data

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