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DATA EVALUATION REPORT

Study: Results of a 13-Week Dietary Toxicity Study in Fischer 344 Rats.

Laboratory: Dow Chemical Company; Midland, Michigan

Date: July 1, 1982

Study No.: HET K-038323-(32)

MRID No.: 00110537

Material Tested: Picloram, Technical. Sample No. AGR 177446 - 92% purity - contaminants not stated

Animals: CDF Fischer 344 rats

Methods:

Fifteen rats/sex/dose were given diets for 13 weeks containing picloram to provide either 0, 15, 50, 150, 300, or 500 mg/kg/day of test material. The rats were examined 2X each day, weekly for body weights and food consumption. Ten animals/sex in all dosage levels were tested for hematological changes and additionally had urinalyses completed at days 86 and 87 of the study. All rats were examined for BUN, SGPT, AP, glucose, total protein, and globulin changes at termination. Organ weights and histopathology changes were determined.

Results:

A dose dependent increase in liver weights was noted at 150 mg/kg and above. These same high doses produced microscopic liver changes.

Conclusions:

The NOEL = 50 mg/kg and the LEL is 150 mg/kg based on liver weight changes and minimal microscopic changes in the liver.

Toxicity Category:

Core Rating: Minimum

(1)

Repairability: None

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DATA EVALUATION RECORD

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CHEM 005101

BRANCH TOX DISC ___ Sub-Chronic Toxicity - Rats

FORMULATION ___ Technical material

Gorzinski, S. J.; Johnson, K. A.; Campbell, R. A.; and Park, C. N. Technical Grade Picloram: Results of a 13-Week Dietary Toxicity Study in Fischer 344 Rats.

SUBST. CLASS = S

DIRECT RVW TIME = (MH)

REVIEWED BY: Joanne E. Betso
TITLE: Toxicologist
ORG:
LOC/TEL: The Dow Chemical Company

SIGNATURE: Joanne Betso DATE: 31 Aug. 1982

APPROVED BY:
TITLE:
ORG:
LOC/TEL:

SIGNATURE: DATE:

CONCLUSIONS

Sub-Chronic Toxicity - Rats

~~1. This study is scientifically valid.~~

1. ~~2.~~ Picloram produced liver effects in rats receiving 150, 300 or 500 mg/kg/day for 13 weeks.
2. ~~3.~~ No observable effects were noted in rats receiving 50 mg picloram/kg/day or less in the diet for 13 weeks (NOEL = 50 mg/kg) for liver effects.
3. ~~4.~~ The kidneys of rats ingesting 300 or 500 mg picloram/kg/day for 13 weeks were slightly enlarged; however, this was not associated with histopathologic changes.

This study is classified as core-minimum.

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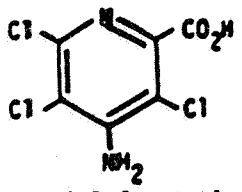
MATERIALS AND METHODS



Picloram (4-amino-3,5,6-trichloropicolinic acid)-technical
Sample No. AGR 177446 - containing 92% picloram

Fifteen CDF Fischer 344 rats per sex were given diets formulated to provide doses of 0 (control), 15, 50, 150, 300 and 500 mg picloram/kg body weight/day for approximately 13 weeks.

The following observations were made:

Appearance, demeanor	2x daily, all rats
Body weights	weekly
Food consumption	weekly
clinical chemistries	BUN, SGPT, AP, Glu, TP, Glob - all rats at termination
Hematology	PCV, RBC, WBC, platelets, Hgb (10 male, 10 female all doses), white cell differential (control, high dose) - days 86, 87
Urinalysis	Sp. gr., pH, glu., prot., ket., bilir., occ. blood, urobilin. - same rats as hematol.

After 13 weeks and following an overnight fast, the rats were weighed and killed by decapitation. Immediately after decapitation, a blood sample was obtained from the severed cervical blood vessels for clinical biochemistries and the eyes examined in situ by means of a moist glass slide technique under fluorescent light illumination. Each rat was examined externally and internally for gross pathologic alterations by a veterinary pathologist. Weights of the brain, liver, kidneys, heart, thymus and testes (males) were recorded from all rats at necropsy and the organ to fasted body weight ratios subsequently calculated. Representative portions of

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the following organs and tissues from each rat were preserved in neutral phosphate-buffered 10% formalin from each rat: adrenal glands, aorta, bone, bone marrow, brain, cecum, cervix, coagulating gland, epididymides, esophagus, eye, heart, kidneys, lacrimal glands, large intestine, larynx, liver, lungs, mammary gland, mediastinal lymph node, mediastinal tissue, mesenteric lymph node, mesenteric tissue, nasal turbinates, ovaries, oviduct, pancreas, parathyroid glands, peripheral nerve, pituitary, prostate, salivary glands, seminal vesicles, skeletal muscle, skin, small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid gland, tongue with lower jaw, trachea, urinary bladder, uterus, vagina, zymbal gland and any gross lesion or mass.

In general, full complement of tissues, with the exception of the Zymbal gland, was prepared from the first ten (numerically) rats/sex of control and high dose level (500 mg/kg/day) groups. Only sections of the liver and kidneys were prepared from 10 rats/sex of the lower treatment groups. Histopathological examination of these sections was performed by a veterinary pathologist.

Statistical Evaluation

Body weights, food consumption, clinical chemistry, hematology (excluding red cell indices and differential white cell counts), urinary specific gravity, organ weights, and organ to fasted body weight ratios were evaluated by Bartlett's test for equality of variances (Winer, 1971). In cases where homogeneity of variances existed, a parametric analysis of variance (Steel and Torrie, 1960), $p<0.10$, was conducted to identify any statistically significant differences between groups. Differences between experimental groups and the corresponding control group were examined using Dunnett's test, $p<0.05$ (ibid). For cases where variances did not exhibit homogeneity, the data were evaluated by a nonparametric analysis of variance (Winer, 1971) and subsequently, Wilcoxon's test (ibid) was used to determine if statistically significant differences

between experimental groups and their corresponding control existed. Outlying values for all parameters measured were identified using the sequential outlier test of Grubb's (1969), $p<0.02$ (two-sided), but were excluded from calculation of group means and statistical comparisons only in the case of body weight and food consumption.

REPORTED RESULTS

Effects of treatment were confined primarily to the liver of male and female rats ingesting picloram. A dose-dependent increase was noted in the absolute and relative liver weights of rats given 150, 300 or 500 mg/kg/day; these groups also had minimal microscopic liver changes. Male rats given the highest two dose levels had increased absolute and relative kidney weights; this was not associated with any histopathological changes.

Based on the data from this study, the liver was the primary target organ for male and female rats given up to 500 mg/kg/day of picloram. No salient sex differences were seen in toxicity. The no-observable-effect level (NOEL) was judged to be 50 mg/kg/day for both sexes.

DISCUSSION

1. This study was conducted in an up-to-date manner, using scientifically appropriate methods.
2. This study was conducted primarily for use in dose setting for a chronic study and therefore it employed fewer animals, used less microscopic pathology and had more dose levels than normal.
3. This study established target organ preference and also has a no-observable-effect dose level and can thus be used in hazard evaluation.

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