

7-27-84

Data Evaluation Report

Compound Brodifacoum. WBA 8119Citation

WBA 8119: Acute Oral Toxicity, G.R. Parkinson, Central Toxicology Laboratory, Imperial Chemical Industries Ltd, CTL/P/216 (revised). Jan 1976

Reviewed by

Robert P. Zendzian 7/23/84
Robert P. Zendzian PhD
Pharmacologist

Core Classification SupplementaryTox Catagory IConclusion

Acute oral toxicity in dogs was between .25 and 1.0 mg/kg and in cats about 25mg/kg.

Materials

WBA 8119 (brodifacoum)

Female beagle dogs (8-12kg)

Male and female cats (2-3kg)

Methods

Compound was dissolved in polyethylene glycol 300 and administered orally by gavage. Animals were observed for 4 weeks. Necropsies were performed on all animals killed in extremis or at termination. Doses used and results are shown in Tables 1 & 2.

Results

Table 1. Female dogs

	Dose (mg/kg)			
	0.25	1.00	2.50	5.00
(no. died/no. treated)	0/2	2/2	2/2	2/2

LD 50 estimated as between 0.25 and 1.0 mg/kg

Toxic signs appeared at about six days in the fatalities consisting of subdued behavior, loss of appetite, pale, respiratory difficulties, hypothermia, blood in feces and minor external hemorrhages. Necropsy of animals killed in extremis revealed hemorrhages, particularly in the neck and thorax.

4) Three rats were dosed orally with 14-C brodifacoum (7.2 uCi/kg; 1.5mg/kg) and urine and feces collected at 24 hour intervals for 5 days.

5) One rats was dosed orally with 14-C brodifacoum (6.6 uCi/kg; 0.25mg/kg) and expired air collected for 48 hours.

6) The bile ducts were cannulated on three rats. After recovery from anesthesia the rats were dosed orally with 14-C brodifacoum (6.6uCi/kg; 0.25mg/kg) and the bile collected at 24 hour intervals for 48 hours.

7) Three rats (80-90gm body weight) were given a single oral dose of 14-C brodifacoum (6.6uCi/kg; 0.25mg/kg)/. A single rat killed, quick frozen, block embedded and sectioned (longitudinal saggital sections) for whole body autoradiography 1, 5 and 10 days after dosing.

8) Twenty-four rats were dosed orally with 14-C brodifacoum (6.0uCi/kg; 0.21mg/kg) and killed in groups of 3 at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours after dosing. Blood (2 ml) was taken by cardiac puncture. Blood was also collected from 3 untreated rats.

9) Six rats were dosed orally with 14-C brodifacoum (6.0uCi/kg; 0.21mg/kg) and killed in groups of 3 at 10 and 17 hours after dosing. Blood (2 ml) was taken by cardiac puncture.

Samples of urine, feces, bile and extracts from various organs were analysed for metabolites by several chromatographic procedures

Results Results are numbered as in the methods section above.

1) Following an oral dose of 0.25mg/kg, the mean percent of dose excreted in the urine was 1.31 after 10 days with the highest excretion on day one (0.88) and excretion stabalizing on days 5 to 10 at 0.02 to 0.04 %/day. In the feces the mean percent of dose after 10 days was 11.01 with the highest excretion on day 2 (4.70%). Fecal excretion decreased throughout the 10 day collection period.

The mean percent of dose remaining in various tissues after ten days was abdominal fat 3.29, liver 22.84, kidney 0.78, heart 0.10 and residual carcass 50.82.

2) Following an oral dose of 0.25mg/kg, the mean percent of dose persent in tissues after 10 days was pancreas 2.33, spleen 0.16 and blood 0.05.

3) Following an oral dose of 0.5mg/kg, the mean percent of dose excreted in the urine was 2.94 after 5 days with the highest excretion on day one (2.05). In the feces the mean

percent of dose after 5 days was 30.75 with the highest excretion on day one (14.95%). One rat died on day four and the remaining two on day five.

4) Following an oral dose of 1.5mg/kg, the mean percent of dose excreted in the urine was 2.81 after 5 days with the highest excretion on day one (2.01). In the feces the mean percent of dose after 5 days was 42.56 with the highest excretion on day two (16.23%). All three rats died on day on day five.

5) Following a single oral dose of 0.25mg/kg to one rat no radioactivity was detected in expired air over 48 hours.

6) Following an oral dose of 0.25mg/kg, the mean percent of dose excreted in the bile was 0.55 for the first 24 hours and 0.77 for the second with a total of 1.36.

7) Following an oral dose of 0.25mg/kg, whole body autoradiograms at one, five and ten days post dose showed that the highest concentrations of radioactivity were present in the liver, pancreas and salivary glands with activity also present in the gastric mucosa, intestinal mucosa, vertebrae, nasal mucosa, kidneys, adrenals, meninges, fat and skins.

8 & 9) Mean blood concentrations of brodifacoum (ng equivalents /ml of blood) following a single oral dose of 0.21mg/kg are given in the following table taken from table 4 of the report. Activity was less than the limit of detection (1.1 ng eq/ml) on day 17.

Hrs after dosing	0.25	0.50	1.0	2.0	4.0	6.0	8.0	10.0	17.0	24.0	240.0
ng eq/ml	2.8	2.2	4.4	5.9	10.1	15.4	16.1	13.1	6.7	5.7	1.3

Analysis for metabolites showed that 50% or more of the retained radioactivity was represented by the parent compound.

Discussion

The dose of 0.25mg/kg brodifacoum administered in most of these experiments approximates the LD₅₀ in the male rat. The compound is almost completely absorbed and only very slowly excreted. The half-life is estimated as 150-200 days with at least 50% of the retained radioactivity represented by the parent compound. This extensive half-life indicates a serious potential for cumulative toxicity.

This study satisfies the Guideline requirements for a single high oral dose in male rats.