Repeated Dose Oral Toxicity of 8-2 Telomer B Alcohol Range-Finding Study in Rats

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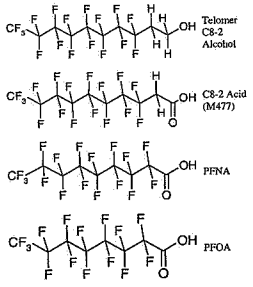
Abstract

Preliminary to a repeated dose toxicity assessment, a range-finder study involving repeated oral doses of 8-2 Telomer B Alcohol was conducted in rats to determine the time needed to reach steady-state as determined by total organofluorine blood fluoride levels. Groups of 10 male and 5 female Crl:CD®(SD)IGS BR rats each were dosed daily with either 0 (control), 5, 25, or 125 mg 8-2 Telomer B Alcohol/kg/day. A number of toxicology end-points such as body weights, liver and kidney weights were recorded during and at the end of the study. Blood samples were analyzed for total fluoride levels weekly. Steady-state concentrations were reached between test days 60 and 84. At steady-state, pooled plasma samples obtained from males and females over the duration of the study were analyzed for Telomer 8-2 Alcohol (parent compound), Telomer 8-2 acid, perfluorooctanoate acid (PFOA), and perfluorononanoic acid (PFNA) and total fluorine levels. The level of parent compound detected did not exceed 0.074 ppm in either males or females. In males, PFOA represented approximately 85% of the total plasma fluorine. In females, PFOA represented approximately 5%. The 8-2 acid of Telomer B Alcohol and PFNA were also found in plasma of both males and females. Significantly lower mean body weights and increased liver weights compared to control were observed in male rats administered 125 mg/kg/day. Based on these data, the following doses were chosen for the 90-day oral toxicity study: 0, 1, 5, 25, and 125 mg/kg/day.

Purpose

To determine appropriate dose levels for use in a 90-day oral subchronic study with 8-2 Telomer B Alcohol.

Structures



Methods

- Test substance, 8-2 Telomer B Alcohol (99.2% pure)
- Test species: Crl:CD rat (male and female)
- Standard husbandry, 5-day quarantine
- Groups: 10 males, 5 females/group [5 males/group allowed 75-day post-dosing recovery period].
  Doses: 0, 5, 25, 125 mg/kg
  Daily gavage beginning with 7-week-old rats
- Doses in methylcellulose suspensions, 5 mL/kg dosing volume.
  Parameters measured (dosing and during recovery)
  Body weights (2 x/week)
  Cage-side exams (daily)
  Total fluoride/parent metabolite evaluation
  Blood samples collected 1 x pre-dosing weekly during dosing
  Organ weights – liver, kidney
- Parent/Metabolite Evaluation
  At steady-state, pooled plasma, fat, liver, and kidney samples from each group were analyzed for
  Telomer 8-2 Alcohol
  Perfluorooctanoic Acid (PFOA)
  Perfluoronononoic acid (PFNA)

Results

Clinical Observations

Dose (mg/kg)	Finding	Sex	Incidence
0	None	M	10/10
		F	5/5
5	None	M	10/10
		F	5/5
25	None	M	10/10
		F	5/5
125	Striated teeth	M	7/10*
		F	4/5*
	Clipped teeth	M	4/10*
		F	0/5

* ($p < 0.05$) different from control

Body Weights

Dose (mg/kg)	After Dosing (Test Day 81) Male	After Dosing (Test Day 81) Female	After Recovery (Post-Dosing Day 75) Male	After Recovery (Post-Dosing Day 75) Female
0	594 ± 44	264 ± 45	554 ± 100	322 ± 41
5	564 ± 59	302 ± 22	595 ± 57	348 ± 29
25	553 ± 34	296 ± 41	573 ± 83	332 ± 50
125	509* ± 55	291 ± 21	549 ± 37	346 ± 31

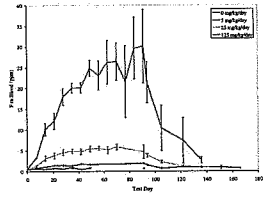
* ($p < 0.05$) different from control

Organ Weights

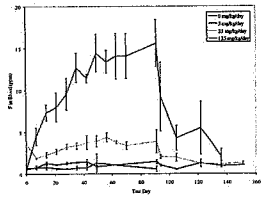
Dose (mg/kg)	Sex	Liver (g/100g bwt) Test Day 81	Liver (g/100g bwt) Post-Dosing Day 75	Kidney (g/100g bwt) Test Day 81	Kidney (g/100g bwt) Post-Dosing Day 75
0	M	3.9(0.28)	3.0(0.13)	0.76(0.03)	0.65(0.06)
	F	--	3.2(0.14)	--	0.70(0.03)
5	M	3.7(0.20)	3.1(0.14)	0.76(0.06)	0.67(0.03)
	F	--	3.2(0.33)	--	0.71(0.07)
25	M	4.1(0.19	2.9(0.13)	0.75(0.04)	0.69(0.05)
	F	--	3.4(0.37)	--	0.73(0.06)
125	M	5.5*(0.39)	3.1(0.32)	0.87(0.11)	0.74*(0.07)
	F	--	3.6*(0.05)	--	0.78*(0.02)

* ($p < 0.05$) different from control

Total Blood Fluorine Analysis in Male Rats Dosed with 8-2 Telomer B Alcohol



Total Blood Fluorine Analysis in Female Rats Dosed with 8-2 Telomer B Alcohol



Analysis of 8-2 Telomer B Alcohol, PFOA, and PFNA in Serum and Selected Tissues

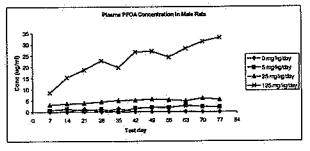
Dose (mg/kg/day)	Male PFOA (ppm)	Male PFOA Converted to ppm F	Male Total Plasma F (ppm)	Female PFOA (ppm)	Female PFOA Converted to ppm F	Female Total Plasma F (ppm)
0	0.07	0.05	NM	0.0	0.0	NM
5	2.19	1.51	NM	0.08	0.05	NM
25	8.47*	5.83	8.11	0.54*	0.37	5.88
125	65.60*	45.16	53.24	1.85*	1.27	23.20

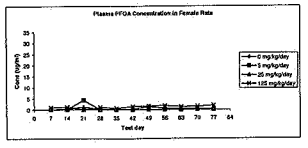
Determined using Wickbold Torch;
* Mean of 2 separate runs.

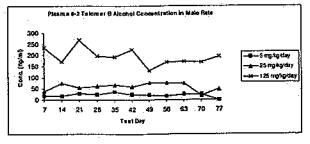
Tissue Analysis from Range-Finder Study (Test Day 81)

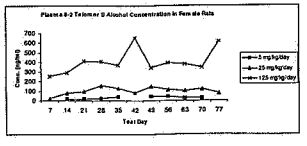
		8-2 Telomer B Alcohol 5 mg/kg/day	25 mg/kg/day	125 mg/kg/day
C8-2A (ppm)	Fat	0.07(0.01)	0.34(0.13)	1.37(0.55)
	Liver	0.02(0.00)	0.13(0.03)	0.77(0.53)
	Kidney	NM	0.01(0.00)	0.07(0.07)
PFOA (ppm)	Plasma	2.19	8.47	65.60
	Fat	0.09(0.04)	0.35(0.12)	1.90(1.66)
	Liver	6.96(1.94)	18.68(10.38)	30.69(20.68)
	Kidney	1.64(0.83)	8.43(4.14)	29.11(17.38)
PFNA (ppm)	Fat	0.00(0.00)	0.00(0.00)	0.01(0.01)
	Liver	0.51(0.09)	0.91(0.23)	1.19(1.25)
	Kidney	0.00(0.00)	0.11(0.09)	0.86(0.62)

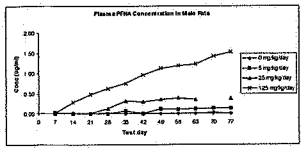
NM = not measured.

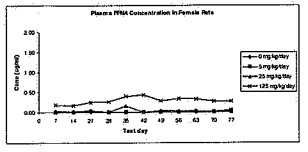


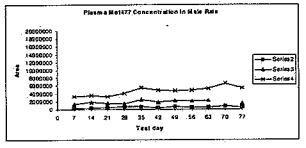


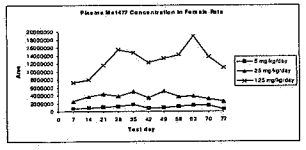












Conclusions

- Doses of Telomer 8-2 Alcohol were well tolerated; number of endpoints were altered at 125 mg/kg.
- Steady-state blood fluorine levels were attained between weeks 8 and 13 of dosing; males reached higher levels than females.
- Metabolites of Telomer 8-2 Alcohol were found in both sexes of rats.
- The 90-day toxicity study would employ dose levels of 0, 1, 5, 25, and 125 mg/kg.