Evaluation of the Subchronic Toxicity and One-Generation Reproductive Effects of a Fluoroalkylethyl Urethane Polymer

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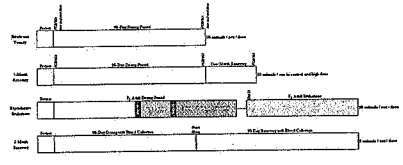
Abstract

A fluoroalkylethyl urethane polymer, used as a carpet protectant, was evaluated for its oral subchronic toxicity and reproductive effects when administered to male and female rats by gavage at dosages of 0, 50, 250, or 1000 mg/kg/day. No compound-related mortality occurred in the study. No adverse clinical signs of toxicity or neurobehavior changes were observed in male or female rats in any dose group. Hepatocellular hypertrophy was observed after 90 days of dosing in male rats at all dose levels. Nasal olfactory epithelium degeneration/necrosis was observed in male and female rats at all dose levels and inflammation of the olfactory epithelium in male rats dosed with 250 and 1000 mg/kg/day. Thyroid hypertrophy was seen in male and female rats in the 250 and 1000 mg/kg/day dose groups. After a 90-day recovery, hepatocellular hypertrophy was still present in male rats in the 250 and 1000 mg/kg/day dose groups. Nasal epithelial lesions were absent and evidence of reversibility of thyroid effects was observed after the recovery period. No test substance-related effects on reproductive parameters were observed. However, mean thyroid organ weight was significantly lower in the 250 and 1000 mg/kg/day dose groups in the F_1 generation. There were no histopathological changes in the thyroid of the F_1 generation rats. Due to the presence of nasal lesions, a no-observed-adverse-effect-level (NOEL) could not be determined for the subchronic toxicity evaluation. For reproductive assessments a NOEL of 50 mg/kg/day was determined based on decreased thyroid weights observed in both male and female F_1 adults. It could not be determined whether the nasal lesions observed are due to systemic toxicity or local toxicity as a result of gavage dosing. Based on the other systemic effects observed at 250 mg/kg/day and above, the potential risk of human health effects from exposure to this product is very low.

Introduction

The objective of this study was to evaluate the potential subchronic and reproductive toxicity of a fluorotelomer-based urethane polymer in male and female rats. The test substance is used as a textile protectant and was administered as formulated product that contained approximately 23% active ingredient and 1.7% hydrocarbon surfactant in water. The test material was administered by gavage, the route selected as the most efficient way to deliver an accurate dosage. In a two-week range-finding study, there was no observable systemic toxicity in rats given a limit dosage of 1000 mg active ingredient/kg body weight/day. Dosages of 50, 250, and 1000 mg/kg/day were selected for this study, based on this ability of rats to tolerate the limit dosage.

Study Design



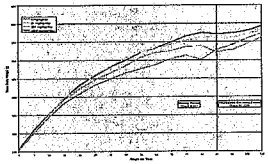
- Body weights, detailed clinical signs, and food consumption were determined weekly throughout the 90-day exposure and 1-month recovery periods.
- Gross and microscopic pathology evaluations were performed at the end of the 90-day exposure, 1-month recovery, and 3-month recovery periods.
- Reproductive evaluations were performed prior to mating and during the mating, gestation, and lactation periods. Developmental landmarks and gross pathology was also assessed on F_1 adults.

Results

Body Weights and Food Efficiency

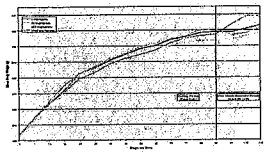
Males

- After the 90-day exposure period, weight gain and food efficiency in male rats administered 1000 mg/kg/day was approximately 23 % and 20 % lower than control rats, respectively.
- Following a one-month recovery period weight gain and food efficiency values were similar to controls.



Females

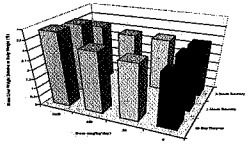
- There were no statistically significant differences in weight gain or food efficiency in female rats at any dose level.



Liver Weights

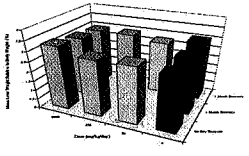
Males

- After the 90-day exposure period, absolute and relative liver weights were increased, compared to controls, in all male rat dose groups.
- After 1-month and 3-month recovery periods, absolute and relative liver weights remained elevated in male rats administered 1000 mg/kg/day compared to controls.



Females

- After the 90-day exposure period, relative liver weights were statistically increased in female rats administered 1000 mg/kg/day compared to controls.



Histopathology

Males

- Test substance-related microscopic findings were present in nose, thyroid gland and liver of male rats.

	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
90-Day Exposure				
Nose:				
Degeneration/necrosis, olfactory epithelium	0/10[a]	8/10 (0.9)[b]	10/10 (1.7)	10/10 (2.1)
Inflammation, subacute/chronic	0/10	0/10	5/10 (0.5)	6/10 (0.6)
Thyroid gland:				
Hypertrophy, follicular	0/10	0/10	5/10 (0.5)	10/10 (1.8)
Alteration, colloid	8/10 (0.8)	8/10 (1.1)	10/10 (1.4)	10/10 (2.8)
Liver:				
Hypertrophy, hepatocellular	0/10	1/10 (0.1)	10/10 (1.8)	10/10 (2.0)
One-Month Recovery				
Nose:				
Degeneration/necrosis, olfactory epithelium	0/10	NA	NA	3/10 (0.3)
Thyroid gland:				
Hypertrophy, follicular	0/10	NA	NA	6/10 (1.1)
Alteration, colloid	6/10 (0.7)	NA	NA	10/10 (2.9)
Liver:				
Hypertrophy, hepatocellular	0/10	NA	NA	10/10 (1.0)
Three-Month Recovery (Satellite)				
Thyroid gland:				
Alteration, colloid	5/5 (1.2)	4/5 (1.2)	4/4 (2.3)	5/5 (2.6)
Liver:				
Hypertrophy, hepatocellular	0/5	0/5	3/4 (0.8)	4/5 (0.8)

a Numerator indicates incidence of rats with microscopic lesion. Denominator indicates number of rats in group.
b Number in parentheses indicates group average severity of lesion.
NA Tissue not available

Females

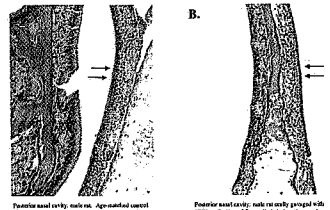
- Test substance-related microscopic findings were present in nose and thyroid gland of female rats.

	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
90-Day Exposure				
Nose:				
Degeneration/necrosis, olfactory epithelium	0/10[a]	2/10 (0.2)[b]	4/10(0.5)	8/10 (1.0)
Thyroid gland:				
Hypertrophy, follicular	0/10	0/10	2/10 (0.2)	7/10 (1.0)
Alteration, colloid	3/10 (0.3)	5/10 (0.5)	6/10 (0.6)	10/10 (1.1)
One-Month Recovery				
Thyroid gland:				
Hypertrophy, follicular	0/10	NA	NA	5/10 (0.6)
Alteration, colloid	6/10 (0.6)	NA	NA	7/10 (1.0)
Three-Month Recovery (Satellite.				
Thyroid gland:				
Hypertrophy, follicular	0/5	0/5	0/5	1/5 (0.2)
Alteration, colloid	3/5 (0.6)	5/5 (1.0)	4/5 (0.8)	3/5 (0.8)

a Numerator indicates incidence of rats with microscopic lesion. Denominator indicates number of rats in group.
b Number in parentheses indicates group average severity of lesion.
NA Tissue not available.

Olfactory Epithelium

- Micrograph of olfactory epithelium from control rat (A) and from rat administered 1000 mg/kg/day test substance (B).



Posterior nasal cavity, male rat. Age-matched control rat orally gavaged with deionized water. Note uniform cellular arrangement of olfactory epithelium (arrows). HE. ~200x

Posterior nasal cavity, male rat orally gavaged with 1000 mg/kg/day of fluoroalkylethyl urethane polymer for 90 days. Note cellular degeneration/necrosis of olfactory epithelium (arrows). HE. ~200x

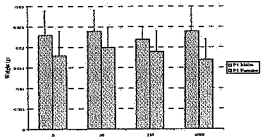
Reproduction

- No test substance-related effects on reproductive parameters were observed.
- There were no adverse effects on estrous cycle or sperm parameters.
- There were no adverse changes in F_1 litter size, pup weights, and survival during lactation.
- There were no test substance-related changes in body weights, food consumption or developmental landmarks in the F_1 generation.

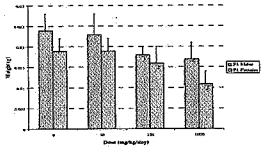
Thyroid Weights (P_1 and F_1 Generations)

- Mean thyroid weight (absolute and relative to body weight) was significantly lower in the 250 and 1000 mg/kg/day dose groups in the F_1 generation, but not in the P_1 generation. However, there were no histopathological changes in the thyroid of the F_1 generation rats.

P_1 Generation



F_1 Generation



Statistically significant difference from control ($p < 0.05$) by Jonckheere-Terpstra trend test.

Summary

- Increased liver weights and/or hepatocellular hypertrophy were observed in male rats of all dose levels and female rats administered 1000 mg/kg/day.
- Thyroid hypertrophy was observed in male and female rats administered 250 and 1000 mg/kg/day.
- Olfactory epithelium degeneration / necrosis was observed in male and female rats of all dose groups. Incidence and severity of nose lesions decreased after one month of recovery and were not observed after three months of recovery.
- No test substance-related effects on reproductive parameters were observed.
- Mean thyroid weight was significantly lower in the 250 and 1000 mg/kg/day dose groups in the F_1 generation, but not in the P_1 generation.

Conclusions

- Increased liver weights and hepatocellular hypertrophy were considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse.
- Thyroid hypertrophy in P_1 generation animals and decreased thyroid organ weights in F_1 generation animals were considered adverse findings and may be caused by exposure to organic iodide impurities in the test substance.
- Olfactory epithelium degeneration/necrosis was also considered adverse but it could not be determined whether the nasal lesions observed were due to systemic toxicity or local toxicity as a result of gavage dosing.
- Based on systemic effects (other than nose) observed at 250 mg/kg/day and above, the potential risk of human health effects from exposure to this product is very low.