Comparison of Dose and Toxicity after Administration of a Fluoroalkylethyl Phosphate Surfactant by Dermal and Inhalation Routes in Rats

C. Finlay, D.P. Kelly, N.E. Everds, J.F. Hansen, and J.C. Stadler

The DuPont Company, Haskell Laboratory for Health and Environmental Sciences, Newark, Delaware, USA

Abstract

Fluorosurfactants are used as specialty wetting and leveling additives in cleaning and coatings formulations. Previously, this fluoroalkylethyl phosphate surfactant was evaluated for subchronic, developmental, and reproductive toxicity in gavage studies; the liver was the most sensitive target organ. Since the intended uses of this surfactant would predict that dermal or respiratory tract exposures are likely, studies were conducted to assess internal exposure and toxicity by these routes. In the 28-day study, the test substance was applied to the skin of male rats each day for 6 hours at doses of 0, 10, 100, and 1000 mg/kg/day (35% ai). There were no adverse effects on mortality, clinical signs, body weights, food parameters, anatomic pathology, or hematology. Aspartate- and alanine-aminotransferases and sorbitol dehydrogenase activities were increased at 100 and 1000 mg/kg/day. The NOEL for dermal exposure was 10 mg/kg/day. In the inhalation study, male rats were exposed nose-only to 0, 0.2, 2, or 20 mg/m³ of aerosol for 6 hrs/day, 5 days/wk for 2 wks. There were no effects on body weights, clinical signs, or clinical pathology parameters. The only histological effects were mild inflammation in the larynx and lung at 2 and 20 mg/m³. The NOEL for inhalation was 0.2 mg/m³. Internal exposures by the dermal, inhalation, and oral routes were compared by fluorine blood analysis (Wickbold Torch Combustion Method). Minimal levels of fluorine were detected at the two lowest doses administered dermally. Fluorine levels were apparent in all rats exposed by inhalation, however, the levels were equal to or less than levels in rats exposed orally. Based on the fluorine dosage results in the above studies and the findings in the respiratory tract after inhalation exposure, inhalation appears to be a more sensitive route of exposure than the dermal or oral routes for this fluorosurfactant.

Introduction

This fluoroalkylethyl phosphate surfactant is used as a specialty wetting and leveling additive in cleaning and coatings formulations. The liver was the most sensitive target organ in previously conducted oral gavage studies. The intended uses of this surfactant would predict that dermal or respiratory tract exposures are likely. Studies were conducted to assess toxicity by these routes and compare internal exposures to a previously conducted 90-day oral study. Only male rats were used because they were the more sensitive sex in the oral studies.

Methods

Total Fluorine in Blood:	Whole blood was combusted using a Wickbold torch, followed by analysis with a fluoride ion selective electrode.
Urine Fluoride:	Determined using a phi12 PH meter and a fluoride-selective electrode.
Test Substance:	35-40% Active ingredients 20% Isopropyl alcohol 40-45% Water
Animals:	Male, Sprague-Dawley rats

Dermal Study Design

Dosages:	0 (control), 10, 100, and 1000 mg/kg/day
Conditions:	6 hrs/day for 28 consecutive days; semi-occluded
Animals:	10 rats per dosage
Recovery Period:	None
Study Parameters:	Mortality, clinical observations, body weights, food consumption, total fluorine in blood (day 22), clinical pathology, anatomic pathology

Dermal Study Results

Mortality:	None
Clinical Observations:	No systemic toxicity
Body Weights:	No effects
Food Consumption:	No effects
Clinical Pathology:	· No adverse effects on hematology · Increased aspartate and alanine aminotransferase activities at 100 and 1000 mg/kg/day were considered potentially adverse (Table 1).
Anatomic Pathology:	No adverse effects on organ weights or gross or microscopic examinations
Fluorine Measurements:	Total Fluorine in Blood (Table 2, Figure 1): Minimal levels of fluorine (slightly above background of 0.5 ppm) in day 21 blood from rats in 10 or 100 mg/kg/day groups. Some fluorine (1.3 ppm) in day 21 blood from rats in 1000 mg/kg/day group. Urine Fluoride (Table 3): Statistically significant at 1000 mg/kg/day. Slightly elevated at 10 or 100 mg/kg/day.
NOEL:	10 mg/kg/day based on increased liver enzymes at 100 and 1000 mg/kg/day

Table 1 - Aspartate and Alanine Aminotransferase Activities

	Dermal Study – Day 29				Inhalation Study – Day 10			
	0 mg/kg	10 mg/kg	100 mg/kg	1000 mg/kg	0 mg/m³	0.2 mg/m³	2 mg/m³	20 mg/m³
AST	109	112	145@	157@	94	94	94	103
(U/L)	14(10)	8(10)	41(10)	79(10)	10(10)	12(10)	15(10)	12(10)
ALT	50	60	100@	111@	38	39	39	41
(U/L)	8(10)	15(10)	37(10)	66(10)	8(10)	7(10)	6(10)	5(10)

AST = aspartate aminotransferase
ALT = alanine aminotransferase

Data arranged as: Mean
Standard deviation (Number of values included in calculations)

@ Statistically significant difference from control at p<0.05 by Dunn's test.

Table 2 - Total Fluorine Levels in Blood

	Dermal Study – Day 22				Inhalation Study – Day 10			
	0 mg/kg	10 mg/kg	100 mg/kg	1000 mg/kg	0 mg/m³	0.2 mg/m³	2 mg/m³	20 mg/m³
F	<0.5	0.7	0.6	1.3	1.3	1.4	1.4	2.0
(ppm)		0.32(2)	0.09(5)	0.09(3)	0.04(5)	0.22(5)	0.15(5)	0.11(5)

F = blood total fluorine

Data arranged as: Mean
Standard deviation (Number of values included in calculations)

Table 3 - Fluorine Levels in Urine

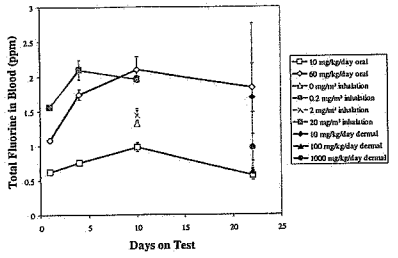
	Dermal Study – Day 29				Inhalation Study – Day 10			
	0 mg/kg	10 mg/kg	100 mg/kg	1000 mg/kg	0 mg/m³	0.2 mg/m³	2 mg/m³	20 mg/m³
UFLU	14.8	17.4	19.2	33.9@	8.3	7.9	8.1	10.5
(µg)	4.0(9)	4.3(10)	5.3(10)	2.1(10)	2.2(10)	2.4(10)	1.2(10)	4.8(10)

UFLU = urine fluorine

Data arranged as: Mean
Standard deviation (Number of values included in calculations)

@ Statistically significant difference from control at p<0.05 by Dunn's test

Figure 1 - Oral, Inhalation, and Dermal Studies



Values represent mean ± standard error of the mean.

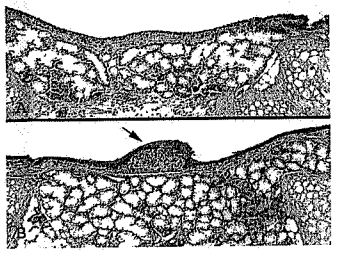
Inhalation Study Design

Concentrations:	0 (control), 0.2, 2, and 20 mg/m³/day
Exposure Mode:	Nose only
Conditions:	6 hrs/day, 9 exposures over a 2-week period
Animals:	· 15 rats per concentration · 10 rats/group designated for toxicity testing; half these rats had a 15-day recovery period · 5 rats/group designated for blood fluorine analysis and had a 15-day recovery period
Study Parameters:	Mortality, clinical observations, body weights, total fluorine in blood (day 10), clinical pathology, anatomic pathology

Inhalation Study Results

Mortality:	None
Clinical Observations:	No systemic toxicity
Body Weights:	No effects
Clinical Pathology:	No effects
Anatomic Pathology:	Organ weights No effects Gross observations No effects Microscopic Observations (Figure 2) Inflammation in lungs characterized by mixed inflammatory cells within scattered alveolar lumina in rats at 2 and 20 mg/m³. Minimal to mild squamous metaplasia of mucosa lining the ventral floor of the larynx at 2 and 20 mg/m³.
Fluorine Measurements:	Total Fluorine in Blood (Table 2, Figure 1): Small amounts of fluorine (slightly above background of 0.5 ppm) in day 9 blood from rats in 0.2 and 2 mg/m³ groups. Some fluorine (2 ppm) in day 9 blood from rats in 20 mg/m³ group. No above-background fluorine present after recovery period. Urine Fluoride (Table 3): Slight elevation in 20 mg/m³ group. No statistically significant differences from control.
NOEL:	0.2 mg/m³ based on respiratory tract effects at 2 mg/m³

Figure 2



Section of larynx (at the base of the epiglottis) from a control rat (A) and a rat exposed to 20 mg/m³ of the test substance (B). Note squamous metaplasia of the ventral laryngeal mucosa and inflammatory cell infiltrate in the submucosa (arrow).

Discussion

This fluoroalkylethyl phosphate surfactant is used as a specialty wetting and leveling Administration of this fluoroalkylethyl phosphate surfactant dermally for 28 days resulted in elevations of liver enzymes but not in adverse liver pathology. Previously, liver necrosis occurred in rats dosed orally. The effects on liver enzymes were only seen at the high dose. A clear no observed adverse effect level (NOEL) was established.

Administration of this fluoroalkylethyl phosphate surfactant by inhalation in 9 exposures over a 2-week period resulted in mild effects on the respiratory tract. There were no liver effects. A clear NOEL was established.

The levels of total fluorine in the blood from rats in the 60 mg/kg/day oral dose group and 20 mg/m³ inhalation group are comparable. However, none of the liver necrosis observed in the oral study was apparent in the inhalation study. The levels of total fluorine from rats dosed with 10 or 100 mg/kg/day dermally compares to blood levels in rats dosed with 10 mg/kg/day orally. As with inhalation, no adverse liver effects were observed from dermal exposure. The inhalation NOEL (0.2 mg/m³) converts to a daily dose of 33 µg/kg/day in a 60 kg man. Therefore, inhalation exposure produces the highest blood levels relative to dose delivered.

Conclusions

Study results indicate that liver effects would not be expected as a result of normal uses. Blood levels indicate inhalation is the more sensitive exposure route on which to base potential health effects for individuals using the surfactant. Clear NOELs have been established for both dermal and inhalation routes of exposure.

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