

8EHQ-1004-00373

AR226-1874

Certified Mail

October 4, 2004

3M

Document Processing Center
EPA East - Room 6428 Attn: Section 8(e)
Office of Pollution Prevention and Toxics
US EPA
1200 Pennsylvania Avenue NW
Washington DC 20460-0001

CONTAINS NO CBI

RE: TSCA 8 (e) SUPPLEMENTAL SUBMISSION:
Docket No. 8EHQ-1180-373, 374

8EHQ-80-373

Dear Docket Coordinators:

On December 4, 2002, 3M provided EPA with preliminary results from repeated dermal contact absorption/toxicology study in rats conducted with four mill-applied and aftermarket carpet/fabric/upholstery protector products that 3M ceased manufacturing as part of its perfluorooctanyl chemistries phase out. The preliminary results indicated that three compounds, believed to be derived from manufacturing residuals of the protector products, were observed in some of the liver and serum samples analyzed post exposure to those products. The three compounds are: 1) PFOS - perfluorooctanesulfonate ; 2) PFHS - perfluorohexanesulfonate; and 3) M-570 - N-methyl-perfluorooctanesulfonamide. The final report for this study contains results that are consistent with the previously reported information.

Enclosed please find the following final report and appendices on CD:

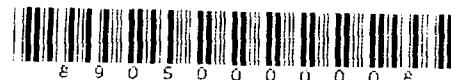
- 28-Day Repeated Dermal Contact in Rats (8 test materials); Dated 08-16-04
 - T-7088 liquid / T-7338 liquid dried on gauze - FX 1860
 - T-7092 liquid / T-7339 liquid dried on gauze - FX 3539
 - T-7340 liquid / T-7341 liquid dried on gauze - FC 1395
 - T-7342 liquid / T-7343 liquid dried on gauze - FC-288
- Note: Reference page 9 of the final report for detail regarding test materials
- Appendix A-D - Sample Re-analysis, Clinical Observation, Body Weight, Liver Weight
- Appendix E - Histopathological findings
- Appendix F - PFOS in liver samples
- Appendix G - Amendments and Deviations
- Appendix H - Exygen Data (Analytical)

Please contact John Butenhoff (651-733-1962) if you have any questions or if we can provide additional information.

Sincerely,

Larry R. Johnson

Larry R. Johnson
Director, Corporate Toxicology and Regulatory Services
Enclosure



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Final Report

28-Day Repeated Dermal Contact Study of 3M Test Articles in Sprague-Dawley Rats

Fraunhofer ITEM - Study No.: 01G 00 0 02

Original ... of 2

Test Facility:

Fraunhofer Institute of Toxicology
and Experimental Medicine
[Fraunhofer ITEM]
Nikolai-Fuchs-Str. 1
30625 Hannover
Germany

Director:

Prof. Dr. Dr. U. Heinrich

Sponsor:

3M Corporate Toxicology
St. Paul, MN 55144-100
USA

This report consists of 25 pages

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General

Title: 28 Day Repeated Dermal Contact Study of 3M Test Articles in Sprague-Dawley Rats

Fraunhofer ITEM - Study No.: 01G 00 0 02

Study Location: Animal Room T2.040-2
Necropsy Room T1.07

Test articles (3M Nos.): -liquids: T-7088.2, T-7090.2, T-7340, T-7342
-cotton gauzes: T-7338, T-7339, T-7341, T-7343

Study Director: Prof. Dr. med. vet. Clemens Dasenbrock

Deputy Study Director: Dr. med. vet. Bernd-D. Görlitz

Monitors of Sponsor: John L. Butenhoff, Ph.D., CIH, DABT
Mike McNamara, MS, DABT

Study Initiation Date: March 29, 2000
Experimental Starting Date : May 8, 2000
Experimental Completion Date: January 18, 2002
(last date on which raw data [at EXYGEN] were recorded)

Study Completion Date: August 16, 2004

1. Certification**1.1 Statement of the Study Director**

Fraunhofer ITEM Study No.: 01 G 00 0 02

Test articles (3M Nos.): -liquids: T-7088.2, T-7090.2, T-7340, T-7342
 -cotton gauzes: T-7338, T-7339, T-7341, T-7343

Title: 28 Day Repeated Dermal Contact Study of 3M Test Articles
 in Sprague-Dawley Rats

Good Laboratory Practice Statement:

The study was conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP) according to Annex 1 of the German Chemicals Law (ChemG) of 25 July 1994, amended on 14 May 2001.

A copy of the Fraunhofer ITEM GLP Certificate is given in chapter 1.4

The study followed the regulations of the German Animal Protection Law (TierschutzGesetz) of 25 May, 1998.

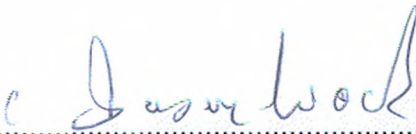
This report provides a correct and faithful record of the results obtained.

I accept the responsibility for the validity of the study.

Date

Signature

August 16, 2004
.....


.....
Fraunhofer-Institute for Toxicology and
Experimental Medicine (Fraunhofer ITEM)
Prof. Clemens Dasenbrock
Study Director

1.2 Statement of the Quality Assurance Unit

Fraunhofer ITEM Study No.: 01 G 00 0 02

Test articles (3M Nos.): -liquids: T-7088.2, T-7090.2, T-7340, T-7342
 -cotton gauzes: T-7338, T-7339, T-7341, T-7343

Title: 28 Day Repeated Dermal Contact Study of 3M Test Articles
 in Sprague-Dawley Rats

The conduct of this study has been subjected to periodic inspections of critical procedures relevant to the study. The findings of these inspections were promptly reported to the study director and the management of Fraunhofer ITEM. The exact dates of inspections and report are given below.

This report has been audited by the Fraunhofer ITEM Quality Assurance Unit. It describes the correct presentation of the procedures and methods employed during the course of the study and accurately reflects the raw data of the study.

Date of Inspection	Type of Inspection	Date of Report
17.12.99 – 29.03.00	Study plan	29.03.2000
10.05.00	Test article identification	10.05.2000
18.05.00	Dermal exposure	18.05.2000
22.05.00 – 20.06.00	Necropsy, raw data	20.06.2000
22.06.00 – 30.06.00,	Chemical analysis of liver samples	03.07.2000
17.07.00 – 18.07.00	for PFOS	18.07.2000
23.07.04 – 16.08.04	Draft report, raw data	16.08.2004

Date

Signature

16.08.2004

M.B. Ketkar

Fraunhofer Institute for Toxicology
and Experimental Medicine (Fraunhofer ITEM)
Dr. M.B. Ketkar
Quality Assurance Unit

1.3 Statement of the Principal Scientists

Fraunhofer ITEM Study No.: 01 G 00 0 02

Test articles (3M Nos.): -liquids: T-7088.2, T-7090.2, T-7340, T-7342
 -cotton gauzes: T-7338, T-7339, T-7341, T-7343

Title: 28 Day Repeated Dermal Contact Study of 3M Test Articles
 in Sprague-Dawley Rats

We the undersigned, hereby declare that the work in this study was performed by us or under our supervision according to the procedures herein described and that this report provides a correct and faithful record of the results obtained.

Fraunhofer Institute of Toxicology and Experimental Medicine

	Date	Signature
Laboratory Animal Veterinarian: Prof. Dr. med. vet. C. Dasenbrock (Study Director)	<u>11.8.04</u>	<u>C. Dasenbrock</u>
Toxicologist: Dr. med. vet. B.-D. Görlitz	<u>24.8.04</u>	<u>B.-D. Görlitz</u>
Chemist: Prof. Dr. rer. nat. K. Levsen	<u>16.8.04</u>	<u>K. Levsen</u>
Pathologist: Dr. med. vet. Heinrich Ernst	<u>23.8.04</u>	<u>H. Ernst</u>
Biostatistician*: Dr. rer. nat. Rupert Kellner	<u>16.8.04</u>	<u>Rupert Kellner</u>

* In October 2001 Dr. Kellner took over the responsibilities of Dr. Kohler who left the test facility.

1.4 Copy of the GLP Certificate

Gute Laborpraxis/Good Laboratory Practice
**GLP-Bescheinigung/Statement of GLP
Compliance**
(gemäß/according to § 19 b Abs. 1 Chemikaliengesetz)



Niedersächsisches
Landesamt für Ökologie

Eine GLP-Inspektion zur Überwachung der Einhaltung
der GLP-Grundsätze gemäß Chemikaliengesetz bzw.
Richtlinie 88/320/EG wurde durchgeführt in:

Assessment of conformity with GLP according to
Chemikaliengesetz and Directive 88/320/EEC at:

☒ Prüfeinrichtung / Test facility

☐ Prüfstandort / Test site

**Fraunhofer-Institut für Toxikologie und Experimentelle Medizin
in D-30625 Hannover, Nikolai-Fuchs-Straße 1**

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/Areas of Expertise (gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

- 1 - Prüfungen zur Bestimmung der physikalisch-chemischen Eigenschaften und Gehaltsbestimmungen
- 2 - Prüfungen zur Bestimmung der toxikologischen Eigenschaften
- 3 - Prüfungen zur Bestimmung der erbgutverändernden Eigenschaften (in vitro und in vivo)
- 5 - Prüfungen zum Verhalten im Boden, im Wasser und in der Luft, Prüfungen zur Bioakkumulation und zur Metabolisierung
- 8 - Analytische Prüfungen an biologischen Materialien
- 9 - Sonstige Prüfungen:
 - Sicherheitspharmakologie, Teilbereich Lunge
 - Molekultoxikologische und molekularbiologische Prüfungen zu Chemikalien, Pflanzenschutzmittel-Wirkstoffen, Bioziden und pharmakologischen Wirkstoffen

- 1 - Physical-chemical testing
- 2 - Toxicity studies
- 3 - Mutagenicity studies
- 5 - Studies on behaviour in water, soil and air; bioaccumulation
- 8 - Analytical and clinical chemistry testing
- 9 - Other studies:
 - Safety pharmacology of the lung
 - Molecular toxicological and molecular biological studies on chemicals, pesticides, biocides and pharmacological active substances

Datum der Inspektion / Date of Inspection
(Tag.Monat.Jahr / day.month.year)

25. – 27. November 2002

Die/Der genannte Prüfeinrichtung/Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

The above mentioned test facility / test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Based on the inspection report it can be confirmed that this test facility / test site is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Niedersächsisches Landesamt für Ökologie/Lower Saxony State Agency for Ecology

Hildesheim, 06.02.03

Im Auftrage

Teuteberg
(Bauamtmann)



2. Introduction

2.1 Objective of the Study

The aim of the study is to screen in Sprague-Dawley rats the potential for dermal toxicity, absorption and metabolism of fluorochemicals from treated, dried test articles and also from the liquid state.

2.2 Guidelines for Conduct of the Study

This non-clinical health and environmental safety study was conducted in compliance with the GLP Principles, German Chemicals Law, Appendix 1 (July 25th, 1994, amended on May 14th, 2001), according to the EU directives 83/571/EU Appendix 3 and 91/507/EU. OECD guideline No. 410 (May 12, 1981) and Annex L 383 A (December 29, 1992; pp 144-147) to EC guideline 92/69/EEG (July 31, 1992) were followed as far as applicable.

The study followed the regulations of the German Animal Protection Law (Tierschutzgesetz of May 25, 1998).

2.3 Storage and Retention of Records and Materials

After completion of the study and issuance of the final report, the study plan including deviations, amendments, the raw data, the final report, all microscopic slides and a sample of each test article was transferred to the archives of Fraunhofer ITEM. It will be properly indexed and catalogued and stored for the minimum period in compliance with the principles of GLP. Thereafter an agreement between the sponsor and Fraunhofer ITEM has to be met with respect to further archivation. No materials will be disposed of without the written consent of the sponsor and Fraunhofer ITEM.

2.4 Study Staff

Laboratory Animal Veterinarian:	Prof. Dr. med. vet. Clemens Dasenbrock
Toxicologist:	Dr. med. vet. Bernd-D. Görlitz
Biostatistician:	Dr. rer. nat. Rupert Kellner
Chemist:	Prof. Dr. rer. nat. Karsten Levsen
Pathologist:	Dr. med. vet. Heinrich Ernst
Quality Assurance:	Dr. M.B. Ketkar

3. Test Articles

- Test article 1: 3M Corporate Toxicology sample number T-7088.2 (former SCOTCHGARD Brand fabric protector aerosol 4101W, Accra Pac Lot F7841, containing FX-1860 and R-23080, 3.16% solids solution) applied to skin as liquid on cotton gauze¹.
- Test article 2: 3M Corporate Toxicology sample number T-7338 (former SCOTCHGARD Brand fabric protector 4101W, Accra Pac Lot F7841, containing FX-1860 and R-23080, 3.16% solids solution) applied to cotton gauze¹ and dried prior to application to skin. (Patches contained 3.59% product solids by gravimetric analysis and 2.64% product solids by analysis of total F and estimation based on product solution % solids and % F in product solids.)
- Test article 3: 3M Corporate Toxicology sample number T-7090.2 (former SCOTCHGARD Brand fabric protector aerosol containing FX-3539, lot unknown, 0.456% solids solution) applied to skin as liquid on cotton gauze¹.
- Test article 4: 3M Corporate Toxicology sample number T-7339 (former SCOTCHGARD Brand fabric protector aerosol containing FX-3539, lot unknown, 0.456% solids solution) applied to cotton gauze¹. (Patches contained 0.641% product solids by gravimetric analysis and 0.98% product solids by analysis of total F and estimation based on product solution % solids and % F in product solids.)
- Test article 5: 3M Corporate Toxicology sample number T-7340 (former mill-applied SCOTCHGARD Brand carpet protector containing FC-1395, Lot 30037, 26.1% solids) applied to skin as liquid on cotton gauze².
- Test article 6: 3M Corporate Toxicology sample number T-7341 (former mill-applied SCOTCHGARD Brand carpet protector containing FC-1395, Lot 30037, 26.1% solids) applied to cotton gauze² and dried prior to application to skin. (Patches contained 0.09% product solids by analysis of total F and estimation based on product solution % solids and % F in product solids.)
- Test article 7: 3M Corporate Toxicology sample number T-7342 (former post-mill application SCOTCHGARD Brand carpet and upholstery protector containing FC-228, Lot NMAO diluted 4:1 with tap water, 1.04% solids solution) applied to skin as liquid on cotton gauze¹.
- Test article 8: 3M Corporate Toxicology sample number T-7343 (former post-mill application SCOTCHGARD Brand carpet and upholstery protector containing FC-228, Lot NMAO diluted 4:1 with tap water, 1.04% solids solution) applied to cotton gauze¹ and dried prior to application to skin. (Patches contained 1.01% product solids by gravimetric analysis and 1.17% product solids by analysis of total F and estimation based on product solution % solids and % F in product solids.)

¹ Tube gauze: Tube-Gauz™ Seamless Tubular Gauze, 1 inch, catalog number 68201 White Size 12, Acme United Corp (0.0236 g/in²). For samples that were applied and dried to gauze prior to dermal application, product solutions were used to saturate the gauze, after which excess was removed by passing through an Atlas Laboratory Wringer, Type LW-1 at 100 pounds weight. The samples were then allowed to air dry at ambient temperature and were placed in zip-lock bags and labelled.

² Tube gauze, 5/8 inch wide, was used.

The test articles were supplied by the sponsor. All test articles were stored at room temperature. The identity and characterization of each test article was documented by the sponsor. For confirmation of the identity of the test articles a sample of each was sent back to the sponsor for re-analysis.

4. Safety Protection, Storage, Handling and Disposal

Safety precaution, storage and handling of the test articles were done according to the sponsor's instructions.

Biological waste material including food, bedding and other disposable materials generated in the animal facility were collected and disposed of in compliance with local, state and federal regulations. Remaining test articles will be returned to the sponsor with the exception of a sample of each test article which will be kept in the archives of Fraunhofer ITEM.

5. Test System

5.1 Animal Model

Sprague Dawley rats (Hsd: Sprague Dawley™ SD™), 6-7 weeks of age at delivery, were purchased from Harlan Winkelmann, Borcheln, Germany. After delivery the animals were carefully inspected by a veterinarian. The study consisted of 8 females and 8 males in each treatment and control group.

Sprague Dawley rats are often used in dermal metabolism and toxicity studies.

At study start the animals were 9-10 weeks old, body weight was approximately 200 g in females and 280 g in males.

5.2 Acclimatization Period

Prior to the treatment period, the rats were acclimatized for about three weeks to the housing conditions in animal room T2.040-2 of Fraunhofer ITEM. During this time, the animals were trained to become accustomed to wearing the harness (saddle) system for 6 hours per day. During the acclimatization period, the animals were observed once daily. The body weights were measured at the end of the acclimatization period. The collected data show that all animals accepted for this study were in a good healthy condition.

5.3 Animal Identification

Each animal in the study was assigned a unique six digit individual identification number by a numbered plate on the cage. The number assigned was GG00NN where GG notes the two digit (01-99) group number, 00 is a common separator and NN are the two digits (01-99) consecutive animal number. In addition, the ears of the animals were tattooed corresponding to the identification number. All data collected from an animal was filed under that number. An identification label with the information of study number, animal number, species, sex, test article, dose, and route of administration was prepared in fourfold for each animal, one copy of which was kept in the animal room and the second and third copies in the necropsy room. The animal room copy was sent with the animal to necropsy. In the necropsy area, the second copy of the animal label was completed, checked with the data and attached to the individual necropsy report. The third copy was attached to the individual tissue bottle. The remaining copy was attached to the individual trimming protocol.

5.4 Housing and Maintenance

Animals were housed individually in Makrolon[®] (polycarbonate) type III (37.5 x 21.5 x 18 cm) cages in room T2.040-2 of the animal house. Absorbent softwood was used as bedding material in the cages (Softwood "altromin 3/4", Altromin International, Lage, Germany). The cages were changed twice weekly.

Food was offered fresh weekly. The diet used ("1324N specially prepared") was supplied by Altromin International, Lage, Germany. Drinking water from the Hannover city water supplier was offered fresh weekly, in Makrolon[®] bottles (approximately 300 ml), ad libitum. Temperature and relative humidity were recorded continuously. The values in the animal room were set at 22 ± 2 °C for temperature and 40 - 70 % for relative humidity.

The animal room lighting was on a 12-hour light/dark cycle controlled by an automatic timing device. Air flow rate was adjusted to 12 - 15 times per hour.

6. Conduct of the Study

6.1 Randomization

Animals were randomized by weight into groups as mentioned in the study design using a computer-generated randomization program. After assignment to treatment groups and prior to the initiation of treatment, all groups were separately evaluated for homogeneity of mean body weight and variances. The weight variation within each sex and within or between groups used did not exceed ± 20 % of the mean weight at the time of randomization.

6.2 Study Design

The study was carried out according to the schedule given in table 1.

Table 1: Study Design

Group	Number Sex	Test Article	3M No.	Duration [#]	Sacrifice at 4, 14, 28, and 42 days after treatment start: n [animals]
A 01*	8 m	Control	(saline)	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
A 02	8 f	Control	(saline)	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
B 03	8 m	1 st Test article	T-7088.2	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
B 04	8 f	1 st Test article	T-7088.2	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
C 05	8 m	2 nd Test article	T-7338	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
C 06	8 f	2 nd Test article	T-7338	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
D 07	8 m	3 rd Test article	T-7090.2	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
D 08	8 f	3 rd Test article	T-7090.2	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
E 09	8 m	4 th Test article	T-7339	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
E 10	8 f	4 th Test article	T-7339	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
F 11	8 m	5 th Test article	T-7340	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
F 12	8 f	5 th Test article	T-7340	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
G 13	8 m	6 th Test article	T-7341	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
G 14	8 f	6 th Test article	T-7341	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
H 15	8 m	7 th Test article	T-7342	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
H 16	8 f	7 th Test article	T-7342	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)
I 17	8 m	8 th Test article	T-7343	6 h/d/28d	2, 2, 2, 2 (= 8 male rats)
I 18	8 f	8 th Test article	T-7343	6 h/d/28d	2, 2, 2, 2 (= 8 female rats)

• Group identifier used in animal numbering

Total number of animals: 144

The duration of treatment was either 4, 14, or 28 days, with an additional recovery group treated for 28 days but allowed to recover for 14 days, post-treatment

6.3 Dermal Exposure

One day before study start animal's fur was clipped from the dorsal area of the trunk. During treatment period clipping was repeated once a week.

The rats were exposed to semi-occluded dermal patches with test article (dried article moistened with saline or liquid article applied on cotton gauze) using a harness (Minnema et al., 1998; "CIH95 Covance Infusion Harness" supplied by UNO, Zevenaar, The Netherlands). The cavity in the upper part of the harness under which the test article was placed, was covered with "3M Brand Post-It flags" (25.4 mm x 43.7 mm). The adhesive side was faced away from the skin. A new flag was used each day. The flags were supplied by 3M. The animals' skin was exposed for 6 hours daily, for up to 28 days. At the end of the daily exposure the harness was removed. Each day a new patch was applied.

Test article dosage was as follows: for the dried cotton gauze approximately 1 square inch was applied daily (groups C, E, G and I); for the liquid 0.1 ml was applied daily (groups B, D, F and H); for controls (group A) 0.1 ml of saline was applied daily.

6.3.1 Dose Level Selection

The test article dosage was fixed according to sponsor's recommendation.

6.3.2 Dosing Preparations

Treated articles (2, 4, 6, 8): Test articles applied to cotton gauze were supplied by 3M Home and Commercial Care Division (3M). Cotton gauze were weighed before and after saturation with test article by 3M to determine loading density. Solids' weight was used to calculate dosage into milligrams per square inch of cotton gauze.

Liquid test articles (1, 3, 5, 7) were supplied by 3M and were diluted in deionized water prior to experimental start as follows:

- | | |
|---|---------------------------------------|
| (1) T-7088.2: 1 part to 5.6 parts water | (5) T-7340: 1 part to 909 parts water |
| (3) T-7090.2: 1 part to 1.8 parts water | (7) T-7342: 1 part to 3.6 parts water |

6.3.3 Test Article Application

Treated articles were applied to the skin after moistening the one square inch article patches with saline.

Liquid test articles were applied as a single dose of 0.1 ml liquid to the one square inch untreated patches. Those treated patches were used for the semi-occluded contact.

Controls were treated with untreated gauze patches (one square inch) moistened with saline.

All fabrics were pre-conditioned with deionized water (using a spray-bottle) to improve the ability to take either saline or liquid test articles into the fabrics.

Harnesses were used for 6 hours to occlude patches to skin.

6.4 Study Duration

The animals were exposed to the test articles for 6 hours per day up to 28 consecutive days. During the 28 day exposure, subgroups with four animals per group (2 per sex) were sacrificed after 4, 14, and 28 days of dermal exposure, and the fourth "recovery" subgroup 14 days after end of the (28 day) exposure.

6.5 Daily Observations

All animals were observed for clinical symptoms twice daily (before and after the dermal exposure on the same day). The animals were clinically observed especially for the following locations, organ systems and symptoms:

- dermal application site

- general condition, fur, grooming activity
- visible mucous membranes
- behavior and locomotor activity (lethargy, coma, convulsions, diarrhea, salivation)
- central nervous symptoms
- breathing pattern

The post exposure-observations were recorded on study specific data sheets.

6.6 Body Weight

Individual body weight was recorded to nearest 0.1 g with an on-line computer program (DATATOX rC. 10) before first exposure and thereafter twice a week.

6.7 Necropsy

Each animal was subjected to a necropsy. During the study period all animals at terminal sacrifice were anesthetized with an overdose of CO₂, exsanguinated and necropsied immediately. The physical condition of the animal prior to euthanasia and the examination of the internal organs was described in detail on individual autopsy protocol sheets. In all cases, dead animals were identified by reference to each animal's identification number.

The treated skin, macroscopically altered tissues, and, after weighing, two 1 cm thick portions of the main lobes of liver were collected from each rat and fixed in 10% neutral buffered formalin.

Additionally, all following organs and tissues were collected from each animal and fixed in 10% neutral buffered formalin (lungs were inflated at 20 cm water pressure with formalin):

Brain, pituitary, tongue, eyes, lacrimal glands, Harderian glands, nasal and paranasal cavities, larynx, pharynx, trachea, thyroid, parathyroids, lungs, thymus, heart, aorta, lung-associated lymph nodes, salivary glands, mandibular lymph nodes, pancreas, spleen, kidneys, adrenals, esophagus, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, mesenterium and lymph nodes, urinary bladder, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, vagina, mammary glands, skeletal muscle, femur including joint, spinal cord, skin, peripheral nerve, sternum with bone marrow, gross lesions, and abnormalities.

6.8 Liver Weight

In addition to the terminal body weight, the liver from each animal was weighed to nearest of 0.1 g with an on-line computer program (DATATOX rC. 10). Relative organ weight data was also computed.

6.9 Histopathology

Tissues for histological examination were fixed in 10% neutral buffered formalin, trimmed according to Bahnemann et al. (1995), embedded in Paraffin, sectioned at 3 - 4 µm, and routinely stained with hematoxylin and eosin.

Histopathological examinations of the following organs were performed on all animals of all groups: heart, liver, spleen, kidneys, adrenals, testes/ovaries and skin. For each animal, 2 sections of the treated skin (clipped area under the harness), one transverse and one

longitudinal to the axis of the hair stroke, were examined. For reason of comparison, 2 further sections (one transverse and one longitudinal) of untreated and unclipped skin from the dorsal area of the trunk were taken and examined for each rat. In addition, macroscopically changed areas of the skin were histopathologically examined.

The slides were examined by light microscopy and the observations were recorded with an on-line computer program (P.L.A.C.E.S. 2000.1).

6.10 Blood and Liver Samples

Blood serum (approximately 2 ml) and liver (same lobe, each animal) samples were collected at necropsy from all animals. These samples were shock-frozen in liquid N₂ and stored at -70 °C. Initially liver samples were analyzed at Fraunhofer ITEM for perfluorooctanesulfonate (PFOS) levels.

Since PFOS was detected in liver samples it was decided, according to the study plan and amendment #1 (Appendix G), to further analyze 52 blood serum samples for PFOS, perfluorohexanesulfonate (PFHS) and M570. Serum samples were analyzed at Exygen Research, State College (PA), USA.

6.10.1 Analysis of Liver Samples

In summary, liver samples were analyzed as follows:

A defined amount of rat liver was weighed to which water was added. The sample was homogenized using an ultra turrax. To an aliquot of the homogenized sample an ion pair reagent (tetrabutylammonium hydrogen sulfate), a sodium carbonate/sodium bicarbonate buffer and ethylacetate was added. The sample was shaken on a shaker for 20 min and then centrifuged at 2200 rpm for 20 min until the phases were separated. 4 mL of the organic phase were transferred into a centrifuge tube and evaporated to dryness using a gentle stream of nitrogen. The residue was redissolved in 1 mL methanol and the solution filtered into a HPLC vial through a nylon membrane filter attached to a syringe. The sample was analyzed by HPLC-electrospray MS in the negative ion mode. (The method is described in more detail in the Fraunhofer ITEM SOP 150 380.01)

6.10.2 Analysis of Serum Samples (Summary)

52 blood serum samples were analyzed at Exygen Research, State College (PA), USA, as follows (Appendix H):

Serum samples (100 µL) were used for the extraction and vortexed for ~ 15 s. To the sample an ion pair reagent (tetrabutylammonium hydrogen sulfate), a sodium carbonate/bicarbonate buffer and MTBE were added. The sample was shaken on a wrist-action shaker for ~ 20 min and then centrifuged for 15 min. An aliquot of the organic layer was taken and evaporated to dryness and then reconstituted with 1 mL of methanol. The sample was analyzed by HPLC - electrospray mass spectrometry in the MS/MS and negative ion mode.

6.11 Statistical Evaluation

Statistical tests on the comparison of treatment groups were performed at the level of $\alpha=0.05$. Body weight and organ weight data were analyzed using analysis of variance as a global test. Pair wise comparison of the means of the treatment groups with the means of the control group were performed using Dunnett's modification of the t-test. Thus the experiment wise error rate was controlled in this multiple testing procedure. Regarding small sample sizes of the treatment and control groups, significant differences in body and organ weight data could only be expected in case of large deviations from the control.

The possible influence of day of treatment on PFOS recovered from liver samples was analyzed by separate analyses of variance of the two injections' mean for each test article and sex. Means < 0.01 were replaced by the value 0.001 for this statistical procedure. Comparisons among the groups were performed using Tukey's Studentized Range (HSD) test. Similarly, PFOS, PFHS, and M570 data from serum samples were evaluated according to the mean/rat. Single measurements resulting in NQ were replaced by 0.0001 for calculation of means used in that analysis.

Statistical evaluation of histopathological findings: significance of differences of the frequencies were evaluated as pair wise comparison between clean air control and treatment groups using Fisher's exact test. These tests were performed at the local significance level of $\alpha=0.05$.

6.12 Amendments

Two study plan amendments were documented during the conduct of the study. Amendment #1 instituted to further analyze 52 blood serum samples for PFOS, perfluorohexanesulfonate (PFHS) and M570 at Exygen Research, State College (PA), USA. Amendment #2 clarified the analytical method (used at Exygen Research) for the analysis of the rat serum samples: Copies are given in Appendix G.

7 Re-Analysis of Test Materials

The re-analysis of test samples resent to 3M on 19th April 2000 by Fraunhofer ITEM was performed by 3M. The analysis resulted in:

Table2a: N-Methyl FOSE, PFOS and PFHS in 3M test articles (1st re-analysis)

Test article	3M No.	3M Sample Identification	N-Methyl FOSE [ppm]		PFOS [ppm]		PFHS [ppm]	
			original	current	original	current	original	current
1 st	T-7088.2	4101W Product	720	735	nd	2	nd	1.2
2 nd	T-7338	4101W Treated Web	740	1,270	<5	11	<5	1.0
3 rd	T-7090.2	European FP Product	60	nd	nd	<1	nd	nd
4 th	T-7339	European FP Treated Web	nd	nd	<5	2	<5	<2.6
5 th	T-7340	FC-1395 Product	930	770	<5	27	nd	nd
6 th	T-7341	FC-1395 Treated Web	nd	nd	nd	<1	nd	nd
7 th	T-7342	SG Carpet P Product	nd	nd	220	610	440	1,900
8 th	T-7343	SG Carpet P Treated Web	nd	nd	200	470	270	1,900
nd = not detected								

The 2nd re-analysis of test samples resent to 3M on 12th September 2003 by Fraunhofer ITEM was performed by 3M. The analysis resulted in:

Table2b: N-Methyl FOSE, PFOS and PFHS in 3M test articles (2nd re-analysis)

Test article	3M No.	3M Sample Identification	Methyl FOS Alcohol [ppm]		PFOS [ppm]		PFHS [ppm]	
			original	current	original	current	original	current
1 st	T-7088.2	4101W Product	720	5,000	nd	1.0	nd	<0.1
2 nd	T-7338	4101W Treated Web	740	1,600	<5	8.6	<5	0.41
3 rd	T-7090.2	European FP Product	60	1,100	nd	<0.5	nd	<0.1
4 th	T-7339	European FP Treated Web	nd	<10	<5	<1	<5	0.24
5 th	T-7340	FC-1395 Product	930	4,000	<5	1.6	nd	0.14
6 th	T-7341	FC-1395 Treated Web	nd	180	nd	<1	nd	<0.2
7 th	T-7342	SG Carpet P Product	nd	47	220	180	440	330
8 th	T-7343	SG Carpet P Treated Web	nd	<10	200	190	270	270
nd = not detected								

All detailed data on N-Methyl FOSE, N-Methyl-FOS Amide, NN-Dimethyl-FOS Amide, PFOS, PFHS, FOS Amide and further semivolatile fluorochemical residuals are given in Appendix A.

8 Results

8.1 In-life Observations

8.1.1 Mortality

No mortality occurred during the test period.

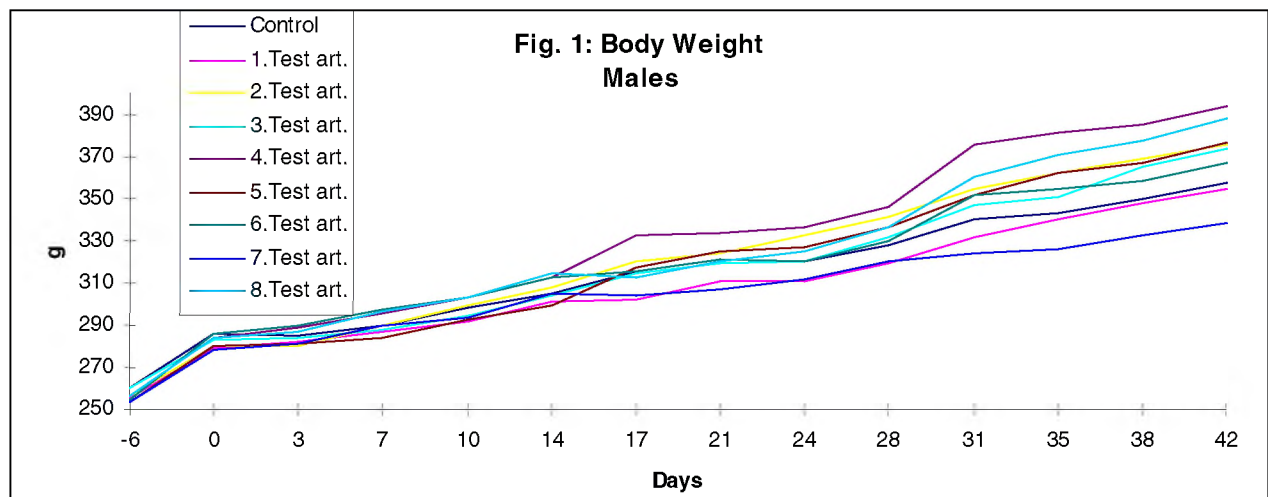
8.1.2 Clinical Observations

The test articles produced no effects on the dermal application site, on the general condition or on the behavior of the rats. The manipulation with the harness however stressed about 20 % of the animals seen as stressed-induced chromodacryorrhea around the eyes.

On the first day of application five animals had edema on the ventral site of the neck caused by pressure of the harness. Over the whole application period single animals had small impressions from the harness, in one case accompanied by a minimal erythema. Two animals had skin lesions with inflammation from the belly bands in the axillary fold (armpit). Summary and individual data on clinical observation are presented in Appendix B.

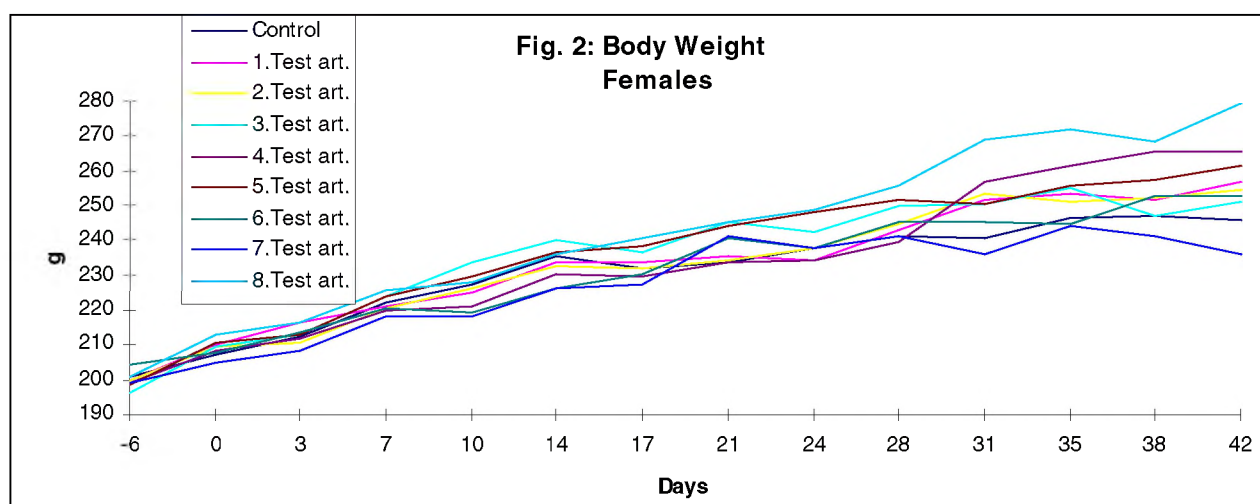
8.1.3 Body Weight

The body weight gain was not influenced by the application of the test articles (see fig. 1 and 2).



Differences in body weight development beyond day 14 are due to the very small number of rats per group; i.e., four rats /group and sex till day 28, only two rats /group and sex till day 42 (=28+14).

None of the group mean body weight was (statistically) significantly different from the controls. Individual and mean body weight data are listed in Appendix C.



8.2 Post Mortem Observations

8.2.1 Gross Pathology

Macroscopically, no test article related effects on the organs were observed in the male and female animals of all groups at final sacrifice.

8.2.2 Absolute and Relative Liver Weights

The liver weight data of the treated rats were in the range of those of the controls. There were no differences detected between sham and treated rats. All individual and summary data are presented in Appendix D.

8.3 Results of the Histopathological Examination

Histopathological findings are summarized in tables 1 and 2 with individual data (table 11) shown in Appendix E.

No histopathological changes could be detected which could be related to treatment with the different test articles, either in the skin or in any other of the examined organs. In the following, the organ-related findings are briefly described:

1. Treated skin

There were no changes which could be related to application of the test articles in any of the treatment groups, either in males or in females (*Tables 1 and 2*, Appendix E). A very common finding of the treated skin was very slight (minimal) to slight hypertrophy/hyperplasia of the epidermis. The increased thickness of the treated skin was more attributable to increased cell volume than to increased numbers of spinous keratinocytes (acanthosis). The hair follicles were rarely involved. Epidermal hypertrophy/hyperplasia occurred in 4/8 to 7/8 males and in 6/8 to 8/8 females per group. Since no differences between the treatment groups and the saline control was observed, epidermal hypertrophy/hyperplasia is considered to be caused by the

repeated clipping procedure and/or local pressure of the harness. In up to 3/8 animals per group, epidermal hypertrophy/hyperplasia was associated with focal or multifocal slight hyperkeratosis. One of 8 males of group D07 (T-7090.2) had slight focal ulceration (ulcerative inflammation) and 1/8 males and females of groups F11 (T-7340) and H16 (T-7342), respectively, showed slight focal erosion of the treated skin. However, since these lesions also developed due to mechanical irritation by the harness (see also 8.1.2) in the untreated skin of several rats, they are not considered to be substance-induced. Other findings of the treated skin included focal/multifocal dermal or subcutaneous inflammatory cell infiltration of predominantly slight degree. These changes were seen in all groups at incidences of up to 3/8 animals per sex and group.

With respect to the time course of the lesions, the highest overall frequency of observed changes was seen after 28 days of treatment with a marked decrease towards the end of the recovery period, indicating reversibility of the observed lesions (*Tables 3-10*, Appendix E).

2. Untreated skin

With the exception of slight to moderate focal subcutaneous inflammatory cell infiltration which occurred in single females of groups F12 (T-7340) and H16 (T-7342), there were no changes observed in the untreated and unclipped skin of the dorsal trunk. Corresponding to macroscopic observations, sections of untreated skin from the axillary region were examined histopathologically. The macroscopic findings corresponded to focal erosions and ulcerations (ulcerative inflammation) of slight to severe degrees with related lesions such as slight to moderate hyperkeratosis, slight to severe (reactive) epidermal hyperplasia, moderate focal dermal fibrosis, slight focal haemorrhage and slight focal dermal inflammatory cell infiltration (*Tables 1 and 2*, Appendix E). These lesions affected nearly all treatment groups, including the control group, at incidences of up to 3/8 per group and were attributable to mechanical irritation by the harnesses. They were not observed in animals of the recovery groups.

3. Heart

Slight focal myocardial degeneration and very slight to slight focal myocardial mononuclear cell infiltration were seen in up to 2/8 and 1/8 males and females, respectively, per group of both the control and most treatment groups. These lesions are considered to be spontaneous, because their types and incidences are not unusual for healthy Sprague-Dawley control rats (Lang, 1992).

4. Liver

All of the observed liver changes were incidental and affected either single animals of different groups (hepatodiaphragmatic nodule, focal necrosis, focal presence of granulation tissue) or were seen at incidences of up to 3/8 (mononuclear cell infiltration).

5. Kidneys

The kidney lesions (cortical scarring, tubular-cell degeneration, tubular basophilia, tubular mineralization, tubular dilatation with intratubular proteinaceous casts and interstitial mononuclear cell infiltration) had incidences of up to 4/8, were evenly distributed among various

groups and represent parts of early spontaneous nephropathy.

6. Adrenals

Incidental findings (incidence up to 3/8) in some groups were slight cortical fatty vacuolation and accessory cortical nodules (incidence up to 2/8).

7. Ovaries

One female of group I18 (T-7343) showed a small unilateral ovarian cyst.

8. Spleen, Testes

No abnormalities were detected in the spleen and testes.

9. Other organs

Corresponding to macroscopic observations in some other (non-protocol) organs, further findings were observed in single rats of some groups which also were spontaneous and unrelated to treatment.

8.4 Analytical Chemistry of Blood and Liver Samples

8.4.1 Concentration of Potassium Perfluorooctanesulfonate (PFOS) in Liver Samples

In table 3 the mean concentrations of PFOS in the livers of two animals per sex and group each are presented as a function of the dermal exposure duration in days.

The tabulated data demonstrate that the concentration of PFOS in the liver of the (saline sham exposed) control group is, as expected, below the limit of quantification (LOQ = <0.01 ppm) in each case. In addition, the concentration of PFOS in the liver of rats treated with T-7340 and T-7341 are mostly below the LOQ, whereas the other 3M test articles T-7088.2, T-7338, T-7090.2, T-7339, T-7342 and T-7343 were detected in quantifiable amounts and increased with the duration of exposure.

All data are listed in Appendix F.

8.4.2 Concentration of PFOS in Blood Serum Samples

The concentrations of PFOS in blood serum demonstrated a basic level in the range of ppb in the controls which seemed to slightly increase with age (table 3). High original PFOS concentration in 3M test articles T-7342 and T-7343 resulted in clearly detectable amounts of PFOS in blood serum which were one order of magnitude lower than found in liver tissue. Individual data are presented in EXYGEN's analytical report, Appendix H.

Table 3: Concentration of PFOS in Liver and Blood Serum Samples from Sprague Dawley Rats [in ppm]

Test article	Matrix	Liver	Serum	Liver	Serum	Liver	Serum	Liver	Serum
	Group	Day 4	Day 4	Day 14	Day 14	Day 28	Day 28	Day 28+14	Day 28+14
Saline (Control)									
Males	A 01	< 0.01	n.a.	< 0.01	n.a.	< 0.01	0.0006	< 0.01	0.0027
Females	A 02	< 0.01	n.a.	< 0.01	n.a.	< 0.01	0.0017	< 0.01	0.0036
T-7088.2									
Males	B 03	< 0.01	n.a.	0.081	n.a.	0.172	n.a.	0.187	n.a.
Females	B 04	< 0.01	n.a.	0.056	n.a.	0.196	n.a.	0.225	n.a.
T-7338									
Males	C 05	< 0.01	n.a.	0.143	n.a.	0.216	0.0048	0.131	n.a.
Females	C 06	< 0.01	n.a.	0.059	n.a.	0.164	0.0440	0.173	n.a.
T-7090.2			n.a.		n.a.				n.a.
Males	D 07	< 0.01	n.a.	0.016	n.a.	0.143	n.a.	0.135	n.a.
Females	D 08	< 0.01	n.a.	< 0.01	n.a.	0.058	n.a.	0.080	n.a.
T-7339			n.a.		n.a.				n.a.
Males	E 09	< 0.01	n.a.	0.041	n.a.	0.057	0.0017	0.066	n.a.
Females	E 10	< 0.01	n.a.	< 0.01	n.a.	0.029	0.0077	0.028	n.a.
T-7340			n.a.		n.a.				n.a.
Males	F 11	< 0.01	n.a.	< 0.01	n.a.	< 0.01	n.a.	0.011	n.a.
Females	F 12	< 0.01	n.a.	< 0.01	n.a.	< 0.01	n.a.	< 0.01	n.a.
T-7341			n.a.		n.a.				n.a.
Males	G 13	< 0.01	n.a.	< 0.01	n.a.	< 0.01	< 0.001	< 0.01	n.a.
Females	G 14	< 0.01	n.a.	< 0.01	n.a.	0.010	0.0065	< 0.01	n.a.
T-7342									
Males	H 15	0.064	0.0033	0.247	0.0110	0.355	0.0172	0.463	0.0264
Females	H 16	0.054	0.0143	0.182	0.0660	0.366	0.1349	0.425	0.1690
T-7343									
Males	I 17	0.296	0.0218	4.529	0.0899	9.374	0.2848	8.993	0.2350
Females	I 18	0.344	0.1093	4.944	0.7213	7.955	1.0850	9.125	1.4840

n.a. = not analyzed

8.4.3 Concentration of PFHS and M570 in Blood Serum Samples

3M test articles T-7342 and T-7343 applied to skin for different periods resulted in clearly detectable amounts of PFHS and M570 in blood serum (table 4).

All individual data are presented in EXYGEN's analytical report, Appendix H.

Table 4: Concentration of PFHS and M570 in Blood Serum Samples from Sprague Dawley Rats [in ppm]

Test article	Serum	PFHS	M570	PFHS	M570	PFHS	M570	PFHS	M570
	Group	Day 4		Day 14		Day 28		Day 28+14	
Saline (Control)									
Males	A 01	n.a.	n.a.	n.a.	n.a.	<0.001	<0.001	<0.001	<0.001
Females	A 02	n.a.	n.a.	n.a.	n.a.	<0.001	<0.001	<0.001	<0.001
T-7088.2									
Males	B 03	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Females	B 04	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T-7338									
Males	C 05	n.a.	n.a.	n.a.	n.a.	0.010	0.0250	n.a.	n.a.
Females	C 06	n.a.	n.a.	n.a.	n.a.	<0.001	0.0393	n.a.	n.a.
T-7090.2									
Males	D 07	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Females	D 08	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T-7339									
Males	E 09	n.a.	n.a.	n.a.	n.a.	<0.001	0,0068	n.a.	n.a.
Females	E 10	n.a.	n.a.	n.a.	n.a.	<0.001	<0.001	n.a.	n.a.
T-7340									
Males	F 11	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Females	F 12	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T-7341									
Males	G 13	n.a.	n.a.	n.a.	n.a.	<0.001	<0.001	n.a.	n.a.
Females	G 14	n.a.	n.a.	n.a.	n.a.	<0.001	<0.001	n.a.	n.a.
T-7342									
Males	H 15	0.0107	<0.001	0.0336	<0.001	0.0707	<0.001	0.0952	<0.001
Females	H 16	0.0126	<0.001	0.0159	<0.001	0.0115	<0.001	0.0013	<0.001
T-7343									
Males	I 17	0.1575	<0.001	0.6750	<0.001	1.3425	<0.001	0.8298	<0.001
Females	I 18	0.2400	<0.001	0.3480	<0.001	0.2413	<0.001	0.0092	<0.001

n.a. = not analyzed

9. Summary and Conclusions

The objective of this 28 day repeated dermal contact study in rats was to evaluate the potential for dermal uptake of 3M fluorochemicals from treated, dried test articles and also from the liquid state. For this, the concentrations of a main metabolite of tested fluorochemicals, PFOS, was determined in liver tissue, and subsequently in blood serum.

The study was conducted in compliance with the GLP Principles, German Chemicals Law, Appendix 1 (July 25th, 1994, amended on May 14th, 2001).

144, 9-10 week-old Sprague Dawley rats (Hsd: Sprague Dawley™ SD™) were exposed to non-occluded dermal article patches (1 square inch) for 6 hours per day up to 28 consecutive days. Four treated, dried 3M test articles and the same four articles from the liquid state were tested. Saline-treated rats served as the sham-exposed group. During the 28 day exposure, subgroups with four animals per group (2 per sex) were sacrificed after 4, 14, and 28 days of dermal exposure, and the fourth "recovery" subgroup 14 days after end of the (28 day) exposure.

Dermal (sham) exposure did not result in differences in the mean body weight between the groups. Independent from the treatment, the fixation of the dermal patches with harnesses caused in several rats little impressions from the harness, in one case accompanied by a minimal erythema, and two animals had skin lesions with inflammation. The manipulation with the harness however stressed about 20 % of the animals seen as transient stressed-induced chromodacryorrhea around the eyes which disappeared over night.

There were no large deviations in terminal body weight and liver weight data.

No histopathological changes were detected which could be related to treatment with the different test articles, either in the skin or in any other of the examined organs. A very common finding of the treated skin was very slight (minimal) to slight hypertrophy / hyperplasia of the epidermis which is considered as related to the dermal application procedure.

PFOS analysis in liver tissue demonstrated a dermal uptake and/or metabolism of 3M articles T-7088.2 & T-7338, T-7090.2 & T-7339, and T-7342 & T-7343 starting at least after 14 days of treatment. PFOS in blood serum was clearly detected in 3M test articles T-7342 & T-7343.

10. References

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11. Appendices

Appendix A: Test Sample Re-analysis

Appendix B: Clinical Observations, Summary and Individual Data

Appendix C: Body Weight Data

Appendix D: Liver Weight Data

Appendix E: Histopathology Data

Appendix F: Analysis of PFOS in Liver Samples

Appendix G: Amendments and Deviations

Appendix H: EXYGEN Report on 52 Blood Serum Samples (PFOS, PFHS, M570)