RESEARCH EVIDENCE IN SUPPORT OF THE SAFETY OF PERFLUOROCARBON CHEMICAL TRACERS

June 5, 2008

Thomas J. Rappolt
Stephen L. Kerrin

Tracer Environmental Sciences and Technologies, Inc.
970 Los Vallecitos Blvd. Suite 100
San Marcos, CA 92069
760-744-9611
www.tracer-est.com

TABLE OF CONTENTS

INTRODUCTION 1
INDUSTRIAL AND COMMERCIAL USES 1
- **Electrical and Electronic Applications** 1
- **Perfluorcarbon Tracers** 1
- **Cosmetics** 1
- **Other Industrial Applications** 2

MEDICAL APPLICATIONS 2
- **Eye surgery** 2
- **Imaging** 2
- **Liquid Breathing and Artificial Blood** 2
- **Artificial Blood** 2
- **Treatment of Decompression Sickness** 3

TOXICOLOGY OF PERFLUOROCARBONS 3
REFERENCES 3
Appendix 1 Acute Inhalation Toxicity of Perflormethylcyclohexane 5
Appendix 2 Oral Toxicity of Perfluoromethylcyclohexane 8
Appendix 3 Acute Inhalation Toxicity of Perfluoro-1,3-diemethylcyclohexane 11
Appendix 4 Acute Oral Toxicity of Perfluoro-1,3-dimethylcyclohexane 14
Appendix 5 In Vitro Microbiological Mutagenicity of Eight Fluorocarbon Taggants 17
Appendix 6 Perfluoromethylcyclopentane: Acute Dermal Irritation Test in Rabbit 20
Appendix 7 Perfluoro-1,3-dimethylcyclohexand MSDS 23

INTRODUCTION

Perfluorcarbons (PFCs) are synthesized from hydrocarbons by replacing all the hydrogen atoms with fluorine atoms. Perfluorocarbons are chemically inert, thermally stable and non-toxic and non-flammable. They were first synthesized in the 1920s and commercially developed in the 1940s as part of the Manhattan Project.

PFCs are used in a variety of industries and medical applications. They are used in paints, for example, to make them spread easier and in textile manufacturing as a fabric protectant. PFCs are also being used or evaluated in several medical applications.

While medical applications require pharmaceutical grade perfluorocarbon preparations [1], it should be noted that the PFCs, themselves, are physiologically inert and non-toxic. Additionally, medical applications involve introduction of pure PFC liquids or minimally diluted gases into the human body whereas atmospheric tracer applications result in minimal inhalation exposure. The Material Safety Data Sheet (MSDS) for a typical PFC tracer (perfluoromethylcyclohexane) [2] indicates in Section 8 (Exposure Controls and Personal Safety) that there is no Exposure Limit Value. Additionally, Section 11 (Toxicology) states that "The substance has been assessed on adequate evidence and found to produce no effect."

INDUSTRIAL AND COMMERCIAL USES

Electrical and Electronic Applications

Perfluorocarbons have high dielectric strengths and high insulating properties, and so can be used in direct contact with high voltage components, either as dielectric fluids or as coolants. They are also used in manufacturing of integrated circuits for plasma cleaning of silicon wafers [3].

Perfluorcarbon Tracers

Perfluorocarbons can be detected at extremely low levels (parts per quadrillion by volume) using electron capture detectors or negative ion mass spectroscopy. Thus, small quantities of PFC can be released and the resultant vapor plume tracked over long distances for investigation of atmospheric transport. They have also been used to characterize underground petroleum geology, study building ventilation, and even recover ransom money.

Cosmetics

Perfluorocarbons have been incorporated into some cosmetic formulations, with the claim that the oxygen dissolved in the perfluorocarbon has an anti-aging effect on the skin [4]

Other Industrial Applications

PFCs are being used as CFC refrigerant replacements, often in conjunction with other gases. They have also found limited acceptance as a fire extinguishing agent. Perfluorocarbons are also used in high end racing ski waxes due to their hydrophobic nature, which is responsible for reduced friction in wet snow conditions.

MEDICAL APPLICATIONS

Eye surgery

Perfluorocarbons liquids are commonly used in eye surgery as temporary replacements of the vitreous humor in retinal detachment surgery. Typically perfluoro-n-octane is injected into the eye, to push out vitreous liquid trapped behind the retina, and to aid removal of membranes (essentially scar tissue)[5]. Perfluoro-1,3-dimethylcyclohexane has been also been in eye surgery[6].

Octafluoropropane (a gaseous PFC) can be diluted in air and injected into the eye where it forms a bubble. The patient then lies face down for about an hour while the gas bubble pushes onto the retina to perform the same task as before [7].

Imaging

Perfluorocarbons are also used to enhance contrast in ultrasound imaging. They are also used, to a lesser extent in magnetic resonance imaging and as an opaquing agent in radiographic imaging.

Liquid Breathing and Artificial Blood

The pronounced ability to dissolve molecular oxygen in combination with their non-toxicity and complete physiological inertness makes perfluorocarbon fluids attractive for applications of respiratory fluids and as components of artificial blood substitutes [8].

Perfluorocarbons dissolve relatively high concentrations of gases. For example, 100 ml of perfluorodecalin at 25°C will dissolve 49 ml of oxygen at STP. This led Leland C. Clark and Frank Gollan (1966) to experiment with liquid breathing, resulting in the submersion of a mouse for several hours in an oxygenated perfluorocarbon [9].

Subsequent studies have led to the use of PFC liquids to enhance oxygen delivery to the lungs as a surfactant product in premature infants, or in patients with Acute Respiratory Distress Syndrome or lung injury [10] [11].

Artificial Blood

Clark and Gollan's experiments also triggered interest in using perfluorocarbons in artificial blood . The Green Cross Corporation attempted to commercialize this technology in the 1980s under the Fluosol tradename, without success[9]. Recently, however, there has been renewed interest in this field[12].

Treatment of Decompression Sickness

Perfluorocarbons accelerate nitrogen washout after venous gas emboli.[13] Success in the treatment of decompression sickness has been shown in several animals[14][15]. This treatment shows great potential as a future adjunctive therapy for decompression sickness in humans [16].

TOXICOLOGY OF PERFLUOROCARBONS

Appendices 1-4 present the results of standard laboratory investigations into the acute oral toxicology and acute respiratory toxicology of two commonly used perfluorocarbon tracers, perfluoromethylcyclohexane (formerly called PP2) and perfluoro-1,3-dimethylcyclohexane. Appendix 5 presents findings of investigation into the mutagenicity of perfluoromethylcyclohexane. Appendix 6 presents findings of dermal irritation testing for another commonly used perfluorocarbon tracer, perfluoromethylcyclopentane. The Material Safety Data Sheet (MSDS) for perfluoro-1,3-dimethylcyclohexane is presented in Appendix 6 and is representative of all perfluoro tracers in current use.

The original documents presented in these appendices are quite long. Therefore, introductory and summary information have been excerpted for this report. Complete text of the documents may be requested from Tracer ES&T.

REFERENCES

1. Peyman, G. A.; Schulman, J. A.; Sullivan, B. Survey. Ophthalmol. 1995, 39(5), 375-395.

2. Perfluoromethylcyclohexane MSDS. F2 Chemicals Ltd, October 2007. http://fluoros.co.uk/data/tracing_and_tagging/TG_PMCH.pdf

3. http://www.research.ibm.com/journal/rd/362/ibmrd3602C.pdf

4. Stanzl, K.; Zastrow, L; RÖding, J; Artmann, C Intl. J. Cosm. Sci., 1996, 18 (3), p137–150

5. Chang, S. Intl. Ophthalmol. Clinic. 1992, 32, 153-163.

6. Rowson, N. J.; Bacon, A. S.; Rosen, P. H. Brit. J. Ophthalmol. 1992, 76, 169-170.

7. Tewari, A.; Shah, G. K. Review Ophthalmol. News 2006, 13(04) (online)

8. Kirsch, Peer (2006) *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*. Wiley-VCH

9. Race for Artificial Blood Heats Up - New York Times.

http://query.nytimes.com/gst/fullpage.html?res=9A0DE7D61138F937A25751C0A962958260&sec=&spon=&pagewanted=2

10. Spahn, Donat R. (1999) "Blood substitutes Artificial oxygen carriers: perfluorocarbon emulsions,"*Critical Care* 1999, **3:**R93-R97doi:10.1186/cc364

11. Moya, Fernando R. (1997), "Repeated Doses of the Perfluorocarbon FC-100 Improve Lung Function of Preterm Lambs 1," Pediatric Research. 42(6):893-898, December 1997

12. "Perfluorochemucal Blood Substitutes", Naito, R., Yokoyama, K., p 57, The Green Cross Corporation, Technical Information Ser. No. 5, June 30, 1978

13. Zhu J, Hullett JB, Somera L, et al (2007). "Intravenous perfluorocarbon emulsion increases nitrogen washout after venous gas emboli in rabbits". Undersea Hyperb Med 34 (1): 7–20.

14. Spiess BD, McCarthy RJ, Tuman KJ, Woronowicz AW, Tool KA, Ivankovich AD (January 1988). "Treatment of decompression sickness with a perfluorocarbon emulsion (FC-43)". Undersea Biomed Res 15 (1): 31–7.

15. Lynch PR, Krasner LJ, Vinciquerra T, Shaffer TH (July 1989). "Effects of intravenous perfluorocarbon and oxygen breathing on acute decompression sickness in the hamster". Undersea Biomed Res 16 (4): 275–81.

16. Moon, R.E. (2000). "Adjunctive therapy in decompression illness: present and future.". South Pacific Underwater Medicine Society journal 30 (2).

APPENDIX 1

ACUTE INHALATION TOXICITY TO THE RAT OF
FLUTEC PP1
FLUTEC PP2 (perfluoromethylcyclohexane)
FLUTEC PP9
AND
FLUTEC PP50

CONFIDENTIAL

ICL2/74122

ACUTE INHALATION TOXICITY TO THE RAT OF FLUTEC PP1 FLUTEC PP2 FLUTEC PP9 AND FLUTEC PP50

Addressee:

B.D. Joyner Esq.,
I.S.C. Chemicals Ltd.,
St. Andrew's Road,
Avonmouth,
BRISTOL,
BS11 9HP.

28 February 1974

Authors:

Zoltan S. Berczy,
Leon M. Cobb,
Cora P. Cherry,

Huntingdon Research Centre,
HUNTINGDON.

SUMMARY AND CONCLUSIONS

Four groups of 10 rats were exposed continuously for 6 hours to the vapour of 4 Flutec samples in purpose designed exposure chambers. A group of 10 control rats was kept for 6 hours in a similar exposure chamber and exposed to clean air. All groups were observed post - exposure for 14 days.

Flutec PP1

An exposure to 2% (20,000 ppm) of the vapour elicited no definite signs of response.

There was an uncharacteristic decrease in the rate of growth of male rats during the second week of the post - exposure observation period.

Flutec PP2

An exposure to 2% (20,000 ppm) of the vapour elicited no definite signs of response.

Flutec PP9

An exposure to 0.3% (3,000 ppm) of the vapour elicited no signs of response.

Flutec PP50

An exposure to 4% (40,000 ppm) of the vapour caused mild temporary eye irritation and dyspnoea during exposure. These signs of response disappeared during post - exposure observation.

Instances of minimal consolidation in the lung of one or two rats from each test group were regarded as being unrelated to treatment.

The results of this investigation indicate that the tested samples of Flutec PP1, PP2, PP9 and PP50 have no appreciable acute inhalation toxicity to the rat.

APPENDIX 2

ACUTE ORAL TOXICITY OF (TG-PMCH) PERFLUOROMETHYLCYCLOHEXANE AND PERFLUORODECALIN IN THE RAT

CONFIDENTIAL 1668/66/196

Acute Oral Toxicity of (TG-PMCH)
Perfluoro(methylcyclohexane) and Perfluorodecalin
in the Rat

Mr. D.S. Robertson
Marketing Development Department
Imperial Smelting Corporation Limited
P.O. Box 19
1 Redcliff Street
BRISTOL 1

Graham H. Wheld
Howard B. Ginn

Huntingdon
Research
Centre
Huntingdon

4 August, 1966.

SUMMARY

Divided oral doses totalling 100ml/kg bodyweight, of perfluoro (methylcyclohexane) or perfluorodecalin administered over a five-hour period failed to produce an observable toxic response. At one and two weeks after dosing, we observed no gross pathological changes which could be attributed to treatment.

For all practical purposes, therefore, the two compounds may be regarded as "Relatively Harmless" (Hodge, H.C. and Sterner, J.H., Am.Ind.Hyg.Ass.Quart., 10:4, 93, Dec.1943)

APPENDIX 3

ACUTE INHALATION TOXICITY TO THE RAT OF PERFLUORO-1,3-DIMETHYLCYCLOHEXANE

CONFIDENTIAL 3326/70/138

ACUTE INHALATION TOXICITY TO THE RAT OF PERFLUORO-1,3-DIMETHYLCYCLOHEXANE

Addressee:

R. Silcock, Esq.,
Imperial Smelting Corporation (NSC) Ltd.,
St. Andrew's Road,
Avonmouth,
BRISTOL.

8 April, 1970.

Authors:

Richard Binns,
Zoltan S. Berczy,

Huntingdon Research Centre,
HUNTINGDON.

SUMMARY

A group of ten rats was exposed continuously for six hours to an atmosphere containing 4% v/v Perfluoro-1,3-dimethylcyclohexane vapour.

There were no signs of irritation during exposure and during a 14-day post-exposure observation period. Apart from a transient weight loss in the male test rats, the performance of the test group of animals was comparable with that of the control group. Terminal autopsy revealed no abnormalities.

It is concluded that the samples of tested Perfluoro-1,3-dimethylcyclohexane have no appreciable acute inhalation toxicity to the rat.

APPENDIX 4

ACUTE ORAL TOXICITY OF PERFLUORO-1,3-DIMETHYLCYCLOHEXANE AND PERFLUORODECALIN IN THE RAT

CONFIDENTIAL 2040/67/240

ACUTE ORAL TOXICITY OF PERFLUORO-1, 3-DIMETHYLCYCLOHEXANE AND PERFLUOROMETHYLDECALIN IN THE RAT

G. Fuller, Esq.,
Assistant Product Development Manager (Chemicals),
Imperial Smelting Corporation (N.S.C.) Limited,
Avonmouth,
Bristol

Ronald E. Davies
Sheena R. Grummant

Huntingdon Research Centre,
Huntingdon.

13 October, 1967.

SUMMARY

Divided oral doses totalling 100ml/kg bodyweight, of perfluorodimethylcyclohexane or perfluoromethyldecalin administered over a six-hour period failed to produce an observable toxic response. Autopsy observations, two weeks after dosing, did not reveal any gross pathological changes which could be attributed to the treatment given.

According to Gleason, Gosselin and Hodge (1963), the two compounds may be categorised as "practically non-toxic".

Reference: Gleason, M.N. Gosselin, R.E., and Hodge, H.C., (1963), "Clinical Toxicology of Commercial Products", Williams and Wilkins, Baltimore.

APPENDIX 5

IN VITRO MICROBIOLOGICAL MUTAGENICITY ASSAYS OF EIGHT FLUOROCARBON TAGGANT SAMPLES

SRI International

PP2
PP3
PP5

IN VITRO MICROBIOLOGICAL MUTAGENICITY
ASSAYS OF EIGHT FLUOROCARBON TAGGANT SAMPLES

Final Report

February 1979

By: Kristien E. Mortelmans, Ph.D.
Microbiologist
Vincent F. Simmon, Ph.D.
Manager, Microbial Genetics Program

Prepared for:

THE AEROSPACE CORPORATION
955 L'Enfant Plaza
Washington, D. C. 20024

Attention: Ms. Susan Derda
Subcontracts Administrator

SRI Project LSC-8044

Approved by:

David C. L. Jones, Director
Toxicology Laboratory

W. A. Skinner, Executive Director
Life Sciences Division

SRI International
333 Ravenswood Ave. • Menlo Park, California 94025
(415) 326-6200 • Cable: STANRES, Menlo Park • TWX: 910-373-1246

SUMMARY

SRI International investigated the mutagenic activity of eight fluorocarbon taggant samples for The Aerospace Corporation, using the Salmonella/mammalian-microsome test. The S. typhimurium tester strains used were TA1535, TA1537, TA1538, TA98, and TA100. Each assay was performed at least twice in the presence and in the absence of a rat liver homogenate metabolic activation system.

The liquid taggant samples were tested at several concentrations in desiccators with the tester strains. The samples were:

- Perfluorodecalin (PFD)
- Perfluorohexylsulfurpentafluoride (PFHSPF)
- Octafluorotoluene (OFT)
- Hexafluorobenzene (HFB)
- Perfluorodimethylcyclohexane (PDCH)
- Perfluoromethylcylohexane (PMCH).

The maximum dose level used for PMCH, PDCH, PFD, and PFHSPF was close to their equilibrium vapor pressure at 37°C. Because of toxicity, HFB and OFT were tested at a maximum dose level considerably below their equilibrium vapor pressure at 37°C.

The solid samples, octafluoronaphthalene (OFN) and decafluorobiphenyl (DFB), were tested in the standard plate incorporation assay. The highest concentrations used per plate were 5000 μg of OFN and 2500 μg of DFB.

None of the eight taggant samples tested appeared to be mutagenic in any of these assays.

APPENDIX 6

PERFLUOROMETHYLCYCLOPENTANE: ACUTE DERMAL IRRITATION TEST IN THE RABBIT

CONFIDENTIAL

PERFLUOROMETHYL CYCLOPENTANE:

ACUTE DERMAL IRRITATION

TEST IN THE RABBIT

PROJECT NUMBER: 149/51

Date Started: 14 November 1989

Experimental Procedures:

Date Completed: 21 November 1989

AUTHOR: J.R. Jones

STUDY SPONSOR:

RTZ Chemicals
ISC Division
P.O. Box 46
St. Andrew's Road
Avonmouth
BRISTOL
BS11 9HP

ISSUED BY:

Safepharm Laboratories Limited
P.O. Box No. 45
DERBY
DE1 2BT
U.K.

Telephone: DERBY (0332) 792896

Facsimile: (0332) 799018

Telex: 377079 SAFPHM G

REPORT NUMBER: 3399-149/51 (13 PAGES)

SUMMARY OF RESULTS

STUDY SPONSOR	:	RTZ CHEMICALS ISC DIVISION
PROJECT NUMBER	:	149/51
TEST MATERIAL	:	PERFLUOROMETHYL CYCLOPENTANE

1. A study was performed to assess the irritancy potential of the test material to the skin of the New Zealand White rabbit. The method used followed that described in the OECD Guidelines for Testing of Chemicals (1981) No. 404 "Acute Dermal Irritation/Corrosion".

2. A single 4-hour, semi-occluded application of the test material to the intact skin of three rabbits produced very slight erythema and desquamation at one treated skin site only.

3. The test material produced a primary irritation index of 0.3 and was classified as a mild irritant to rabbit skin. No corrosive effects were noted.

   The test material was regarded as non-irritant according to EEC labelling regulations. No symbol and risk phrase are required.

APPENDIX 6

PERFLUORO-1,3-DIMETHYLCYCLOHEXANE MSDS

FLUTEC TG o-PDMCH™

1 – Identification of the substance and the company

Trade name:	FLUTEC TG o-PDMCH™
Primary uses:	
Company:	F2 Chemicals Ltd.
Address:	Lea Lane, Lea Town Preston, PR4 0RZ, UK
Telephone:	+44 (0) 1772 775804
Fax:	+44 (0) 1772 775809
Emergency Telephone:	+44 (0) 1772 775833

2 – Composition/information on ingredients

Substances	*CAS number*
Perfluoro-1,2-dimethylcyclohexane	306-98-9

3 – Hazards identification

Not hazardous according to *Chemicals (Hazard Information and Packaging for Supply) Regulations 2002*

4 – First-aid measures

a) Inhalation:	In case of severe exposure; remove from exposure, rest and keep warm. Apply artificial respiration if breathing has ceased. Obtain medical attention if effects are other than slight.
b) Skin contact:	Remove contaminated clothing and wash off with soap and water. Obtain medical attention if adverse symptoms arise.
c) Eye contact:	Irrigate thoroughly with water. Obtain medical attention if adverse symptoms arise.
d) Ingestion:	Wash out mouth with water. Obtain medical attention if adverse symptoms persist.

5 – Fire-fighting measures

a) Suitable Extinguishers:	Carbon dioxide Alcohol resistant foam Powder Halons Water fog Water jets Inert material – Sand, earth, etc. Non-combustible material
b) Unsuitable Extinguishers:	None.
c) Hazardous Decomposition:	Toxic fumes, including hydrogen fluoride fumes, may be produced on thermal decomposition, such as contact with flames, and in particular where hydrogen-containing compounds are also present.
d) Protective equipment:	Use approved self-contained breathing apparatus.

6 – Accidental release measures

a) Personal precautions:	Wear laboratory coat. Respiratory protection not normally required. Wear impermeable gloves. Wear chemical safety spectacles or goggles. FLUTEC TG o-PDMCH™ spillages can produce very slippery surfaces which may be hazardous to personnel.
b) Environmental precautions:	Do not allow spillage to enter drains and watercourse. If water is contaminated inform relevant authority immediately.
c) Method of clean-up:	Absorb in inert material eg. sand, vermiculite absorbent granules, place in plastic container for transfer.

7 – Handling and storage

a) Handling:	Do not smoke, eat or drink when handling. Avoid contact of vapour or liquid with red hot surfaces, flames or electrical arcs as this may give rise to toxic gases such as hydrogen fluoride. Do not use sodium or similar metals or their hydrides for removing water from the liquid; other desiccants are acceptable. Where possible, systems should be designed to reduce the risk of releases to the atmosphere.
b) Storage:	Store in original, tightly closed, labelled container.

8 – Exposure controls and personal protection

a) Exposure Limit Values:	None
b) Exposure Controls:	Recommend using in a well-ventilated area
c) Occupational exposure:	Light eye protection (safety glasses) and gloves (any chemically resistant gloves are suitable)
d) Environmental exposure:	Where applicable, use in closed systems with vapour returns.

9 – Physical and chemical properties

Appearance:	Clear, colourless liquid
Odour:	Odourless
pH	n/a
Boiling Point:	102°C
Flash point	Non-flammable
Explosive properties	None
Oxidising properties	None
Vapour Pressure:	48 mbar
Density:	1.828 kg/l @25°C
Pour Point:	-30°C
Dynamic viscosity	1.92 mPa s @25°C
Vapour density	ca. 0.0131 kg/l @25°C
Evaporation rate	Fast
Solubility in Water:	Insoluble (< 25 ppm)
Solubility in Organic Solvents:	Sparingly soluble in most common solvents. Miscible with CFCs.

10 – Stability and reactivity

a) Stability:	Extremely stable.
b) Conditions to Avoid:	Naked flames, hot surfaces (>400°C).
c) Materials to Avoid:	Lithium, sodium, potassium, calcium, and barium.

11 – Toxicological information

The substance has been assessed on adequate evidence and found to produce no effect.

12 – Ecological information

a) Ecotoxicity:	No specific data available
b) Mobility:	Volatile; material readily lost to the atmosphere Low surface tension; material readily able to seep into ground water
c) Persistence:	Material liable to persist in the environment for considerable time; not subject to biodegradation.
d) Bioacculation:	Material not expected to accumulate in biota.

13 – Disposal considerations

Observe all national and regional regulations.
Do not discharge into drains or watercourses.
Small quantities can be sent to an authorised landfill site.
Larger quantities should be incinerated by a licensed waste disposal organisation at a site equipped with an after-burner and scrubber.

14 – Transport information

This material is not regulated by IATA/ICAO (air), ADR (road), IMDG (sea) or RID (rail).
There is no applicable UN number, class or transport name.

15 – Regulatory information

a) Hazard symbols:	None
b) Risk and Safety phrases:	None.
c) Other regulations:	Health and Safety at Work Act 1974. Within the UK, the use of this material must be assessed under COSHH regulations, with reference to COSHH Essentials.

16 – Other information

a) Suitability for purpose:	F2 Chemicals Ltd cannot guarantee the suitability of this material for any particular purpose. It is the responsibility of the customer to satisfy himself that the product is suitable for his purpose. In the event of doubt the customer may contact F2 Chemicals for advice.