

Existing Chemical
Draft Secondary Notification Assessment
NA/482S



Australian Government
Department of Health and Ageing
NICNAS

HFE-7100

DRAFT



HFE-7100

JULY 2006

Any requests for variation must be made with respect to the draft report and accompanied by a completed application form (NICNAS Form 4a).

Form 4a is available from
http://www.nicnas.gov.au/Forms/Existing_Chemicals.asp
or from the address below.

Requests for variation should be sent to:
NICNAS, GPO Box 58, Sydney NSW 2001
Tel: (02) 8577 8848
Fax: (02) 8577 8888

DRAFT

© Commonwealth of Australia 2005

ISBN XXXXXXXXX

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at <http://www.ag.gov.au/cca>

Draft

Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are conducted in conjunction with the Australian Government Department of the Environment and Heritage (DEH), which carries out the environmental assessment.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture, and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health and/or environmental effects.

Chemicals that have been assessed as new or existing chemicals may require a reassessment of the risk of the chemical under the secondary notification provisions of the Act.

This assessment report has been prepared by the Director of NICNAS, in accordance with the secondary notification provisions of the Act. Under the Act manufacturers/importers of the chemical are required to notify the Director of new information and apply for assessment. New information can include a new use, an increase in quantity imported, the commencement of Australian manufacture, increased environmental exposure, and/or additional information becoming available on hazards.

Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested, the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made, appear in the *Commonwealth Chemical Gazette*.

In accordance with the Act, publication of this report revokes the declaration of this chemical for secondary assessment, therefore, manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under Section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of assessment reports for new and existing chemical assessments are freely available from the web (www.nicnas.gov.au) and may be inspected by the public at the OASCC Library (Office of the Australian Safety and Compensation Council), Department of Employment and Workplace Relations (formerly known as the National Occupational Health and Safety Commission (NOHSC) library). Summary Reports are published in the *Commonwealth Chemical Gazette* (http://www.nicnas.gov.au/Publications/Chemical_Gazette.asp), which are also available to the public at the OASCC library.

Hardcopies are available from NICNAS from the following address:

GPO Box 58, Sydney, NSW 2001, AUSTRALIA

Tel: +61 (02) 8577 8800

Freecall: 1800 638 528

Fax: +61 (02) 8577 8888

Other information about NICNAS (also available on request) includes:

NICNAS Service Charter;

Information sheets on NICNAS Registration;

Information sheets on Priority Existing Chemicals and New Chemicals assessment programs;

Safety information sheets on chemicals that have been assessed as Priority Existing Chemicals;

Details for the NICNAS Handbook for Notifiers; and

Details for the *Commonwealth Chemical Gazette*.

Other information on the management of workplace chemicals can be found at the following web site:

<http://www.nohsc.gov.au>

Overview and Recommendations

Overview

Background

HFE-7100 was assessed as NA/482 under the NICNAS New Chemicals program as a standard notification in 1997. As a result of new toxicity data and information on a new use pattern becoming available, HFE-7100 has now been reassessed under the secondary notification provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) relevant to existing chemicals, as more than five years have elapsed since the original assessment.

Use

HFE-7100 was originally notified under the new chemical assessment program for use as a cleaning and a heat transfer agent. In addition to its current use, HFE-7100 will now be used as a solvent for the manufacture of cosmetic products, including personal care products (skin, hair and bath care), fragrances and room scents. HFE-7100 is not manufactured in Australia. HFE-7100 will be imported as a finished product for cosmetic use, however it is envisaged that formulation of the raw chemical for cosmetic use will occur at a later stage.

Exposure

Exposure to the formulated product is likely in the event of an accident while loading, unloading and storage of the packaged cosmetic product, cleaning up in the event of a spill or during distribution. Dermal and inhalation exposure may occur for sales staff when demonstrating the use of a product, or using the product on clients. However, the number of workers likely to be exposed to the chemical through sales cannot be accurately ascertained. While the products containing the chemical are likely to be used regularly, actual applications (eg dermal or aerosol) may normally occur for very short periods.

Compounders would have the highest level of exposure to the chemical if it is imported as raw material to be formulated locally. Between twenty and one hundred personal care industry workers may be involved in the formulation of the chemical, and may be exposed for 8 h/day, 5 d/week. Workers involved in the formulation of cosmetic products may have dermal or inhalation exposure to the chemical, when opening and closing drums, manually pouring the chemical into the mixer, connecting and disconnecting transfer lines and when overfilling retail containers during packaging operations. Blending operations are described as both open and closed systems.

Quality control testing, filling and packaging operations were not described in the submission. However, if these operations are performed, exposure to small amounts of the chemical when carrying out these activities is possible. Skin contamination of maintenance workers may also occur when cleaning equipment and during routine maintenance work.

Exposure to transport workers is likely in the event of an accident during transport of either the formulated product, or the raw material.

Skin contamination of maintenance workers may also occur when cleaning equipment and during routine maintenance work.

Public exposure to the chemical is anticipated as it will be used Australia-wide in fragrances, skin, hair, bath other personal care products and room/air fresheners, at levels of 1%-95%. Skin contact with the cosmetic product will be the main route of public exposure followed by inhalation for room/air freshener applications.

With an import volume of between 300-4000 kg of the formulated product, >1 tonne to <5 tonnes per annum for the raw material and the use pattern, environmental exposure is expected to be minimal. Release to landfill will be in a diffuse manner around the country. Release to the aquatic compartment will be negligible.

Health effects

HFE-7100 has low acute oral and inhalation toxicity. It is not an eye or skin irritant and is not a skin sensitiser. Results of a pharmacokinetic study to determine a convenient marker for dermal absorption of HFE-7100 indicated that a fluorine marker does not exist in the liver, however, following intravenous (IV) administration of the chemical, a major metabolite, heptafluorobutyric acid (HFBA) was detected which would provide a marker for dermal absorption. HFE-7100 is not mutagenic based on in vitro and in vivo assays. HFE-7100 is not determined to have reproductive toxicity and does not cause developmental effects. HFE-7100 has no potential to cause cardiac sensitisation based on studies conducted on beagle dogs exposed to concentrations of up to 10% v/v HFE-7100 in air.

HFE-7100 is not classified as a hazardous chemical under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) and is not listed in the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (FORS, 1998).

Environmental effects

When used in the indicated manner in cosmetic products, the new compound is not expected to be a risk to the aquatic or soil environmental compartments, but will effectively contribute to a very small amount of Australia's greenhouse gas emissions and probably contribute a similar amount to the global pool of short chain PFCAs.

Recommendations

This section provides the recommendations arising from the assessment of HFE-7100. Recommendations are directed principally at regulatory bodies and importers and formulators of HFE-7100. Implicit in these recommendations is that best practice is implemented to minimise occupational and public exposure and environmental impact.

Recommendations to importers and State and Territory Authorities

Hazard communication – Material Safety Data Sheet (MSDS)

Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994) and the Commonwealth, State and Territory regulations introduced in accordance with these national model regulations, employees shall have ready access to Material Safety Data Sheets (MSDS) for hazardous substances at their workplace.

Although HFE-7100 is not classified as a hazardous substance and there is no legal requirement to provide an MSDS, it is good practice to do so, as an MSDS is a well-accepted and effective method for the provision of workplace information.

Recommendation to importers and users

Occupational controls

The risk of adverse effects for occupational use of HFE-7100 is low. The control measures for HFE-7100 are as follows:

Avoidance of spillage and splashing of the chemical. Spillages and splashes should be cleaned up promptly using chemical-resistant impervious gloves.

If engineering controls and safe work practices are insufficient to reduce exposure, employers should ensure that Personal Protective Equipment (PPE) such as gloves and overalls are used by workers to minimise occupational exposure. The PPE used should be in accordance with Australian, Australian/New Zealand or other approved standards.

The use of LEV is recommended during the formulation of cosmetic products from the raw material.

Disposal

Accidental leaks and spillages should be cleaned up promptly with absorbents and put into containers for disposal. The empty drums and their residues should be disposed in accordance with government regulations.

Contents

PREFACE	III
OVERVIEW AND RECOMMENDATIONS	V
CONTENTS	VIII
ACRONYMS AND ABBREVIATIONS	XI
GLOSSARY	XIII
1. INTRODUCTION	1
2. APPLICANT	3
3. CHEMICAL IDENTITY AND COMPOSITION	4
4. PHYSICAL AND CHEMICAL PROPERTIES	5
5. MANUFACTURE, IMPORTATION AND USE	7
5.1 Manufacture and importation	7
5.2 Use and packaging	7
6. EXPOSURE	8
6.1 Environmental exposure	8
6.1.1 Release	8
6.1.2 Fate	8
6.2 Occupational exposure	11
6.2.1 Exposure to the formulated product	11
6.2.2 Exposure during formulation into end use products	11
6.3 Public exposure	12
6.3.1 Consumer exposure	12
7. EVALUATION OF ANIMAL TOXICOLOGICAL DATA	15
7.1 Pharmacokinetics (ND)	15
7.2 Dermal absorption (ND)	16
7.3 Acute toxicity	17
7.3.1 Acute oral	17

7.3.2	Acute dermal	17
7.3.3	Acute inhalation	17
7.4	Skin irritation	18
7.5	Eye irritation	18
7.6	Skin sensitisation	18
7.7	Repeated-dose toxicity	19
7.7.1	28-day oral repeated-dose toxicity (ND)	19
7.7.2	28-day repeat dose inhalation toxicity study in rats	20
7.7.3	13-week repeat dose inhalation toxicity study in rats (ND)	21
7.8	Genotoxicity	22
7.9	Reproductive effects (ND)	22
7.10	Developmental effects (ND)	24
7.11	Cardiac sensitisation study	25
8.	EVALUATION OF HUMAN TOXICOLOGICAL DATA	27
8.1	Skin irritation (ND)	27
8.2	Skin sensitisation (ND)	27
9.	HAZARD CLASSIFICATION	29
9.1	Effects from repeated or prolonged exposure	29
9.2	Reproductive toxicity	30
9.2.1	Fertility	30
9.2.2	Developmental	30
10.	ENVIRONMENTAL EFFECTS ASSESSMENT	31
11.	RISK CHARACTERISATION	32
11.1	Occupational	33
11.1.1	Formulation into end use products	33
11.1.2	End use products	33
11.2	Public	33
11.2.1	Dermal	34
11.2.2	Inhalation	34
11.3	Environmental	35
12.	DISCUSSION AND CONCLUSIONS	37
13.	RECOMMENDATIONS	39
13.1	Recommendations to importers and State and Territory Authorities	39
13.1.1	Hazard communication – Material Safety Data Sheet (MSDS)	39

13.2	Recommendation to importers and users	39
13.2.1	Occupational controls	39
13.2.2	Disposal	39
14.	SECONDARY NOTIFICATION	40
	APPENDIX 1	41
	APPENDIX 2	42
	APPENDIX 3	43
	REFERENCES	50

Draft

Acronyms and Abbreviations

AICS	Australian Inventory of Chemical Substances (NICNAS)
APTT	Activated Partial Prothrombin Time
BOD	Biochemical Oxygen Demand
BCF	Bioconcentration factor
bw	bodyweight
CAS	Chemical Abstracts Service
CFC	Chlorofluorocarbons
CHL	Chinese hamster lung
COF2	Carbonyl fluoride
CIT	Cumulative Irritation Score
DEH	Australian Government Department of the Environment and Heritage
DMSO	Dimethyl sulfoxide
DNCB	Dinitrochlorobenzene
EC	European Commission
FORS	Federal Office of Road Safety
GD	Gestation day
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
GWP	Global Warming Potential
HCIPT	Human Cumulative Irritancy Panel Test
HFBA	Heptafluorobutyric acid
HRIPT	Human Repeat Insult Patch Test
IPCC	Intergovernmental Panel on Climate Change
IPCS	International Programme on Chemical Safety
IV	Intravenous
LC50	Lethal concentration
LD50	Lethal dose
LEV	Local exhaust ventilation

MOE	Margin of exposure
MSDS	Material Safety Data Sheet
ND	New Data
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOHSC	National Occupational Health and Safety Commission
OASCC	Office of the Australian Safety and Compensation Council
OECD	Organisation for Economic Cooperation and Development
PFOA	Perfluorooctanoic acid
PFCA	Perfluorinated carboxylic acid
PN	Post natal
PPE	Personal Protective Equipment
PPM	Parts per million
RBC	Red blood corpuscle
TFA	Trifluoroacetic acid
US EPA	United States Environment Protection Authority
WHO	World Health Organization

Glossary

In this report, NICNAS used the IPCS Risk Assessment Terminology (WHO, 2004) glossary which includes Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment and Part 2: IPCS Glossary of Key Exposure Assessment Terminology. The IPCS Terminology can be accessed at: <http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf>

Adverse effect	Change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
Assessment	Evaluation or appraisal of an analysis of facts and the inference of possible consequences concerning a particular object or process.
Concentration	Amount of a material or agent dissolved or contained in unit quantity in a given medium or system.
Dose	Total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population.
Dose-Response Relationship	Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent. Related Terms: <i>Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship.</i>
Exposure	Concentration or amount of a particular agent that reaches a target organism, system or (sub) population in a specific frequency for a defined duration.

Exposure assessment	<p>Evaluation of the exposure of an organism, system or (sub) population to an agent (and its derivatives).</p> <p>Exposure Assessment is the third step in the process of Risk Assessment.</p>
Exposure period	The time of continuous contact between an agent and a target.
Fate	Pattern of distribution of an agent, its derivatives or metabolites in an organism, system, compartment or (sub) population of concern as a result of transport, partitioning, transformation or degradation.
Hazard	Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.
Hazard assessment	A process designed to determine the possible adverse effects of an agent or situation to which an organism, system or (sub) population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard in contrast to risk assessment where exposure assessment is a distinct additional step.
Hazard characterization	<p>The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose-response assessment and its attendant uncertainties.</p> <p>Hazard Characterisation is the second stage in the process of Hazard Assessment, and the second step in Risk Assessment.</p> <p>Related terms: <i>Dose-Effect Relationship, Effect Assessment, Dose-Response Relationship, Concentration -Effect Relationship.</i></p>

<p>Hazard identification</p>	<p>The identification of the type and nature of adverse effects that an agent has inherent capacity to cause in an organism, system or (sub) population.</p> <p>Hazard identification is the first stage in hazard assessment and the first step in process of Risk Assessment</p>
<p>Risk assessment</p>	<p>A process intended to calculate or estimate the risk to a given target organism, system or (sub) population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.</p> <p>The Risk Assessment process includes four steps: hazard identification, hazard characterization (related term: dose-response assessment), exposure assessment, and risk characterization. It is the first component in a risk analysis process.</p>
<p>Risk characterization</p>	<p>The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system or (sub) population, under defined exposure conditions.</p> <p>Risk Characterization is the fourth step in the Risk Assessment process.</p>
<p>Risk management</p>	<p>Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard.</p> <p>Risk management comprises three elements: risk evaluation; emission and exposure control; risk monitoring.</p>

Toxicity	Inherent property of an agent to cause an adverse biological effect.
Uptake (absorption)	The process by which an agent crosses an absorption barrier.

Draft

1. Introduction

The chemical, HFE-7100, a mixture of two inseparable isomeric chemicals: methoxynonafluoroisobutane, and methoxynonafluorobutane, was previously assessed as a new chemical (NA/482) under Section 23 of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) as a standard notification, and a report was published in June 1997. The two isomers were assessed as a single chemical entity, due to their inseparable nature and similar boiling points. Both isomers are listed individually in the Australian Inventory of Chemical Substances (AICS). HFE was imported in a ready-to use form, as a component of a liquid finished product, containing 50% of the chemical. No manufacturing or formulation was conducted in Australia.

Based on the data provided at that time, a hazard classification was conducted in accordance with the National Occupational Health and Safety Commission (NOHSC) *Approved Criteria for Classifying Hazardous Substances*, and HFE-7100 was considered a non-hazardous substance. Recommendations were made relating to the use of PPE and safe work practices. These recommendations were based on the intended use of HFE-7100 as a cleaning and heat transfer agent.

In December 2004, the applicant advised NICNAS of the proposed additional use of HFE-7100 as a cosmetic ingredient. In support of the application for Secondary Notification, additional toxicity, biodegradation and atmospheric degradation data were submitted. As five years have elapsed since the original assessment, this chemical is now being assessed as an existing chemical (Secondary Notification). The proposed additional use and the availability of new toxicity data warrants reassessment which has been carried out under Section 68A of the Act, covering secondary notification of existing chemicals. HFE-7100 will be imported as a finished product, as there are currently no Australian formulators for the chemical. However, formulation may be conducted at a later stage. Similar to the earlier assessment, the assessment of HFE-7100 for cosmetic use will be conducted as a single assessment of the mixture of both isomers. All toxicity studies that have been provided were conducted on the combined isomers, and the applicant is unable to provide toxicity or ecotoxicity data on the individual isomers.

Declaration and Secondary Notification

Declaration as a secondary notification was initiated when NICNAS received advice of the proposed additional use and the availability of new studies conducted on HFE-7100 that were not submitted during its assessment as a new chemical. The studies are:

1. Pharmacokinetics
2. Dermal absorption
3. 28-day repeat dose oral study
4. 13-week repeat dose inhalation study
5. Reproductive toxicity study

6. Developmental toxicity study
7. Atmospheric degradation
8. Biodegradability
9. Human Repeat Insult Patch Test
10. Human Cumulative Irritancy Panel Test

A notice was published in the *Chemical Gazette* of 1 March 2005 requiring all persons who introduce HFE-7100 into Australia either by manufacture or import, to apply for secondary notification.

Objectives

The objectives of this assessment are to review the new data made available since the publication of the New Chemical Assessment Report in 1997, and where appropriate, revise the original assessment to:

- characterise the hazards of HFE-7100 to human health and the environment when used as a cosmetic ingredient;
- characterise potential occupational, public and environmental exposure to HFE-7100 when used as a cosmetic ingredient;
- characterise the risks of adverse effects resulting from exposure to workers, the general public and environment when used as a cosmetic ingredient; and
- make appropriate recommendations to manage potential risks to workers, the general public and the environment.

International perspective

HFE-7100 was notified in the USA and has been notified in the EU for cosmetic applications.

Peer review

During all stages of preparation, this report has been subject to internal peer review by NICNAS.

2. Applicant

One company applied for secondary notification assessment of HFE-7100. The applicant supplied additional use and toxicity data, and information on biodegradation and atmospheric degradation of HFE-7100. Under Section 36 of the Act, the applicant was provided with a draft copy of the report for correction of errors and variation of content.

Applicant details are:

3M AUSTRALIA PTY LTD

25-27 Bridge St

Pymble

NSW 2073

Draft

3. Chemical Identity and Composition

Chemical Name:	Mixture of methoxynonafluoroisobutane & methoxynonafluorobutane
Marketing or Other Names:	3M Cosmetic Fluid CF-61 HFE-7100 3M Brand Speciality Liquid T-6334
Molecular Weight:	250
Molecular Formula:	(C ₅ H ₃ F ₉ O) (C ₅ H ₃ F ₉ O)
Degree of purity	>99%

Draft

4. Physical and Chemical Properties

HFE-7100 is manufactured as a mixture of two inseparable isomers with essentially identical properties. The mixture is a clear colourless liquid.

Appearance @20°C and 101.3 kpa	clear colourless liquid
Boiling point:	58.34-58.59°C
Density:	1.5305 g/cm ³ at 20°C
Particle size:	Not applicable
Vapour pressure:	27.736 kPa at 25°C
Water solubility:	8.47 mg/L at 20°C
Partition co-efficient (n-octanol/water):	Log P _{ow} = 3.54 at 20°C
Hydrolysis as a function of pH:	T _{1/2} 1-day to 1-year, at pH 4.0, 7.9, 9.9 (see comments below)
Adsorption/desorption:	log K _{oc} 2.56 at 20°C
Dissociation constant:	Not provided
Flash point:	>60°C
Surface Tension	72.6 mN/m
Autoignition temperature:	397°C
Explosive properties:	Not explosive
Flammability limits:	Not flammable
Reactivity/stability:	Not reactive

The method used in determining the hydrolysis may have resulted in loss of HFE-7100 through volatilisation, leading to an erroneous conclusion that the substance was hydrolysed. No hydrolysis was observed during biodegradation testing, and laboratory experiments conducted have shown that the substance is stable under highly acidic conditions.

While the high partition coefficient, and high adsorption/desorption coefficient indicate that HFE-7100 will associate with sediments or organic carbon, the volatility suggests that the chemical will also volatilise to the atmosphere. No dissociation constant was provided for HFE-7100. The chemical does not contain readily dissociable moieties.

Draft

5. Manufacture, Importation and Use

5.1 Manufacture and importation

HFE-7100 is not manufactured or formulated in Australia. Information provided by the applicant indicates that HFE-7100 will be imported in formulated products in volumes ranging from 300-3000kg.

It is proposed that HFE-7100 will be imported in the future as raw material at 100% concentration to be formulated into cosmetic products locally. The proposed import volume of the raw material is expected to range from >1 tonne to <5 tonnes.

5.2 Use and packaging

HFE-7100, as a formulated product, will be used as a solvent or solvent carrier in fragrances, hair care products, room/air fresheners, skin care products and personal care/bath care products. The concentration of the chemical in fragrances is expected to be 20%-95%, in room/air fresheners 5%-70% and in personal care products 1%-30%. The product will be available for retail distribution packed in glass, plastic, bottle/tubes contained in cardboard cases.

The raw material will be imported in 200 L drums. Both the formulated products and the raw material will be transported by road, rail, and sea.

6. Exposure

6.1 Environmental exposure

6.1.1 Release

The chemical is expected to be sold Australia wide. Release during formulation into various cosmetic products will result in unused residues in the containers, washings and batch residues. There are no estimates of waste available. However, these would be contained by standard physical engineering means and are expected to be minimal with some being released to the atmosphere through volatilisation of the notified chemical.

The major release of the chemical is expected through its end use in cosmetic formulations. The high vapour pressure of the chemical would indicate that residues of the chemical would be evaporated off the face, hands and body and thus released to the atmosphere. The applicant also indicates that residues in empty containers will be disposed of with the container with household garbage. Due to the high volatility of the chemical it is anticipated that the residues will eventually be released to the atmosphere.

6.1.2 Fate

The Level 1 Fugacity Model predicts that, at equilibrium, 99.999% of the chemical will partition to the atmosphere, with the remainder found in soil. This is expected due to the high vapour pressure and low water solubility of the chemical. As such, no chemical released would be expected to remain in the aquatic system.

Atmospheric lifetime

The chemical has been estimated to have a relatively short atmospheric lifetime of around 4.1 years (US EPA 2005). Wallington and co-workers have published an atmospheric lifetime for the notified chemical of ≈ 5 years for the reaction with hydroxyl radicals (Wallington et al. 1997). By comparison CFCs can have an atmospheric lifetime of 15 to 400 years, and carbon dioxide approximate lifetimes of 50-200 years (IPCC 2005). The atmospheric lifetime of carbon dioxide is difficult to define because it is exchanged with reservoirs having a wide range of turnover times.

Atmospheric fate

The applicant has proposed an atmospheric degradation pathway for the chemical (see Figure 1)

The core of this reaction scheme is based on the work of Wallington et al. (1997), who determined that the atmospheric lifetime of the chemical is by its reaction with hydroxyl radicals and estimated a lifetime of ≈ 5 years. The product of the reaction gives the alkyl radical ($R_fO\dot{C}H_2$), which they showed will be converted to the corresponding peroxy radical ($R_fOCH_2O_2\cdot$) in less than 1 μs . These radicals rapidly react with NO to produce NO_2 and by inference alkoxy ($R_fOCH_2O\cdot$) radicals. These radicals were shown to rapidly react with oxygen in the atmosphere to generate the corresponding formate (R_fOCHO). The authors were able to show that the formate is relatively uncreative (inert) to atmospheric hydroxyl radicals and will be slow as reflected in an atmospheric lifetime of >3 years. This is in agreement with the recent work of Chen et al. (2004) who have shown that the atmospheric lifetimes of analogous formates C_2F_5OCHO and $n-C_3F_7OCHO$ for the reaction with hydroxyl radicals are 3.6 and 2.6 years respectively. These formates were generated from the reaction of the parent perfluoro ethers $C_2F_5OCH_3$ and $n-C_3F_7OCH_3$ with hydroxyl radicals. These authors also reported that CF_3COF and COF_2 were observed as products of the reaction of $C_2F_5OCH_3$ with hydroxyl radicals and C_2F_5COF and COF_2 as products of the reaction of hydroxyl radicals with $n-C_3F_7OCH_3$.

Another suggested pathway leads to the formation of the C4 perfluorinated carboxylic acids.

Global warming potential (GWP)

The GWP of the notified chemical has been reported for a number of time horizons. These are summarised in Table 1 (Samson 2005).

Table 1: GWP values for the notified chemical over various time horizons

Time Horizon	20 years	100 years	500 years
GWP	1300	390	120

Ozone depletion potential

Because of the absence of chlorine and bromine groups, the chemical is considered to have zero ozone depleting potential (US EPA 2005).

Biodegradation

In the previous assessment, testing to OECD TG 301D (closed bottle test) concluded that the notified substance was not readily biodegradable, with 22% degradation (based on BOD) after 28 days.

Bioaccumulation

In the previous assessment, a bioconcentration study was performed on carp (*Cyprinus carpio*). The high exposure level of 0.5 $\mu g/mL$ gave a maximum bioconcentration factor (BCF) of 118, while the low exposure level (0.05 $\mu g/mL$) gave a maximum bioconcentration factor (BCF) of 71 after an exposure period of 8 weeks. On the basis of these results, it was concluded that the test substance was

not bioaccumulative. Testing was carried out in a closed system due to the volatility of the test substance

6.2 Occupational exposure

According to information provided by the applicant, the chemical will be currently imported as a formulated product and later as raw material to be formulated into cosmetic products.

6.2.1 Exposure to the formulated product

Exposure to the formulated product is likely in the event of an accident while loading, unloading and storage of the packaged cosmetic product, and cleaning up in the event of a spill or during distribution. Dermal and inhalation exposure may occur for sales staff when demonstrating the use of a product, or using the product on clients, however, the number of workers likely to be exposed to the chemical through sales cannot be accurately ascertained. While the products containing the chemical are likely to be used regularly, actual applications (eg dermal or aerosol) may normally occur for very short periods.

6.2.2 Exposure during formulation into end use products

Exposure to the raw material is likely during packaging, dispensing, or cleaning up in the event of a spill. Warehousing and distribution of the chemical involves loading, unloading, transport and storing of the imported chemical. The raw material will be transported by air, sea, rail or road from the warehouse to local formulators for incorporation into cosmetic products.

Between 20 and 100 workers will be involved in the formulation of the chemical into cosmetic products. These workers are expected to be exposed for 8 h/day, 5 d/week. Compounders would have the highest level of exposure to the chemical. No information was provided on whether this would be a batch process.

Workers involved in the formulation of cosmetic products may have dermal and inhalation exposure to the chemical when opening and closing drums, manually pouring the chemical into the mixer, connecting and disconnecting transfer lines and when accidentally overfilling retail containers during packaging operations. Blending operations are described as both open and closed systems. The MSDS recommends the use of local exhaust ventilation at transfer points and when the product is heated.

Quality control testing, filling and packaging operations were not described in the submission, as formulation is likely to occur in the future. However, if these operations are performed, exposure to small amounts of the chemical when carrying out these activities is possible. Skin contamination of maintenance workers may also occur when cleaning equipment and during routine maintenance work.

The MSDS states that workers wear suitable gloves, and eye and face protection when handling the chemical. Respiratory protection is also to be worn if ventilation is inadequate and thermal degradation is expected.

6.3 Public exposure

Public exposure to the chemical is anticipated as it will be used Australia-wide in fragrances, skin, hair, bath and other personal care products and room/air fresheners at levels of 1%-95%. Skin contact with the cosmetic product will be the main route of public exposure followed by inhalation for room/air fresheners applications.

The potential for exposure of the public to the chemical during normal industrial storage, handling and transportation is negligible, except in the case of an accident. The packaging will protect the contents from being released during normal handling.

6.3.1 Consumer exposure

Consumer products are in the form of lotions, creams, aerosol sprays, liquids, gels and soap bars. Consumer exposure is expected to be widespread and will predominantly occur by dermal or inhalation exposure. The oral route of exposure is not anticipated except in the case of accidental ingestion by children or adults. Inhalation exposure is possible during application of hair/deodorant sprays and room air fresheners.

Consumer exposure was estimated based on the data provided by the applicant i.e. the different applications and the concentration of the chemical in each proposed application.

HFE-7100 is to be currently imported as a formulated product. In the future, the raw material will be imported and formulated into the various cosmetic products locally. The proposed applications and the concentration of the chemical in each application is provided in Table 2

Table 2: Concentration of the chemical in the products

Products	Range of HFE-7100 concentration (%)
Fragrances	20-95
Hair care products	1-30
Room/air fresheners	5-70
Skin care products	1-30
Personal care/bath products	1-30

HFE-7100 is mainly used in the above applications as a solvent or solvent carrier. There are no Australian data on the typical amounts used per application, frequency of use and duration of the different applications used by the public. Consumer exposure by the dermal route was estimated using modelled data collected by the European Cosmetics and Toiletries Association (COLIPA-1987) and submitted to the European Commission. These data have been utilised in the European Union by the Scientific Committee on Cosmetic Products and Non-Food products Intended for Consumers (SCCNFP) in their Guidance Notes for the Testing of Cosmetic Ingredients and their Safety Evaluation (2003) and also in the European Chemical Bureau's Technical Guidance Document on Risk Assessment (European Commission, 2003). It is assumed that the use pattern of the various cosmetic applications is similar to the use in Australia.

In determining dermal exposure for consumers, exposure from the above products was estimated according to the product type provided in the model: fragrances (perfumes, fragranced cream), hair care products (shampoo, hair spray), skin care products (body lotion, face cream), personal care/bath care products (shower gel, toilet soap, antiperspirant/deodorant).

Values used in determining exposure are, an average human body weight of 60 kg, and a dermal absorption rate of 5%. A dermal absorption rate of <5% was determined from a dermal absorption study conducted on rats, however, assuming a worst case scenario, a dermal absorption rate of 5% was used to determine the internal dose.

Exposure was determined for the maximum concentration of HFE-7100 in the products. Details of the quantity per application, concentration of HFE-7100 in the product, frequency of use, retention factor, external and internal doses are presented in Table 3.

The quantity per application (g), frequency of use (events per day) and estimated retention after wash-off are cosmetic data from the Health Canada Cosmetic Exposure Workbook (McLaughlin, 2006).

The external and internal doses were calculated based on the concentration of HFE-7100 in the products and the HC Cosmetic Survey Data (referenced above).

Table 3: Estimated internal dose from dermal exposure to products containing HFE-7100

Product	Quantity per application (g)	HFE-7100 conc. in product (%)	Frequency of use (events per day)	Estimated retention after wash-off	External dose (mg/kg bw/d)	Internal dose (mg/kg bw/d)
Fragrances	8	95	0.29	1	3.67	0.1835
Hair care products	8	30	2	0.01	0.5	0.025
Skin care products	8	30	2	1	28	1.4
Personal						

care/bath products	17	30	6	0.01	2.5	0.125
-----------------------	----	----	---	------	-----	-------

HFE-7100 is volatile and therefore inhalation exposure to the vapour is possible. Inhalation exposure from room air fresheners was estimated based on the formula from the European Chemicals Bureau Technical Guidance Document on Risk Assessment (European Commission, 2003), the Toxicologist's Pocket Handbook (MJ Derelanko, 2000) and the Environmental Health Risk Assessment enHEALTH, 2002.

The body burden from inhalation exposure during use of room fresheners in aerosol form was estimated as 0.1415 mg/kg/d. The assumptions used and details of the calculations are provided in Appendix 1.

Draft

7. Evaluation of Animal Toxicological Data

Data submitted for the original new chemical assessment included studies conducted on HFE-7100, identified as L-13532 or T-6334 in the submission, except for the acute inhalation study which was conducted on a chemical analog, perfluorobutyl methyl ether. New data (denoted by ND) on pharmacokinetics, dermal absorption, chronic and reproductive/developmental toxicity conducted on HFE-7100 were provided for the Secondary Notification. Summaries of the original data and assessment of the new studies are presented below for completeness.

7.1 Pharmacokinetics (ND)

A pharmacokinetic study was conducted in New Zealand White rabbits (4/sex), to assess systemic exposure to HFE-7100 and to determine whether a convenient marker for HFE-7100 exists when administered as a single intravenous injection at various doses. HFBA, a major metabolite, was identified in the serum and was present up to 48 h. HFBA was therefore considered a convenient marker for HFE-7100, following intravenous administration (3M Environmental Technology & Services, 1996a).

The animals were divided into 5 groups, Group 1 (Control Group), and 4 test groups (Groups 2-5). The control group was administered dimethyl sulphoxide (DMSO) and the test group varying doses of HFE-7100, as a single injection into the marginal ear vein of the right ear. The doses administered were 1.0 mg/kg (Group 2), 2.0 mg/kg (Group 3), 5.0 mg/kg (Group 4) and 10 mg/kg (Group 5). The test material was mixed with dimethyl sulphoxide (DMSO) to obtain the following dose levels: 0, 1, 2, 5 and 10 mg/kg.

Blood samples were collected pre-dose and at 4, 8, 12, 24 and 48 h and on day 8 post injection. In addition, blood samples were collected on day 16 or day 29 (day of sacrifice), and serum samples and cellular fractions were frozen for analysis using electrospray mass spectrometry.

On day 16, 2 animals/sex/dose were sacrificed and the remaining 2 animals/sex/dose were sacrificed on day 29. Clinical observations were conducted pre-dose and at approximately 0.5, 2 and 4 h after IV injection. Mortality was checked twice daily and body weights were checked pre-dose and on day 16 or day 29. At necropsy, the whole liver, bile and kidneys were collected and frozen on dry ice for extraction and fluorine analysis. Liver samples were collected from the control group on day 29, from the 10 mg/kg dose group on day 16 and day 29, and from the 5 mg/kg dose group on day 29 for fluoride analysis. Fluoride in liver was extracted from each sample using a modified Dohrmann organic halide analyser and fluoride content was measured using both the Orion meter and Skalar segmented flow analyser.

All animals gained weight during the study and appeared normal throughout the study.

Results of the serum samples analysed by the electrospray mass spectrometry showed HFBA present in quantities ranging from 0.0015 to 0.0543 mg/kg in Group 2 male and female rabbits at 4, 8 and 12 h post dosing, and in Groups 3, 4 and 5 from 0.0088 to 0.6352 in male and female rabbits, at 4, 8, 12, 24 & 48 h post-dosing.

Results obtained from analysis of fluorine in the liver (estimated using the Orion meter and Skalar segmented flow analyser) showed trace amounts of organic fluorine 28 d after treatment, with no significant differences in fluorine concentrations between the control group and the 10 mg/kg and 5 mg/kg dose groups on day 28. Therefore, liver data does not provide a useful marker for HFE-7100, 28 d after treatment.

7.2 Dermal absorption (ND)

The pharmacokinetic study indicated that HFBA was present in the serum of rabbits from 4-48 h after IV injection of the chemical. Therefore, it was assumed that if the chemical were dermally absorbed, HFBA would be present in serum at some point between 4 and 48 h after dermal exposure. A dermal absorption study was conducted to assess the systemic absorption/toxicity and relative skin irritancy of HFE-7100 when applied to rabbit skin (3 M Environmental Laboratory, 1996).

The study was conducted using New Zealand White rabbits (4/sex). The back of each rabbit was clipped free of hair and a single dose of distilled water (control) (Group 1) or test material 15.0 mg/kg/d (Group 2) was applied daily to the skin of the rabbits for 5 consecutive days. The treatment site was covered by an occlusive dressing for approximately 23 h.

Clinical observations were conducted pre-dose and at approximately 1, 2.5 and 4 hours after each administration on days 1 to 5. Additional clinical observations and twice a day mortality checks were conducted daily thereafter until the scheduled sacrifice interval (day 10 or 29). The initial dermal irritation reading was made before the first treatment and subsequent readings for dermal irritation were made approximately 30 minutes after each patch removal on days 2 to 6 and on day 10. A blood sample (2.5 mL) was collected from each animal prior to application, approximately 12 h after the daily application on days 1 to 4 and at approximately 4, 6, 12, 24, 48, 72 and 96 h after treatment on day 5. Blood samples were also collected on day 10 from each animal sacrificed on day 29. The blood samples were analysed for HFBA levels.

In addition, 20-40 mL of blood was collected from each control animal and 20 mL of blood from each treated animal at each scheduled sacrifice (day 10 or day 29). Separate samples of serum and cellular fractions from all animals were obtained and frozen for subsequent testing.

Two animals/sex/group were sacrificed on day 10 and the remaining animals were sacrificed on day 29.

At necropsy, the whole liver, bile and a section of the dermal application site and both kidneys from all animals were collected and weighed (volume only determined for bile). All tissue samples collected were frozen for subsequent testing.

There were no test-related changes in body weight gain and all animals appeared normal throughout the study. Slight to severe erythema and oedema, slight to marked atonia and coriaceousness (leather-like changes) slight desquamation and slight to moderate fissuring reactions were observed in the control animals exposed to distilled water. Areas of subcutaneous haemorrhage and possible necrosis were seen in two control animals. No explanation for the unexpected dermal irritation in the control group was provided. Application of HFE-7100 produced only slight erythema in four Group 2 animals. At necropsy on day 10, 2 females from the control group (Group 1) exhibited thickened, tan-coloured, crusted skin and multiple red to dark red areas on the test sites. These observations were not seen in the test group (Group 2).

Dermal administration of five daily doses of HFE-7100 resulted in no detectable levels of HFBA in the serum of rabbits at any time after dosage. As no detectable HFBA was found in serum 4-48 h after dermal application, it was assumed that only a small percentage (<5%) of HFE-7100 might have been absorbed. The necropsy findings of the liver and kidneys were not presented in the report.

7.3 Acute toxicity

7.3.1 Acute oral

HFE-7100 has very low oral toxicity in young adult albino rats (5/sex) when treated with a single dose of 5000 mg/kg body weight (bw) of the chemical by gavage. No mortality was observed during the study. All animals appeared normal throughout the study, except for one animal, which exhibited soft stool on the day of test administration. All animals gained weight during the study. There were no visible lesions observed at necropsy. Based on the results of the study, the LD50 for HFE-7100 was determined to be >5000 mg/kg bw. The results of the study indicate that HFE-7100 has low acute oral toxicity (Hazelton Wisconsin, 1995a).

7.3.2 Acute dermal

An acute dermal toxicity study was not performed. No new data were submitted for this assessment.

7.3.3 Acute inhalation

An acute nose only inhalation study in rats was conducted on a chemical analogue, perfluorobutyl methyl ether. One group of 5/sex of albino rats (Group 1) and one group of four male and six female rats (Group 2) were exposed to different vapour concentrations of the test material for 4 h using nose-flow-past exposure methods. The exposure concentrations were 2050 ppm (Group 1) and 10 100 ppm (Group 2) measured as T-5333 (calibration standard). All animals were euthanised at the end of the study and all major organs in the abdominal and thoracic cavities were observed for macroscopic abnormalities. No significant observations or mortality were noted either immediately, or during the 14d post-exposure period. No

abnormal macroscopic findings were observed at necropsy. Based on this study, the 4-hour LC50 for perfluorobutyl methyl ether was determined to be >10 000 ppm. The results of the study indicate that HFE-7100 has low acute inhalation toxicity (IRDC, 1995).

7.4 Skin irritation

HFE-7100, at a dose of 0.5 mL was applied to an area of intact dorsal skin of three male New Zealand rabbits, and the test area covered with semi-occlusive dressing for 4 h. At the end of the 4-hour exposure period, the dressing was removed and the test site irrigated with lukewarm water. Skin reactions were assessed at 30 minutes (recorded as a 4-hour score), 24, 48 and 72 h after removal of the dressing. The untreated skin of each animal was used as a control. The results were scored according to Draize method. A very slight erythema (Grade 1) was observed in two animals at the 4-hour observation period, which resolved within 24 h. No other dermal reactions were observed. The results of the study indicate that HFE-7100 is not a skin irritant (Hazelton Wisconsin, 1995b).

7.5 Eye irritation

Three male New Zealand white rabbits received 0.1 mL each of undiluted HFE-7100 in the everted lower lid of the right eye. The left eye remained untreated and served as a control. The eyelids were gently held together for one second to prevent loss of material. The eyes remained unwashed and were observed for ocular irritation at 1, 24, 48 and 72 h after treatment. Ocular irritation was graded and scored according to the Draize method. A sodium fluorescein examination was used to aid in identifying possible corneal injury at the 24 h observation period. The test material produced slight conjunctival irritation (Grade 1) in 2 animals and mild chemosis (Grade 1) in 1 animal at the 1 h observation period. The results of the study indicate that HFE-7100 is not an eye irritant (Hazelton Wisconsin, 1993).

7.6 Skin sensitisation

The skin sensitisation potential of HFE-7100 was evaluated in 3 phases. A total of 26 albino guinea pigs were divided into 4 groups consisting of an irritation screening group of two animals, a test group of 10 animals, a naïve control group of 10 animals, and a positive control group of 4 animals.

In the first phase, an irritation study was conducted to determine the irritation threshold of the test material. The test material (0.4 mL) was applied undiluted onto adhesive patches which were placed on a shaved area on the bodies of two guinea pigs. The patches remained in place for approximately 6 h following which the sites were washed and dermal reactions noted at approximately 24 and 48 h after application.

In the induction phase, the test material (0.4 mL) was applied undiluted onto adhesive patches which were placed on the induction site along the dorsal anterior left quadrant of each animal in the test group (10 animals). The site was then occluded. The patches remained in place for approximately 6 h, following which the area was washed with warm water and patted dry with a disposable paper towel. The positive control (4 animals) group was treated with 0.4 mL of an 80%

2,4-dinitrochlorobenzene (DNCB) solution and treated in the same way as the test group. The animals in the test and positive control groups received one application/week for 3 weeks for a total of 3 applications. The naïve control group (10 animals) were not treated during this phase.

The challenge phase followed two weeks after the administration of the third induction dose. The test material (0.4 mL) was administered on the dorsal anterior right quadrant of each animal in all groups in the same manner as the induction phase. Dermal reactions according to Buehler scoring were conducted at 24 and 48 h after challenge applications.

No signs of irritation were observed in the test group during the induction phase. At 100% challenge concentration, all scores in both test and naïve control animals were zero. Individual dermal reactions were noted for the positive control animals; however, this group of animals was considered to have been sensitised because of the moderate to strong dermal reaction they exhibited to the DNCB application in the challenge phase. The results of the study indicate that HFE-7100 is not a skin sensitiser (Corning Hazelton, 1996).

7.7 Repeated-dose toxicity

7.7.1 28-day oral repeated-dose toxicity (ND)

In a preliminary study conducted to determine the dose levels for a 28-day study Sprague-Dawley rats (3 per sex per group) were dosed daily via a gastric tube with 0, 8, 40, 200 and 1000 mg/kg bw HFE-7100 suspended in 0.1% Tween 80 aqueous solution for 14 consecutive days. The dosing volume was set at 10 mL/kg. No abnormalities were noted clinically. A slight increase in liver weight in both sexes in the highest dosed group (1000 mg/kg bw) was observed. Accordingly, the dosing regimen for the main study was set at 8, 40, 200 and 1000 mg/kg bw HFE-7100.

In the main study 6 rats/sex/group were dosed with 0, 8, 40, 200 and 1000 mg/kg bw HFE-7100 in 0.1% Tween 80 aqueous solution for 28 consecutive days. In addition, three recovery groups (6 per sex per group) received 0, 200 and 1000 mg/kg bw HFE-7100 at the same dosing schedule and were maintained without treatment for a further 14 days. All animals were observed for clinical toxicity, body weight changes and food consumption. Haematology, blood chemistry and urinalysis were conducted. Thorough pathological examinations (macroscopic and microscopic) were also performed on all animals at necropsy.

No deaths occurred in any group throughout the observation period. Body weight, food consumption and urinalysis were comparable to the control group.

In the 8 mg/kg bw/d group, decreased blood sodium levels and increased potassium levels were observed in males. Decreases in absolute (13%) and relative (12%) spleen weights were reported in females.

In the 40 mg/kg bw/d group, a decrease in the red blood cell (RBC) count activated partial prothrombin time (APTT), and decreased serum calcium were observed in males. Decreases in absolute (20%) and relative (19%) spleen weights were reported in females.

In the 200 mg/kg bw/d group, increase in blood potassium level in males and a decrease in total protein in females were observed. In addition, a decrease in absolute (18%) and relative (17%) spleen weights in females were seen at the end of the treatment period.

In the 1000 mg/kg bw/d group, irregular respiration, and salivation were observed in males after day 26. In addition, increased albumin, alanine aminotransferase (ALAT/ GPT) and potassium levels were also observed in males. At the end of the treatment period, increase in absolute and relative liver weights were observed in males. Females had increased relative liver weights only. Decreases in absolute (17%) and relative (14%) spleen weights were also noted in females. Macroscopic examinations revealed enlarged livers in two males and one of them had enlarged bilateral thyroid lobes. Histopathological examinations of the liver and thyroid revealed centrilobular hypertrophy of the hepatocytes in all males, and hypertrophy of the follicular cells in the thyroid of the male with the enlarged thyroid. No histopathological changes were observed in the spleen.

Centrilobular hypertrophy of the hepatocytes was observed, but this was considered to be an adaptive response to the treatment. Chemical substances capable of inducing drug metabolising enzymes are also capable of inducing hypertrophy of the follicular cells in the thyroid through the hypothalamo-hypophysial axis (Capen et al, 1991).

In the recovery group, no clinical signs were observed, however, a decrease in body weight in females in the 1000 mg/kg bw/d recovery group was noted. At the end of the recovery period, increases in relative brain and adrenal weights were observed in females in the 1000 mg/kg bw/d group. No histological findings in the liver and thyroid were observed at the end of the recovery period.

Although a decrease (>10%) in absolute and relative spleen weights were noted in females in all groups, a dose response was not observed. This observation was therefore not considered significant. No data were provided for splenic weights in males.

The No-Observed-Adverse-Effect Level (NOAEL) of HFE-7100 was determined to be 200 mg/kg bw/d based on the absence of systemic toxicity or histopathological effects at this level (Mitsubishi Chemical Safety Institute, 1996).

7.7.2 28-day repeat dose inhalation toxicity study in rats

Toxicity from repeated inhalation doses of HFE-7100 was evaluated in a study using groups of Sprague-Dawley rats, 5/sex/group. The animals were exposed for 6 h/day, 5 d/week, for 4 weeks via whole-body inhalation to mean concentrations of 0, 1489, 2935, 9283 and 28 881 ppm (0, 15.3, 30, 94.9, 295.3 mg/L, respectively) of HFE-7100 v/v in air. A control group was exposed to air only.

There were no deaths during the study. Changes in body weight gain and food consumption were comparable to the control group. Isolated incidence of functional observatory changes including piloerection, altered gait, increased foot splay and hair loss were observed.

In the highest dose group (28 881 ppm), statistically significant increase in neutrophils and basophils were observed in females only. In addition, statistically significant increase in glucose and phosphorus, decrease in cholesterol and increase

in liver weights were observed in males only. This effect was more severe in males dosed at 28 881 ppm than in females of the same dose group.

Urinary pH and urinary protein were elevated in the highest dose males, and an increase in urinary protein was observed in both sexes at 9283 ppm. A statistically significant increase in total urinary fluoride output was observed in both sexes at 2935, 9283 and 28 881 ppm.

At necropsy, liver samples were examined for protein. Palmitoyl CoA oxidase activity of the liver from 3 animals/sex/group was also determined. Statistically significant increase in total amount of supernatant protein in males exposed at 28 881 ppm compared with controls was seen. Evidence of increase in palmitoyl CoA oxidase activity was observed in all 3 males at 28 881 ppm. Palmitoyl CoA oxidation activity is used as a peroxisomal enzyme marker (Citron, 1995).

Histopathological examination revealed centrilobular hepatocyte enlargement in a number of animals exposed to 2938 and 28 881 ppm. The presence of centrilobular hypertrophy was considered to be an adaptive response, which is consistent with the observations in the oral repeat dose study indicating that metabolic enzymes in the liver were induced by the test material.

The findings of this study indicated that at high doses, HFE-7100 induced metabolic activity with subsequent breakdown of the parent molecule as evidenced by increase in urinary fluoride. The study report concluded that due to the variability of activity and the small number of animals in each treatment group, the non-statistically significant increase in palmitoyl oxidase activity provided no conclusive evidence that the test substance was acting as a peroxisome proliferator (Huntingdon Life Sciences, 1996a).

7.7.3 13-week repeat dose inhalation toxicity study in rats (ND)

Groups of Sprague-Dawley rats (5/sex/group) were exposed to the vapour of HFE-7100 for 6 h/day, 5 d/week for 13 consecutive weeks to concentrations of 0, 1500, 4500, 7500 and 15 000 ppm (0, 15.4, 46.1, 76.8 and 153.7 mg/L) by whole body inhalation. A control group was exposed to air only. Concurrent exposure of pregnant female rats to 4500, 7500 and 15 000 ppm (46.1, 76.8 and 153.7 mg/L) in an embryo foetal development study were also conducted, which is described later.

No effects of treatment were evident in clinical signs, body weight gain or food consumption. Haematology, biochemistry and urinalysis investigations did not reveal any treatment-related changes. Functional observation tests did not indicate any treatment-related neurotoxicity. Between exposures, incidental clinical signs were observed including hair loss, damaged tail, overgrown lower teeth, missing upper teeth and swollen eyes from an orbital sinus bleed. Behavioural changes such as slight incidence of vocalisation during removal from the cage, soft faeces and incidence of hair loss were confined to exposure at 15 000 ppm. Food consumption and body weights of treated groups were comparable with the control group.

A dose-related increase in total urinary fluoride was observed in all treated groups compared with the control group. However, the increase in urinary fluoride output was determined to be a consequence of metabolism of the test substance and not a toxic effect.

There were no deaths during the study. Statistically significant increases in spleen, kidney, and liver weights and an increase in palmitoyl CoA oxidase activities were observed in males exposed to 15 000 ppm. Although there were statistically significant weight increases in the liver, spleen and kidneys, no histopathological findings were detected that could explain the organ weight changes in the spleen and kidneys. The histopathological change seen in the liver consisted of minor degrees of centrilobular hepatocyte hypertrophy. This finding is not uncommon and is considered associated with metabolic processing within the liver. This observation is consistent with the effects obtained from the other repeated dose studies.

A No Observed Adverse Effect Level (NOAEL) of 7500 ppm was determined based on an increase in palmitoyl CoA activities (indicating peroxisome proliferation) observed at the highest dose (Huntingdon Life Sciences, 1996c).

7.8 Genotoxicity

Two in vitro studies and one in vivo study were submitted with the original application (Huntingdon Life Sciences, 1996; Mitsubishi Chemical Safety Institute, 1996). In a bacterial (*Salmonella* and *E.coli*) gene mutation assay, doses ranging from 1.25 to 20 mg/plate showed no increase in the incidence of gene mutations in *Salmonella* tester strains TA1535, TA1537, TA98, TA100, or in *E. coli* bacterial strain WP2, with or without metabolic activation. The test was carried out using 3 cultures per dose per strain. An independent repeat test confirmed the absence of mutagenicity in all tester strains at all doses.

In the chromosome aberration assay, Chinese hamster lung (CHL) cells were treated with HFE-7100 at concentration levels between 0.63 mg/mL and 10 mg/mL. There was no increase in the incidence of chromosomal damage following treatment with HFE-7100 for either the 24 or 48-hour treatment, in the absence of metabolic activation. In addition, no induction of chromosomal aberration was observed after 6-h treatment with metabolic activation.

In the in vivo assay, HFE-7100 was injected into the peritoneal cavity of Swiss mice, 5/sex at doses of 1250, 2500 or 5000 mg/kg bw. The negative control group received the vehicle, aqueous 1% methylcellulose. The positive control group was dosed orally (by intragastric gavage) with Mitomycin C.

Bone marrow smears were obtained from all treated animals at each sampling time (24, 48 or 72 h after treatment). There was no significant increase in the frequency of micronucleated polychromatic erythrocytes at all sampling times compared with the control group. There was no significant decrease in the ratio of polychromatic to normochromatic erythrocytes after treatment. The positive control produced highly significant increases in the frequency of micronucleated polychromatic erythrocytes together with decreases in the ratio of polychromatic to normochromatic erythrocytes. Based on the above results, HFE-7100 is not determined to be mutagenic using in vitro and in vivo assays.

7.9 Reproductive effects (ND)

An inhalation one-generation reproductive study was conducted with HFE-7100 to study the effects on male and female fertility, general reproductive performance, and on the pre- and post natal development of the offspring (TNO, 2003). Four

groups (28/sex/group) of Wistar rats were exposed by nose-only inhalation to HFE-7100 at atmospheric concentrations of 0 (control), 3000 (31.0 g/m³; low dose), 7500 (77.5 g/m³; mid dose) and 12 500 ppm (129.1 g/m³; high dose).

Prior to mating, each group of males and females were exposed to the appropriate concentrations of test material for 6 h/day, 5 d/week (10 weeks for males while the females were only exposed for 2 weeks). Control animals were exposed to air only until the day before sacrifice.

During the mating period, males were exposed daily for 6 h until the day before sacrifice. The females were exposed daily for 6 h during the mating and gestation periods until gestation day (GD) 19. The female rats were allowed to litter and rear their pups until weaning. During the lactation period, the animals were not exposed.

At the end of GD 19, females were examined twice daily for signs of parturition and litters were examined for dead pups once a day.

The total litter size and numbers of each sex, stillbirths, livebirths, grossly malformed pups, and pups showing abnormalities were recorded on post natal (PN) day 1. In addition, the number of live and dead pups, and the number of pups showing malformations were recorded on days 4, 7, 14 and 21-post-partum. The litters were weighed on days 1, 4 (before and after culling), 7 and 14-post-partum.

At weaning (PN day 21), all pups were weighed individually, checked for overt signs and sacrificed. After weaning, F0 females were sacrificed and necropsied.

Results

Except for the decreased number of sparsely haired males seen in the mid-dose group during the pre-mating period (no reason provided in the study) and which was not considered treatment-related, no other changes in appearance, general condition or behaviour were noted in both the control and treatment groups during the pre-mating gestation and lactation periods.

No significant differences were observed in mean body weights and food consumption for males during the pre-mating period. Similarly, no significant differences in mean body weights and food consumption for females during pre-mating, gestation and lactation periods, were observed, except for a decrease in food consumption of females of the low dose group during the second week of pre-mating period.

Fertility and reproductive performance in all test groups were comparable with the control groups. Pre-coital time was similar among the groups ranging from 1.93 – 2.81 d. There were no differences in the number of pregnant females, the number of males that became sire, the number of females with liveborn and the number of females surviving delivery among the group. The mating index, female fecundity index, female fertility index, male fertility index and gestation index were comparable among the groups and ranged from 75% to 100%. No difference was observed in the duration of gestation. The number of stillborn pups and post implantation loss were comparable among the groups and there were no dams with all still born pups.

The number of pups delivered per litter was comparable among the groups. No significant differences in the number of lost pups after culling (PN day 4-21) and the number of live pups per litter during the lactation period were observed.

The macroscopic observation in stillborn pups and pups that died during lactation did not indicate any abnormality in the development of the pups. No significant differences in pup body weight and body weight changes were observed among the groups.

Gross examination of parental animals at necropsy did not reveal any treatment-related findings. The changes observed were mostly isolated or common pathology findings in rats of this strain and age.

No treatment-related effects on terminal body weight and organ weights of parental animals were observed. There were no effects observed on the weight of reproductive organs, except a significant decrease in the prostate weight (absolute and relative) of the animals in the mid dose groups. However, this effect was not seen in any of the other treatment groups. Histopathological examination of the prostate did not show any abnormalities.

Microscopic observations of parental animals showed increased striation of the dentine of the upper incisors of all rats of the high dose groups (10 animals) and in 4 animals of the mid dose groups. One male rat in the high dose group had malocclusion of the incisors associated with tooth fracture, haemorrhages, callus formation and nasal luminal obstruction. Striation of the dentine was not seen in low dose and control groups. Striation of dentine in the teeth was due to development of decalcification bands, which was regarded as a characteristic feature of dentine damage by fluorine compounds (Jarzynka et al 1990). All other histopathological changes occurred at similar incidences among the groups, including controls and were common findings in rats of this strain and age.

The No Observed Adverse-Effect Level (NOAEL) for parental toxicity of HFE-7100 is 3000 ppm (31.0 g/m³; low dose) based on the presence of striation of the dentine of the upper incisors in higher doses. The No Observed Adverse Effect Level (NOAEL) for reproductive and developmental toxicity is 12 500 ppm (129.1 g/m³). Based on the above results, HFE-7100 is not determined to have reproductive toxicity.

7.10 Developmental effects (ND)

An inhalation developmental toxicity study was conducted to evaluate the effects of HFE-7100 on pregnant rats and embryofetal development of the rat (Huntingdon Life Sciences Ltd, 1998). Twenty-five time-mated pregnant female rats (CrI: CD® BR VAF.Plus strain) per group were exposed by whole body inhalation to atmospheric concentrations of 0 (control) and 30 000 ppm (307.4 mg/L) HFE-7100 for 6 h/day, from days 6 to 19 of gestation.

Clinical signs, and food and water consumption were observed daily from day 1 of gestation. Body weights were measured on days 1 and 2 of gestation and every 2 days thereafter.

On day 20 of gestation, all animals were sacrificed, and examined for congenital abnormalities and pathological changes in maternal organs. The ovaries and uteri were examined to determine the number of corpora lutea, number of distribution of

live young rats, number and distribution of embryofoetal deaths, individual foetal weight from which the litter weight was calculated and gravid uterine weight. Live young were examined externally and weighed.

Results

No treatment related clinical signs were observed during the study and food consumption was comparable in treated and control groups. At 30 000 ppm, a reduction in mean body weight gain between days 10 to 12 of gestation, compared with controls, were observed. However, a degree of recovery was apparent with body weights being comparable for both groups at day 20 of gestation.

Macroscopic examination of maternal organs did not reveal any significant changes. The incidence and distribution of findings were mostly isolated.

Twenty-three females per group (control and treated) had live litters at day 20. There were no instances of total litter loss in any group. Pre-implantation loss and implantation rate (events determined prior to treatment) were comparable for both groups.

There were no treatment-related changes in the number of corpora lutea, number of distribution of live young, number and distribution of embryofoetal deaths, foetal weights, gravid uterine weights and sex ratio (as assessed by % males/litter) in the treated animals, compared with the control group.

There were 0/286 and 3/297 malformed foetuses (0/23 and 3/23 litters affected) in the control and 30 000 ppm groups, respectively. At 30 000 ppm, the mean percentage incidence of foetuses with supernumerary ribs was higher than in controls although the difference was not statistically significant. There was no obvious effect of treatment on the type and incidence of visceral anomalies.

The presence of supernumerary ribs is common in rat teratology studies. These effects in foetuses have been found to be reversible after birth (Wickramaratne, 1988). In the absence of any other skeletal or visceral abnormalities, HFE-7100 is not considered to have developmental effects under the conditions of the study.

7.11 Cardiac sensitisation study

HFE-7100 was evaluated for its potential to cause cardiac sensitisation to beagle dogs by nose-only inhalation (Huntingdon Life Sciences, 1996). A preliminary test was first conducted in 9 beagle dogs to determine the appropriate doses to be used for the Cardiac Sensitisation Study. The dogs were exposed by nose-only inhalation to air for 17 minutes, along with various concentrations of adrenaline (1-12 µg/kg) administered by intravenous injection, before and during inhalation. From the preliminary study, six dogs were selected and exposed to atmospheric concentrations of 1%, 2%, 5% and 10% v/v HFE-7100 in air, along with adrenaline concentrations of 1, 2, 4 and 12 µg/kg. The selected dogs represented each class of responders (weak, moderate and strong responders). All six animals were exposed separately and sequentially to the test substance (1%, 2% and 5% v/v) and 2 of the six animals were also exposed to 10% v/v of the test substance.

In dogs exposed to 10% v/v HFE-7100, general restlessness, cold extremities, limb rigidity, head and whole body tremors, head shaking, arched back, general state of agitation and salivation were observed. These clinical signs suggested that higher

exposures to the test substance would not be tolerated. Similar signs were seen in dogs exposed at 5% v/v but the signs were generally less severe. Positive evidence of cardiac sensitisation is indicated by the presence of multiple multifocal ectopic beats, or ventricular fibrillation, following adrenaline administration, during inhalation of the test substance. The absence of the above effects is indicative of a negative result. No cardiac sensitisation reactions were observed in any of the exposed groups. Results of the study indicate that HFE-7100 has no potential to cause cardiac sensitisation in beagle dogs.

Draft

8. Evaluation of Human Toxicological Data

8.1 Skin irritation (ND)

A Human Cumulative Irritancy Panel Test (HCIPT) was conducted to determine and compare the cumulative (Consumer Product Testing, 2005a).

A total of twenty-seven subjects, both male and female aged between 21 and 58 years participated in the study, Twenty-three participants completed the study, while the remaining discontinued due to personal reasons, unrelated to the study.

The upper back served as the treatment site. Approximately 0.2 mL of the test material MTDID 3519 = 3M™ Cosmetic Fluid CF-61 Lot# 20008, or an amount sufficient to cover the contact surface was applied on the 3/4" x 3/4" absorbent pads of adhesive dressing and applied to the treatment sites to form occlusive patches. The test material was applied to the treatment site from Monday to Friday to maintain twenty-one consecutive days of direct contact. Patches applied on Friday remained in place until the following Monday. Evaluation of the test sites was conducted prior to each patch application.

If a test site exhibited an evaluation score of '3' which indicated marked erythema, with possible oedema, then application of test material to this site was discontinued and an observed score of '3' was recorded for the remaining study days.

Observations conducted at the end of the study showed the total score was 2, with 2 subjects scoring of 0.5 each, and 1 subject with a score of 1. The total score was within the Cumulative Irritation Total (CIT) scoring system for scores ranging from 0-49 (Essentially no evidence of cumulative irritation under conditions of use). Results indicated that MTDID 3519 = 3M (TM) Cosmetic Fluid CF-61 Lot# 20008 did not have a clinically significant potential for cumulative dermal irritation.

8.2 Skin sensitisation (ND)

A Human Repeat Insult Patch Test (HRIPT) was conducted to determine by repetitive epidermal contact, the potential of the test material MTDID 3519 = 3M (TM) Cosmetic Fluid CF-61 Lot# 20008 to induce primary or cumulative irritation, and/or allergic contact sensitisation (Consumer Product Testing, 2005b).

Two hundred and twenty-four subjects, male and female aged between 16 and 79 years, participated in the study. Two hundred and ten subjects completed the study. The remainder discontinued for various reasons unrelated to the study. Approximately 0.2 mL, or an amount sufficient to cover the contact surface was applied on 3/4" x 3/4" absorbent pads of adhesive dressing to the upper back, between the scapulae, to form occlusive patches.

Induction phase

Patches were applied three times per week for a total of nine applications. The site was marked to ensure the continuity of patch application. Following supervised removal of the first induction patch, participants were instructed to remove all subsequent induction patches at home, 24 h after application. Evaluation of the test site was made prior to re-application. If a participant was unable to report on an assigned day, one make-up day was permitted which was added to the induction period.

Challenge phase

Approximately two weeks after the final induction patch application, a challenge patch was applied to a virgin test site adjacent to the original patch site, following the same procedure described for induction. The patch was removed and the site scored 24 and 72 h post application. No visible skin reaction was noted in any of the subjects throughout the test period. Results indicated that MTDID 3519 = 3M (TM) Cosmetic Fluid CF-61 Lot# 20008 did not cause dermal irritation or allergic contact sensitisation.

Draft

9. Hazard Classification

This section discusses the classification of the health effects of HFE-7100, according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). The NOHSC Approved Criteria are cited in the NOHSC National Model Regulations for the Control of Workplace Hazardous Substances (NOHSC, 1994) and provide mandatory criteria for determining whether a workplace chemical is hazardous.

The classification for health effects is based on experimental studies (animal, and in vitro and vivo tests). HFE-7100 was determined to be non-hazardous based on acute oral and inhalation toxicity, eye and skin irritation effects, sensitiser genotoxicity (in vitro and in vivo), and cardiac sensitisation data provided with the original submission.

HFE-7100 is not classified as a skin irritant or sensitiser based on new human data provided by the applicant.

The hazard classification for the new data (ND) provided for the Secondary Notification for chronic toxicity (28-day oral repeated dose and 13-week inhalation repeated dose toxicity), reproductive effects and developmental effects are presented below.

Classification of HFE-7100 in accordance with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (OECD, 2003) can be found in Appendix 2. This is provided for guidance only, is not mandatory and has no legal status at present.

9.1 Effects from repeated or prolonged exposure

According to the NOHSC Approved Criteria, a substance is classified as hazardous when substance-related deaths or serious damage (clear functional disturbances or morphological changes which have functional toxicological significance) are likely to be caused by repeated or prolonged exposure by an appropriate route.

In the 28-day repeat oral dose toxicity study, the differences in clinical observations, haematology, clinical chemistry, body weight and organ changes were either not dose-dependent, within the normal range or were resolved during the recovery period. These changes were therefore considered incidental. In males of the high dose group (1000 mg/kg bw), centrilobular hypertrophy of the hepatocytes and hypertrophy of the follicular cells in the thyroid were observed, which were regarded as adaptive changes. In addition, these effects were not observed in the recovery group, which suggest that this effect is reversible. The No Observed Effect Level (NOEL) was determined to be 200 mg/kg bw/d based on the absence of systemic toxicity or histopathological changes at this dose level.

In the 13-week (90-day) repeat inhalation dose toxicity study, isolated clinical signs were observed in rats exposed to HFE-7100 at the high dose group i.e. 15 000 ppm. A dose-related increase in total urinary flouride was observed in all treated groups, which indicated that HFE-7100 was metabolised. Hypertrophy of

centrilobular hepatocytes in both sexes, and statistically significant increases in relative liver weights and palmitoyl CoA oxidase activities were observed in males in the highest dose group. A No Observed Adverse Effect Level (NOAEL) of 7500 ppm was determined based on an increase in palmitoyl CoA activities (indicating peroxisome proliferation) observed at the highest dose.

Classification

HFE-7100 does not meet the NOHSC Approved Criteria (NOHSC, 2004) for danger of serious damage to health by prolonged exposure (R48)

9.2 Reproductive toxicity

According to the NOHSC Approved Criteria, reproductive toxicity includes impairment of male and female reproductive functions or capacity, and the induction of non-heritable harmful effects on the progeny. Reproductive toxicity may be classified as effects on male or female fertility and developmental toxicity.

9.2.1 Fertility

In the reproductive toxicity study in rats by inhalation exposure, no treatment related effects were observed during pre mating, mating, gestation and lactation periods. Fertility and reproductive performance in all test groups were comparable with the control group. Increased striation of the dentine of the upper incisors of rats in the mid (7500 ppm) and high (12 500 ppm) dose groups were observed. Striation of the dentine is due to the development of decalcification, which is a dentine damage caused by flourine compounds. The NOAEL for parental toxicity is 3000 ppm based on the presence of increased dentine striation at the higher doses (7500 ppm and 12 500 ppm).

Classification

HFE-7100 does not meet the Approved Criteria (NOHSC, 2004) for classification of substances that cause concern for human fertility (R62).

9.2.2 Developmental

In a developmental toxicity study in rats by inhalation exposure, there were no treatment related changes in any of the litter parameters, except for a non significant increase in incidence of foetuses with supernumerary ribs at 30 000 ppm. The presence of supernumerary ribs is a common observation in rat teratology studies and in the absence of any other skeletal or visceral abnormalities, the presence of supernumerary ribs is not considered to be a developmental effect under the conditions of the study. The NOAEL for development toxicity is 12 500 ppm.

Classification

HFE-7100 does not meet the Approved Criteria (NOHSC, 2004) for classification for developmental effects (R63).

10. Environmental Effects Assessment

The following ecotoxicity studies (Table 4) have been previously supplied by the applicant and is included here for completeness. The tests were carried out to OECD Test Methods.

Table 4: Ecotoxicity test results

Test	Species	Results (mg./L)
Acute Toxicity (S; N)	Fathead minnow (<i>Pimephales promelas</i>)	96 h LC50>7.9
Immobilisation (S; N)	Water Flea (<i>Daphnia magna</i>)	48 h EC50>10
Growth Inhibition (S; N)	Algae (<i>Selenastrum capricornutum</i>)	72h ErC50>8.9

Flow through; S=Static; N=Nominal Concentration.

To avoid volatilisation of the chemical, tests were performed in closed vessels with no head space.

During testing in fish, sub lethal effects (abnormal swimming behaviour) was observed. Over the test period, only 1.25% loss in concentration of the test substance occurred. One concentration only was tested, at the limit of solubility.

No sublethal effects were observed with *Daphnia*. An average of 29% loss in concentration of the test media (over three tested concentrations) occurred.

No observations were made during algal testing. Due to the restricted gas exchange situation because of the closed test vessel, the algae media was enriched with sodium bicarbonate to allow for algal growth. A glass marble was placed in each test chamber to aid in algal suspension.

While no sub lethal effects were observed with *Daphnia* and no observations were made during algae testing, the chemical may exhibit slight toxicity to fish, with a NOEC <7.9 ppm. The volatility of the chemical suggests any of the substance entering waterways will not remain long enough for toxic effects to occur.

11. Risk Characterisation

HFE-7100 is manufactured as a mixture of two inseparable isomeric chemicals with identical properties. A risk assessment of the mixture containing the two isomers was conducted, and not individual assessments of the isomers. The mixture is a clear colourless liquid. It has a high vapour pressure but is stable under highly acidic conditions.

The data provided in the original assessment indicated that HFE-7100 had very low acute oral and inhalation (based on analogue data) toxicity. The chemical was slightly irritating to the eyes and skin, but not a skin sensitiser. In a 28-day repeat dose inhalation study, there was no conclusive evidence that HFE-7100 was acting as a peroxisome proliferator. It is not genotoxic and has no potential to cause cardiac sensitisation.

HFBA, a major metabolite of HFE-7100 was identified as a convenient marker for HFE-7100 following intravenous administration. Dermal absorption of HFE-7100 is assumed to be <5% as no detectable levels of HFBA were found in the serum of rabbits following dermal application of multiple doses.

In a dermal absorption study, slight to severe dermal irritation, and a very slight dermal irritation were observed in the control and treated animals, respectively. At necropsy, thickened, tan-coloured, crusted skin, and multiple red to dark red areas on the test sites were observed in animals in the control group. These observations were not seen in the test group and the reason for the dermal irritation observed in the control group was not determined.

In a 13-week inhalation study, there was evidence that HFE-7100 acted as a peroxisome proliferator in males at the highest dose tested (15 000 ppm). However, since the effect was confined to males exposed to a very high dose and in the absence of other significant changes in the study, or any overt effects in other repeat dose studies, HFE-7100 is not expected to cause serious damage to health by prolonged exposure. It has no developmental or reproductive effects. HFE-7100 was determined to be non-hazardous.

In an HRIPT, 210 subjects were treated with the test material MTDID 3519 = 3M (TM) Cosmetic Fluid CF-61 Lot# 20008. No visible skin reactions were noted at the end of the Induction or Challenge phase in any of the subjects. Under conditions of the study, the test material did not indicate a potential for dermal irritation or allergic contact sensitisation.

In a 21-day HCIPT, 23 subjects were treated with the test material MTDID 3519 = 3M (TM) Cosmetic Fluid CF-61 Lot# 20008, for 21 days. A 21-day CIT Score was determined for each subject, and an irritation score obtained on a daily basis. At the end of the study the CIT was 2 with two subjects scoring 0.5 each and 1 subject with a score of 1. Based on the 'Generalised Interpretation of Scores' provided in the study, the CIT score of 2 was considered as 'essentially no evidence of cumulative irritation'. Under the conditions of the study, the test material did not indicate a clinically significant potential for cumulative dermal irritation.

11.1 Occupational

HFE-7100 will currently be imported in formulated cosmetic products and as raw material at a later stage, to be formulated into cosmetic products. The formulation process is largely automated but manual intervention may also be required.

Occupational exposure to HFE-7100 during transport and storage is low due to the handling of sealed packages. Similarly, distribution, warehouse and retail workers will also have low exposure as these workers will only handle sealed products. Risk of adverse effects during transport and storage of HFE-7100 is minimal as potential exposure to the chemical is unlikely or very low, except in cases of accidental spills.

11.1.1 Formulation into end use products

During formulation of HFE-7100 into cosmetic products, dermal contact and inhalation exposure are the most likely routes of exposure. Ocular exposure may also occur due to accidental splashes. Exposure to HFE-7100 during filling and packing into retail containers is expected to be minimal, as the filling operation is typically automated.

Although, HFE-7100 is considered a non-hazardous chemical any occupational risk due to dermal and inhalation exposure during the formulation process can be reduced by wearing appropriate PPE including gloves, and protective clothing and respiratory protection when handling the chemical. Local exhaust ventilation (LEV) during formulation will also minimise exposure and the risk of adverse effects.

11.1.2 End use products

Occupational exposure to end use products containing HFE-7100 may occur in sales people demonstrating the use of the product. The concentration of HFE-7100 in end use products is between 0.5% to 95%. While the products containing the chemical are likely to be used regularly, actual applications (eg. dermal and aerosol) will only normally occur via short intermittent applications. Therefore, the risk of adverse effects during this activity is likely to be low.

11.2 Public

It is expected that during import, transport, storage, and formulation of cosmetic products, exposure to the general public will be limited, except in the event of an accidental spill.

Cosmetic products containing HFE-7100 will be sold in the public domain, consequently there is potential for widespread public exposure. Skin contact with cosmetic products will be the main route of public exposure followed by inhalation for room/air freshener applications.

The risk to human health from exposure to HFE-7100 has been characterised using margin of exposure (MOE) methodology commonly adopted in international assessments (EC, 2003)

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. In deciding whether MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process, such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability.

11.2.1 Dermal

Consumer products containing HFE-7100 are in the form of lotions, creams, aerosol sprays, liquids, gels and soap bars. The risk for consumers would be mainly through the dermal route during application of these products. The risk is dependent on the amount used and the frequency of use of the different products. Since no Australian data on the typical amounts used per application, frequency of use and duration of contact of the different products used by consumers were available, Health Canada Cosmetic data were used (see Table 6.1). The MOE for dermal toxicity is based on the NOAEL of 200 mg/kg bw/d from a 28-day repeat-dose study in rats. Based on this NOAEL, the MOEs for fragrance use and for use of skin products were determined to be 1090 and 143 respectively.

11.2.2 Inhalation

The risk of inhalation exposure for consumers using room/air fresheners was determined from modelled data for cosmetic use, collected by the European Cosmetics and Toiletries Association (Colipa, 1997). No data were available for exposure during spraying of room/fresheners, therefore exposure data from deodorant sprays was used in the model. The main route of exposure is inhalation, therefore, the inhalation NOAEL of 7500 ppm (76 844 mg/m³) determined from a 13-week repeat-dose inhalation toxicity study in rats exposed for 6 h per day, was chosen for the risk characterisation. Assuming 100% absorption, the average body weight of a rat as 0.35 kg and a rat respiratory rate of 0.29 m³/day, (Derelanko MJ, 2000) the absorbed dose was determined as follows :

$$\begin{aligned} & \frac{76\,844\text{ mg/m}^3 \times 0.29\text{ m}^3/\text{day} \times 6\text{h}}{0.35\text{ kg} \times 24\text{ h}} \\ & = 15\,918\text{ mg/kg/d} \end{aligned}$$

Inhalation exposure for the public using room air fresheners determined from modelled data was 0.1445 mg/kg/d. Based on the NOAEL of 15 918, the margin of exposure (MOE) was as follows:

$$\begin{aligned} \text{Margin of exposure} &= \frac{15\,918\text{ mg/kg/d}}{0.1445} = 110\,157 \end{aligned}$$

Since the MOE for consumers was >100 000, it is determined that there is no risk of adverse health effects from this route of exposure.

11.3 Environmental

When released, the chemical is expected to partition almost entirely to the atmosphere. It has an expected lifetime in the atmosphere of 4-5 years, which is far lower than for many other solvents and greenhouse gases. The chemical will degrade through a series of atmospheric reactions to give polar perfluorinated species such as the C4 and lower perfluorinated carboxylic acids (PFCAs), TFA, perfluorinated alcohols and COF₂. These are expected to be removed from the atmosphere through precipitation (von Sydow, 2000).

The applicant suggests that one of the breakdown pathways of the branched isomer of the notified chemical leads to the formation of trifluoroacetic acid (TFA). This chemical is extremely stable in the environment and has been shown to be ubiquitous in precipitation; detected in samples of rain from Ireland and Poland and snow from Canada, Sweden, New Zealand and East Antarctica (von Sydow et al. 2000). These authors also noted that there was some evidence to suggest that TFA is also derived from natural sources. TFA has also been widely found in ocean waters (Scott et al. 2005, Frank et al. 2002).

While PFCAs are also stable, they are widespread contaminants and have been detected in arctic seals, whales and birds. These have largely been the 9-15 carbon chain length acids. Perfluorobutanoic acid does not appear to have been found in biota to date.

Perfluorooctanoic acid (PFOA) has also not been found to be a major contaminant, as this is rapidly and nearly completely eliminated in urine. The lack of detection of the lower homologues is attributed by Verreault et al (2005) to "a comparable high depuration and excretion rate, and perhaps also low bioavailability, bioaccumulation potential and exposure, as a result of low environmental concentrations".

The chemical has an ozone depletion potential (ODP) of zero (US EPA 2005).

Its global warming potential (GWP) is rated as 1300 on a 20 year time horizon, 390 on a 100 year time horizon and 120 on a 500 year time horizon (ie, a radiative forcing of 1300, 480 and 120 times that of carbon dioxide on 20, 100 and 500 year time horizons respectively). The drop in GWP with increasing time horizons reflect the relatively short atmospheric lifetime. In the worst case, assuming that 4.2 tonnes of the notified chemical are used and released to the atmosphere each year in Australia, when averaged over a 20 year period this is roughly equivalent to the effect of releasing $4.2 \times 1300 = 5460$ tonnes of CO₂. To put this emissions in perspective, in 2003 the Australian greenhouse gas emissions amounted to the equivalent of 550×10^6 tonnes of carbon dioxide (AGEIS 2005). Therefore, the contribution to greenhouse gases from the introduction of the chemical for the proposed use will be equivalent to less than 0.001% of the current emissions.

Additionally, this chemical will be used to replace ozone depleting substances which are likely to exhibit longer atmospheric lifetimes and higher global warming potentials. The environmental risk resulting from the use of this chemical is rated as low.

Hydrofluoroethers are approved by the US EPA as they are not ozone-depleting, offer reduced lifetimes compared to perfluorocarbons and are generally minimally toxic (US EPA 2005). However, the chemical contains a perfluorinated moiety which has been identified as a potential source of short chain PFCAs in the environment. It is likely that degradation of the chemical will result in the release of degradation products that will ultimately contribute to this PFCA load in the environment. It is likely that the ultimate degradation products will include C4 perfluorobutanoic acids and TFA. The latter is already a widespread contaminant around the globe and the contribution from this source is likely to be low. By contrast there is little information about environmental levels of C3 and C4 perfluoroalkyl acids, alcohols or related substances. However, available literature indicates that C7 perfluoroalkyl acids and below such compounds are not expected to bioaccumulate but will be persistent and spread across the world.

Draft

12. Discussion and Conclusions

HFE-7100 is not currently manufactured or formulated in Australia. HFE-7100 is used as a solvent/solvent carrier and will be imported as a formulated product for use as fragrances, personal body care products, and room aerosols in varying concentrations. The concentration of the chemical in cosmetic preparations will range from 1% to 95%. The products will be packaged in plastic and glass containers and distributed for sale. In the future, HFE-7100 will be imported as raw material in 200 L metal drums for formulation into cosmetic products.

HFE-7100 is a clear colourless liquid with a boiling point of 58°C, water solubility of 8.47 mg/L @ 20°C, and vapour pressure of 27.736 kPa@25°C.

Health hazards

HFE-7100 has very low acute oral toxicity (LD50 >5000 mg/kg bw). An acute dermal toxicity study was not performed. An acute inhalation study in rats was conducted on a chemical analogue, perfluorobutyl methyl ether. Based on the results of this study, it was determined that HFE-7100 has low acute toxicity by inhalation. It is not an eye or skin irritant, and is not a skin sensitiser. In a 28-day oral repeated-dose toxicity study in rats, the No Observed Adverse Effect Level was identified as 200 mg/kg bw/d based on the absence of systemic toxicity or histopathological effects at this level. In a 13-week repeat dose inhalation toxicity study in rats, the No Observed Adverse Effect Level (NOAEL) was determined to be 7500 ppm based on an increase in palmitoyl CoA oxidase activities at the higher dose. Although there were statistically significant macroscopic weight increases in the liver, spleen and kidneys, no histopathological findings were detected that could explain the organ weight changes in the spleen and kidneys. The histopathological change seen in the liver consisted of minor degrees of centrilobular hepatocyte hypertrophy. This finding is not uncommon and is considered associated with metabolic processing within the liver. HFE-7100 was not determined to be genotoxic based on in vitro and in vivo assays. No reproductive effects were noted in an inhalatory one-generation study conducted with HFE-7100. In a developmental study, the mean percentage incidence of foetuses with supernumerary ribs was higher than in controls, although the difference was not statistically significant. However, the occurrence of supernumerary ribs is a common observation in rat teratology studies, besides these effects in foetuses have been found to be reversible after birth. In the absence of any other skeletal or visceral abnormalities, the presence of supernumerary ribs is not considered to be a developmental effect.

HFE-7100 is not classified as a hazardous chemical according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). HFE-7100 is not classified as hazardous according to the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (OECD, 2002). This system is not mandated in Australia and carries no legal status.

HFE-7100 is not listed in the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (FORS, 1998).

Environmental hazard and risk

No sublethal effects were observed with *Daphnia*, however, the chemical may exhibit slight toxicity to fish with a NOAEC of <7.9 ppm. The volatility of the chemical suggests that any of the chemical entering waterways will not remain long enough for toxic effects to occur.

HFE-7100 when used in cosmetic products is not expected to be a risk to the aquatic or soil environmental compartments, but will effectively contribute in minimal amounts to Australia's greenhouse gas emissions and probably contribute in a similar amount to the global pool of short chain PFCAs.

Occupational risk

Occupational exposure to the formulated product, or the raw material is likely during packaging, dispensing, transport or cleaning up in the event of an accident or spill. There is potential for exposure to the raw material during the formulation process. Exposure for end users is likely when the sales staff demonstrate the use of the product. During formulation, dermal contact and inhalation exposure are the most likely routes of exposure. Although HFE-7100 is a non-hazardous chemical, exposure to the chemical can be reduced by the use of PPE. Risk of adverse effects during occupational use is considered to be low.

Public risk

Consumer products containing HFE-7100 will be available in the form of lotions, creams, liquid or gel. It will also be available as soap bars or aerosol room fresheners. Public exposure to the chemical is anticipated as it will be used Australia-wide. Skin exposure will be the main route of exposure followed by inhalation exposure for room air fresheners. Following the assessment of consumer exposure for the various cosmetic products and room air fresheners, the risk was found to be very low, and no specific risk management actions are required for consumer protection.

13. Recommendations

This section provides the recommendations arising from the assessment of HFE-7100. Recommendations are directed principally at regulatory bodies and importers and formulators of HFE-7100. Implicit in these recommendations is that best practice is implemented to minimise occupational and public exposure and environmental impact.

13.1 Recommendations to importers and State and Territory Authorities

13.1.1 Hazard communication – Material Safety Data Sheet (MSDS)

Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994) and the Commonwealth, State and Territory regulations introduced in accordance with these national model regulations, employees shall have ready access to MSDS for hazardous substances at their workplace.

Although HFE-7100 is not classified as a hazardous substance and there is no legal requirement to provide an MSDS, it is good practice to do so, as an MSDS is a well-accepted and effective method for the provision of workplace information.

13.2 Recommendation to importers and users

13.2.1 Occupational controls

The risk of adverse effects for occupational use of HFE-7100 is low. The control measures for HFE-7100 are as follows:

Avoidance of spillage and splashing of the chemical. Spillages and splashes should be cleaned up promptly using chemical-resistant impervious gloves.

If engineering controls and safe work practices are insufficient to reduce exposure, during the formulation process, employers should ensure that PPE such as gloves and overalls are used by workers to minimise occupational exposure. The PPE used should be in accordance with Australian, Australian/New Zealand or other approved standards.

The use of LEV is recommended during the formulation of cosmetic products from the raw material.

13.2.2 Disposal

Accidental leaks and spillages should be cleaned up promptly with absorbents and put into containers for disposal. The empty drums and their residues should be disposed in accordance with government regulations.

14. Secondary Notification

Under Section 65 of the Act, the Secondary Notification of HFE-7100 may be required where an applicant or other importer or manufacturer of HFE-7100, becomes aware of any circumstances that may warrant a reassessment of its hazards and risks. Specific circumstances include:

- a. Manufacture of HFE-7100 has begun, or is likely to begin in Australia.
- b. Additional information has become available on the adverse health and/or environmental effects of HFE-7100.
- c. The use of HFE-7100 has changed, or is likely to change significantly.
- d. The amount of HFE-7100 introduced into Australia has increased, or is likely to increase significantly.

The Director must be notified within 28 days of the introducer becoming aware of any of the above circumstances.

Draft

Appendix 1

Calculation of inhalation exposure for consumers exposed to room air fresheners

The concentration in air after using a certain amount of the room air freshener was determined from the following equation:

$$C_{inh} = \frac{Q_{prod} \times FC_{prod}}{V_{room}}$$

where C_{inh} is the concentration in the room air, Q_{prod} the amount of product used per room, FC_{prod} the percentage of substance in the product, and V_{room} the room volume.

$$\begin{aligned} C_{inh} &= \frac{3000 \text{ mg} \times 70\%}{58 \text{ m}^3} \\ &= 36.2 \text{ mg/m}^3 \end{aligned}$$

Since no data were available for the amount of air freshener used per room (Q_{prod}), data for a typical amount of deodorant spray used per application (3 g) from the EU Technical Guidance Document on Risk Assessment, Part 1 was used in the equation. The value of 70% (FC_{prod}) was the highest concentration available for room air fresheners, and 58 m^3 (V_{room}) the room volume (living), taken from the Netherlands data published in the Technical Guidance Document on Risk Assessment, Part 1.

The inhalatory uptake of the chemical (I_{inh}) based on the concentration in the room air is determined from the following equation :

$$I_{inh} = \frac{F_{resp} \times C_{inh} \times I_{H_{air}} \times T_{contact} \times n}{BW}$$

where I_{inh} is the inhalatory uptake of substance, F_{resp} the respirable fraction of inhaled substance, C_{inh} is the concentration in the room air, $I_{H_{air}}$, the ventilation rate of the person, $T_{contact}$ duration of contact per event, n mean number of events per day and BW the body weight.

$$\begin{aligned} I_{inh} &= \frac{1 \times 36.2 \text{ mg/m}^3 \times 23 \text{ mg/m}^3 \times 0.25 \times 1}{60 \text{ kg} \times 24\text{h}} \\ &= 0.1445 \text{ mg/kg/d} \end{aligned}$$

The respirable fraction (F_{resp}) is 1 (assuming 100% absorption) air concentration (C_{inh}) of 36.2 mg/m^3 , a ventilation rate of 23 mg/m^3 (enHEALTH, 2002), duration per application assumed to be 15 min, and the number of events per day (n) estimated as 1, taken from the data collected by Colipa (EC, 2003), as no data were available for room air fresheners.

Appendix 2

Classification under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

HFE-7100 is not classified as a hazardous substance in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (OECD, 2003). This system of classification will come into force when the GHS is adopted by the Australian Government and promulgated into Commonwealth legislation. GHS documentation is available at:

<http://www.unece.org/trans/danger/danger.htm>

Draft

Appendix 3

This MSDS was provided by 3M Australia Pty Ltd. It is reproduced here as a matter of public record. The format of this MSDS is acceptable under the NOHSC's *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 2003). The accuracy of this information remains the responsibility of the applicant.

3M AUSTRALIA PTY LIMITED
950 Pacific Highway
Pymble NSW 2073
Phone: 136 136

24HR EMERGENCY: 1800 097 146 (Australia only)

3M NEW ZEALAND LTD
250 Archers Road
Glenfield Auckland N.Z.
Phone: (9) 444 4760

MATERIAL SAFETY DATA SHEET

Document ID : 16-3761-0 Issue date : 16/11/2004
Version : 2.02 Supersedes date : 2/11/2004
Document status : Issued

This MSDS has been prepared by 3M Australia Pty Ltd Toxicology Dept.

1 PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME
3M (TM) COSMETIC FLUID CF-61

DIVISION
BI - 3M Specialty Materials

3M Product ID
98-0212-2982-2 98-0212-2983-0 98-0212-2984-8 98-0212-2985-5
98-0212-3050-7 98-0212-3218-0 98-0212-3232-1

RECOMMENDED USE: For industrial use only. Not intended for use as a medical device or drug. Specific use - Cosmetic fluid

2 HAZARDS IDENTIFICATION

NOTE: Not classified as Hazardous according to criteria of NOHSC Australia.

R Codes: 53

Risk Phrases: May cause long-term adverse effects in the aquatic environment.

S Codes: 51-61

Safety Phrases: Use only in well ventilated areas. Avoid release to the environment. Refer to special instructions/safety data sheets.

3 COMPOSITION

Ingredient Name	CAS number	Percentage
METHYL NONAFLUOROISOBUTYL ETHER	163702-08-7	20 - 80
METHYL NONAFLUOROBUTYL ETHER	163702-07-6	20 - 80

4 FIRST AID MEASURES

EYE CONTACT

Flush eyes with large amounts of water. If signs/symptoms persist, get medical attention.

SKIN CONTACT

Wash affected area with soap and water. If signs/symptoms develop, get medical attention.

INHALATION

If signs/symptoms develop, remove person to fresh air. If signs/symptoms persist, get medical attention.

IF SWALLOWED

No need for first aid is anticipated.

5 FIRE FIGHTING MEASURES

FIRE FIGHTING PROCEDURES

Water may be used to blanket the fire. Wear full protective equipment (Turnout Gear) and a self-contained breathing apparatus (SCBA). No unusual effects are anticipated during fire extinguishing operations. Avoid breathing the products and substances that may result from the thermal decomposition of the product or the other substances in the fire zone. Keep containers cool with water spray when exposed to fire to avoid rupture.

6 ACCIDENTAL RELEASE MEASURES (SPILL)

Personal Precautions

Observe precautions from other sections of this Material Safety Data Sheet.

Spill Response

Working from around the edges of the spill inward, cover with commercially available absorbent material until it appears dry. Seal the container. Evacuate unprotected and untrained personnel from hazard area. The spill should be cleaned up by qualified personnel. Ventilate area with fresh air. Contain spill. Collect as much of the spilled material as possible. Clean up residue with an appropriate organic solvent. Read and follow safety precautions on the solvent label and MSDS. Place in a metal container. Dispose of collected material as soon as possible.

7 HANDLING AND STORAGE

Precautions for Safe Handling

Contents may be under pressure, open carefully. Keep container tightly closed when not in use. For industrial or professional use only. No smoking: Smoking while using this product can result in contamination of the tobacco and/or smoke and lead to the formation of the hazardous decomposition products mentioned in Section 11 of this MSDS. Avoid continuous exposure of the material to extreme conditions of heat, ie, above 150C (welding, open flame, misuse or equipment failure). Avoid exceeding a watt density of 50 watts/inch² from a heater surface. Continuous exposure to 150C results in very slight decomposition of this product, therefore, is a very conservative use temperature threshold. Applications involving exposure of the fluid to temperatures exceeding 150C or watt densities exceeding 50 watts/inch² have been safety implemented. Applications may exceed these use parameters should be reviewed with 3M Technical Service.

Conditions for Safe Storage

Store away from strong bases.

Incompatibility - Materials to Avoid

Store away from heat.

8 EXPOSURE CONTROLS/PERSONAL PROTECTION

Special Information, Exposure/Protection

The extent to which the following recommendations for exposure control and protection are observed should depend on the risk assessment undertaken for the specific conditions under which this product is used, including occupational hygiene measurements.

Recommended Ventilation

If appropriate, use local exhaust ventilation. Provide appropriate local exhaust ventilation at transfer points. Provide appropriate local exhaust when product is heated. For those situations where the fluid might be exposed to extreme overheating due to misuse or equipment failure, use with appropriate local exhaust ventilation sufficient to maintain levels of thermal decomposition products below their exposure guidelines. Use general dilution ventilation and/or local exhaust ventilation to control airborne exposures to below Occupational Exposure Limits. If ventilation is not adequate, use respiratory protection equipment.

Eye Protection

Keep out of eyes. During operations in which eye exposure is likely, the following should be worn alone, or in combination, as appropriate: Safety glasses with side shields. Eye protection should comply with AS/NZS1337.

Skin Protection

Gloves not normally required.

Respiratory Protection

Under normal use conditions, airborne exposures are not expected to be significant enough to require respiratory protection. If thermal degradation products are expected, use fullface supplied air respirator.

Prevention of Accidental Ingestion

Do not eat, drink or smoke when using this product. Wash your hands thoroughly with soap and water after product use and before eating or smoking.

9 PHYSICAL/CHEMICAL PROPERTIES

Appearance and Odour	Clear, colourless liquid; slight ethereal odour
pH	Not applicable
Vapour pressure	202 mmHg @ 25C
Vapour density	8.6 (Air=1)
Boiling point	61 C @ 760mmHg
Melting point	-135 C
Water Solubility	<12 ppm
Specific gravity	1.5
Flash point	Not applicable
Flammable Limits - LEL	None
Flammable Limits - UEL	None
Autoignition temperature	405 C (ASTM E659-84)
Volatile organic compounds (VOC) content	Exempt
Evaporation rate	49 (Air=1)
Viscosity	0.6 centipoise @ 23C

10 STABILITY AND REACTIVITY**Stability**

Hazardous polymerisation will not occur. Stable.

Materials to Avoid

Strong bases.

Hazardous Decomposition Products

Hydrogen fluoride at elevated temperatures. Perfluoroisobutylene (PFIB) at elevated temperatures. Perfluorinated Acid Fluorides (PFIB) at elevated temperatures. Perfluorinated Acid Fluorides (PFIB) has a NOHSC Threshold Limit Value of 3 ppm (as fluoride). The odour threshold for HF is 0.04ppm, provided good warning properties for exposure. Decomposition of this product at temperatures above 300C can form perfluoroisobutylene (PFIB), but PFIB will only accumulate with continuous exposure to excessive heat in a sealed vessel. The formation rate for PFIB is about 1000 times less than the rate for primary thermal decomposition products such as HF. During normal use conditions, no health hazard is associated with the use of this material due to PFIB exposure.

11 TOXICOLOGICAL INFORMATION

Effects from Eye Contact

Contact with the eyes during product use is not expected to result in significant irritation.

Effects from Skin Contact

Contact with the skin during product use is not expected to result in significant irritation.

Effects from Inhalation

Vapours from heated material may cause respiratory system irritation. Signs/symptoms may include cough, sneezing, nasal discharge, hoarseness, wheezing, breathing difficulty, nose and throat pain, coughing up blood, and nonrespiratory effects such as painful and watery eyes. If thermal decomposition occurs: illness may occur after a single overexposure by inhalation to relatively large quantities of this material.

Effects from Ingestion

No adverse health effects are expected from swallowing.

12 ECOLOGICAL INFORMATION

Ecotoxicity Data

This substance has chemical moieties that are resistant to biodegradation and is likely to only undergo partial biodegradation in the environment. The high potential of this substance to move from water to the atmosphere means its potential to bioconcentrate is likely to disappear rapidly from aerobic environments. Take precautions to prevent direct release of this product to the environment.

AQUATIC TOXICITY

Testing results indicate that this product has insignificant toxicity to aquatic organisms at its saturation point (Lowest LC50, EC50 or IC50 > substance water solubility). This substance is highly volatile and has a high Henry's Law constant and is thus expected to move rapidly through vaporisation from solution

 in an aquatic compartment or from a soil surface in a terrestrial compartment to the atmosphere.

ATMOSPHERIC FATE

Zero Ozone Depletion Potential (ODP).
 Atmospheric Lifetime: approximately 4.7 yr and 3.7 yr for n-butyl and isobutyl isomers, respectively. Global Warming Potential (GWP): 320 (100 year ITH, WMO 1998 method). Atmospheric degradation products are expected to include: for methyl nonafluoroisobutyl ether: predominantly iso-perfluorobutyric acid, CO₂, HF, and perhaps also CF₃COOH; for methyl nonafluorobutyl ether; n-perfluorobutyric acid, CO₂, and HF.

Persistence/Biodegradability

This substance has chemical moieties that are resistant to biodegradation and is likely to only undergo partial biodegradation in the environment.

Environmental Data
 Not determined

----- 13 DISPOSAL CONSIDERATIONS -----

Disposal methods

To reclaim or return, check product label for contact. As a disposal alternative, incinerate in an industrial or commercial facility in the presence of a combustible material. Combustion products will include HF. Facility must be capable of handling halogenated materials.

Potential for Recycling
 Reclaim if feasible.

----- 14 TRANSPORT INFORMATION -----

ADG (Road/Rail)

UN NUMBER	NONE ALLOCATED
PROPER SHIPPING NAME	NONE ALLOCATED
DANGEROUS GOODS CLASS	NONE ALLOCATED
SUBSIDIARY RISK	NONE ALLOCATED
PACKING GROUP	NONE ALLOCATED
IATA (Airfreight)	

UN NUMBER	NONE ALLOCATED
PROPER SHIPPING NAME	NONE ALLOCATED
DANGEROUS GOODS CLASS	NONE ALLOCATED
SUBSIDIARY RISK	NONE ALLOCATED
PACKING GROUP	NONE ALLOCATED

IMO (Seafreight)

UN NUMBER	NONE ALLOCATED
PROPER SHIPPING NAME	NONE ALLOCATED
DANGEROUS GOODS CLASS	NONE ALLOCATED
SUBSIDIARY RISK	NONE ALLOCATED
PACKING GROUP	NONE ALLOCATED

15 REGULATORY INFORMATION

Product Certifications
AICS - Yes

16 OTHER INFORMATION

REASON FOR REISSUE

21/11/03 Added new information to hazardous decomposition products section.

2/11/04 This MSDS has been revised because 3M has adopted the 16-section ANSI/ISO format. The potential hazards of the product have not changed. We encourage you to re-read the MSDS and review the information.

16/11/04 Updated safety phrases.

The information on this data sheet represents our current data and best opinion as to the proper use in handling of this product under normal conditions. Any use of the product which is not in conformance with this data sheet, which involves using the product, or otherwise that in accordance with instructions of use on product packaging is the responsibility of the user. If clarification or further information is needed to ensure that an appropriate risk assessment can be made, the user should contact the Snr Regulatory Services Officer on (02) 9677-5179.

References

3M Environmental Technology & Services (1996a) A Single-dose Intravenous Pharmacokinetic Study of T-6334 in Rabbits: Final Report-Analytical Study (Study No.: AMDT-040996.1, 18 Dec 1996). St. Paul, MN, 3M Environmental Laboratory. (Unpublished report submitted by 3M).

3M Environmental Technology & Services (1996b) A 5-Daily Dose Dermal Absorption Study of T-6334 in Rabbits – Final Report-Analytical Study (Study Number: AMDT-073096.1). St. Paul, MN, 3M Environmental Laboratory. (Unpublished report submitted by 3M).

AGEIS (2005) Australian Greenhouse Emissions Information System. Australian Government Department of Environment and Heritage, Australian Greenhouse Office, Parkes, ACT. <http://www.greenhouse.gov.au/inventory> , Accessed 2006 Jun 21.

FORS (1998) Australian Code for the Transport of Dangerous Goods by Road and Rail, 6th ed. Canberra, ACT, Federal Office of Road Safety, Australian Government Publishing Service.

Capen CC, DeLellis RA & Yarrington JT (1991) In: Haschek W, & Rousseaux C ed. Handbook of Toxicologic Pathology, San Diego, Academic Press, pp 723-725.

Chen L, Kutsuna S, Tokuhasi K & Sekiya A (2004) Kinetics study of the gas-phase reactions of C₂F₅OC(O)H and n-C₃F₇OC(O)H with OH radicals at 253-328 K, Chem.Phys.Lett., **400**: 563-568.

Citron, M(1995) Perplexing Peroxisome Proliferators, Environ Health Perspect, **103**(3): 103-3

COLIPA (1987) European Cosmetics and Perfumary Association. Current website: <http://www.colipa.com/site/index.cfm?SID=15588> , Accessed 2006 Jun 21.

Consumer Product Testing Co (2005a) 21-Day Cumulative Irritation Patch Test, Protocol No. TCLX02-007 (Experiment Reference No.: C05-0815.01-.04. 3M Study ID: 05-158, 7 Nov 2005). Fairfield, NJ, Consumer Product Testing Company Incorporated, 3M Medical Department. (Unpublished study submitted by 3M).

Consumer Product Testing Co (2005b) Repeated Insult Patch Test, Protocol No. TCLX02-006 (Experiment Reference No.: C05-0817.02, 3M Study ID: 05-157, 1 Dec 2005). Fairfield, NJ, Consumer Product Testing Company Incorporated, 3M Medical Department. (Unpublished study submitted by 3M).

Corning Hazelton Inc (1996) Dermal Sensitization Study of T-6334 in Guinea pigs – Closed Patch Technique (EPA Guidelines), (Project No. CHW 50904621, 25 Jan 1996). Madison, WI, Corning Hazelton Incorporated, 3M. (Unpublished study submitted by 3M).

Derelanko MJ & MA. Hollinger, ed. (2000) Toxicologist's Pocket Handbook. Boca Raton, CRC Press.

Environmental Health Risk Assessment (enHEALTH) (June 2002) Guidelines for assessing health risks from environmental hazards. Canberra, Department of Health and Ageing and enHEALTH Council.

European Commission (2003) European Chemical Bureau's Technical Guidance Document on Risk Assessment. Luxembourg, European Commission-Joint Research Centre, Institute for Health and Consumer Protection, European Chemicals Bureau (ECB).

Frank H, Christoph EH, Holm-Hansen O & Bullister JL (2002) Trifluoroacetate in ocean waters, *Environ Sci Technol*, **36**(1): 12-50.

Hazelton Wisconsin, Inc. (1993) Primary Eye Irritation/Corrosion Study of T-6334 (OECD Guidelines) in Rabbits (Project No. HWI 50904620, 9 Nov 1995). Madison, WI, Hazelton Wisconsin Incorporated (Unpublished report submitted by 3M).

Hazelton Wisconsin Inc. (1995a) Acute Oral Toxicity Study of T-6334 in Rats (OECD Guidelines) (Project No. HWI 50904618, 8 Dec 1995). Madison, WI, Hazelton Wisconsin Incorporated (Unpublished report submitted by 3M).

Hazelton Wisconsin Inc. (1995b) Primary Dermal Irritation/Corrosion Study of T-6334 in Rabbits (Project No. 50904619, 9 Nov 1995). Madison, WI, Hazelton Wisconsin Incorporated (Unpublished report submitted by 3M).

Huntingdon Life Sciences Ltd (1996) A 13-Week Repeat Dose Inhalation Toxicity Study in Rats (Project No.: MIN 196/961181, 28 Nov 1996). Huntingdon, Cambridgeshire, Huntingdon Life Sciences Limited, 3M Toxicological Services (Unpublished report submitted by 3M).

Huntingdon Life Sciences Ltd (1996) A 28-Day Repeat Dose Inhalation Toxicity Study in Rats. (Project No.: MIN 181/952688 3 Apr 1996). Huntingdon Cambridgeshire, Huntingdon Life Sciences Limited, 3M Toxicological Services (Unpublished report submitted by 3M).

Huntingdon Life Sciences Ltd (1996) Assessment of Cardiac Sensitisation Potential in Dogs (Project No.: MIN 182/953117 17 Apr 1996). Huntingdon, Cambridgeshire, Huntingdon Life Sciences Limited, 3M Toxicological Services (Unpublished report submitted by 3M).

Huntingdon Life Sciences Ltd (1996) Mouse Micronucleus Test (Project No.: MIN 195/960755) Huntingdon, Cambridgeshire, Huntingdon Life Sciences Limited, 3M Toxicological Services (Unpublished report submitted by 3M).

Huntingdon Life Sciences Ltd (1998) A Study for Effects on Embryofoetal Development of the Rat (Inhalation Administration) (Project No.: MIN 236/971252, 10 Mar 1998). Huntingdon, Cambridgeshire, Huntingdon Life Sciences Limited, 3M Toxicological Services (Unpublished report submitted by 3M).

IPCC (2001) Technical Summary: C1. Observed Changes in Globally Well-Mixed Greenhouse Gas Concentrations and Radiative Forcing. In: *Climate Change 2001: Working Group 1: The Scientific Basis*. Boulder, Intergovernmental Panel on Climate Change. http://www.grida.no/climate/ipcc_tar/wg1/016.htm, Accessed on 2006 Jun 21.

IRDC (1995) Nose Only Acute Inhalation Toxicity Evaluation on T-6101 in Rats (Project no. 137-177, 26 Jun 1995). Mattawan MI, International Research & Development Corporation, 3M Company. (Unpublished report submitted by 3M).

Jarzynka W, Put A & Ceglecka M (1990) Micromorphology of dentine in rats with chronic exposure to ammonium fluoride. *CZAS Stomatol.* **43** (5): 255-60. (abstract only accessed through Pub Med).

McLaughlin A (2004) *Cosmetics Exposure Workbook*, Environmental Assessment Unit/New Substances Assessment and Control Bureau (EAU/NSCAB), Health Canada. (personal communication).

Mitsubishi Chemical Safety Institute (1996) Toxicity Study of T-6334 by Oral Administration to Rats for 28 days, (Study No. 5L587, 15 May 1996). Minato-ku, Tokyo. Sumitomo 3M Limited. (Unpublished report submitted by 3M)

NOHSC (1999) List of Designated Hazardous Substances[NOHSC:10005(1999)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

NOHSC (1994) Control of Workplaces Hazardous Substances. National Model Regulations for the Control of Workplace Hazardous Substances [NOHSC:1005(1994)], National Code of Practice for the Control of Workplace Hazardous Substances [NOHSC:2007 (1994)]. Canberra., ACT, Australian Government Publishing Service.

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission. <http://www.nohsc.gov.au/PDF/Standards/MSDSCodeNOHSC20112003.pdf> Accessed 2006 Jun 22.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)] 3rd edition. National Occupational Health and Safety Commission. http://www.nohsc.gov.au/PDF/Standards/approved_criteriaNOHSC1008_2004.pdf Accessed 2006 Jun 22.

OECD (2003) Amendment to the GHS. Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals. Third Session, 10-12 July, 2002. UN/SCGHS/3/INF.16 Prepared as Annex 3 of OECD Document ST/SG/AC.10/C.4/2001/26. Paris, Organisation for Economic Cooperation and Development, 6 pp.

Samson PJ (2006) Global Warming Potential of Greenhouse Gases and the Energy (Im)Balance of Our Current Atmosphere. In: University of Michigan, Global Change 1 lectures. http://www.globalchange.umich.edu/globalchange1/current/lectures/samson/global_warming_potential/ Accessed 2006 Jun 22

Scott BF, Macdonald RW, Kannan K, Fisk A, Witter A, Yamashita N, Durham L, Spencer C & Muir DC (2005) Trifluoroacetate profiles in the Arctic, Atlantic, and Pacific Oceans. *Environ Sci Technol*, **39**(17): 6555-60.

SCCNFP (2003). Opinion concerning Diethyl Phthalate, adopted by the SCCNFP during the 26th Plenary Meeting of 9 December 2003. (SCCNFP/0767/03). Brussels, The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers, 7pp.

TNO Nutrition and Food Research (2003) Inhalatory one-generation reproduction study with T-6334 in rats (TNO Report: V 4367, 14 Apr 2003) Utrechtsweg 48, Zeist, NL TNO Nutrition and Food Research Institute, 3 M Corporate Toxicology (Unpublished report submitted by 3M)

US EPA (2005) Protection of Stratospheric Ozone: Notice 16 for Significant New Alternatives Policy Program. United States Environmental Protection Agency. <http://www.epa.gov/fedrgstr/EPA-AIR/2002/March/Day-22/a6848.htm> Accessed 2006 Jun 22

Verreault J, Houde M, Gabrielsen GW, Berger U, Haukas M, Letcher RJ & Muir DCG (2005) Perfluorinated Alkyl Substances in the Plasma, Liver, Brain and Eggs of Glaucous Gulls (*Larus hyperboreus*) from the Norwegian Arctic. Environ. Sci. Technol, **39**(19): 7439-7445.

von Sydow, LM, Grimvall, AB, Borén, HB, Laniewski, K, & Nielsen, AT (2000). Natural background levels of trifluoroacetate in rain and snow. Environ. Sci. Technol. **34**(15): 3115-3118.

Christensen LK, Sehested Jnielsen OJ, Bilde M, Wallington TJ, Guschin A Molina LT & Molina MJ (1998) Atmospheric chemistry of HFE-7100 (C₄F₉OCH₃) - reaction with OH radicals, UV spectra and kinetic data for C₄F₉OCH₂· and C₄F₉CH₂O₂· radicals, and the atmospheric fate of C₄F₉OCH₂O· radicals. J. Phys. Chem. A **102**: 8264-8274

Draft