The extensive toxicology data behind alternative short-chain fluorinated product technology

SOT RASS-MISS Webinar
9 December 2015

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Summary

• Fluorinated surfactants and polymers are valuable technologies with unique and important societal and product life-cycle benefits.

• Global manufacturers are rapidly moving from long-chain to alternative (e.g., short-chain) technologies.
  – Regulators are approving manufacture and use
  – Toxicological and environmental properties along the product life cycle need to be understood.

• Chemours has developed comprehensive toxicological data for short-chain fluorotelomer-based Products, Raw Materials and Degradation Products.
  – Rapid elimination from living systems is a key attribute
  – Each has unique toxicological endpoints – *product toxicology is different from raw material which is different from degradation product*

• Risk characterization shows large margins of exposure for 6:2 FTOH and PFHxA
Presentation Outline

• Background
• Alternatives Assessment
• Hazard Assessment
  – toxicological data for short-chain fluorotelomer-based products, raw materials and degradation product.
• Risk Characterization – Margin of Exposure
• Summary
Perfluoroalkyl and Polyfluoroalkyl Substances in the Environment: Terminology, Classification, and Origins

http://dx.doi.org/10.1002/ieam.258

Open Access article
Toxicology of Short-Chain Alternatives – Key References

• **Toxicology Data for Alternative "Short-Chain" Fluorinated Substances.**

• **Assessment of POP Criteria for Specific Short-Chain Perfluorinated Alkyl Substances.**
The focus is on Long-Chain* Perfluorinated Chemicals

- as defined by OECD* and the USEPA, and commitments by companies to eliminate substances associated with PFOA and PFOS by 2015.
- PFOS and PFOA detected broadly in people and the environment. PFOS is considered persistent, bioaccumulative, and toxic (PBT) (OECD, Stockholm Convention)
- A major global manufacturers have committed to phase out or already have phased out of PFOA and PFOS and products related to them (see US EPA 2010/15 Stewardship Program).
- Hence, the objective of regulators and industry is to eliminate the manufacture and use of long-chain substances and move to alternative technologies, such as short-chain fluorinated substances.

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Alternatives – Desired Attributes

• Have a more favorable environmental, health and safety (EHS) profile; with a focus on the “B” and “T” properties. P matters too.

• Rapid elimination from living systems.

• First and foremost, the alternative technologies must deliver the performance required for the end-use application.
### Perfluoroalkyl acids (PFAAs) elimination half-life in plasma

<table>
<thead>
<tr>
<th>Elimination</th>
<th>“short-chain”</th>
<th>“long-chain”</th>
</tr>
</thead>
<tbody>
<tr>
<td>t$_{1/2}$ (Days)</td>
<td>PFBA</td>
<td>PFBS</td>
</tr>
<tr>
<td>Rat</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Monkey</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Human</td>
<td>3 - 4</td>
<td>26</td>
</tr>
</tbody>
</table>

# Fluorinated Carbons | 3 | 4 | 5 | 6 | 7 | 8 |

There is a BIG difference between “long” and short” chain PFAAs! Short chain PFAAs eliminate rapidly and are significantly less toxic.

Fluorinated Carbons
Alternatives – Additional Considerations

• Performance (KPIs)
  – All the things that matter to the end-user
  – From the simple …… to the most demanding requirements

• Hazard Assessment

• Exposure Assessment
  – Worker, consumer, environment

• Life-cycle environmental impacts
  – Carbon footprint, water footprint, etc.

• And more…..
Knowledge Foundation – what is needed

Along the Product Life-Cycle
Product Composition

- Active Ingredient
- Residual raw materials
- By-product impurities
- Other ingredients (e.g., surfactants)

Have they been determined? How? How much?
## Hazard Assessment considerations

<table>
<thead>
<tr>
<th>Mammalian Toxicity</th>
<th>Aquatic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td><strong>Acute</strong></td>
</tr>
<tr>
<td>- Oral, Inhalation</td>
<td>- Fish</td>
</tr>
<tr>
<td>- Eye, Skin irritation</td>
<td>- Daphnia (invertebrate)</td>
</tr>
<tr>
<td>- Skin sensitization</td>
<td>- Algae</td>
</tr>
<tr>
<td><strong>Genotoxicity</strong></td>
<td><strong>Repeated-dose, Chronic</strong></td>
</tr>
<tr>
<td><strong>Repeated-dose</strong></td>
<td>- Fish 90d ELS; 21d Daphnia</td>
</tr>
<tr>
<td>- Oral, dermal, inhalation</td>
<td>- Bioconcentration / Bioaccumulation</td>
</tr>
<tr>
<td>- Development</td>
<td></td>
</tr>
<tr>
<td>- Reproduction</td>
<td></td>
</tr>
<tr>
<td>- Cancer</td>
<td></td>
</tr>
<tr>
<td>- Toxico- and Pharmacokinetcs</td>
<td></td>
</tr>
</tbody>
</table>

### worker and consumer exposure

### Environmental exposure
### Greenscreen® Assessment – An Example

Assign based on established regulatory classification criteria

<table>
<thead>
<tr>
<th>Group I Human</th>
<th>Group II and III Human</th>
<th>Ecotox</th>
<th>Fate</th>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenicity</td>
<td>Mutagenicity / Genotoxicity (M)</td>
<td>Reproduction</td>
<td>Development (D)</td>
<td>Endocrine Activity</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>R</td>
<td>D</td>
<td>E</td>
</tr>
</tbody>
</table>

#### Example #1

| PRODUCT | | | | | | | | | | | | | | | | | | | | |
| RAW MATERIAL | | | | | | | | | | | | | | | | | | | | |

DEGRADATION PRODUCT

DEGRADATION PRODUCT
## Greenscreen® Assessment – An Example

### Example #2

<table>
<thead>
<tr>
<th>Assign based on established regulatory classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I Human</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Carcinogenicity (C)</td>
</tr>
<tr>
<td>Low</td>
</tr>
</tbody>
</table>

### PRODUCT

<table>
<thead>
<tr>
<th>C</th>
<th>M</th>
<th>R</th>
<th>D</th>
<th>E</th>
<th>AT</th>
<th>SnS</th>
<th>SnR</th>
<th>IrS</th>
<th>IrE</th>
<th>AA</th>
<th>CA</th>
<th>P</th>
<th>B</th>
<th>Rx</th>
<th>F</th>
</tr>
</thead>
</table>

### RAW MATERIAL

| | | | | | | | | | | | | | | | | | |

### DEGRADATION PRODUCT

| | | | | | | | | | | | | | | | | | |

### DEGRADATION PRODUCT

| | | | | | | | | | | | | | | | | | |
Hazards = Toxicology Studies

- Conduct Studies on Products and Raw Materials as they are made and sold every day; and Stable Degradation Products
- From this Data, Develop a Hazard Assessment - define a safe human exposure level
  - NOAEL = No Observable Adverse Effect level (mg/kg/day)

**Exposure Routes**

- Inhalation
- Oral
- Dermal

**Study Types**
- Tier 1 - Acute
- Tier 2 - Repeated-dose
Synthesis of 6:2 Fluorotelomer-based Manufacturing Raw Materials & Products

CF₃CF₂I + CF₂=CF₂

→

C₆F₁₃ I

Perfluorohexyl iodide - PFHxI

→

C₆F₁₃ CH₂CH₂I

6:2 Fluorotelomer iodide – 6:2 FTI

→

C₆F₁₃ CH₂CH₂OH

6:2 Fluorotelomer alcohol – 6:2 FTOH

→

Raw Material

→

Surfactant Products

→

Polymeric Products

C₆F₁₃ CH₂CH₂OC(O)CR=CH₂

6:2 FTMAC (Meth)acrylate monomer

R = H, CH₃

→

Commercial Sales Product

PFHxA, perfluorohexanoate F(CF₂)₅CO₂⁻
Synthesis of 6:2 Fluorotelomer-based Manufacturing Raw Materials & Products

\[
\text{CF}_3\text{CF}_2\text{I} + \text{CF}_2=\text{CF}_2 \rightarrow \text{C}_6\text{F}_{13}\text{I} \quad \text{Perfluorohexyl iodide - PFHxI}
\]

\[
\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{I} \rightarrow \text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OH} \quad \text{Surfactant Products}
\]

\[
\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OC(O)CR=CH}_2 \quad \text{Polymeric Products}
\]

\[
\text{PFHxA, perfluorohexanoate } F(\text{CF}_2)_5\text{CO}_2^-
\]
Aqueous polymer dispersion

Commercial Product

$\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2$- side chains appended to the polymer backbone

• Acute Mammalian
  – Oral LD50 (rat): $>11,000 \text{ mg/kg}$
  – Mild eye irritant, non-irritating to Skin (rabbit)
  – Local Lymph Node Assay (LLNA) (mouse): negative for skin sensitization

• Acute aquatic
  – Fish: 96 hr LC50: $>100 \text{ mg/L}$
  – Daphnia: 48hr EC50: 4.3 mg/L
  – Algae 72 hr EC50: $>100 \text{ mg/L}$

• Genetic Toxicity
  – Ames and Chromosome aberration negative.

• Repeated-Dose Mammalian
  – Oral 90-day sub-chronic, One generation reproduction, Development
  – NOAEL 1000 mg/kg/day – Limit Dose

• Genetic Toxicity
  – Very low acute oral and dermal toxicity.
  – Low acute aquatic toxicity.

• Very low repeated-dose toxicity.

• Not a selective developmental or reproductive toxicant.

• Not damaging to DNA, not genotoxic or mutagenic.

• Rapid elimination, not bioaccumulative.
Synthesis of 6:2 Fluorotelomer-based Manufacturing Raw Materials & Products

\[
\text{CF}_3\text{CF}_2\text{-I} + \text{CF}_2=\text{CF}_2 \rightarrow \text{C}_6\text{F}_{13} \text{I} \quad \text{Perfluorohexyl iodide - PFHxI}
\]

\[
\text{C}_6\text{F}_{13} \text{CH}_2\text{CH}_2\text{I} \quad \text{6:2 Fluorotelomer iodide – 6:2 FTI}
\]

\[
\text{C}_6\text{F}_{13} \text{CH}_2\text{CH}_2\text{OH} \quad \text{6:2 Fluorotelomer alcohol – 6:2 FTOH}
\]

\[
\text{Raw Material} \quad \text{Surfactant Products}
\]

\[
\text{Raw Material} \quad \text{Commercial Sales Product}
\]

\[
\text{Degradation Product} \quad \text{PFHxA, perfluorohexanoate } \text{F(CF}_2)_5\text{CO}_2^{-}
\]

\[
\text{C}_6\text{F}_{13} \text{CH}_2\text{CH}_2\text{OC(O)}\text{CR}=\text{CH}_2 \quad \text{Polymeric Products}
\]

\[
\text{R} = \text{H, CH}_3
\]
Chemours Study Data

Raw Material 6:2 Fluorotelomer Alcohol*  
C₆F₁₃CH₂CH₂OH

**Acute Mammalian**
- Oral LD50 (rat): 1,750 mg/kg; Dermal LD50: 5,000 mg/kg
- Mild eye irritant; No Skin Irritation (rabbit)
- Local Lymph Node Assay (LLNA) (mouse) : negative
- Inhalation: 4Hr. ALC > 3.6 mg/L vapor

**Genetic Toxicity**
- Ames and Chromosome Aberration both negative

**Acute Aquatic**
- Fish: 96Hr LC50 4.84 mg/L
- Daphnia: 48Hr EC50 7.84 mg/L
- Algae: 72-hour EC50 4.52 mg/L

**Summary**
- Not damaging to DNA, not genotoxic or mutagenic.
- Rapid elimination, not bioaccumulative.
- Repeated-dose toxicology similar to published results for other fluorotelomer alcohols studied.
- Not expected to be harmful to human health or the environment at environmentally relevant concentrations.

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**Repeated-Dose Mammalian (rat)**
- Oral 90-day sub-chronic: **NOAEL 5 mg/kg/day**
  - Target: Teeth (F⁻), blood, liver
- Reproduction, One-generation: **NOAEL 25 mg/kg/day**
- Development: **NOAEL 25 mg/kg/day**
- Inhalation – 5 day, 28 day: **NOAEL 10ppm**
- **Oral and inhalation target organs the same, no route-specific toxicity**

**Pharmacokinetics (rat)**
- Single and repeated dose oral and inhalation.
- Rapid metabolism and bioelimination
Synthesis of 6:2 Fluorotelomer-based Manufacturing Raw Materials & Products

\[ \text{CF}_3\text{CF}_2\text{I} + \text{CF}_2=\text{CF}_2 \]
\[ \rightarrow \quad \text{C}_6\text{F}_{13}\text{I} \quad \text{Perfluorohexyl iodide - PFHxI} \]
\[ \rightarrow \quad \text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{I} \]

6:2 Fluorotelomer iodide – 6:2 FTI

6:2 Fluorotelomer alcohol – 6:2 FTOH

\[ \rightarrow \quad \text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OH} \quad \text{Surfactant Products} \]

\[ \rightarrow \quad \text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OC(O)CR=CH}_2 \]

6:2 FTMAC (Methyl)acrylate monomer

R = H, CH₃

Polymeric Products

Degradation Product
PFHxA, perfluorohexanoate F(CF₂)₅CO₂⁻
### Chemours Study Data

**Raw Material 6:2 Fluorotelomer Methacrylate**

\[ C_{6}F_{13}CH_{2}CH_{2}OC(O)C(CH_{3})=CH_{2} \]

### Acute Mammalian

- Oral LD50 rats and mice: > 5,000 mg/kg
- Eye Irritation: non irritating
- Skin Irritation: non irritating
- Acute Dermal LD50: > 5,000 mg/kg
- Local Lymph Node Assay: not a skin sensitizer

### Acute Aquatic

- Fish: 96Hr LC50: > 14.5 mg/L
- Daphnia: 48Hr EC50: > 120 mg/L
- Algae: 72-hour EC50: > 24.6 mg/L

### Genetic Toxicity

- **In-vitro**
  - Bacterial Reverse Mutation Assay: Negative
  - Chromosome Aberration Positive (Structural w/o act.): Positive
- **In-vivo**
  - Mouse Lymphoma, Mouse Micronucleus and Chrom. Ab.: Negative

### Summary

- Low acute and aquatic toxicity.
- Not damaging to DNA, not genotoxic or mutagenic.
- **Metabolized rapidly to 6:2 FTOH**
- Repeated-dose toxicology similar to 6:2 FTOH

**Repeated-dose (rat)**

- 14d Oral repeated-dose NOAEL 1000mg/kg/day
- Target: Teeth (F-), liver wt.
Synthesis of 6:2 Fluorotelomer-based Manufacturing Raw Materials & Products

\[
\text{CF}_3\text{CF}_2\text{-I} + \text{CF}_2=\text{CF}_2 \\
\downarrow \\
\text{C}_6\text{F}_{13}\text{I} \quad \text{Perfluorohexyl iodide - PFHxI} \\
\downarrow \\
\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{I} \quad \text{6:2 Fluorotelomer iodide – 6:2 FTI} \\
\downarrow \\
\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OH} \quad \text{6:2 Fluorotelomer alcohol – 6:2 FTOH} \\
\downarrow \\
\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OC(O)CR=CH}_2 \quad \text{6:2 FTMAC (M eth)acrylate monomer} \\
\text{Commercial Sales Product} \\
\text{Polymeric Products} \\
\text{Surfactant Products} \\
\text{Degradation Product} \\
\text{PFHxA, perfluorohexanoate} \quad F(\text{CF}_2)_5 \text{CO}_2^-
Degradation Product – Perfluorohexanoate (PFHx)*

Chemours Study Data

Repeted-Dose Mammalian (oral)

– **2-year chronic** (rat)
  - NOAEL M 15 mg/kg/day; F 30 mg/kg/day

– **90-day sub-chronic** (rat)
  - NOAEL 100 mg/kg/day
  - Target: body weight, liver

– **One-Generation Reproduction** (rat)
  - NOAEL 100 mg/kg/day; no effects on reproductive parameters

– **Repro/Development** (mouse)
  - NOAEL 100 mg/kg/day

– **Development** (rat)
  - NOAEL 100 mg/kg/day

– **Pharmacokinetics** (rat, mouse, monkey)
  - Single and repeated dose studies completed. Rapid elimination M&F all species.

### Summary

- Low aquatic toxicity.
- Not damaging to DNA, not genotoxic or mutagenic.
- Not a selective developmental or reproductive toxicant
- Rapid elimination, not bioaccumulative.
- Not expected to be harmful to human health or the environment at environmentally relevant concentrations
Degradation Product – Perfluorohexanoic Acid (PFHxA) $\text{C}_5\text{F}_{11}\text{CO}_2\text{H}$

**Study Data from Others**

- **2-year chronic** (rat)
  - NOAEL M 15 mg/kg/day; F 30 mg/kg/day
  - No carcinogenic effects observed

- **90 day sub-chronic acid** (rat)
  - NOAEL 50 mg/kg/d M, 200 mg/kg/d F

- **Pharmacokinetics** (rat, monkey)
  - Rapid elimination.

- **90d Early-life stage fish**
  - OECD 210
  - NOEC 10 mg/L

**Summary**

- Rapid elimination, not bioaccumulative.
- No carcinogenic effects observed.
- Not expected to be harmful to human health or the environment at environmentally relevant concentrations.
Risk Characterization: 6:2 Fluorotelomer Alcohol
(for illustrative purpose)

- Hazard Assessment (non-cancer)
  - Based on the NOAEL of 5 mg/kg, the corresponding HED was calculated to be approximately 1.4 mg/kg bw/day.
  - An additional assessment factor of 2 was applied to extrapolate from the subchronic exposure to a chronic exposure and resulted in a final HED of 0.7 mg/kg bw/day.
  - This was converted to an equivalent air concentration by using an allometric scaling factor and the results are presented in the table below.
  - This assessment indicates there is little to no human health risk expected even at the highest ambient air concentrations of 6:2 FTOH reported.
Risk Characterization
Margin of Exposure – 6:2 FTOH Inhalation

Margin of exposure (MOE) comparison for 6:2 FTOH in outdoor and indoor air

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Exposure assessment range (ng/m³)²</th>
<th>Alveolar ventilation (m³/day)</th>
<th>HEC² (mg/m³)</th>
<th>Margin-of-exposure range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outdoor</td>
<td>GM 0.100 – High 0.388</td>
<td>20</td>
<td>2.5</td>
<td>6.3E+06 – 2.5E+07</td>
</tr>
<tr>
<td>Indoor</td>
<td>0.984 – 23</td>
<td>20</td>
<td>2.5</td>
<td>1.1E+05 – 2.5E+06</td>
</tr>
</tbody>
</table>

²Values adapted from Shoeib et al. (2011).

HED from rodent BMD analysis = 0.7 mg/kg/day (derivation described in text) was used to calculate HEC = 0.7 mg/kg bw/day × 70 kg human × 1 day/10 or 20 m³ alveolar ventilation. Alveolar ventilation values are from Derelanko (2000).

Example MOE Calculation

The NOAEL of 5 mg/kg bw/day in rats, adjusted for allometric scaling and a subchronic-to-chronic assessment factor of 2 gave a human-equivalent oral dose = 0.7 mg/kg [= 5.0 mg/kg bw × (0.456 kg rat/70 kg human)⁰.²⁵ + 2]. This oral dose was translated to human equivalent exposure concentrations of 2.5 mg/m³ [e.g. = 0.7 mg/kg bw/day × 70 kg human × 1 day/20 m³ alveolar ventilation]. This HEC was then divided by the indoor air concentration to arrive at the margin of exposure (MOE). Further details of this calculation can be found a publication for 8:2 FTOH (Himmelstein et al. 2012b).
Risk Characterization
Margin of Exposure – Perfluorohexanoic acid
(for illustrative purpose)

• Hazard Assessment (non-cancer)
  – Point of Departure = 100 mg/kg/d
  – Apply 1000x safety Factor = 0.1 mg/kg/d

• Exposure Assessment
  – Drinking Water, 100ppt, 2L, 20% of diet
  – 70 kg adult

• Margin of Safety = ~ $10^6$
Summary

• Fluorinated surfactants and polymers are valuable technologies with unique and important societal and product life-cycle benefits.
• Global manufacturers are rapidly moving from long-chain to alternative (e.g., short-chain) technologies.
  – Regulators are approving manufacture and use
  – Toxicological and environmental properties along the product life cycle need to be understood.
• Chemours has developed comprehensive toxicological data for short-chain fluorotelomer-based Products, Raw Materials and Degradation Products.
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Thank you : )

Contact Information

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