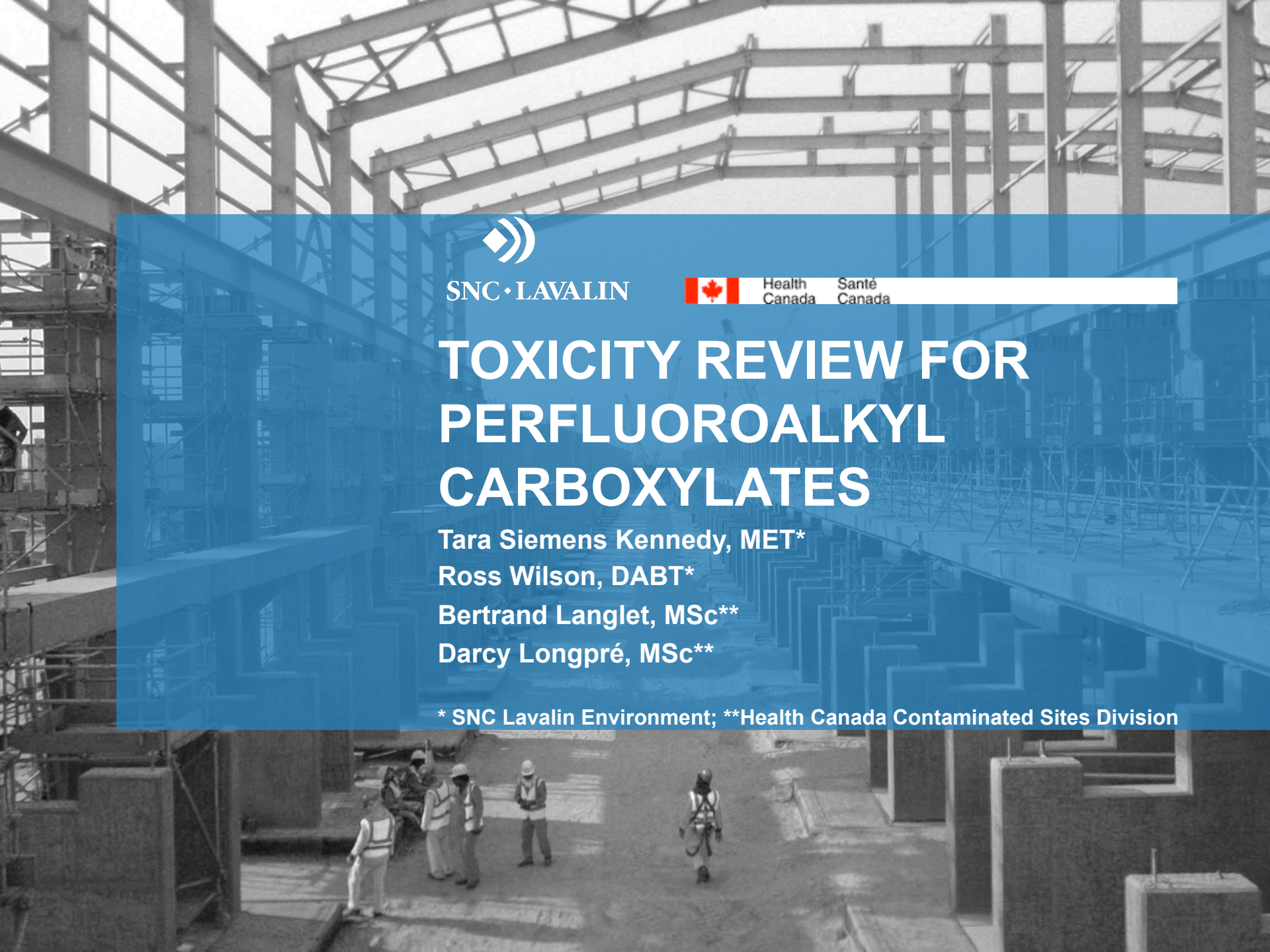


SNC·LAVALIN

Health Canada Santé Canada

TOXICITY REVIEW FOR PERFLUOROALKYL CARBOXYLATES

Tara Siemens Kennedy, MET*

Ross Wilson, DABT*

Bertrand Langlet, MSc**

Darcy Longpré, MSc**

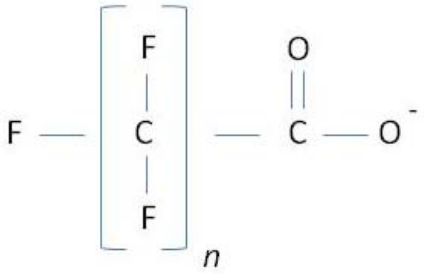
* SNC Lavalin Environment; **Health Canada Contaminated Sites Division

Perfluoroalkyl Compounds (PFCs) - Background

- PFCs have unique chemical and physical characteristics – used in various industrial and consumer applications
- Ubiquitous distribution of PFCs in human tissues, wildlife and the environment
- PFCs have the defining characteristics of persistent organic pollutants (POPs):
  - Toxic
  - Resistant to biodegradation
  - Bioaccumulative
  - Long half-lives in humans

Perfluoroalkyl Carboxylates - PFCAs

- **PFCAs are one class of PFCs**
- **PFCAs are fully fluorinated alkyl chains with a carboxylate or carboxylic acid functional group**



PFBA – perfluorobutanoate (C4)
PFPeA – perfluoropentanoate (C5)
PFHxA – perfluorohexanoate (C6)
PFHpA – perfluoroheptanoate (C7)
PFOA – perfluorooctanoate (C8)
PFNA – perfluorononoate (C9)
PFDA – perfluorodecanoate (C10)

- **In the environment, PFCAs are present in their dissociated form**
- **PFCAs are named based on their carbon chain length**

PFCA Environmental Contamination

- C4-C13 PFCAs have the potential to be present at contaminated sites in Canada (SLR, 2011)[1]
- Sources:
  - fire-fighting foams (e.g. AFFF)
  - electroplating facilities
  - various industries (e.g. textile, pulp and paper), etc.
- USEPA and Minnesota Department of Health → TRVs for PFOA and PFBA
- Current review conducted to compile toxicity data on PFCAs → for future development of environmental quality guidelines

[1] SLR Consulting (Canada) Ltd. 2011. Environmental Occurrence and Toxicity Summary Report for Perfluorinated Chemicals, Excluding PFOS and PFOA. Prepared for Health Canada Contaminated Sites Division. February 2011.

Understanding PFCA Toxicity

- Efficiently absorbed and are not metabolized
- Elimination half-life ($T_{1/2}$) > with decreasing fluorinated carbon chain length
- Major species differences in $T_{1/2}$ (e.g. PFOA $T_{1/2}$ in humans = 3.8 yrs, in male rats = 4-6 days)
- Gender differences in $T_{1/2}$ in some species (e.g. PFOA $T_{1/2}$ in female rats = 2-4 hrs, in male rats = 4-6 days)
- Data generally supports that the toxicity of PFCAs is positively correlated with longer elimination half-life (i.e., longer carbon chain)

Using Animal Data to Derive TRVs

- Species/gender differences in $T_{1/2}$ make it difficult to extrapolate animal data to human health
- Use of internal doses (i.e., serum concentrations) from the animal studies is recommended
- The duration of the study should allow for steady-state serum concentrations to be achieved
- When human kinetic data is available, a toxicokinetic interspecies uncertainty factor (UF) can be calculated based on the difference in the $T_{1/2}$ in the animal and humans

Scope of Current Review

- **Compilation of toxicological data for PFCAs in humans and mammalian species**
  - Review of primary literature and agency (e.g. ATSDR, USEPA, WHO, RIVM) databases
  - Summarize available data for C4 to C18 PFCAs
  - Evaluate if databases for individual PFCAs sufficient for development of toxicity reference values (TRVs)
- **Evaluation of alternative approaches to evaluating PFCAs that lack TRVs**

Results – Toxicity Databases for PFCAs

- **TRVs have been derived by the USEPA and/or the Minnesota Department of Health for PFBA (C4) and PFOA (C8)**

PFCA	Toxico-kinetic	Develop-mental	Repro-ductive	Acute (1- <14 d)	Sub-Chronic (≥14-≤90 d)	Chronic (> 90 d)	Epidem-iological	Other
PFPeA	-	-	-	-	-	-	X	X
PFHxA	X	-	X	X	X (90 d)	-	X	X
PFHpA	-	-	-	X	-	-	X	X
PFNA	X	X	X	X	X (14 d)	-	X	X
PFDA	-	X	-	X	-	-	X	X
PFUnDA	-	-	-	X	-	-	X	X
PFDoDA	-	-	X	-	X (males)	-	X	X
C13-C18	-	-	-	-	-	-	X	X

Results – Toxicity Databases (cont).

- **PFHxA (C6)**
  - Two 90 day repeat oral dose rat studies
  - Toxicokinetic studies in rats and mice
  - Animal serum concentrations and/or human toxicokinetic data not available

- **PFNA (C9)**
  - Two 14 day repeat oral dose rat studies
  - Developmental toxicity studies in rats and mice (unknown duration)
  - Toxicokinetic studies in rats and mice
  - Animal serum concentrations and/or human toxicokinetic data not available

Alternative Approaches to Assess PFCAs without TRVs

- **PFHxA (C6)**
  - **Kinetic data for rat and mouse indicates $T_{1/2}$ 7 to 9 times shorter than PFOA**
  - **Human elimination $T_{1/2}$ expected to be shorter than for PFOA**
  - **PFHxA less toxic than PFOA - use of TRV for PFOA conservative**
  - ***Alternative:*** **use results of two 90 day rat studies for PFHxA in conjuction with toxicokinetic interspecies UF for PFOA to derive an oral TRV**

Alternative Approaches to Assess PFCAs without TRVs (cont.)

- **PFNA (C9)**
  - Kinetic data for rat and mouse indicates $T_{1/2}$ 3.6 to 5 times longer than PFOA
  - Human $T_{1/2}$ expected to be longer than for PFOA
  - PFNA more toxic than PFOA - use of TRV for PFOA *not* conservative
  - *Alternative:* Apply an additional 5 x UF to the human equivalent dose calculated for PFOA
  - If duration of developmental toxicity studies sufficient, results could be used in conjunction with 5 x toxicokinetic UF for PFOA

Alternative Approaches to Assess PFCAs without TRVs (cont.)

- **Ranking Based on Elimination Half-Life**
  - **Currently used by the German Environment Agency (UBA) to develop DW guidelines for C4 to C8 PFCAs (reported in Wilhelm *et al*., 2010)[3]**
  - **Based on two assumptions:**
    - Rates of elimination of the shorter-chain PFCAs are enhanced compared to PFOA
    - Shorter-chain PFCs are less toxic than PFOA
  - **Starting point = DW guidelines for PFBA (7 ug/L) and PFOA (0.3 ug/L) (based on available TRVs)**

[3]Wilhelm M, Bergmann S, Dieter HH. 2010. Occurrence of perfluorinated compounds (PFCs) in drinking water of North Rhine-Westphalia, Germany and new approach to assess drinking water contamination by shorter-chained C4-C7 PFCs. *International Journal of Hygiene and Environmental Health* 213:224-232.

Alternative Approaches to Assess PFCAs without TRVs (cont.)

- **Ranking Based on Elimination Half-Life – *Other Considerations***
  - Available $T_{1/2}$ data for PFCAs generally in agreement with assumption that > carbon chain length = > $T_{1/2}$
  - One exception to this is PFHxA (C6), which has a shorter $T_{1/2}$ in rats and mice than PFBA (C4)
  - Because PFHxA $T_{1/2}$ is shorter than PFBA, approach would be conservative in this case

Alternative Approaches to Assess PFCAs without TRVs (cont.)

- **Ranking Based on Elimination Half-Life – *Other Considerations***
  - **Available data largely supports the > C-chain length = > $T_{1/2}$ = > toxicity assumptions, but there are exceptions**
  - **PFHxA (C6 PFCA) < $T_{1/2}$ than PFBA (C4 PFCA)**
  - **PFHxS (C6 PFSA) > $T_{1/2}$ than PFOS (C8 PFSA)**
  - **Results of some studies [e.g. bacterial multiple endpoint reporter assay (Nobels et al., 2011)[4]] indicate that longer chain PFCAs (and PFSAs) not more toxic**

[4]Nobels I, Dardenne F, Coen WD, Blust R. 2010. Application of multiple endpoint bacterial reporter assay to evaluate toxicological relevant endpoints of perfluorinated compounds with different functional groups and varying chain lengths. *Toxicology in vitro 24: 1786-1774.*

Conclusions and Recommendations

- The toxicity databases for the individual PFCAs are generally insufficient to derive TRVs
- Possible exceptions = PFHxA and PFNA, however, the lack of internal dose data and human kinetic data would need to be accounted for
- In the absence of data for the individual PFCAs, a ranking approach based on elimination $T_{1/2}$ is recommended
- Ranking approach should be used cautiously and reviewed as new data on the kinetics and toxicity of PFCAs becomes available

Acknowledgements

Ross Wilson, SNC-Lavalin Environment

Bertrand Langlet and Darcy Longpré – Health Canada Contaminated Sites Division

Questions?

WE CARE
NOUS VEILLONS

WE CARE embodies SNC-Lavalin's key corporate values and beliefs. It is the cornerstone of everything we do as a company. **Health and safety, employees,** the **environment, communities and quality:** these values all influence the decisions we make every day. And importantly, they guide us in how we serve our clients and therefore affect how we are perceived by our external partners. **WE CARE** is integral to the way we perform on a daily basis. It is both a responsibility and a source of satisfaction and pride by providing such important standards to all we do.

WE CARE about the health and safety of our employees, of those who work under our care, and of the people our projects serve.

WE CARE about our employees, their personal growth, career development and general well-being.

WE CARE about the communities where we live and work and their sustainable development, and we commit to fulfilling our responsibilities as a global citizen.

WE CARE about the environment and about conducting our business in an environmentally responsible manner.

WE CARE about the quality of our work.