[FHI, KM] [3]

Institution: Norwegian Institute of Public Health (FHI/NIPH)
Administrative unit: Division of Climate and Environmental Health
Title of case study: PFAS – from research to regulation
Period when the underpinning research was undertaken: 2009-2017
Period when staff involved in the underpinning research were employed by the submitting institution: 1995-present
Period when the impact occurred: 2018-2022

5. Summary of the impact

PFAS, "forever chemicals", are prevalent in the environment and a human health concern. The Division has led PFAS research for over 15 years. Our multidisciplinary approach: identifying exposure sources, assessing PFAS levels and the association between exposure and health, and *in vitro* experiments to find mechanisms of action and support causality. We contributed to European impact through research findings and involvement of our experts in EFSA risk assessments, resulting in tolerable weekly intakes, food and drinking water legal limits and EU bans on some PFAS. Global impact is supporting evidence for the Stockholm Convention on PFAS.

2. Underpinning research

Per- and Polyfluoroalkyl Substances (PFAS), are used in consumer products for their water/grease-resistant properties. These "forever chemicals" persist in the environment and living organisms, raising health concerns. Before 2010, in Europe, restrictions were focused on the most prevalent PFAS – PFOS, regulating manufacture and use, with little attention to human exposure. The Division discovered key insights allowing a more accurate assessment of PFAS exposure and health effects.

Exposure

Although PFAS was widely detected in the environment and wildlife, prior to Haug et al. (2010, 2011) human exposure sources were not well described.

Food, particularly seafood, is an important source of PFAS (Haug et al. 2010). Seafood was identified as a significant dietary source by comparing food frequency questionnaire data and PFAS food level databases to individuals' blood levels. ***However, there are multiple pathways including house dust*** (Haug et al. 2011). In 2011, the group estimated PFAS intake from various sources, including dust, in the individual's environment and compared these to their blood levels, highlighting the indoor environment as another key exposure source.

Poothong et al. (2017) determined 25 PFAS in blood and described for the first time in so many PFAS how these partition into the different matrices ("parts") of blood. A new insight was also that some PFAS are in the red blood cell part, and not just the serum/plasma ("liquid" part). This provided conversion factors, important for comparing data from different studies.

Pregnant women and their young children

While previous studies focussed on adults, Haug et al (2011), Brantsæter et al. (2013), Gützkow et al. (2012), and Papadopoulou et al. (2016) provided new data on the vulnerable subpopulations of pregnant women and children.

Maternal concentrations of PFAS are most influenced by pregnancy and lactation *(Brantsæter et al. 2013).* Mothers who had previously given birth had lower concentrations of various PFAS compared to first time mothers. Breastfeeding was linked to reduced PFAS levels, and time since the last pregnancy with increased levels. This demonstrated for the first time that PFOA bioaccumulates in humans.

PFAS are differentially transferred from mother to child during pregnancy *(Gützkow et al. 2012).* Several PFAS were detected in both maternal and cord blood, showing a correlation between them. The levels in cord blood were 30% to 79% of the maternal levels, indicating placental transfer.

Breast milk is the most important source of PFAS for breastfed infants, although breast milk concentrations are a fraction of maternal blood concentrations *(Haug et al. 2011*). ***By the age of 3 years, 98% of toddlers had higher levels of PFAS than their mothers*** *(Papadopoulou et el. 2016).* Every month of breastfeeding was associated with a 4 % increase in toddlers.

Health effects
The Division's research on PFAS health effects is extensive, with study of immune response having the most impact.

Increased exposure to PFAS leads to lower vaccine response (Granum et al. 2013). Higher maternal levels of two PFAS were negatively associated with infant's rubella antibody response at 15 months. This suggested an impact of PFAS on the immune response in children post-vaccination even at low levels.

Three of these studies used data from the Norwegian Mother, Father and Child Cohort Study (MoBa).

Research projects: BROFLEX, A-TEAM, MoBa-substudies
Research carried out: 2009-2017
Key researchers, position (years in the Division):
Anne Lise Brantsæter, PhD student (2002-2007), Postdoc (2007-2009), Scientist (2009-2012), Senior Scientist (2012—)
G Brunborg, Department of Chemicals and Radiation, Director (2010-2015)

Berit Granum, PhD student (1996-2000), Postdoctoral fellow (2000-2005), Scientist (2005-2011), Senior Scientist (2011—)
Kristine B Gützkow, Postdoc (2007-2010), Scientist (2010-2015), Senior scientist (2016-2021) Department director (2021—)
Line S. Haug, PhD student (2007-2011), Scientist (2011-2013), Senior Scientist (2013—)
Helle K. Knutsen, PhD student (1989-1995), Postdoc (1996-1999), Senior Scientist (1999-)
Unni C Nygaard, PhD student (1999-2005), Scientist (2005-2011), Senior Scientist (2011-2020)
Eleni Papadopoulou, postdoc (2013-2016)
Somrutai Poothong, PhD student (2013-2018), Engineer (2018-2019)
Azemira Sabaredzovic, Engineer (2009-2013), Over Engineer(2013-2017), Senior Engineer(2017-)
Cathrine Thomsen, PhD student (1997-2002), Postdoctoral fellow (2002-2004), Scientist (2004-2007), Senior Scientist (2007-2014), Department Director (2014—)

3. References to the research (indicative maximum of six references)

Authors: **Brantsaeter AL**, Whitworth KW, Ydersbond TA, **Haug LS**, **Haugen M**, **Knutsen HK**, **Thomsen C**, **Meltzer HM**, **Becher G**, **Sabaredzovic A**, Hoppin JA, Eggesbø M and Longnecker MP
Title: Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women
Year: 2013
Journal: Environment International, 54, 74–84
https://doi.org/10.1016/j.envint.2012.12.014 *146 Citations*
Authors: **Haug LS**, **Thomsen C**, **Brantsaeter AL**, **Kvalem HE**, **Haugen M**, **Becher G**, **Alexander J**, **Meltzer HM** and **Knutsen HK**
Title: Diet and particularly seafood are major sources of perfluorinated compounds in humans
Year: 2010

Journal: Environment International, 36, 772–778
https://doi.org/10.1016/j.envint.2010.05.016 *244 Citations*
Authors: **Haug LS**, Huber S, **Becher G** and **Thomsen C**
Title: Characterisation of human exposure pathways to perfluorinated compounds — Comparing exposure estimates with biomarkers of exposure
Year: 2011
Journal: Environment International, 37, 687–693
https://doi.org/10.1016/j.envint.2011.01.011 *274 Citations*
Authors: **Granum B**, **Haug LS**, **Namork E**, **Stølevik SB**, **Thomsen C**, Aaberge IS, van Loveren H, **Løvik M** and **Nygaard UC**
Title: Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood
Year: 2013
Journal: Journal of Immunotoxicology, 10, 373–379
https://doi.org/10.3109/1547691X.2012.755580 *203 Citations*
Authors: **Gützkow KB**, **Haug LS**, **Thomsen C**, **Sabaredzovic A**, **Becher G** and **Brunborg G**
Title: Placental transfer of perfluorinated compounds is selective – A Norwegian Mother and Child sub-cohort study
Year: 2012
Journal: International Journal of Hygiene and Environmental Health, 215, 216–219
https://doi.org/10.1016/j.ijheh.2011.08.011 *152 Citations*
Authors: **Papadopoulou E**, **Sabaredzovic A**, **Namork E**, **Nygaard UC**, **Granum B** and **Haug LS**
Title: Exposure of Norwegian toddlers to perfluoroalkyl substances (PFAS): the association with breastfeeding and maternal PFAS concentrations
Year: 2016
Journal: Environment International, 94, 687–694
https://doi.org/10.1016/j.envint.2016.07.006 *62 Citations*
Authors: **Poothong S**, **Thomsen C**, **Padilla-Sanchez JA**, **Papadopoulou E** and **Haug LS**
Title: Distribution of Novel and Well-Known Poly- and Perfluoroalkyl Substances (PFASs) in Human Serum, Plasma, and Whole Blood
Year: 2017
Journal: Environmental Science & Technology, 51, 13388–13396
https://doi.org/10.1021/acs.est.7b03299 *106 Citations*

4. Details of the impact (indicative maximum 750 words)

Impact 1: Tolerable weekly intakes (TWIs) for PFAS
→Drinking water limits for PFAS
→Maximum levels of PFAS in certain food stuffs
Beneficiaries: General population of Europe, pregnant women, infants
Dates: 2018 (TWIs PFOA and PFOS), 2020 (TWIs sum four PFAS), 2021 (drinking water limits), 2022 (maximum levels in certain food).

The European Food Safety Agency (EFSA) sets safety thresholds to improve food safety by conducting risk assessments to set TWIs for chemicals in food. A substantial part of the European population exceeded the TWIs for PFAS, so the European Commission acted to reduce exposure in food and water. The Drinking Water Directive took effect on 16 January 2021 and included a limit for all PFAS. The Maximum levels of PFAS in certain food stuffs took effect on 7 December 2022.

Process

The research above is highly cited and disseminated widely in reputable journals, at conferences, and directly for national authorities including the Norwegian Food Safety Authority. In addition, individual researchers, Dr Line S. Haug and Dr Helle K. Knutsen are recognised PFAS experts. Dr Knutsen was the chair of the CONTAM Panel at EFSA, 2015—2018. Dr Haug was a member of the

EFSA working group on PFAS under the CONTAM Panel that assessed research, performed the risk assessment, and developed the Scientific Opinions. The research described above in Section 1 (except Poothong et al. 2017), were included in the evaluation of PFOA and PFOS, contributing to setting TWIs (EFSA 2018). Fish and seafood were highlighted as key exposure sources and a decreased immune response as a critical effect for children. This research documented that levels in Norway were comparable to the levels in Europe, and that for a considerable proportion of the population exposure exceeds the TWIs.

Between 2018 and 2020, EFSA extended the PFAS evaluation, including PFNA and PFHxS in a new TWI for the sum of four PFAS (EFSA 2020). Dr Haug and Dr Knutsen were members of the EFSA working group and all above research contributed to the assessment and Scientific Opinion. In addition, original data from Granum et al. (2013) was included in the benchmark dose modelling for setting the TWI. EFSA emphasised that toddlers and other children are the most exposed population groups, and exposure during pregnancy and breastfeeding is the main contributor to PFAS in infants (Haug et al. 2011, Brantsæter et al. 2013, Gützkow et al. 2012, Papadopolou et al. 2016).

In all risk assessments, many sources of data are assessed, however, research described here were novel findings and important for the assessment. The Scientific Opinions were the direct driver for risk management and stricter regulation of PFAS in food and drinking water.

Impact 2: Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
→The European Commission set a ban for use of long-chain PFCAs, PFOA and PFHxS
Beneficiaries: General population of Europe
Dates: 2020 (PFOA), 2021 (long-chain PFCAs), 2022 (PFHxS)
Process

Dr Haug and Dr Kristine Gützkow contributed to the PFOA restriction proposal, which came from Norway (Norwegian Environment Agency) and Germany. They developed the background document on human health, with Brantsæter et al. (2013) key in showing that PFOA bioaccumulates in humans.

Some research was included in the documentation for the ban for use of long-chain PFCAs: breast milk as the main source for infants (Haug et al., 2011), and monitoring and trend data (Haug et al. 2011), and human biomonitoring data (Papadopoulou et al. 2016).

Norway drafted the PFHxS restriction proposal. Dr Haug quality assured the text on human exposure. Supporting documents referred to breastmilk as an important exposure pathway to PFHxS for infants (Brantsæter et al. 2013), the importance of the indoor environment for exposure (Haug et al. 2011) and included data on cord blood levels (Gützkow et al. 2012).

The impact continues with a restriction on all PFAS in Europe expected in 2025 (ECHA, 2024).

Impact 3: Stockholm Convention on POPs – PFOA and PFHxS
→Global regulation/restrictions for use of PFOA and PFHxS
Beneficiaries: Global
Dates: 2019 (PFOA), 2022 (PFHxS)
Process

PFOA and PFHxS were proposed for inclusion in the Stockholm Convention on POPs. Background documents highlighted the role of indoor environment (Haug et al., 2011), PFOA bioaccumulation and breastfeeding as an important pathway (Brantsæter et al. 2013), levels increase with age and diet is the most important source (Haug et al. 2010, 2011). For PFHxS, Brantsæter et al. 2013, Granum et al. (2013), Gützkow et al (2012) were all cited.

The PFAS case illustrates the synergy between research and advisory roles in public health prevention.

5. Sources to corroborate the impact (indicative maximum of ten references)

Impact 1: Tolerable Weekly Intakes for PFAS

First PFOA and PFOS TWI, 2018

Authors: EFSA Panel on Contaminants in the Food Chain (CONTAM), **Knutsen HK**, Alexander J, Barregård L, Bignami M, Brüschweiler B, Ceccatelli S, Cottrill B, Dinovi M, Edler L, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Nebbia CS, Oswald IP, Petersen A, Rose M,
Roudot AC, Vleminckx C,Vollmer G, Wallace H, Bodin L, Cravedi JP, Halldorsson TI, **Haug LS**, Johansson N, Loveren Hv, Gergelova P, Mackay K, Levorato S, Manen Mv, Schwerdtle T.
Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. 2018. EFSA Journal https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2018.5194

Second PFAS TWI, 2020

Authors: EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel); Schrenk D, Bignami M, Bodin L, Chipman JK, Del Mazo J, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Leblanc JC, Nebbia CS, Nielsen E, Ntzani E, Petersen A, Sand S, Vleminckx C, Wallace H, Barregård L, Ceccatelli S, Cravedi JP, Halldorsson TI, **Haug LS**, Johansson N, **Knutsen HK**, Rose M, Roudot AC, Van Loveren H, Vollmer G, Mackay K, Riolo F, and Schwerdtle T. Risk to human health related to the presence of perfluoroalkyl substances in food. 2020. EFSA Journal https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2020.6223
p.346 K.2. Benchmark dose modelling: Vaccination response: "Data on rubella are from the study by Granum et al. (2013) and obtained from the authors. Analysis performed by the CONTAM Panel."
Press release: EFSA News, 17 Sept 2020. PFAS in food: EFSA assesses risks and sets tolerable intake.
https://www.efsa.europa.eu/en/news/pfas-food-efsa-assesses-risks-and-sets-tolerable-intake

Drinking Water Directive

DIRECTIVE (EU) 2020/2184 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2020 on the quality of water intended for human consumption.
https://eur-lex.europa.eu/eli/dir/2020/2184/oj
COMMISSION REGULATION (EU) 2022/2388 of 7 December 2022 amending Regulation (EC) No 1881/2006 as regards **maximum levels of perfluoroalkyl substances in certain foodstuffs**
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R2388

Impact 2: Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

PFOA

ECHA, 2018. Committee for Risk Assessment (RAC), Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on Perfluorooctanoic acid (PFOA), PFOA salts and PFOA-related substances
https://echa.europa.eu/documents/10162/e40425c6-590f-8df7-2cd9-0eef79527685

PFHxS

ECHA, 2020. Committee for Risk Assessment (RAC), Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related substances
https://echa.europa.eu/documents/10162/4e84f904-7cd7-9be6-dd9b-2cc711c0859b

Long Chain PFCAs

ECHA, 2018. Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on C9-C14 PFCAs including their salts and precursors
https://echa.europa.eu/documents/10162/02d5672d-9123-8a8c-5898-ac68f81e5a72

All PFAS restriction

ECHA, 2024. Registry of restriction intentions until outcome
https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18663449b

Impact 3: Stockholm Convention on POPs (PFAS)

PFOA https://www.pops.int/Implementation/IndustrialPOPs/PFAS/Overview/tabid/5221/Default.aspx
Document name: UNEP/POPS/POPRC.12/11/Add.2: Risk profile for PFOA, its salts and PFOA-related compounds (opens as pdf)
PFHxS https://chm.pops.int/Implementation/IndustrialPOPs/PFAS/Overview/tabid/5221/Default.aspx
Document name: UNEP/POPS/POPRC.14/6/Add.1: Risk profile for PFHxS, its salts and PFHxS-related compounds (opens as pdf)