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Human studies and critical effects

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Outline

- Potential critical effects in the EFSA 2018 opinion
- Observations in humans
  - Human outcomes reviewed
  - Effects on immune system
- Critical effects

EFSA 2018 opinion on PFOS and PFOA

- In the EFSA 2018 opinion on PFOS and PFOA, four outcomes in humans were considered potential critical effects:
  - Increased serum cholesterol
  - Impaired antibody response after vaccination
  - Increased serum ALT
  - Decreased birth weight
- CONTAM Panel derived TWIs based on effects on serum cholesterol
  - PFOS: 13 ng/kg bw per week
  - PFOA: 6 ng/kg bw per week
- TWIs were also protecting towards the other potential critical effects

Explanatory note EFSA 2018

Due to the nature of the scientific uncertainties described in this opinion and in the minutes of the expert meeting of 24 September 2018, EFSA/CONTAM/3503 (https://www.efsa.europa.eu/sites/default/files/news/efsa-contam-3503.pdf), and the possible application of the forthcoming Scientific Committee guidance on combined exposure to multiple chemicals, the **conclusions of this assessment will be reviewed** in parallel with the finalisation of the EFSA scientific opinion on The risks to human health related to the presence in food of perfluoroalkylated substances other than PFOS and PFOA (EFSA-Q-2017-00549). The indicative timeline for this is December 2019. Until such time, the conclusions and derived tolerable weekly intakes shall be considered provisional.

Human studies: Metabolic outcomes

- **Clear evidence** for an association between exposure to PFASs and increased serum levels of **cholesterol**
- **Insufficient evidence** to conclude on associations between exposure to PFASs and increased **risk of cardiovascular disease**

- **Evidence** for an association between exposure to PFASs and increased serum levels of the liver enzyme **ALT**
- Magnitude of the associations was small (~3%)
- Few studies found associations with **ALT outside the reference range**
- There were **no associations with liver disease**

- **Insufficient evidence** for associations with diabetes, obesity and metabolic syndrome

Human studies: Fertility, pregnancy outcomes

- New studies on PFOS and PFOA confirm the previous conclusions that "there **may well be a causal association** between PFOS and PFOA and **birth weight**"
- **No evidence** for an adverse association for other PFASs and birth weight

- **No evidence for associations** between PFASs and **fertility and reproductive outcomes** in both males and females

Other effects in humans

- **No evidence** for associations between PFASs and:
  - **neurodevelopmental outcomes**
  - **growth in infancy and childhood**
  - **neurobehavioral, neuropsychiatric, cognitive outcomes**
  - **thyroid function**
- **No evidence** for **carcinogenicity** of PFOS and PFOA in humans
- Limited information was identified for other PFASs
- **Insufficient evidence** for associations between exposure to PFASs and:
  - **changes in kidney function**
  - **low bone mineral density**
  - **osteoporosis**

Re-evaluation cholesterol, birth weight, ALT

- Although the association with **increased cholesterol** was observed in a large number of studies, the CONTAM Panel now considers the **uncertainty regarding causality larger**
- This is primarily due to a postulated biological process around the enterohepatic cycling of both PFASs and bile acids, the latter affecting serum cholesterol levels

- The observed association with **reduced birth weight** might (as mentioned before) at least partly be explained by changes in the physiology during pregnancy
- Remaining decrease in birth weight after adjusting for confounders was not large and the adversity of such a decrease might be questioned
- Little evidence for increase in the proportion of children with low birth weight (<2500 g)

- Increase in **ALT levels** in general population studies seems supported by effects in animals, but was not observed in most of the occupational studies
- In the critical study (Gallo et al., 2012), the increase in subjects with high ALT leveled off at relatively low serum concentrations and did not increase further

Immune outcomes in humans

- New epidemiological studies provide further support for the conclusion that PFOS and PFOA are associated with **reduced antibody response** to vaccination
- Evidence for other PFASs (at much lower levels) is weaker
- Some studies **suggest** that serum levels of PFOS and PFOA are associated with **increased propensity for infection**
- **Insufficient evidence to conclude on associations** between exposure to PFASs **and asthma and allergies**

Vaccination response in humans

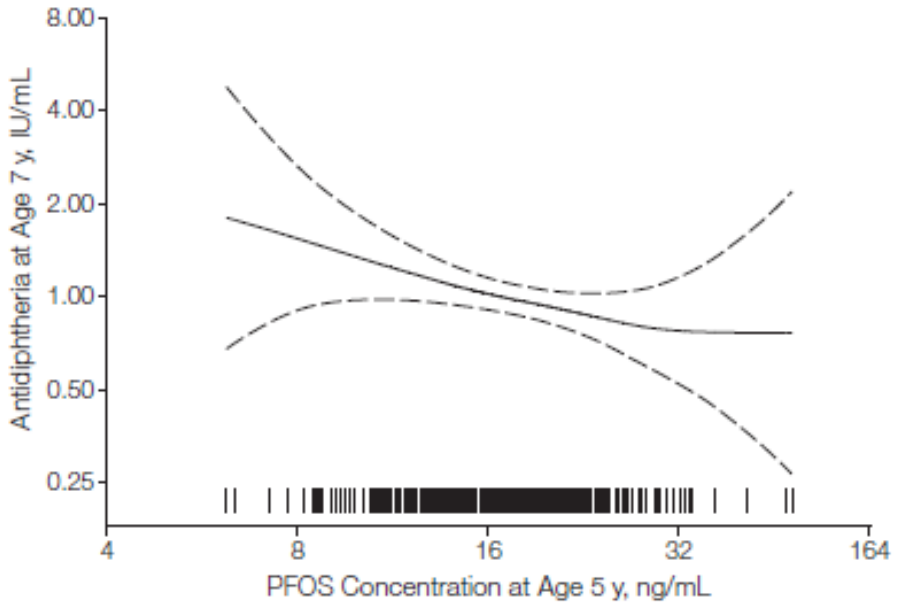
- Results from 6 vaccination response studies have been reported
- 4 studies show relatively **strong inverse associations** with **antibody response** following booster vaccination to tetanus and diphtheria in both children (Grandjean et al., 2012; Granum et al., 2013; Abraham et al., 2020) and adults (Kielsen et al., 2016)
- 1 study showed **modest inverse associations** with antibody titres after influenza vaccination in adults (Looker et al., 2014)
- Null findings by Stein et al. (2016b) on influenza vaccination do not contradict results, as most subjects did not respond to the vaccination
- Associations with antibody titres falling **below protective levels** also reported (Grandjean et al., 2012; Looker et al., 2014)

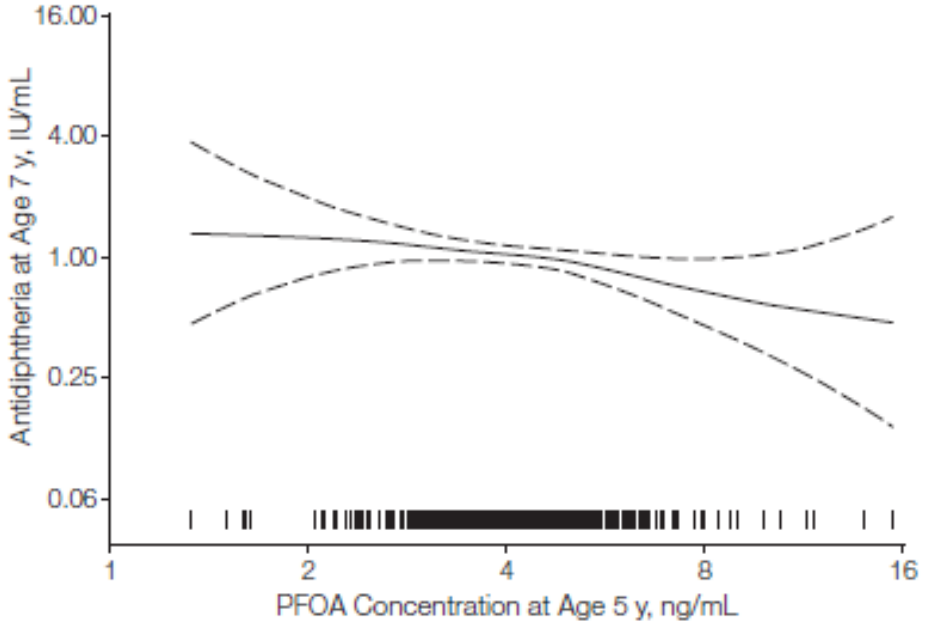
Vaccination response in humans II

- Are findings on vaccination response among the Faroese children **confounded by other seafood contaminants**?
  - Stability of those findings after adjustment for PCBs (Grandjean et al., 2012)
  - Replication of findings in breastfed infants (Abraham et al., 2020)
  - Possible confounders like PCBs, dioxins, organochlorine pesticides, lead and mercury had no effect on the observed associations (Abraham et al., 2020)
  - Replication of findings in a small group (12) Danish adults (Kielsen et al., 2016)

Pivotal studies used to derive NOAECs: Grandjean et al., 2012

- Examined in **children on the Faroe Islands** associations between both pre- (gestation week 32) and postnatal (5 years) serum concentrations of PFASs and offspring antibody concentrations against tetanus and diphtheria following booster vaccination (**n=456-587**, 1997-2000)





- Significant association serum levels at 5 years and diphtheria antibody titres at 7 years (28/25% decrease per doubling of the serum PFOS/PFOA level)
- Also for antibodies against tetanus

Pivotal studies used to derive NOAECs: Grandjean et al., 2012

- On request CONTAM Panel received **additional data for the sum of PFOA, PFNA, PFHxS and PFOS** from the authors
- **NOAEC** at the age of 5 years for the **sum of PFOA, PFNA, PFHxS and PFOS of 27.0 ng/mL** was identified, based on decreased diphtheria antibody titres at the age of 7 years

Quintiles	Sum_PFASs (ng/mL)	N	mean	SD	t-test P	%change
1	16.1	86	0.31	1.65	referent	
2	20.2	86	-0.37	1.84	0.02	-38
3	23.4	86	-0.22	2.14	0.08	-31
4	27.0	86	-0.09	1.90	0.16	-24
5	34.8	86	-0.70	1.89	0.0005	-50

titres based on $\log_2$

Pivotal studies used to derive NOAECs: Abraham et al., 2020

- In a cohort of **101 infants from Germany**, associations between plasma concentrations of PFHxS, PFOS, PFOA and PFNA and antibodies to diphtheria, tetanus and haemophilus influenzae type b (Hib) were studied
- Mothers and their infants (341 to 369 days old) were recruited in 1997-1999
- 21 infants were formula fed (≤2 weeks of breastfeeding) and 80 breastfed for > 4 months

Plasma concentrations (ng/mL)	PFOA	PFNA	PFOS	PFHxS
non-breastfed infants (n=21)	3.8	0.2	6.8	1.7
breastfed infants (n= 80)	16.8	0.6	15.2	2.1

Plasma concentrations (ng/mL)	PFOA	PFNA	PFOS	PFHxS
mothers who did not breastfeed (n=21)	4.9	0.4	17.2	1.8
mothers who breastfed (n= 80)	3.2	0.3	14.1	1.0

Studies used to derive NOAECs: Abraham et al. 2020

- Inverse association between **serum levels of PFOA** and **antibody titres against HiB, diphtheria and tetanus** in serum of 1-year-old children predominantly breastfed
- On request CONTAM Panel received **additional data for the sum of PFOA, PFNA, PFHxS and PFOS** from the authors
- **NOAEC of 31.9 ng/mL** at the age of 1 year **for the sum of PFOA, PFNA, PFHxS and PFOS**

	PFASsum																
Groups	Hib						Tetanus IgG1						Diphtheria				
	Quantile	grp.mean	N	mean	sd	p.value	Quantile	grp.mean	N	mean	sd	p.value	Quantile	grp.means	N	mean	sd	p.value
	Q1	10	20	1.92	0.75	0.025	Q1	10	20	1.06	0.32	0.041	Q1	10	20	0.44	0.4	0.06
	Q2	19.8	20	1.67	0.59	0.247	Q2	19.8	20	0.99	0.41	0.573	Q2	19.8	20	0.57	0.36	
5	Q3	31.9	20	1.78	0.74	0.547	Q3	30.9	20	1.06	0.44	0.955	Q3	30.9	20	0.56	0.4	
	Q4	40.5	20	1.38	0.79	0.034	Q4	39.8	20	1.01	0.35	0.677	Q4	39.8	20	0.46	0.42	
	Q5	50.4	18	1.49	0.63	0.065	Q5	49.7	20	0.77	0.35	0.01	Q5	49.7	20	0.2	0.55	

titres based on $\log_{10}$

Critical effects

- Effects on immune system critical for assessment
- in humans: NOAECs for **sum of PFOA, PFNA, PFHxS and PFOS**:
  - 31.9 ng/mL in 1-year-old children
  - 27.0 ng/mL in 5-year-old children
- in mice: NOAECs for **PFOS**:
  - 17.8 ng/mL (Peden-Adams et al. 2008)
  - (674 ng/mL (Dong et al. 2009) but less good protocol and less sensitive strain)
- Also effect PFOA on mammary gland development at low serum levels (LOAEC 66 ng/mL)
- **Weight-of-evidence more robust for immune effects**; preference to use human data for this assessment (less uncertainty)

Critical effects II

- Effects on immune system were observed at the lowest serum levels in both animals and humans
- Findings were considered robust
- Possible confounders like PCBs, dioxins, organochlorine pesticides, lead and mercury had no effect on the observed associations

- A **decrease in vaccination response** is seen as **adverse** by the scientific community, as summarized by WHO/IPCs 2012 in the guidance for immunotoxicity risk assessment for chemicals
- This may particular apply to vulnerable groups, i.e. infants and the elderly, considering their higher infection risk

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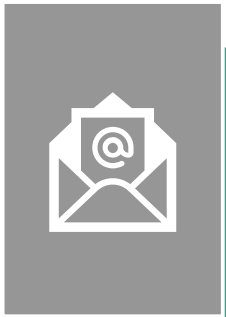

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