LITERATURE REVIEW AND REPORT ON THE POTENTIAL HEALTH EFFECTS OF PERFLUOROALKYL COMPOUNDS, MAINLY PERFLUOROOCTANE SULFONATE (PFOS)

A review initially prepared in 2010 and updated in 2015, 2016 and now in 2017

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Report Contents

Glossary of acronyms

ACHHRA   Australian Centre for Human Health Risk Assessment
ADHD   Attention Deficit Hyperactivity Disorder
AFFF   Aqueous Film-Forming Foam
ALSPAC   Avon Longitudinal Study of Parents & Children (UK)
ALT   alanine aminotransferase
ATSDR   Agency for Toxic substances and Disease Registry (US)
BCF   bio-concentration factor
BMD   Bone mineral density
BMI   Body Mass Index
C8   an epidemiological study of residents around a U.S. production plant
CFA   Country Fire Authority (Vic)
CHD   coronary heart disease
CI   Confidence interval (usually 95%)
CM-risk   cardiometabolic risk score (aggregate of scores for blood pressure & BMI)
Conc(s)   Concentration(s)
COT   Committee on Toxicity (UK)
(p,p')DDE   Dichlorodiphenyldichloroethylene (DDT metabolite)
DHEA   dehydroepiandrostenone
DHHS   Department of Health & Human Services (Vic)
DoH   Department of Health (Commonwealth)
DXA   dual X-ray absorptiometry
EDC(s)   Endocrine disrupting chemical(s)
     BPA   bisphenol A
     BPAF   fluorinated bisphenol A (replacement chemical)
     DEHP   diethylhexyl phthalate
     MEHHP [mono(2-ethyl-5-hydroxyhexyl) phthalate] - DEHP metabolite
     MOiNP [mono(4-methyl-7-oxo-octyl) phthalate] – DEHP metabolite
     DINP   di-isononyl phthalate

EFSA   European Food Safety Authority
EPA   Environmental Protection Agency (US)
DNBC   Danish National Birth Cohort
et al   indicator of multiple authors
FACTRA   Fellow, Australasian College of Toxicology & Risk Assessment
FE(F)V$_1$/FVC   Forced expiratory (Flow) volume-1 sec); Forced Vital Capacity – measures of respiratory efficiency
FFQ   food frequency questionnaire
FSANZ   Food Standards Australia & New Zealand
GBCA   Generic & Biomarkers study for Childhood Asthma (Taiwan)
GFR   Glomerular Filtration Rate
GM   Geometric mean
HbA1C   glycated haemoglobin
HBGV   Health-based Guidance Value
HCB(H)   Hexachlorobenzene (hexachlorocyclohexane)
HED   Human Equivalent Dose
HEPA   Heads of EPAs of Australia & New Zealand
(H)HRA   (Human) Health Risk Assessment
HOMA-IR   homeostatic model assessment of insulin resistance
IARC   International Agency for Research on Cancer

IGF-1	insulin-like growth factor 1
IgG(E)(F)(M)	immunoglobulin G (E) (F) (M)
Il-	Interleukins
INMA	INfancia y Medio Ambiente, Environment and Childhood birth cohort Study (Spain)
IUD	intrauterine development
L(H)DL	Low (High) density lipoprotein
LOAEL	Lowest Observable Adverse Effect Level
LOQ	Limit of Quantitation
LRC	linear regression coefficient
mg/µg	milligram/microgram
MMR	measles, mumps and rubella (vaccine)
NHANES	National Health and Nutrition Examination Survey (US)
NOAEL	No Observable Adverse Effects Level
NTP	National Toxicology Program (US)
OC	oral contraceptive
(a)OR	(adjusted) Odds Ratio
PBPK	physiologically-based pharmacokinetic
PCB	polychlorinated biphenyl

PFAS   perfluoroalkyl substances (also PFCs in some references)

    PFCA   perfluoroalky carboxylic acids

	PFD(e)A	perfluordecanoic acid
	PFDoDA	perfluorododecanoic acid
	PFHpA	perfluoroheptanoic acid
	PFNA	perfluorononanoic acid
	PFOA	perfluorooctanoic acid
	PFTrDA	perfluorotridecanoic acid
	PFU(nD)A	perfluoroundecanoic acid
	PFPrOPrA	perfluoro-2-propoxypropanoic acid (PFOA replacement)

    PFSA   perfluoroalkyl sulfonic acids and sulfonates

	Me-PFOSAA	N-methyl-perfuorooctane sulfonamidoacetic acid
	PFB(u)S	perfluorobutanesulfonate
	PFHxS	perfluorohexanesulfonic acid
	PFOS	pefluorooctanesulfonate
	PFOSA	perfluorooctansulfonamide
	FOSES	perfluorooctanesulfonamidoethanols

FTOH		fluorotelomer alcohols
DiPAPS		polyfluoroalkyl phosphate esters (PFCA precursors)

POP	Persistent Organic Pollutant
PPAR	Peroxisome Proliferator-Activated Receptor
PPARα-KO	genetically-modified mouse strain with PPARα receptor deleted
QAEHS	Queensland Alliance for Environmental Health Sciences
RfD	Reference Dose (US equivalent to TDI)
SD	Standard Deviation
SGA	small for gestational age
TDI	Tolerable Daily Intake (see also RfD)

TEF   Toxicity Equivalence Factor

TH   Thyroid hormones
      TGN   Thyroglobulin
      T(F)T3 Total (Free) triiodothyronine
      T(F)T4 Total (Free) thyroxine
      TSH   Thyroid Stimulating Hormone

TTP   Time to pregnancy
U(S)F   Uncertainty (Safety) Factor
UK   United Kingdom
US(A)   United States (of America)
WHO   World Health Organization
WTCD   World Trade Center Disaster

Executive Summary

This is an extension to reports prepared in 2015 and 2016 to review the literature on the health effects of perfluorooctane sulfonate (PFOS) and related perfluoralkyl substances (PFAS). It summarizes new studies published primarily in the period Sept 2016 to Nov 2017 and comments on recent regulatory actions, including the February 2017 updating of Tolerable Daily Intake (TDI) estimates for PFOS, PFOA and PFHxS developed by the Australian food regulator (FSANZ). This 2017 update should be read in conjunction with the two earlier Monash University reports from the Australian Centre for Human Health Risk Assessment (ACHHRA). Approximately 50 new epidemiological studies are summarized in a table format, with added comments on the extent to which these new reports extend the knowledge base of the health effects of PFAS.

The new epidemiology studies have not added any substantially new or concerning information on the potential health effects of PFOS. There have been some papers addressing endpoints that received only passing attention in my previous reviews (metabolic dysfunctions, including effects on glycaemic controls), some papers that expand on the previously covered main associations with adverse health effects (thyroid disease, reproductive and fertility changes, neurodevelopmental effects, effects on blood lipids, and immunomodulation), along with 1-2 papers on some new indicators (coronary heart disease, endometriosis and effects on bone and lung disease). In the main, these studies report inconsistent findings, with associations (not necessarily causal) between individual PFAS varying in strength from study to study, and for some endpoints, a range of positive and negative findings for these same PFAS. The 'comments' section also includes references to recent reviews of some endpoints where the conclusions are more forceful than mine on the same range of evidence.

Papers dealing with immunomodulatory effects and cancer have received additional attention in this 2017 update, because these are endpoints that commonly feature in media reports that cause some degree of alarm in communities living around point sources of (mainly) PFOS contamination associated with the legacy use of Aqueous Film-Forming Foams (AFFFs) used to fight fuel fires. There is currently no consensus on whether there are causative associations between exposure to any PFAS, and these endpoints. There have been international reviews; for example, an oft-cited (in the media) International Agency for Research on Cancer (IARC) evaluation of PFOA-related carcinogenicity (categorised as *possibly causing human cancer*), while other reviews have reached even less certain categorisations, or even a conclusion for a lack of evidence. One recent Italian study, outlining an increased relative risk (RR) for deaths (from cancers and other diseases) in communities exposed over time to known PFAS water pollution, has been analysed in more detail, with some methodological issues pointing to a reduction in the strength of the evidence that should be accorded the rather startling conclusions from this study.

Similarly, for immunomodulatory effects, some reviews (e.g. US NTP 2016 and FSANZ 2016) have reached consensus on the strength of the animal studies, but varying degrees of consensus on the strength of the epidemiological evidence. The lack of consensus on the epidemiology outcomes is largely due to disparities, even within the same study, on which immune marker has been affected, and by which PFAS. In some cases, the inconsistency may be confounded by an inability to rule out concurrent exposure to other Persistent Organic Pollutants (POPs) known to influence immune

responses, and by conflicting findings for the same, or related endpoints, across different studies.

Some additional papers have been covered outlining how different sources of exposure and exposure pathways can become more significant under some circumstances. For example, there are some papers that extend the knowledge base of PFAS concentrations in breast milk, and the contributions this route can make to increasing body burden in suckling infants. There are papers dealing with ingestion of foods and drinking water, and inhalation routes from household dusts. A significant number of these papers are the work of Jochen Mueller's group at the Queensland Alliance for Environmental Health Sciences (QAEHS) and provide useful background data on PFAS disposition in the Australian context.

There are a few miscellaneous papers that could be of interest, or that may help to explain some health outcomes in terms of possible mechanisms of PFAS interactions with receptor-linked pathways; for example the PPARα-activated physiological systems.

Finally, there is an update on the extent to which PFAS other the PFOS may need to be taken into consideration in new human health risk assessments (HHRA). The fact that these other PFAS, including new polyfluoro- and telomeric substitutes for the perfluorinated alkyl acids appear to be more consistently found in human biota and environmental samples, suggests that there will be an increasing focus on their potential health effects. Currently, the knowledge to develop separate TDI values for these emerging PFAS contaminants is insufficient, nor is there any reliable information on whether one could use relative potencies in the form of a Toxicity Equivalence Factor (TEF) to assess the risks of complex mixtures of PFAS.

1.   Preamble

In March 2015, DHHS commissioned the Australian Centre for Human Health Risk Assessment (ACHHRA) at Monash University, to review the literature on the health effects of perfluorooctane sulfonate (PFOS) and related perfluoralkyl substances (PFAS). The acronym PFC was used in the initial report but the acronym PFAS is now preferred to distinguish these specific chemicals from a subset of per- and poly-fluorocarbon compounds (that have different chemistry (may include atoms other than carbon & fluorine) and properties. A useful, and comprehensive summary of the chemistry, manufacture, use and environmental occurrence of PFAS, including fluorotelomers, can be found in the review by Buck *et al* (2011).

The initial report, submitted in October 2015, was intended to provide background information to assist DHHS manage health-related issues pertaining to the legacy use of aqueous film-forming foams (AFFFs) used at the Country Fire Authority's (CFA) Fiskville Training Centre. It focussed primarily on epidemiological studies that addressed PFOS effects on selected health outcomes, but it also included a brief summary of the historical uses of PFAS, the toxicology of PFOS and the related acid, perfluorooctanoic acid (PFOA), estimates of PFOS and PFOA exposures in various populations, and a summary of international regulatory actions to limit the use of PFOS and PFOA.

A subsequent updated report, submitted in November 2016, included around 130 additional papers, mostly published since August-September 2015 to October 2016, and maintained the emphasis from the 2015 report on analysing the published epidemiological studies describing the relationship between PFAS and various diseases or disease markers.

This current (2017) update of the Monash University report under the DHHS contract (June 2016) to undertake periodical updates of the PFAS literature, summarizes new studies published primarily in the period Sept 2016 to Nov 2017. It also comments on recent regulatory actions, including:

- The February 2017 updating of Tolerable Daily Intake (TDI) estimates for PFOS, PFOA and PFHxS developed by the Australian food regulator (FSANZ) and endorsed by the Australian Department of Health (DoH) and enHealth Council for use in risk assessment activities in Australia; and
- The establishment of a DoH webpage to provide guidance on the management of PFAS-related health issues, accompanied by the development of a National Environmental Management Plan (August 2017).

2.   Summary of new epidemiological studies

A new literature survey (in October-November 2017) discovered around 50 new studies that were not included in the 2015 and 2016 Reports. These studies are summarized in Table 1, with a commentary on any key outcomes in Section 2.1.

Table 1: Summary of recent (mostly 2016-17) epidemiological studies on the potential health effects of PFAS exposures
[not included in previous Monash reports 2015-16]

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Immunomodulation			
Incidence of infectious disease up to age 4 in children from the Hokkaido Study on Environment and Children's Health	Hospital-based birth cohort (n=1558) Hokkaido Japan; 2003 – 2009; 11 PFAS measured in maternal plasma at 28-32 weeks pregnancy; infectious disease from maternal questionnaire	The incidence of infectious diseases (total 67% for at least one disease) was otitis media (41.4%), pneumonia (18.4%) respiratory syncytial virus infection (12.6%) and varicella (37.8%); after adjusting for confounders, OR (1st-4th quartiles) for PFOS increasing total infections in both sexes was 1.61 (CI: 1.18, 2.21); for PFHxS, the OR was 1.55 (CI: 0.98, 2.45) (girls only); no effect for other PFAS; no effects on individual disease patterns, only 29% of children had received vaccination against varicella. Dose-response trends were claimed to be significant, but inspection of the plotted data was generally unconvincing, with similar increases in OR apparent in all 3 upper quartiles compared to lowest quartile.	Goudarzi *et al* 2017a
Incidence of asthma & allergy in children (questionnaire at ages 5 & 13y; skin prick test 13y);	Infant cohort from the Faroe Island (n=559; 1997-2000); 5 PFAS measured in maternal blood (pregnancy week 34-36) and in children age 5 & 13 years; IgE levels measured in cord blood and at age 5y	Elevated PFAS previously associated with increased asthma risk; study aimed to investigate interactive effect of MMR vaccination (ordinarily has some protective effect; but numbers unvaccinated in this study quite small); Overall, no association between higher PFAS and asthma or allergies, but in a small sub-group (n=22) of MMR-unvaccinated children higher levels of all 5 PFAS (only at age 5 & not pre-natal) associated with increased OR for asthma at ages 5 and 13; associations reversed by MMR vaccination; no effects on IgE levels	Timmermann *et al* 2017
Thyroid disease and thyroid hormone changes			
Serum levels of thyroid hormones TSH, T3 (F/T), T4 (F/T) & testosterone	Cross-sectional; serum PFAS NHANES database 2011-12	Some weak (only some statistically significant) associations were found between PFOS, PFNA and TSH (positive; adolescent males; negative adolescent females); PFOS, PFOA & PFNA increases positively associated with FT4, but only in females 20-<40y; PFOA positively associated with FT3 & TT3, but only in females 60-80y. No effects seen on testosterone levels	Lewis *et al* 2015 [This study similar to Jain 2013, reviewed in 2015 & 2016 reports]
Association of 16 PFAS with thyroid hormone levels in children with congenital hypothyroidism	Case-control study; n=27 cases; 13 controls; South Korean hospital 2009-10;	Total PFAS 2.6-44.7 ng/mL in cases; 2.4-22.4 ng/mL controls; higher levels in cases achieved statistical significance only for PFOA, PFNA, PFDA and PFUnDA.	Kim *et al* 2016
Association of serum TSH and thyroid hormones with exposure to 19 POPs (including 7 PFAS)	Cross-sectional study of 391 mother-infant pairs in a Norwegian Newborn Screening program (2007-09);	Several POPs affected TSH and TH levels; effects were small and variable; and generally within normal clinical range; maternal TSH & some TH showed reductions in highest quartile only; different hormones associated with PFDA, PFUnDA (but no effect for total PFAS); OC effects > total POPS; PFOS increased maternal TSH, but no effect on infants; complex statistical analysis to assess confounding variables	Berg *et al* 2017
Review of published studies of PFAS effects on thyroid hormones & thyroid dysfunctions	Assessed studies: 3 cross-sectional, 1 case-control and 6 cohort	Only a small number of studies with comparable data; some consistency of a positive association between maternal and teenage PFAS exposure (mainly PFOS & PFHxS) and plasma TSH levels (mainly aged ≥11y); authors suggested further studies needed to confirm effects	Ballesteros *et al* 2017

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Review of published studies of PFAS effects on thyroid hormones & thyroid dysfunctions	Review of 5 US studies (general population) and 10 other studies in pregnant women	Confirms a range of (relatively inconsistent) positive & negative associations between some PFAS and thyroid hormone status; notes difficulties that observational studies unable to assess possible confounding effects of other POPs and EDCs; speculates on possible mechanisms involving inhibition of TH synthesis, transport and protein binding.	Lee et al 2017
Altered birth outcomes and fertility changes			
Review of published studies of PFAS* effects on fertility *note comment below in 2.1.3 on possible analytical artefacts*.	Study inclusion criteria included: PFAS & reproductive hormone measurements, semen characteristics or time-to-pregnancy (TTP); 16 studies in men; 11 studies in women	Overall, the studies lacked consistency of outcomes; the evidence that PFAS exposure could affect semen quality or levels of reproductive hormones was inconclusive, although there were some subtle associations between higher PFOS and lower testosterone or abnormal semen morphology in some studies; 4 out of 8 studies in women suggested a prolonged TTP with higher PFOS or PFOA, but only 1 study found such an association when nulliparous women were considered; the authors concluded that any association with female fecundability in parous women is most likely not causal.	Bach et al 2016 [a follow-up review to the 2015 & 2016 studies on human foetal growth considered in my 2015 & 2016 reports]
PFOSA effect on fecundability	Plasma PFOSA at 18 weeks gestation and self-reported TPP; n=451 primiparous women from Norwegian Mother and Child Cohort Study (MoBa).	PFOSA only measurable in approx. half the women; median 0.03 ng/mL. Age- and BMI-adjusted relationship between interquartile PFOSA and TPP 0.91 (CI: 0.71-1.17). The outcomes of this study were consistent study with the previously (2016) summarised study by Vestergaard et al (2012), but failed to confirm a previously reported prolongation of TPP associated with PFOSA (but not other PFAS) and 4 other chemicals (Louis et al 2013).	Whitworth et al 2016
Effect of PFAS on birth weight	Birth weights and serum levels 7 PFAS measured in cord blood (n=118) in Chiel Woman's Hospital, Seoul, S. Korea; June-Nov 2008	Seven PFAS detected in serum, with mean PFOA (1.11.ng/mL) and PFOS (0.87 ng/mL) being dominant. No association found between birth weight and any PFAS.	Lee et al 2016
Effect of POPs (incl 8 PFAS) on birth weight	Birth weight and multiple POPs measured in maternal blood during ante-natal visits to hospitals in Greenland. Poland & Ukraine; n=1321; 2002-2004	Adjusted associations between term birth weight and chemicals exposures suggested 2-SD increases in MEHHP (phthalate metabolite), PFOA and p,p'-DDE were associated with lower birth weight (-87g; -43g and -1335g respectively). MOiNP (another phthalate metabolite was associated with an increased birth weight (46g); elastic net regression modelling was used to demonstrate the effects	Lenters et al 2016
Effect of PFOA, PFOS and some EDCs on birth weight	Birth weight and multiple POPs measured in maternal blood during ante-natal visits to hospitals in Sweden (n=159) and Norway (n=265)	Odds of Small for Gestational Age (SGA) birth weight were increased for PFOA in Swedish mothers (OR 2.85 CI 1.68 -16.4) but not in Norwegian mothers (OR 0.66 CI 0.33 -1.33). PFOS was not implicated in either cohort, but achieved near statistical significance in the Swedish cohort (OR 2.52 CI 0.93-6.77). None of the other chemicals (PCB_{153}, p,p'-DDE, HCB, β-HCH, t-NC) had effects in the Norwegian cohort, but all increased SGA odds in the Swedish cohort. Male offspring appeared to be more susceptible.	Lauritzen et al 2017
Effects of PFAS on birth weight; differentiation of linear- and branched-chain isomers	Birth weight and PFAS measured in cord blood for mother-infant pairs in Guangzhou, China; n= 321; Jul-Oct 2013	Higher levels of branched-chain PFOS isomers were associated with a lower birth weight (-126g; CI -196 to -57g per ng/mL), while the effect of linear PFOS isomers was less (-57g CI -103 to -11g per ng/mL). The effect was greater in male infants. Both total and linear PFOA was also associated with lower birth weight, but not other linear PFAS (PFNA, PFHxS, PFUnDA, PFHpA, PFBA, PFDoDA). The authors noted their results were consistent with those of 11 other published studies (graphical depiction).	Li et al 2017

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Effects of PFAS on birth weight	Birth weight and PFAS measured in cord blood for mother-infant pairs in Beijing, China; n= 170; Feb-June 2012	Mean serum concentrations (ng/mL) of PFAS were: PFOA 1.285; PFOS 1.228; PFHxS 0.23; PFNA 0.224; PFDA 0.1; and PFUnA 0.085. Small correlation coefficients showed PFHxS (0.16 p=0.038) and PFOA (0.202 p=0.008) prolonged gestation time, and for male infants only, PFHxS correlated positively and PFUnA negatively with birth length. However, both univariate and multivariate regression analysis showed no statistically significant associations with birth weight, birth length or PI. The authors noted that the lower levels of PFAS in their study, compared to other published studies, may have been responsible for the failure to replicate other findings.	Shi *et al* 2017
Effects of PFAS on birth weight;	Birth weight and PFOS, PFOA, PFHxS and PFNA measured in maternal serum collected during 1st trimester ante-natal visits to hospitals in Spain; n=1202; 2003-2008.	Median PFOS 6.05 ng/mL and PFOA 2.35 ng/mL were most commonly found PFAS; no clear effects on any PFAS on birth outcomes, but PFOA, PFHxS and PFNA showed weak, non-statistically significant birth weight reductions (8.6 – 10.3g per doubling of exposure); PFOS showed an OR of 1.9 (CI: 0.98 – 3.68) for low birth weight in boys only; there was no association with maternal GFR (shown by Verner *et a*l 2015 to influence fetal growth; summarised in 2016 report)	Manzano-Salgado *et al* 2017a
Effects of PFAS on birth weight, with a special emphasis on the influence of adipokines	Birth weight, maternal blood PFOA & PFOS and cord blood adipokines measured in 168 mother-infant pairs in the Sapporo (Japan) cohort of the Hokkaido Study on Environment and Children's Health; Jul 2002 - Oct 2005	Median maternal PFOS and PFOA levels were 5.1 and 1.4 ng/mL and median total adiponectin and leptin levels were 19.4ng/mL and 6.2 ng/mL. Adjusted linear regression showed that PFOS increased total adiponectin levels (but not leptin levels) and decreased the infant Ponderal Index (PI; birth wt/length); the authors speculated that the effects of PFAS on birth weight may be associated with altered adiponectin-related metabolic functions.	Minatoya *et al* 2017
Effects of PFAS on birth weight, with a special emphasis on the influence of adipokines	Birth weight, maternal PFOA, PFOS & PFHxS and cord blood adipokines measured 1705 mother-infant pairs in the MIREC (Canadian) study; 2008-2011;	Median maternal plasma PFAS concs. (ng/mL) were: PFOS 4.6; PFOA 1.7, PFHxS 1.0; Bayesian Hierarchical Regression analysis showed little if any effects on birth weights; adjusted β slope values ranged from -0.1 to -0.04 CI ranges all included the null; similar analysis of relationships with leptin and adiponectin levels were also null; the authors suggested follow-up at a later stage of growth	Ashley-Martin *et al* 2017
Effects of PFAS on birth weight, with a special emphasis on the influence of maternal fasting glucose and lipid levels	11 PFAS were measured in maternal (27th week) & cord blood, as well as fasting plasma glucose, HDL lipoprotein cholesterol and triglycerides; n= 652; prospective cohort from the Healthy Start project at the University of Colorado Hospital; 2009 - 2014	Only 5/11 PFAS were detected in >50% of maternal plasma samples; only PFOA, PFNA & PFHxS levels were inversely associated with birth weight, and adiposity at birth was around 10% lower in the highest tertiles; PFOA, PFNA, PFDeA and PFHxS were inversely associated with maternal glucose, but not with lipids; the authors suggested that up to 11.6% of the effects of PFAS on neonatal adiposity could be attributed to decreased maternal glucose levels. PFOS had no effect on any of the measured variables in this study.	Starling *et al* 2017

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Review of published rodent and human studies on the effects of PFAS on birth weight	Birth weight, LBW and SGE outcomes assessed in 5 Cross-sectional and 13 cohort studies; compared with birth/fetal weight data from 12 PFOA studies in mice & 13 PFOS mouse studies	For PFOA, the pooled linear regression coefficient (LRC) was -12.8g (CI: -23 to 2.4; 12 studies) for a 1ng/mL increase in untransformed data and -27.1g (CI: -50.6 to -3.6; 9 studies) for transformed data (1 ln ng/mL). For PFOS, the untransformed pooled LRC was -0.92g (CI: -3.4 to 1.6; 8 studies), and for transformed data -46.1g(CI: -80.3 to -11.9). No consistent pattern emerged for study location or timing of blood sampling. Mouse studies confirmed that both PFOA (>5mg/kg/d) and PFOS reduced fetal body weights; analysing the data according to a framework for integrating epidemiological and toxicological data (Adami *et al* 2011) the authors concluded that the discrepancy between human and rodent blood levels eliciting the effects (100-1000x higher in rodents) reduces the biological plausibility of any causal association in humans.	Negri *et al* 2017
Hormonal and menstrual changes			
Effect of PFAS on sex hormones and insulin-like growth factor -1 (IGF-1) in pre-pubertal children at age 6-9y; exclusion criteria: boys with testosterone >50ng/dL and girls with menarche	Prospective cohort of 2,292 children in the C8 Health Project; mid-Ohio valley USA; sampled 2005-2006; 4 PFAS, estradiol, testosterone and IGF-1 measured in serum	Median PFAS concs (boys/girls, ng/mL) were: PFOS 22/21; PFOA 35/30; PFHxS 8/7; PFNA 1.7/1.7; significant negative associations were found in boys between PFOA & testosterone (-4.9% CI: -8.7 to 0.08); PFOS was negatively associated with testosterone (-5.8% CI: -9.4 to -2), estradiol (-4.0% CI:-7.7 to -0.1) and IGF-1 (-5.9% CI: -8.3 to -3.3); PFNA with IGF-1 (-3.5% CI: -6 to -1); In girls, the significant negative associations were: PFOS and testosterone (-6.6% CI: -10.1 to -2.8) and IGF-1 (-5.6% CI: -8.2 to -2.9); PFNA and IGF-1 (-3.8% CI -6.4 to -1.2), the dose-response relationships across PFAS quartiles was generally monotonic, but not always clearcut.	Lopez-Espinosa *et al* 2016
Effect of PFAS on menstrual cycles in women planning to become pregnant	Cross-sectional study of 950 women from 2 clinics in Shanghai, China; 2013-2015; 10 PFAS measured in plasma; menstrual cycle characteristics collated via questionnaires	The OR for higher levels of PFAS associated with self-reported history of irregular menstrual cycles were: PFOA 1.52 (CI: 1.08 – 2.15); PFOS 1.29 (CI: 0.98 – 1.70); PFNA 1.50 (CI: 1.03 – 2.07); PFHxS 1.80 (CI: 1.17 – 2.77). Similar OR were reported for PFOA, PFOS, PFNA and PFHxS for longer menstrual cycles, but negative OR were reported for self-reported history of menorrhagia (0.37, 0.57, 0.47, 0.14 respectively; the authors noted the difficulties of accurately estimating menstrual blood loss vi self-reporting, and misclassification was therefore a likely factor.	Zhou *et al* 2017
Endometriosis			
PFAS and endometriosis	Case control study; 495 women aged 18-45y scheduled for laparoscopy/laparotomy vs 131 age-/residence/matched controls; San Francisco & Salt Lake City hospitals, 2007-2009; 9 PFAS measured in blood	The OR (after adjustment for age, BMI & parity) in the operative sample were: PFOA 1.62 (CI: 0.99 – 2.66); PFNA 1.99 (CI: 0.91 – 4.33); slightly higher before adjustments; PFOS (1.86 CI: 1.05 – 3.30) and PFOA (2.58 CI: 1.18–5.64) increased the odds for moderate/severe endometriosis, although the odds were also attenuated with parity adjustment (OR = 1.50 and 1.86, respectively). The authors offered no explanation for the apparent selectivity of the PFAS effect, and suggested the association awaits confirmation	Louis *et al* 2012

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
PFAS and endometriosis, with emphasis on possible influence of oral contraceptive (OC) treatment of pelvic pain modifying menstrual blood loss	PBPK model used to simulate plasma levels of PFOA and PFOS from birth to age at study participation (range 18–44 years); prevalence & GM OC use based on NHANES data; in simulations, menstrual fluid loss (ml/cycle) in women taking OCs was assumed to be 56% of loss in non-users;	In the simulated population, PFAS level distributions matched controls in the epidemiologic study; OC use among women with endometriosis was 29% over 6.8 (SD: 3.1) years; among those without endometriosis OC use was 18% over 5.3 (SD: 2.8) years; the OR for an association between PFAS levels and endometriosis attributable to differential contraceptive use were 1.05 (CI: 1.02 - 1.07) for a $\log_e$ (ln) unit increase in PFOA and 1.03 (CI: 1.02 - 1.05) for PFOS. These were lower than the OR reported in the Louis et al 2012 Study summarized above; the authors concluded that OC use had no significant impact on any association between PFAS exposure and endometriosis.	Ngueta *et al* 2017
Neurodevelopmental & neurobehavioural effects			
PFAS and Attention Deficit Hyperactivity Disorder (ADHD) at age 7y.	Cross-sectional study of 282 children (out of 1526 mother-infant pairs) from the Taiwan Birth Panel Study (TBPS) & Taiwan Early-life Cohort (TEC); 2004-2005 recruitment; follow-up at age 7 (2011-2012); 3 validated questionnaires to assess ADHD; cord blood PFOA, PFOS PFNA & PFUA selected (out of 12 PFAS) for analysis based on detection rates and data availability	Mean cord blood levels (ng/mL) in the pooled cohort were: PFOS 4.8, PFOA 1.55, PFNA 4.5, PFUA 8.0 with generally higher levels in the TBPS cohort; there was no association between PFOA, PFOS or PFUA with ADHD symptoms, but PFNA was inversely associated with inattention and oppositional defiant disorder scores in a SNAP-IV test and with hyperactivity/inattention in SDQ scores. The authors cautioned about drawing conclusions about any causal relationship, citing the varied results from other previous studies on behavioural effects of PFAS (see further discussion in my 2016 report).	Lien *et al* 2016
PFAS and post-natal behavioural changes (including ADHD) at age 18mo.	Cross-sectional study of 59 children from the LINC (Linking Maternal Nutrition to Child Health) cohort; 2011-13; 7 PFAS measured in cord blood and child development through 1st 18 months assessed via questionnaires at 3mo intervals;	Mean (median, range) cord blood levels (ng/mL) in the cohort were: PFOS 1.6 (1.6, 0.57-3.2), PFOA 0.9 (0.87, 0.2 – 2.3), PFHxS 0.14 (0.145, 0.036-0.26), with 4 other PFAS generally at lower levels; there were no significant associations found between ΣPFAS and ADHD scores; a significant negative association was found for ΣPFAS with externalizing problem behaviour, but only in the crude data; after stratification for sex, boys with the 2nd & 3rd tertiles of PFOA had lower scores on this attribute, while girls showed the same effects in both the crude and adjusted data; the authors cautioned about drawing conclusions from a study with such small numbers.	Quaak *et al* 2016
PFAS and early-life development of communication skills in girls	Cross-sectional analysis of 432 girls from the nested case-control ALSPAC (UK) study; 1991-92; maternal serum PFAS (15 wk gestation) compared to communicative development test scores at age 15 & 38 mo.	Multivariate linear regression analysis showed associations that varied with maternal age at delivery; In daughters of younger mothers (< 25y), no effects seen with PFOA, PFHxS, PFNA; but for PFOS, every incremental 1 ng/mL was associated with a 3.82 point (CI: −6.18 to −1.47) lower vocabulary score at 15 mo and a 0.80 point (CI: −1.74 to 0.14) lower language score at 38 months; essentially, the study showed both positive and negative effects on some tests of communication development associated with selective PFAS; the patterns of response were inconsistent across PFAS type and maternal age	Jeddy *et al* 2017

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Personal behaviours in adults and their impacts on PFAS exposures	Cross-sectional study of 37 adults recruited in 2015 across North Carolina USA; 8 PFAS measured in serum; behavioural & other demographics collected at home interview;	Only 6 PFAS found in >50% of samples; GM values (ng/mL) were comparable to NHANES data (PFOS 5, PFOA 1.6, PFHxS 3.2, PFDA 0.3, PFNA 0.7, PFHxA 0.14); males generally had higher levels than females; Few levels were associated with specific behaviours; e.g. use of filtration devices was associated with 28% lower PFOA, but higher (122%) PFHxA; PFHxS levels were higher in those who vacuumed less often or ate more microwaved foods; the authors' interpretation was that personal behaviours may be an important determinant of PFAS exposure	Siebenaler et al 2017
Potential artefactual influences on relationship between PFAS exposure and ADHD	Simulated data from the Danish National Birth Cohort to test the hypothesis that exposure-related early fetal loss during pregnancy could bias post-natal tests	The analysis showed that, even if PFAS do not cause ADHD but significantly reduce fetal survival, negative bias could occur, although the magnitude of the bias was generally small; adjustment for common causes of the outcome and fetal loss can reduce the bias	Liew et al 2016
Altered lipids			
Comparison of maternal & cord blood glucocorticoids (precursors for cholesterol synthesis	Hospital-based birth cohort (n=185) Sapporo Japan; July 2002 – Oct 2005	Prenatal maternal exposure to PFOS (but not PFOA) produced a dose-related decrease in cortisol $1^{st}-4^{th}$ quartile (-24 ng/mL CI: -.48, -12) and cortisone (-63 ng/mL CI -133, -27) cord blood levels and higher dehydroepiandrostenedione (DHEA) levels (1.3 ng/mL CI: 0.2, 1.8); the DHEA trend for PFOA was negative (-1.2 ng/mL CI: -0.25, -1.7). No effects on androstenedione levels	Goudarzi et al 2017b
Asthma and lung function			
Association of PFAS with asthma; emphasis on 16-kDa club cell secretory protein (CC16), an asthma biomarker	Case control study of 231 asthmatic children vs 225 controls from the Generic & Biomarkers study for Childhood Asthma (GBCA) Northern Taiwan, 2009-2010; 9 PFAS measured in serum; CC16 in urine; asthma symptoms at structured interview	Asthmatic subjects had generally higher PFAS serum levels than controls; e.g. medians PFOS 36.9 boys 28.2 girls vs 29.9 and 28.8 respectively (p=0.002); PFOA 1.3 and 0.8 vs 0.5 and 0.5 (p<0.001); similar findings for PFHxS & PFDoA, smaller differences for other PFAS; urinary CC16 was negatively associated with PFOS, PFOA, PFDA and PFNA, especially among asthmatic and non-asthmatic males; among girls, PFDA was the only PFAS associated with CC16 (-ve); significant (p<0.15) interactive effects on CC16 were found for asthma and PFOS, PFOA PFBS and PFHxA in all subjects.	Zhou et al 2017a A follow-on study from the Zhu et al 2016 study reported below
Association of PFAS with asthma; emphasis on sex hormone status	Case control study of 231 asthmatic children vs 225 controls from the Generic & Biomarkers study for Childhood Asthma (GBCA) Northern Taiwan, 2009-2010; 9 PFAS, estradiol and testosterone measured in serum;	Among asthmatics, PFAS were positively associated with estradiol levels and negatively associated with testosterone; the changes were small for PFOS (0.001 to 0.004 ln hormone level change per ng/mL PFAS increase), but somewhat larger for PFNA (0.025 – 0.142), which was the only PFAS effect in non-asthmatics (increasing estradiol 0.206 pmol/L per ng/mL PFNA); the authors concluded that reproductive hormones amplify the association between PFAS exposures and asthma among adolescents	Zhou et al 2017b A follow-on study from the Zhou et al 2016 study reported below
Association of PFAS with sex hormone status	Cross-sectional study of 225 adolescents from the Generic & Biomarkers study for Childhood Asthma (GBCA) Northern Taiwan, 2009-2010; 10 PFAS, estradiol and testosterone measured in serum;	Median levels of PFOS (males 29.9,females 28.8 ng/mL) and PFTA (m 6.0; f 4.5 ng/mL) levels were highest of all the PFAS; a positive association between PFNA and estradiol was the only significant interaction, but when stratified for sex, more significant associations were found in males (PFOS, PFDA, PFHxA, PFNA) for interactions with testosterone and estradiol (PFOA, PFHxS); in females, only a weak negative association was found for PFNA for testosterone.	Zhou et al 2016

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Association of PFAS with asthma; emphasis on T-helper cell cytokine status	Case control study of 231 asthmatic children vs 225 controls from the Generic & Biomarkers study for Childhood Asthma (GBCA) Northern Taiwan, 2009-2010; 10 PFAS, T-Helper cell cytokines T_H1 (interferon IFN-Y & interleukin IL-2) and T_H2 (IL-4 & IL-5) measured in serum;	Asthmatic subjects had generally higher PFAS serum levels than controls (same data as Zhou et al 2017b above; but not stratified for gender); the pattern of TH1 and TH2 cytokines and serum IgE levels differed in asthmatics and non-asthmatics; serum PFAS were positively associated with T_H2 cytokines and inversely with T_H1 cytokines among male asthmatics, but among females, no significant associations were found between PFAS & T_H2 cytokines; the authors concluded that increased PFAS may promote TH cell dysregulation and alter the availability of key T_H1 and T_H2 cytokines; the impact on asthma development appeared to be greater in males.	Zhu et al 2016 A precursor to the two Zhou et al studies reported above
Effect of PFAS on lung function in children (association with asthma?)	Case-control study of 132 asthmatic children and 168 non-asthmatic controls; recruited 2009-2010 in Genetic & Biomarkers Study for Childhood Asthma (GBCA), Taiwan; lung functions measured by spirometry and via questionnaire;	Serum PFAS in cases higher than in controls; adjusted OR ranged from 0.99 for PFHxA (CI 0.8 to 1.21) to 2.76 for PFOA (CI 1.82 to 4.17); the OR for PFOS was 1.3 (CI: 1.0 to 1.69); OR for PFHxS, PFNA and PFTA were all sig >1.0; PFAS levels were significantly negatively associated with three pulmonary function measurements (forced vital Capacity (FVC); forced expiratory volume in 1s (FEV1); forced expiratory flow 25–75% (FEF25–75), but only among children with asthma; adjusted slope coefficients between lung function and PFAS ranged from −0.055 (CI: −0.10 to −0.01) for FVC and PFOS; to −0.223 (CI: −0.400 to −0.045) for FEF25–75 and PFOA.	Qin et al 2017 (see also Zhou and Zhu studies above)
Diabetes, insulin resistance and glycaemic intolerance			
Association between PFAS exposure and the incidence and type of diabetic disease	Case-control analysis of C8 project data; Aug 2005-Aug 2006; blood levels of PFOA, PFOS, PFHxS and PFNA compared in 6,460 cases with diabetes (Type 1 n=820; Type 2 n=4,291 and 1,349 with missing data, or only blood sugar at study entry) vs 60,439 controls	Overall, PFAS levels were lower in those with diabetes, especially those with Type 1; age- & sex-adjusted ORs (CI) for Type 1, Type 2 and uncategorized diabetes and elevated PFAS were: PFOS: 0.65 (0.6-0.7), 0.86 (0.8-0.9) 0.93 (0.86-1.03) PFOA: 0.7 (0.65-0.74) 0.9 (0.89-0.91) 0.9 (0.88-0.97) PFHxS: 0.59 (0.54-0.64) 0.74 (0.71-0.77) 0.84 (0.78-0.9); PFNA: 0.65 (0.57-0.74) 0.94 (0.88-1.0) 0.95 (0.85-1.06). Further adjustments for eGFR and other covariates did not eliminate these inverse associations; the authors suggested the effects could be related to a protective effect on pancreatic islet cell viability (shown in mouse studies), or to an increased oxygen-carrying capacity sparing anoxia in these cells	Conway et al 2016
Association between PFAS exposure and the incidence of Type 2 diabetes in high-risk adults	Baseline plasma PFAS levels measured in 957 subjects in a multicentre Diabetes Prevention Program; July 1996 – May 1999; subjects randomized to placebo or lifestyle intervention groups; glycaemic indicators measured annually up to 4.6y of trial	Plasma PFAS levels were comparable with the NHANES database; at baseline, doubling of PFOS & PFOA plasma levels were associated with small changes (higher) in insulin resistance; β-cell function, fasting proinsulin, and glycated haemoglobin; there was no strong evidence of associations between plasma PFAS and diabetes incidence or prospective change in glycaemic indicators during the follow-up period;	Cardenas et al 2017
Does lactation lower diabetes risk by promoting the elimination of POPs?	Breastfeeding history was assessed in 4479 women from the NHANES database (1999-2006); diabetes identified by self-reporting or HbA1C >.5%; 24 POPs measured among sub-samples of 668-1073 subjects	The OR (CI) for having diabetes in women with & without a lactation history were: 0.83 (0.61-1.13) for 1-2 lactation periods (≥ 1 month) and 0.63 (0.44 – 0.91) for ≥ 3 lactation periods; lifetime lactation history was inversely associated with serum levels for 17/24 organochlorines, PCBs and PFAS; comparing ≥ 3 lactations with no lactations, the reduction in diabetes ranged from 12% (PCB-196) to 30% (chlordane), with the PFAS effect intermediate (PFOS 20%, PFOA 21%, PFNA 13%);	Zong et al 2016

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Adiposity, metabolic dysfunctions & growth			
PFAS effects on adiposity in early and mid-childhood	Cross-sectional study of 1,006 children (median age 3.2y) and 876 children (median age 7.7y) from Project Viva cohort, Massachusetts, USA; child growth characteristics compared with pre-natal (1999 – 2002) maternal PFAS levels	The pre-natal maternal PFAS median concs (ng/mL) were: PFOS 24.8, PFOA 5.6, PFHxS 2.4, PFNA 0.6; Small increases in adiposity were seen in girls (not boys) only at mid-childhood for all pre-natal PFAS; for PFOA the incremental changes across the quartiles were 0.21 kg/m2 (CI: -05 to 0.48) for BMI, 0.76 mm (CI: -0.17 to 1.7) for subscapular/triceps skinfold thickness; and 0.17 kg/m2 (CI: -0.02 to 0.36) DXA total fat mass index; the authors acknowledged that the effects were small and not across all the growth periods	Mora *et al* 2016 (see also Fleisch et al 2017 below)
PFAS effects on metabolic functions in mid-childhood, with emphasis on adipokines	Cross-sectional study of 665 mother-child pairs in Project Viva, Massachusetts USA, recruited 1999-2002; maternal PFAS measured at 1ˢᵗ prenatal visit (9.6 weeks gestation); child plasma at 7.7y (median age)	Maternal pre-natal and children's concs (med. ng/mL) PFOS 24.4 & 6.2; PFOA 5.3 & 4.2; PFHxS 2.5 & 2.2; PFNA 0.6 & 1.7; PFDeA only measured in children (0.3); an interaction resulting in lower insulin resistance in children (HOMA-IR) was most pronounced for PFOA -15.6% per interquartile range; CI -25.4 to -4.6 in females; -6.1% CI: -16.2 to 5.2 in males; there were no associations found between any pre-natal maternal PFAS levels and leptin, adiponectin or HOMA-IR in children; overall the study found no PFAS-related adverse effects on metabolic function in mid-childhood	Fleisch *et al* 2017 (see also Mora et al 2017 above)
PFAS effects on adiposity in girls at age 9	Cross-sectional study of 359 girls age 9 in Avon Longitudinal Study of Parents & Children (UK); maternal plasma PFAS measured at 1991-92 enrolment 15 weeks gestation;	Maternal PFAS (median ng/mL) were: PFOS 19.7; PFOA 3.7, PFHxS 1.6, PFNA 0.5; levels sl higher where mothers breast-fed & sl lower with earlier menarche; no associations were found between any PFAS and % total body fat in girls; some minor variations were noted for PFOS & PFOA when the data stratified according to maternal education.	Hartman *et al* 2017
Effects of PFAS on cardio-metabolic functions associated with the World Trade Center Disaster (WTCD)	Case-control study of children born between 11 Sept 1993 & 10 Sept 2011 (day before WTCD) 123 enrolled WTC Health Registry vs 185 matched controls; fasting blood collected to analyse 11 PFAS, blood lipids & insulin resistance (HOMA-IR)	Most detected PFAS were higher in cases vs controls; e.g. median ng/mL PFOS 3.73 vs 2.78; PFOA 1.81 vs 1.39; PFHxS 0.67 vs 0.53; no difference were observed for body weight characteristics; adjusted multivariable regression analyses showed significant positive associations for PFOA with triglycerides (15.1% change), total cholesterol (9.2%), and LDL cholesterol (11.5%); PFHxS levels were associated with decreased HOMA-IR (-8.6%), PFOA & PFNA were associate with increased brachial artery distensibility.	Koshy *et al* 2017
Effects of PFAS on cardio-metabolic functions & BMI in children	Cross-sectional study from the INMA (Spanish) birth cohort 2003-2008; 2150 women recruited 1ˢᵗ trimester; mother-child pairs assessed at age 6mo, 4 & 7y; n=1154 with wt gain 6mo, n=1230,with BMI age 4, n=1086 with BMI age 7; blood lipids in sub-set n=627.	PFOS (GM 5.8 ng/mL) & PFOA (2.32 ng/mL) most commonly found PFAS; overall, no associations found between pre-natal PFAS and combined CM risk score (standardized sum lipids, blood pressure & body weight); some individual values were significant; e.g. doubling PFHXS & triglycerides; doubling PFNA and CM-risk score; the authors noted that PFASS levels were measured early in pregnancy, before changes in GFR likely, but adjusting for GFR made no difference to the results	Manzano-Salgado *et al* 2017b

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Hyperuricaemia			
Relationship of PFAS with hyperuricaemia in children	Cross-sectional study of 225 Taiwanese children aged 12-15y; recruited 2009-2010; 10PFAS & serum uric acid measured	6 PFAS found in >96% of samples, but 3 in <20%; highest was PFOS (ng/mL medians) 28.2 in boys, 29.9 in girls; hyperuricaemia (≥6mg/dL) also higher in boys (20.6%) than in girls (9.8%); Multivariate regression analysis showed that only PFOA showed significant association with serum uric acid; $\beta=0.14$ $p<0.05$; aOR for hyperuricaemia 2.16 CI: 1.29 to 3.61; no significant effects in girls; aOR for boys 2.76 (CI: 1.37 to 5.56); possible mechanisms could include interactions with renal organic anion transporters, or hepatic oxidative stress, but further research needed	Qin *et al* 2016
Effects on bone			
Do PFAS affect bone cell differentiation as a result of bone and bone marrow accumulation?	Bone and soft tissue biopsies from a female cadaver (49y old) were analysed for PFAS	PFOA (<LOQ - 0.41 ng/g), PFOS (<LOQ – 0.19 ng/g) and PFNA (<LOQ – 12 ng/g) were most commonly found in bone samples; PFOA was more prominent in bone marrow, while PFOS was more evenly distributed between trabecular bone and marrow; accumulation; no effect on *in vitro* osteoclast differentiation was related to PFAS; the paper includes a useful Table summarising bone PFAS in other human populations (Spanish, Finnish and US firefighters and general populations; and *in vitro* animals studies	Koskela *et al* 2017
A review of the effects of various environmental pollutants on chemokines related to bone healing	Survey of papers reporting effects of various chemicals with bone chemokines (mostly *in vitro* studies)	Pollutants covered included: PFAS (classified as an endocrine disrupting chemical) and other EDCs (BPA, BPAF, DEHP, DINP), some VOCs (benzene, xylenes etc) and some POPs (TCDD, PCBs), some heavy metals (Co, Ti) and asbestos; no studies identified relating to PFAS, but noted one study (Khalil *et al* 2016, reviewed in my 2016 report) that noted serum PFAS levels were inversely correlated with bone mineral density (BMD) of the femur and lumbar spine	Smith *et al* 2017
Liver & kidney			
Effects of PFOA on liver disease	Cross-sectional study of modelled PFOA serum levels in subject from the C8 Health Project (recruited 2005-2006; health surveys 2008-11); n=30,723 (incl 1,892 workers) for liver biomarkers; n=32,254 (incl 3,713 workers) for reported liver disease.	Serum PFOA modelled based using environmental fate & transport models and participant residential histories; no evidence of an effect of cumulative exposure (with or without a 10-year lag) on all liver disease (*n* = 647 cases), nor on enlarged liver, fatty liver, and cirrhosis only (*n* = 427 cases); no association with liver disease markers bilirubin or γ-glutamyltransferase; but a weak positive association with another liver disease marker (ALT) was found; 6% increase in ALT from 1st to 5th quintiles PFOA levels; OR for above-normal ALT 1.16 (CI 1.02 to 1.33)	Darrow *et al* 2016
Coronary heart disease			
Effects of PFAS exposure on coronary heart disease (CHD)	Prospective case-control study of 231 male Swedish farmers & rural residents recruited in 1990-91 and diagnosed with CHD between 1992 - 2009; 253 controls without CHD from same cohort; 8 PFAS measured in stored serum or serum collected at 2002-03 follow-up;	Noted that the epidemiological literature on relationships between PFAS exposure and CVD is inconsistent; therefore set out to study PFAS levels and CHD; cases generally had higher risk factors for CHD (elevated BP, cholesterol, tobacco use, type 2 diabetes); all PFAS levels were comparable in two groups, with all OR not significantly different from 1; PFHpA was the exception (a chance finding?), with 0.06 ng/mL higher in cases than in controls (0.04 ng/mL) and this led to higher RRs for the 3rd (OR 2.72 CI: 1.52 to 4.84) and 4th (OR 2.45 CI: 1.40 to 4.29) quartiles; PFOS levels were comparable (22.8 & 22.0 ng/mL); overall, the study failed to support previously reported relationships between PFAS and CHD.	Mattsson *et al* 2015

Disease or health indicator	Study details, (exposure years where available)	Outcomes and comments	Reference
Cardiovascular disease			
Do branched-chain isomers of PFAS have a greater effect on blood pressure (BP) changes?	Reports of PFAS causing hypertension have been inconsistent; this study set out to investigate BP changes in a cohort of workers in the Isomers of C8 Health Project in Shenyang, China; BP & PFAS measured in 1228 workers & 384 general residents; aged 22-96y; Jul 2015 – Oct 2016	Approx. 60% males & 36% females in sample classified as hypertensive; Adjusted odds ratios (aORs) for hypertension per ln-unit (ng/mL) increase in serum PFAS ranged from 1.10 (CI: 1.04 to 1.17) for PFBA to 1.26 (CI: 1.12 to 1.42) for 3 + 4 + 5m PFOS; branched PFOS isomers (aORs 1.26 for 3 + 4 + 5m-PFOS, 1.19 for 6m-PFOS, and 1.19 for Σ2m-PFOS) displayed a stronger inverse association than linear PFOS isomers (aOR 1.11 for n-PFOS). When stratified by sex, the positive associations were only found in females, except for aOR = 1.09 (CI: 1.02 to1.16) for PFNB in males.	Bao *et al* 2017 NB this is the first paper, to my knowledge, to differentiate the effects of linear from branched-chain PFAS

2.1   General comments on these studies:

The epidemiology studies published since my last review (2016) have not added any substantially new or concerning information on the potential health effects of PFOS. There have been some papers addressing endpoints that received only passing attention in my previous reviews (metabolic dysfunctions, including effects on glycaemic controls), some papers that expand on the previously covered main associations with adverse health effects (thyroid disease, reproductive and fertility changes, neurodevelopmental effects, effects on blood lipids, and immunomodulation), along with 1-2 papers on some new indicators (coronary heart disease, endometriosis and effects on bone and lung disease).

In relation to these new disease indicators, only the potential for PFAS to increase the risk of endometriosis was consistent across the two papers that studied this effect. There remains the possibility that changes in menstruation-linked PFAS elimination could provide a 'reverse causality' explanation, although the study of interaction with oral contraceptive use suggested that any such interaction would be small.

As noted in my 2016 Report, associations between PFAS exposures and changes in thyroid hormones were inconsistent, although small changes were commonly found to have statistical (but not clinical) significance. The three studies reviewed in Table 1, and the two recent reviews of the published literature, failed to clarify these inconsistencies.

The largest number of new studies relate to effects of PFAS on foetal growth and post-natal development. While there were a few studies that reported reduced birth weight associated with selected PFAS, the effects appeared to be quite weak and there were also some well-conducted studies that failed to show any significant effects for any PFAS. Some of the papers focussed on the ability of PFAS to modify adipokines and other metabolic processes (including modulation of glycaemic controls), with subsequent effects on pre- and postnatal weight gain.

In relation to effects of PFAS on lung function and asthma, most of the new studies confirmed higher levels of PFAS exposure among asthmatics and investigated possible links with hormonal changes and cytokines. While there appeared to be some positive associations, they were largely confined to asthmatics and not in non-asthmatic subjects, and there were some puzzling gender-related differences in response.

My 2016 report commented on the disparate results of studies investigating a link between PFAS exposures and diabetes related to glycaemic control, including insulin resistance. If anything, the new papers reviewed above add to the confusion. One reports an apparent protective effect of PFAS, another reports a small increased risk of diabetes among high-risk men, and another suggests the previous lactation history could be protective by promoting the elimination of PFAS.

There was one additional study, from the C8 Health Study cohort, that provided some confirmation of an issue raised in my 2016 Report, that these PFAS exposures (mainly PFOA) may cause liver disease. However, the Darrow *et al* (2017) paper only established a propensity to increase one liver disease marker (serum AST), with no association with frank liver disease.

There have been different interpretations of the state of the epidemiological literature. For example, Rapazzo *et al* (2017) undertook a systematic review of studies on PFAS and child health outcomes. They identified 64 studies for inclusion and performed risk of bias analysis on those studies, concluding that the risk of bias across studies was low to moderate. They identified six categories of health outcomes[1] - immunity/infection/asthma, cardio-metabolic, neurodevelopmental/attention, thyroid, renal, and puberty onset. While there were a limited number of studies for any one particular health outcome, they concluded that there is evidence for positive associations between PFAS and dyslipidemia, immunity (including vaccine response and asthma), renal function, and age at menarche. One factor they noted in particular was that, while PFASs are mixtures of multiple compounds, few studies examine them as such, leaving open the possibility that mixture effects remain largely unknown.

Using an evaluation methodology called the 'Navigation Guide' Lam *et al* (2017) identified 18 epidemiology studies and 21 animal toxicology studies relevant to a study of the effects of PFOA on foetal growth. Both the human and nonhuman mammalian evidence was rated as "moderate" in relation to quality and "sufficient" in relation to strength. Integration of these evidence ratings produced a final strength of evidence rating that PFOA is "known to be toxic" to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.

In a critical review of the methodologies for evaluating the current state of the science regarding PFAS effects on human early life exposure processes (until 18 years of age) Winkens *et al* (2017) commented particularly on methods for assessing exposures. They noted that efficient placental transfer of PFAS results in relatively high prenatal exposure compared with many neutral organic contaminants. The few biomonitoring studies that specifically target infants, toddlers and other children suggest relatively high serum concentrations of PFOS and PFOA in early life, with peak concentrations generally occurring sometime before the child reaches 20 months. This peak in serum concentrations is most likely explained by exposure via breastfeeding, ingestion of house dust and/or specific contact events with consumer products leading to high body weight normalized estimated daily intakes (EDIs). Although children have higher PFAS EDIs adults, these are not always reflected by higher serum levels of PFASs in children in cross-sectional biomonitoring studies due to the confounding effect of age and birth

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[1] These same study categories have been reviewed in my 2016 & 2017 reports

cohort, and different exposure histories due to production changes. Longitudinal exposure studies measuring internal and external exposure (for multiple pathways and PFAS) at several time points during early life were strongly encouraged by these authors to understand temporal changes in exposure of individual children.

2.2 Immunomodulatory effects

The immune modulatory effects received particular attention in my 2016 report, primarily because they have been alleged to impact immune responses to vaccination in children and that they have been observed at the lowest reported blood PFAS concentrations. Indeed, Phillipe Grandjean has argued that US EPA HBGV values may be 1-2 orders of magnitude too high to protect children against these claimed immunomodulatory effects of PFAS occurring at current 'background' levels of exposure (Grandjean 2016). His group at the University of Southern Denmark Public and the Harvard School of Public Health have been responsible for most of the studies reporting positive effects on immune responsiveness, although in my 2016 report, I noted there were a range of reports from other sources that demonstrated inconsistencies with regard to which PFAS and which vaccines were associated with these responses. I also commented on the difficulty of assessing effects due to PFAS in the light of potential confounding effects of exposures to other immunomodulatory chemicals, including polychlorinated biphenyls (PCBs) and other POPs.

Since 2016, there have been three comprehensive reviews of the immunomodulatory effects of PFAS. The US National Toxicity Program (NTP 2016) concluded that :

> "*The NTP concludes that PFOS[2] is presumed to be an immune hazard to humans based on a high level of evidence that PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOS on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from studies in experimental animals that PFOS suppresses disease resistance and natural killer (NK) cell activity. The evidence indicating that PFOS suppresses multiple aspects of the immune system supports the overall conclusion that PFOS alters immune function in humans. Although the mechanism(s) of PFOS-associated immunotoxicity is not clearly understood, suppression of the antibody response and NK cell function are both potential mechanisms by which PFOS may reduce disease resistance*."

In contrast, a review by Chang *et al* (2016)[3] covering essentially the same set of epidemiological studies, concluded that:

> "*With few, often methodologically limited studies of any particular health condition, generally inconsistent results, and an inability to exclude confounding, bias, or chance as an explanation for observed associations, the available epidemiologic evidence is insufficient to reach a conclusion about a causal relationship between exposure to PFOA and PFOS and any immune-related health condition in*

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[2] A similar conclusion was reached in relation to the evidence for PFOA.

[3] It should be noted that Ellen Chang, who has also published a 2014 review of PFOA carcinogenicity that differed from the IARC assessment, is identified as a consultant (Exponent Inc), while most of the authors are associated with University Schools of Medicine or Public Health.

humans. When interpreting such studies, an immunodeficiency should not be presumed to exist when there is no evidence of a clinical abnormality. Large, prospective studies with repeated exposure assessment in independent populations are needed to confirm some suggestive associations with certain endpoints."

The third review is that published by FSANZ, as part of its evaluation of the critical toxicological effects of PFAS in developing the new TDI values (see below). This review was conducted by consultants Drew & Hagen (2016) and it reached conclusions that were more circumspect than those above:

> *"The weight of evidence indicates PFOS can adversely modulate immune system responsiveness and therefore presents a toxicological hazard for immune effects. However there are marked differences between studies with respect to the exposures necessary to cause such effects, and the quantitative aspects of pivotal studies have not been confirmed in independent investigations."*

Some cogent points raised in the Drew & Hagen review relate to disparities in the database, where studies achieving quite high blood levels of PFAS have been unable to replicate some findings seen in studies where the blood levels were substantially lower. The potential for different routes and modes of exposure (gavage vs diet) were discussed, as was potential impact of the dislocation between the time PFAS exposures and the immune responses were measured.

My overall conclusion about the effects of PFAS on the human immune system remains essentially the same as in my 2016 report. The variability in the relationships between individual PFAS serum levels, antibody responses and other measured immunological responses in human cohorts (mainly in children), suggests that the finding are too inconsistent to meaningfully ascribe causative relationships. The US and FSANZ conclusions also remarked on the low-moderate levels of evidence in human studies. The consequent classification of PFOS and PFOA as '*presumptive immune hazards to humans*', suggests that the classification is mainly based on the higher levels of supportive evidence in the animal studies.

2.3   Cancer

Community concerns have generally been exacerbated by media reports that commonly refer to the alleged 'cancer-causing' properties of PFAS. These media reports rarely specify the nature of the evidence, nor do they differentiate the carcinogenic classification of PFOA (the only PFAS so far classified by IARC in Category 2B – *possibly carcinogenic to humans*) from the evidence for carcinogenicity of PFOS, the principle contaminant around Defence bases and airports in Australia. Media reports also do not report cancer classification by other agencies or reviews, such as the draft US ATSDR 2015 statement that: "*There is no conclusive evidence that perfluoroalkyls cause cancer in humans".*[4]

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[4] This 2015 ATSDR review is still in draft form. Current advice on the ATSDR webpage (https://www.atsdr.cdc.gov/pfc/docs/pfas_clinician_fact_sheet_508.pdf) cites the IARC & US EPA evaluations and concludes .... *Additional research is needed to clarify if there is an association*.

While it has only been PFOA that has so far been assessed by IARC, one group of Mexican scientists have attempted to apply the IARC criteria to an assessment of the carcinogenicity of PFOS (Arrieta-Cortes *et al* 2017). For what it is worth, their assessment of PFOS was that the epidemiological, animal and mechanistic evidence is *inadequate*, suggesting that PFOS is not currently classifiable for carcinogenicity (equivalent to IARC Group 3).

The issue of PFAS carcinogenicity was addressed in my 2015 and 2016 reports, where I reviewed much of the evidence considered by IARC in relation to PFOA, and included a range of other papers that mostly concluded no relationship with cancer. This 2017 update reviews some additional reports relating to potential carcinogenicity of PFAS that were not covered in my 2016 review.

In a follow-up study to the one on breast cancer incidence in Inuit women that I reviewed in 2016, Bonefeld-Jørgensen *et al* (2014) reported on breast cancer incidence related to PFAS exposure in a larger group of Danish women. In a nested case-control study within the Danish National Birth Cohort (DNBC) Study from 1996-2002, ten PFAS were analysed in the serum of 250 women diagnosed with breast cancer and compared with 233 matched controls. PFOS, PFOA, PFHxS, PFNA and PFOSA were detected in all samples, with mean levels (ng/mL) 30.6, 5.2, 1.2, 0.5 and 3.5 respectively in the controls. Relative risk (RR; neither crude nor adjusted) estimates for breast cancer in this study failed to show any relationship with PFAS exposure, except for a weak association for PFOSA (crude RR 1.03, CI: 1.0 – 1.07; adjusted RR 1.04 CI: 0.99 – 1.08), and an inverse relationship for PFHxS (adjusted RR 0.66 CI: 0.47-0.94).

In a review of the relationships between breast cancer and environmental pollutants, Rodgers *et al* (2018) noted that many common environmental chemicals are mammary gland carcinogens in animal studies, but the long latency and multifactorial etiology make evaluation of these chemicals in humans challenging. However, they also noted that mammary carcinogens in animals often activate relevant hormonal pathways, or enhance mammary gland susceptibility to carcinogenesis. They reviewed 158 papers published since 2007, focusing on whether the study designs captured relevant exposures and disease features suggested by toxicological and biological evidence of genotoxicity, endocrine disruption, tumor promotion, or disruption of mammary gland development. They identified papers that suggested a higher risk with environmental exposures to DDT, dioxins and air pollution, with RR estimates ranging from 2.14 to 5.0 and occupational exposures to solvents and other mammary carcinogens, such as gasoline components (risk estimates ranged from 1.42 to 3.31). They were only able to identify 4 recent studies relating to PFAS, including the two studies reviewed in my 2016 Report (Bonefeld-Jørgensen *et al* 2011 and Ghisari *et al* 2014), and the Bonefeld-Jørgensen *et al* (2014) reviewed above. The other was an occupational study of PFOA exposure in 3M plants that did not control for breast cancer risk factors or specify whether estimates were among male or female workers.

There is one recent study that presents some rather disturbing data on a possible link between PFAS exposure and cancer (Mastrantonio *et al* 2017). This ecological study surveyed deaths (over the period 1980-2013 from a local population of 143,605 in 2011) from cancer and other diseases in 24 municipalities in the Veneto region of Italy where there had been a long-standing (since 1964) local PFAS contamination of groundwater from a nearby manufacturing facility. These death rates were compared with similar data from 56 surrounding 'uncontaminated' municipalities (population 588, 012). The study

reported significantly elevated relative risks (RR), allegedly adjusted for age, socioeconomic status and smoking habits, as follows:

Table 3 Number of deaths (Deaths), standard mortality rates (SMRate) and relative standard errors (SE) for the PFAS contaminated and uncontaminated municipality areas in the total population (males and females) in the period 1980–2013. Relative risk (RR) and 95% confidence intervals are also reported. Statistically significant RR are evidenced in bold

Mortality causes	Contaminated area			Uncontaminated area			
	Deaths	SMRate	SE	Deaths	SMRate	SE	RR
All causes	41841	1032.55	5.06	143072	932.56	2.47	**1.11 (1.10–1.12)**
Liver cancer	337	8.43	0.46	1544	10.07	0.26	**0.84 (0.74–0.94)**
Kidney cancer	258	6.39	0.40	918	5.96	0.20	1.07 (0.93–1.23)
Bladder cancer	282	7.15	0.43	1029	6.88	0.21	1.04 (0.91–1.19)
Pancreatic cancer	663	16.52	0.64	2590	16.93	0.33	0.98 (0.90–1.06)
Leukemia	376	9.24	0.48	1358	8.74	0.24	1.06 (0.94–1.19)
Non-Hodgkin's lymphoma	268	6.69	0.41	1138	7.38	0.22	0.91 (0.79–1.04)
Breast cancer	813	19.68	0.69	3031	19.15	0.35	1.03 (0.95–1.11)
Diabetes	887	21.76	0.73	2622	17.17	0.34	**1.27 (1.17–1.37)**
Cerebrovascular disease	4592	113.51	1.68	14284	94.05	0.79	**1.21 (1.17–1.25)**
Myocardial infarction	3358	83.23	1.44	11211	73.38	0.69	**1.13 (1.09–1.18)**
Alzheimer's disease	267	6.59	0.40	801	5.30	0.19	**1.24 (1.08–1.43)**
Parkinson's disease	203	5.05	0.35	647	4.33	0.17	**1.17 (1.00–1.37)**

There were additional Tables where the data were broken down by gender, with generally slightly higher RR estimates for those conditions that achieved statistical significance. It is noteworthy that the two cancers considered by IARC to constitute the *limited evidence* in the PFOA Monograph (kidney and testicular cancer in men), were not significantly elevated in the Italian study (RR 1.07 CI: 0.9 to 1.28; 1.86 CI: 0.81 to 4.27).

It is somewhat unusual that that so many unrelated cancer and non-cancer deaths achieved statistically significant RR value >1. I have some issues (see below) with the authors' interpretation and conclusions from the study:

- The study is ecological, generally considered to be the weakest design from an epidemiological viewpoint, because of the lack of individual level data for either outcome or exposure.
- The designation of municipalities as 'contaminated' areas was based on reports from local water authorities where PFAS measured in drinking water exceeded arbitrary 'standards (30 ng/L for PFOS and 500 ng/L for PFOA and other PFAS), although the actual PFAS concentrations were not reported. The 'uncontaminated' areas also reported PFAS levels that exceeded LOQ (71 out of 2460 samples from 205 sampling points in 1st sampling; 40 out of 2712 samples from 226 sampling points). In some samples in the 'uncontaminated' area, PFAS actually exceeded the arbitrary standards (e.g. highest PFOA 1173 ng/L; highest PFUnA 640 ng/L), and it is not clear whether these results were used to exclude the municipalities from the death rate analysis.
- The 'contaminated' municipalities are all clumped together, suggesting this may be a town, whereas the 'uncontaminated' municipalities are spread all over the region. There were a large number of municipalities in the region that were not included.
- No data were presented on PFAS water levels in the contaminated region, nor in people living there, so it is not possible to determine whether the body burden of any PFAS is actually elevated in the contaminated region. It may be possible to draw inferences from studies elsewhere where these data have been presented. For example, Strubleski *et al* (2017) reported blood levels of several PFAS from a region of Sweden where local water contamination had been measured at >20ng/L PFOS and >40ng/L PFHxS. While PFHxS plasma concentrations in people living in the region were significantly higher than in controls from outside the region, the median differences were not marked (2.0 – 6.4 ng/mL compared to 1.7). PFOS levels were also not markedly different (14 – 14.5 ng/mL vs 12) and were suggested to be in decline. Worley *et al* (2017) also reported serum and urine levels of PFAS from a region in Decatur, Alabama where local water contamination had occurred as a result of discharge from a manufacturing plant to a local wastewater

treatment facility. Serum PFAS sampled in 2010 and 2016 (ng/mL GMs PFOA 16.3 & 11.7; PFOS 39.8 & 23.4; PFHxS 6.4 & 7.7; PFNA 1.7 & 0.8) were generally higher than NHANES data from 2009-10 and 2013-14 cohorts (PFOA 3.07 & 1.94; PFOS 9.32 & 4.99); PFHxS 1.66 & 1.35; PFNA 1.26 & 0.675), but the differences were not marked, and in decline. If these data can be extrapolated to the Italian situation, it suggests that the difference in PFAS exposures may not be very large between the 'contaminated' and 'uncontaminated municipalities (see also comments in 3.2 below).

- The RR data appear to have been adjusted for age, but although comparisons were made between the two areas on the basis of a 'deprivation index' and a rather crude estimate of smoking rates, the authors do not appear to have adjusted for these in the analyses presented in the tables.

- Noting that deaths from cardiovascular disease and myocardial infarction are elevated, this is strongly suggestive of smoking being a relevant factor. Also, diabetes deaths are elevated, so that in itself would be expected to increase the vascular deaths.

- The adjustments for socioeconomic status and smoking were rather crudely based, but there were no other risk factors considered for outcomes found to be elevated.

- The authors did not present an external analysis of the 'contaminated' area against the whole region first. This could have determined the expected numbers of death based on population rates and then these could have been used to calculate the SMRs. Just going straight into an internal analysis comparing the two areas tells you nothing about how they compare with the overall general population. One area may be higher than the other, but if both are lower than what you would expect based on an SMR analysis, then the excess for one area isn't very meaningful.

- For the cancer analysis, mortality data were used, which is a poorer measure than incidence (acknowledged by the authors). Health care differences between the areas could be important in this circumstance.

2.4   Possible confounding factors in studies

The Danish group that has published several papers on reproductive outcomes and foetal growth raised a warning about potential analytical artefacts that could influence study reliability (Bach *et al* 2017). They noted a consistent decline in measured PFAS in paired samples where whole blood was transported before plasma separation and freezing, compared to the paired samples where the plasma was immediately processed and frozen. The differences were seasonal (greater in winter than summer) and different for specific PFAS (e.g. PFOS declined 29%, while PFOA showed no decline. The overall changes across 12 PFAS were variations ranging from -77% to +38%.

The issue of possible 'reverse causality' was raised in relation to several of the studies reviewed in my 2015 and 2016 Reports. That is, the apparent increased incidence of disease or other biomarker in the highest blood level quartiles or tertiles, may have resulted simply because the disease has caused PFAS to accumulate to a higher level in those parts of the cohort. This concept of 'reverse causality was further explored in a recent paper by Ruark *et al* (2017). Using physiologically-based pharmacokinetic (PBPK) models of PFOS and PFOA, they used Monte Carlo simulations, including estimated distributions of age at menopause, to replicate the data on delayed menopause from two published studies (Taylor *et al*, 2014[5]; and Knox *et al*, 2011). The analysis showed that the reported associations between PFAS and delayed menopause could be substantially explained by pharmacokinetic factors. Essentially, the increased PFAS retention in women with delayed menopause could be explained by the relatively late loss of a significant pathway for elimination (via menstrual blood loss).

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[5] Reviewed in my 2016 Report

The issue of 'reverse causation' was also addressed by Dhingra *et al* (2017), who investigated the effects of menopause and changing kidney function in relation to PFOA serum concentrations. Both earlier menopause and reduced eGFR were shown to be significantly associated with higher PFOA levels (measure, but not modeled), suggesting that these contribute to higher retention of PFOA by reducing elimination pathways.

The potential confounding effect of concurrent exposure to persistent organic pollutants (POPs) such as PCBs and organochlorines has been raised in relation to a number of the endpoints studied for PFAS. Arrebola *et al* (2014, 2015) have reported a clear role for POPs, such as PCBs, DDE and HCB, in modifying serum lipids and in promoting insulin resistance. None of the studies on PFAS-related changes in serum lipids or insulin resistance reported above (except the Zong *et al* 2016 study of the impact of lactational history) have attempted to control for exposure to other POPs.

In a review of the potential impacts of endocrine disrupting chemicals (EDCs) on pre- and post-natal foetal development, Braun (2017) included PFAS as substances considered to increase adiposity in early childhood. However, he conceded the difficulties of evaluating and quantifying these effects on foetal development, in the face of confounding factors such as mixed exposures and possibly differing periods of susceptibility.

2.5   Mechanistic insights

Neither my 2015, 2016 Reports nor this 2017 update, purport to delve deeply into experimental studies or possible mechanisms for PFAS effects on biological systems. PPARα is a ligand-dependent transcription factor that is activated by various endogenous as well as exogenous compounds. It is involved in the regulation of a variety of biological processes, such as nutrient metabolism, energy homoeostasis, immunological response and xenobiotic metabolism. My 2016 report noted that some effects of PFAS appear to be related to activation of the PPARα receptor complex, while other effects probably have an independent action. Differences between humans and rodents in responses to PPARα receptor-mediated toxicity have made the human relevance of some health effects caused by PFAS controversial.

The four studies summarized below add some context to this information.

- Response differences in hepatic toxicity in mouse strains 18 months after gestational PFOA exposure in CD-1 and 129/Sv strains of mice were compared with wild type (WT) and PPARα-knockout (KO) strains. Pregnant mice were exposed daily to PFOA doses (0.01–5mg/kg/BW) from gestation days 1–17, with the female offspring necropsied at 18 months for pathological review of liver sections. Hepatocellular adenomas were observed in PFOA-exposed PPARα-KO 129/Sv and CD-1 mice, but were absent in untreated controls from those groups and WT 129/Sv mice. Hepatocellular hypertrophy was significantly increased by PFOA exposure in the CD-1 strain and an increased severity was found in the WT 129/Sv mice. PFOA significantly increased non-neoplastic liver lesions in PPARα-KO mice (hepatocyte hypertrophy, bile duct hyperplasia and hematopoietic cell proliferation). Evidence of different types of liver toxicity in PPARα-KO mice suggests that pathways other than PPARα receptor activation may be involved (Filgo *et al* 2015).

- The molecular mechanisms of PFOA-induced hepatotoxicity in mice may be relevant to human health. Both *in vivo* (male and female Balb/c mice dosed with PFOA at 0.05, 0.5, or 2.5 mg/kg/d for 28d) and *in vitro* (human hepatocyte cells, HL-7702) techniques were used to assess these mechanisms. Serum PFOA concentrations *in vivo* were claimed[6] to be at environmentally relevant levels (1200 & 970 ng/mL for male & female mice at 0.05 mg/kg/d). Liver samples examined for histological and proteomic changes showed dose-dependent hepatocyte apoptosis and peroxisome proliferation. At high doses, genotoxicity resulting from ROS generation was due to suppression of Complex I subunits in the electron transport chain and activation of PPARα in both genders. However, at 0.05 mg/kg/d, Complex I suppression occurred only in females, making them more sensitive to PFOA-induced apoptosis. *In vitro* assays using HL-7702 cells confirmed that apoptosis was also induced through a similar mechanism. The authors claimed that these dose and gender-dependent toxicities may help to explain some epidemiological phenomena, i.e., liver cancer is not often associated with PFOA exposure in professional workers (Li *et al* 2017).

- Past studies have suggested a direct relationship between plasma cholesterol and PFOA serum concentrations in humans and an inverse one in rodents fed standard rodent chow. In order to examine dietary modification of PFOA-induced effects on cholesterol and altered sterol metabolism, C57BL/6 and BALB/c mice were fed PFOA in a fat- and cholesterol-containing diet. When fed these high fat diets, PFOA ingestion resulted in marked hypercholesterolemia in male and female C57BL/6 mice, but less marked hypercholesterolemia in male BALB/c mice. Strain-specific PFOA-induced changes in cholesterol concentrations in mammary tissues and ovaries paralleled changes in plasma cholesterol levels. PFOA-induced hypercholesterolemia appeared to be the result of increased liver masses and altered expression of genes associated with hepatic sterol output, specifically bile acid production. mRNA levels of genes associated with sterol input were reduced only in C57BL/6 females, the mice with the greatest increase in plasma cholesterol levels and mRNA levels of sterol-related genes were reduced in ovaries of C57BL/6 but not in BALB/c mice and not in mammary tissues. The results suggest that PFOA exposure causes a hypercholesterolemic response in mice fed fat and cholesterol, with the effects further modified by the genetic background and gender of the mice (Rebholz *et al* 2016).

- While the study did not specifically address PFAS-induced responses, knowledge of the tissue-specific and temporal aspects of PPARα receptors during human prenatal development could be useful to understand mechanisms of PFAS effects during this period. PPARα receptors were examined in human embryonic & foetal intestines, in liver and in kidney from the 5th to 20th week of prenatal life. PPARα expression was detectable as early as the 7th week of intrauterine development (IUD) in the intestines, 5th week of IUD in the liver and 6th week of IUD in the kidney. Changes in PPARα expression in the intestines and kidney were gestational age-related, commencing around the time functions commence in these tissues. In the liver, strong positivity was found in parts of the

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[6] These levels may be in the range of occupationally exposed workers, but they are orders of magnitude higher than those found in normal populations

developing blood elements (Cizkova *et al* 2015).

3. Comments on exposure sources

In my 2016 Report, there was some limited discussion of sources of exposure and body burdens from around the world. This discussion included survey of some papers that discussed the significance of breastfeeding as an exposure source for infants. A number of additional papers are reviewed below to shed further light on this and other sources.

3.1 Breast milk

My 2016 report included data on PFOS concentrations in breast milk across some 15 regions worldwide (but no Australian data). The current group of additional papers extend this database (but still no published Australian data).

- **France**: 48 breast milk samples from the ELFE Study; PFOS detected in 43/48 samples (90%), median 0.079 ng/mL (range <0.05 to 0.33); PFOA & PFHxS detected in 98-100% of sample, with medians 0.075 and 0.05 ng/mL (Antignac *et al* 2017) – NB paper also includes Table summarising worldwide literature on breast milk PFAS to date); while the dataset were limited, the authors reported no associations between PFAS exposure and birth weights in the infants.

- **Korea**: 293 breast milk samples from 128 mothers in the CHECK cohort; PFOS detected in 100% of samples; mean 0.057 ng/mL (range 0.015 to 0.38); 16 other PFAS detected in some samples at much lower levels (except PFOA <0.01 – 0.657; PFNA <0.01 – 0.127; PFHxS <0.01 – 0.133; PFUnDA <0.01 – 0.119). PFAS levels correlated with maternal age, BMI and parity, tended to increase after the first month of nursing, and were apparently increase with the frequency of snack consumption and eating out (packaging materials as source?) (Lee *et al* 2018).

- **Faroe Islands**: While breast milk concentrations were not measured in this study, changes in serum concentrations of several PFAS in exclusively breast-fed infants at ages 11, 18 and 60 months showed the influence of this source on overall exposures; most PFAS increased at around 30% per month, except for PFHxS, where sources other than breast-milk appeared to be more important; infant serum levels tended to decline after breastfeeding ceased (Mogensen *et al* 2015).

While not a study aimed at the significance of breast milk as a source of PFAS in infant diets, a study by Romano *et al* (2016) aimed to determine whether maternal exposures to PFAS could influence the **duration** of breastfeeding. The hypothesis under investigation was that hormonally-related PFAS effects on breast structure could limit breastfeeding duration. They found that women in the highest PFOA quartile serum concentration had a RR of 1.77 (CI: 1.23 to 2.54) of ending breastfeeding by 3 months, and a 1.41 RR (CI: 1.06 to 1.87) of ending breastfeeding by 6 months. The effects of PFOS were marginal (RR at 3 mo 1.32 CI: 0.97 to 1.79).

A different approach to estimating the significance of breast milk as a PFAS source was taken by Verner *et al* (2017). They developed a generic pharmacokinetic model to quantify the influence of three chemical-specific parameters (biological half-life,

milk:plasma partition coefficient, and volume of distribution) on lactational exposure to chemicals and resulting plasma levels in children. A two-compartment pharmacokinetic model was used to simulate lifetime maternal exposure, placental transfer, and lactational exposure to the child. Monte Carlo simulations (10,000) were used to study the influence of varying these three parameters. Children's dose and plasma levels were compared to their mother's by calculating child:mother dose ratios and plasma level ratios, with differences analysed by linear regression and decision trees. Half-life was found to be the most influential parameter on children's lactational dose and plasma concentrations, followed by milk:plasma partition coefficient and volume of distribution. While specific data for PFAS were not included, the models used previous estimates of parameters to predict maximum infant/mother dose ratios of 87 for PFOA, 23 for PFOS and 38 for PFHxS.

3.2   Drinking water

Drinking water is not ordinarily a significant source of exposure to PFAS for a community not exposed to contaminated sites. In a survey of potable water samples from 34 locations around Australia, Thompson *et al* (2011) identified measurable levels of PFAS (mainly PFOS and PFOA) in 49% and 45% of samples, with a maximum PFOS concentration of 16 ng/L, PFHxS at 13 ng/L and PFOA at 9.7 ng/L. They calculated that, under normal circumstances, drinking water contributed around 2-3% of total PFOS/PFOA daily intake, with a maximum of 22-24%.

Where there is a significant source of local contamination, drinking water levels can be much higher and therefore contribute much more to local body burdens. It is beyond the scope of this report to comment on the extensive literature around drinking water levels, the processes used by local authorities to establish drinking water and recreational water quality standards, or the experience gained around Australian Defence bases in measuring local groundwater and surface water concentrations, with consequent impacts on exposures to local inhabitants.

One example of such a study is the report of drinking water PFAS (mainly PFOA) around a manufacturing facility in Arnsberg, Germany, where some 40,000 residents had been exposed to drinking water contaminated by PFAS from the plant (Hölzer *et al* 2008). The PFOA blood levels were generally 4.5 – 8.3 times higher than those in a reference German population, with PFOA levels in tap water (500-640 ng/L) a significant predictor of these levels, along with age and gender. PFHxS and PFBS were also detected at a higher frequency and at higher levels in blood samples from the Arnsberg residents.

PFAS may not be the only water contaminants of concern in waters around PFAS production plants. River and drinking water samples taken around a PFAS production plant in the Netherlands in 2016 showed only moderate levels (ng/L) of some PFAS (e.g. PFOA <0.03 – 12; PFBS 1 – 26; PFHxS 0.02 – 2.2), but much higher levels (<0.02 – 812) of perfluoroalkyl (mono and poly) ether carboxylic acids, including GenX (also named PFPrOPrA or HFPO− DA), used as a substitute for PFOA in the manufacturing processes (Gebbink *et al* 2017).

3.3   Other sources

In recent years there has been a distinct downward trend in the human body burden of PFAS, especially for PFOS and PFOA. This decline has been evident in the NHANES

database, reproduced in my 2015 and 2016 Reports, and more recently in a paper from Gomis *et al* 2017) noting an inconsistency between the concentration decline in human serum and in wildlife samples. They suggest this could be indicative of a historical exposure pathway for humans linked to consumer products that has been reduced or eliminated as a result of product stewardship and regulatory actions. In the current study, past human exposure trends were reconstructed in the USA and Australia, by inferring the historical intake from cross-sectional biomonitoring data of PFOS, PFOA and PFHxS using a population-based pharmacokinetic model. For PFOS in the USA, the reconstructed daily intake peaked at 4.5 ng/kg-bw/day between 1988 and 1999 while in Australia it peaked at 4.0 ng/kg-bw/day between 1984 and 1996. For PFOA in the USA the peak reconstructed daily intake was 1.1 ng/kg-bw/day in 1995 and in Australia it was 3.6 ng/kg-bw/day in 1992, with a decline starting in 2000 and 1995 in the two countries.

In a recent global survey of inhalation, dietary and drinking water sources of PFAS exposures, Jian *et al* (2017) noted that diet and drinking water are still the main routes of human exposure. They included PFAS profiles in indoor air and dust samples collected from home, office, and vehicles, in addition to food (vegetables, dairy products, beverages, eggs, meat products, fish, and shellfish) and drinking water. The results showed that neutral PFAS, such as fluorotelomer alcohols (FTOHs) and perfluorooctane sulfonamide ethanols (FOSEs) can contribute significantly to total PFAS intake, in addition to PFOS and PFOA. Dietary exposure to PFAS in fish and shellfish remain the most significant dietary source. Well water and tap water contained relatively higher concentrations of PFAS than other types of drinking water, suggesting that intake from this source can be influenced by the drinking water treatments and packaging sources associated with bottled water.

There are three general methods used to estimate dietary intakes of PFAS
   i.   by measuring daily intakes through a 1-day duplicate diet study (separately in solid and liquid foods),
   ii. by estimating intake after combining food contamination with food consumption data, as assessed by 2-day weighted food diaries and
   iii. by a Food Frequency Questionnaire (FFQ).

Using these three methods, Papadopoulou *et al* (2017) showed the three most abundant PFAS in duplicate diet samples in Norwegian population were PFOA, PFOS and PFHxS, with median total intakes (ng/day) of 5.6, 11 and 0.78. Estimates of PFOA intake derived from food diary and FFQ were significantly higher than those derived from the duplicate diet method, but the reverse was true for PFOS. PFOS and PFOA concentrations were higher in solid than in liquid samples and PFOS was the main contributor to dietary intake from solid food samples (median 14 pg/g), while PFOA was the dominant one in liquid food samples (median 0.72 pg/g). High intakes of fats, oils, and eggs were statistically significantly related to high intakes of PFOS and PFOA from solid foods, while high intake of milk and consumption of alcoholic beverages, as well as food in paper containers, were responsible for the higher PFOA intakes from liquid foods.

In a study of the significance of the inhalation route of PFAS exposure, Padilla-Sánchez *et al* (2017) measured PFAS levels, including fluorotelomer alcohols (FTOHs), perfluoroalkyl sulfonamidoethanols (FOSEs), and perfluoroalkyl sulfonamides (FOSAs), in 61 residential indoor air and 15 personal air samples collected in the Oslo area of Norway. FTOHs were detected in all samples, and the median concentrations in residential indoor air were 2970, 10400, and 3120 pg/m^3 for 6:2, 8:2, and 10:2 FTOH,

respectively. The authors noted these values were similar to, or higher than, previously reported data from the same geographical area and worldwide. FOSEs and FOSAs were detected in 49−70% and 7−13% of the residential indoor air samples, respectively. The median FTOH concentrations observed in personal air were 1970, 7170, and 1590 pg/m^3 for 6:2, 8:2, and 10:2 FTOH, respectively, which is 30 to 50% lower than the median concentrations in residential indoor air. No FOSEs or FOSAs were detected in the personal air samples. Intakes of PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, and PFOS through inhalation and biotransformation of PFAS precursors in air were estimated, with median intakes of 1.7, 0.17, 5.7, 0.57, 1.8, 0.18, and 2.3 pg/kg bw/d estimated in residential indoor air, and 1.0, 0.10, 3.3, 0.33, 0.88, and 0.09 pg/kg bw/d based on personal air sampling. Median PFOA intakes from residential indoor air (5.7 pg/kg bw/d) and personal air (3.3 pg/kg bw /d) were claimed to be around 5 orders of magnitude lower than the tolerable daily intake (TDI) reported by EFSA, the European Food Safety Authority.

4 Australian Government initiatives assisting management of PFAS-contaminated areas

The development of TDIs for use in Australian HHRA reports (see discussion in 4.1 below) has been accompanied by other initiatives, including establishment of a National PFAS Management Plan[7] by a National Chemicals Working Group of the Heads of EPAs Australia and New Zealand (HEPA). This plan has been developed in consultation with relevant Australian Government, State and Territory agencies. There has also been an Australian Government Department of Health website[8] established to co-ordinate health-based information on PFAS. This website describes the formation of an Expert Panel[9] to advise on PFAS-related health matters, and an epidemiological study of residents around the Oakey and Williamtown Defence bases, in conjunction with a voluntary blood testing program.[10]

4.1 Health-based guideline values (HBGV)

A range of HBGV have been developed over the past ten years to assist with management of PFAS-contaminated sites and waters. These HBGV have included investigation values for soil, drinking water, food commodities and serum concentrations. Since the methodologies for the derivation of these HBGV is generally standardised with respect to intake and exposure estimates, a crucial component has been the establishment of toxicological reference values for PFOS and PFOA (but not so far for other PFAS), such as the Tolerable Daily Intake (TDI), or its US equivalent, the oral Reference Dose (RfD).

The TDI/RfD values for both PFOS and PFOA have been on a downward spiral since the first such values were established by the UK Committee on Toxicity (COT) in 2006, for PFOS at 300 ng/kg bw/day and PFOA at 3000 ng/kg bw/day, with the US EPA revising these down to 20 ng/kg bw/day for both PFOS and PFOA in 2016 (Dong *et al*,

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[7] http://www.epa.vic.gov.au/~/media/Files/Your%20environment/Land%20and%20groundwater/PFAS%20in%20Victoria/PFAS-Management-Plan-2017.pdf

[8] http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas.htm

[9] http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-expert-panel.htm

[10] http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-epi-study.htm

2017). The reason for the changing TDI/RfD values has partly been the selection of different toxicological endpoints, from rat, mouse or monkey studies, by different national agencies. There has been some criticism of these selections, including the reasons for discounting lower NOAELs for immunotoxicity in mice and mammary gland development in mice (Lilienthal *et al* 2017).

However, a major reason for the differences has been the method of calculating a Human Equivalent Dose (HED) representative of the NOAELs from these studies, where toxicokinetic adjustments have been made based on estimates of the critical blood concentrations in these studies. The application of different Uncertainty Factors (UF) to these estimates has been another factor.

Critical to the conversion of NOAELs in animal studies to an estimated HED is knowledge of the serum half-lives ($t_{1/2}$). There is a useful collation of serum $t_{1/2}$ values in a review by Lee & Choi (2017). The Table from that review is reproduced below, and it clearly illustrates the faster elimination of short-chain PFAS, compared to the longer-chain and the marked species differences (only some of the data in the Table refers to elimination $t_{1/2}$ estimates in humans (e.g. PFBA, PFHxA, PFOA, PFBS, PFHxS and PFOS, marked with an asterisk*).

Table 1. Perfluoroalkyl substances - classification and physicochemical characteristics

Compound	CAS RN	Molecular weight (g/mol)	log Kow[b]	Serum elimination half-lives	
				Male	Female
Perfluoroalkyl carboxylic acids (PFCAs)					
Short chain PFCAs (CnF$_{2n+1}$COOH, n<7, PFCAs)[a]					
Perfluorobutanoic acid (PFBA)	375-22-4	214.04	3.391±0.597	*68±35 hr[c] †6 hr (IV)[c], 9 hr (Oral)[c]	*87±31 hr[c] †1 hr (IV)[c], 2 hr (Oral)[c]
Perfluoropentanoic acid (PFPeA)	2706-90-3	264.05	4.391±0.657	-	-
Perfluorohexanoic acid (PFHxA)	307-24-4	314.05	4.985±0.710	*<28 days[d], †1 hr (IV)[g]	†0.4 hr (IV)[g]
Perfluoroheptanoic acid (PFHpA)	375-85-9	364.06	5.714±0.759	†0.10 days (IV)[h]	†0.05 days (IV)[h]
Long chain PFCAs (CnF$_{2n+1}$COOH, n≥7, PFCAs)					
Perfluorooctanoic acid (PFOA)	335-67-1	414.07	6.444±0.806	*3.8±1.7 yr[e] †5.63 days (IV)[h]	*3.3 yr[e] †0.08 days (IV)[h]
Perfluorononanoic acid (PFNA)	375-95-1	464.08	7.174±0.844	†29.5 days (IV)[h], 30.6 days (Oral)[i]	†2.44 days (IV)[h], 1.4 days (Oral)[i]
Perfluorodecanoic acid (PFDA)	335-76-2	514.08	7.904±0.860	†39.9 days (IV)[h]	†58.6 days (IV)[h]
Perfluorododecanoic acid (PFDoDA)	307-55-1	614.1	9.363±0.888	-	-
Perfluorotridecanoic acid (PFTrDA)	72629-94-8	664.11	10.093±0.901	-	-
Perfluorotetradecanoic acid (PFTeDA)	376-06-7	714.11	10.823±0.914	-	-
Perfluoroalkyl sulfonic acids (PFSAs)					
Short chain PFSAs (CnF$_{2n+1}$SO$_3$H, n<6, PFSAs)					
Perfluorobutane sulfonic acid (PFBS)	375-73-5	300.1	1.689±0.719	*24±7 days[f] †5 hr (IV)[f], 5 hr (Oral)[f]	*46 days[f] †4 hr (IV)[f], 8 hr (Oral)[f]
Long chain PFSAs (CnF$_{2n+1}$SO$_3$H, n≥6, PFSAs)					
Perfluorohexane sulfonic acid (PFHxS)	355-46-4	400.11	3.053±0.814	*8.2±5.1 yr[e] †29 days (IV)[j]	*12.8±0.6 yr[e] †2 days (IV)[j]
Perfluorooctane sulfonic acid (PFOS)	1763-23-1	500.13	4.512±0.862	*5.4±3.7 yr[e] †38 days (Oral)[k], 41 day (Oral)[k]	*5.9±1 yr[e] †62 days (Oral)[k], 71 days (Oral)[k]
Perfluorodecane sulfonic acid (PFDS)	335-77-3	600.14	5.972±0.891	-	-

CAS RN, chemical abstracts service registry number.
*Serum elimination half-lives in human. †Serum elimination half-lives in rat. [a]Buck et al. (2011)[11]. [b]At 25℃, calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2016 ACD/Labs). [c]Chang et al. (2008)[13]. [d]Nilsson et al. (2010)[14]. [e]Olsen et al. (2007)[15]. [f]Olsen et al. (2009)[16]. [g]Chengelis et al. (2009)[17]. [h]Ohmori et al. (2003)[18]. [i]Tatum-Gibbs et al. (2011)[19]. [j]Sundström et al. (2012)[20]. [k]Chang et al. (2012)[21].

More recent estimates of elimination $t_{1/2}$ values for humans can be found in a paper by Gomis *et al* (2017), using modelled data from USA and Australian blood level monitoring sources. The intrinsic elimination half-lives for PFOS and PFOA for men were 3.8 and 2.4 years for the USA, and 4.9 and 2 years for Australia. Elimination $t_{1/2}$ values in women were up to 13% lower for PFOS and up to 12% lower for PFOA compared to the corresponding $t_{1/2}$ values in men. They also showed that menstruation is a depuration pathway for PFOA for women, similarly but to a lesser extent compared to previous

reports for PFOS. However menstruation, cord-blood transfer and breastfeeding together do not fully explain the apparently more rapid elimination of PFOA and PFOS by women compared to men.

Until early in 2017, the TDI values used most commonly in Australia to establish soil and water HBGV or in HHRA reports, were the values (PFOS 150 ng/kg bw/day; PFOA 1500 ng/kg bw/day) derived by EFSA in 2008, using the more conventional adjustment of dividing the NOAELs by a 200x UF. In April 2017, the Australian Government endorsed new TDI values for PFOS (20 ng/kg bw/day) and PFOA (160 ng/kg bw/day), based on an evaluation by FSANZ, and incorporating the more contemporary toxicokinetic dose adjustment. These new TDI values were also used to establish HBGV for drinking water (PFOS 70 ng/L; PFOA 560 ng/L) and recreational water (10x higher). While FSANZ concluded that there is insufficient information to establish a separate TDI for PFHxS at this time, for the first time it has been assumed that the toxic effects of PFOS and PFHxS are additive, and the PFOS HBGV incorporates the sum of PFOS and PFHxS.

FSANZ also established some "trigger points for investigation of PFOS, and PFHXs in various food commodities along with some higher values for PFOA (see Table[11] copied from FSANZ report;

Table 1. Proposed trigger points for investigation

Food	Food classification	Proposed trigger points for investigation (µg/kg)		Derivation
		PFOS, PFOS+ PFHxS combined	PFOA	
Fish and Seafood	Crustaceans#	65	520	Children 2-6 years, median consumption
	Finfish (all)	5.2	41	Children 2-6 years, P90 consumption
	Fish liver#	280	2240	Population 2+ years, median consumption assumed to be 5 g (weight of one liver)*
Animal Products	Meat mammalian	3.5	28	Children 2-6 years, P90 consumption
	Milk	0.4 or LOD if higher	2.8	Children 2-6 years, P90 consumption
	Honey	33	264	Children 2-6 years, P90 consumption
	Offal mammalian#	96	765	Population 2+ years, median consumption
	Poultry eggs	11	85	Children 2-6 years, P90 consumption
Fruits and vegetables	Fruit (all)	0.6 or LOD if higher	5.1	Children 2-6 years, P90 consumption
	Vegetables (all)	1.1 or LOD if higher	8.8	Children 2-6 years, P90 consumption

occasionally consumed food, trigger points for investigation for crustaceans applied to molluscs due to the small number of consumers of molluscs
* no food consumption data available, source: FSANZ report on Edith River, Northern Territory 2013, https://dpir.nt.gov.au/__data/assets/pdf_file/0006/260187/TraceElementsNTFish.pdf

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[11] http://www.health.gov.au/internet/main/publishing.nsf/content/2200FE086D480353CA2580C900817CDC/$File/Consoldiated-report-perflourianted-chemicals-food.pdf)

5.   Some miscellaneous papers on PFAS of possible interest

While they do not fit readily into any of the themes developed in this 2017 review update, some papers are summarized below that may shed light on some developing problem areas of PFAS human health risk assessment:

- 154 per- and polyfluoroalkyl substances (PFASs), including 122 emerging PFASs used in fluorosurfactant-based firefighting foams (FSBFs) were measured in nine different foam concentrates. Environmental samples were also taken around two airports, a training centre, and an oil storage depot where there had been a history of FSBF use. In the foam concentrates, only three PFASs were measured with concentrations ranging from 22,500 to 3,188,000 **m**g/L. Thirteen emerging PFASs were also identified in these samples. Each foam concentrate was a mixture of at least two classes of PFASs. In three concentrates, none of the 122 emerging PFASs were identified as the main ingredient, but a PFAS precursor oxidation assay revealed the presence of high amounts of unidentified PFASs. The PFAS concentrations found around the investigated sites were the highest recorded in France and resulted in the closure of some drinking water resources (Dauchy *et al* 2017)

- The available Australian data on serum levels of PFAS and related PFCAs is growing. 54 pooled serum samples from Australia collected in 2002-2013 (n=4920 individuals) were analyzed for PFASs and categorized according to gender and age. Analytes included perfluorocarboxylic acids (PFCAs), perfluorosulfonic acids (PFSAs), and two groups of PFCA precursor compounds; polyfluoroalkyl phosphate diesters (diPAPs), and fluorotelomer sulfonic acids (FTSAs). Several PFASs that were not reported in previous studies of Australian serum samples were found in this sample set including; diPAPs, FTSAs, perfluoropentane sulfonic acid (PFPeS), perfluoroheptane sulfonic acid (PFHpS), perfluoroheptane carboxylic acid (PFHpA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), and perfluorotridecanoic acid (PFTrDA). Observed temporal trends included - a significant reduction between 2002 and 2013 for 8:2 FTSA, PFHxS), PFHpS, PFOS, and PFOA; longer-chained PFDA and PFUnDA started to decrease more recently, between 2006 and 2013, while PFDoDA increased during the same time period; higher levels of 8:2 FTSA and PFHpA were found in younger age groups (0-4 and 5-15y) compared to adults (>15y); but the reverse was found for the more common older PFAS (PFHpS, PFOS, PFUnDA, PFDoDA and PFTrDA). Typical gender-specific patterns were seen for PFOA, PFHxS, PFHpS and PFOS, with levels tending to be lower in women. Changes in manufacturing processes probably account for some of these temporal differences, but differences in bioaccumulation potential between homologues could also be a factor, especially for the older age groups (Eriksson *et al* 2017).

- Leachate from 27 landfills from around Australia have been investigated as sources of 9 PFAS. PFHxA was the dominant PFAS found (mean 1700 ng/L; range 73-25,000), but levels of up to 8 other PFAS were routinely found, with levels generally higher in active (vs closed) landfills accepting primarily municipal waste. Landfill accepting primarily construction and/or demolition waste had higher PFAS levels than municipal landfills, with similar time trend for younger

landfills compared to older ones. Eight of the landfills discharged leachate to wastewater treatment plants (WWTPs). For PFHxA, estimates of annual mass discharge from individual landfills was up to 62g, with estimates up to 31 kg on a national basis. These data provide a useful overview of the potential for landfill leachates to be a significant source of PFAS other than the conventional PFAS related to AFFs (Gallen *et al* 2017).

6. Implications for HHRA of PFAS other than PFOS and PFOA

The number of different PFAS that are routinely measured in biological and environmental samples is now quite large; general up to 10-12, or even more, in some studies. While there is ample evidence that PFOS and PFOA levels in human serum have been in decline for some decades, due to stronger product stewardship and regulatory actions to phase them out of manufacture and products (including AFFFs), that is not true for other PFAS, particularly those that continue to be manufactured and used because of a more favourable environmental persistence profile.

These other PFAS, including new polyfluoro- and telomeric substitutes for the perfluorinated alkyl acids, still appear consistently in human biota and environmental samples. It is inevitable that there will be an increasing focus on their potential health effects. Currently, the knowledge to develop separate TDI values for these emerging PFAS contaminants is insufficient, nor is there any reliable information on whether one could use relative potencies in the form of a Toxicity Equivalence Factor (TEF) to assess the risks of complex mixtures of PFAS.

To illustrate these problems, two papers are summarized below that illustrate the potential impact of these different PFAS.

- A novel perfluoroalkyl ether carboxylic acid (ammonium perfluoro-2-[(propoxy)propoxy]-1-propanoate; HFPO-TA) has been reported in surface water and common carp (*Cyprinus carpio*) collected from the Xiaoqing River and in residents residing near a fluoropolymer production plant in Huantai County, China. Water levels of HFPO-TA (5200−68500 ng/L) were approximately 120−1600x higher downstream compared to upstream, as a result of discharge of this fluoropolymer into plant effluent. The total annual discharge of HFPO-TA was estimated to be 4.6 t, accounting for 22% of total PFAS discharge. In the wild common carp collected downstream from the point source, HFPO-TA was detected in blood (median: 1510 ng/mL), liver (587 ng/g ww), and muscle (118 ng/g ww), with a higher bioconcentration factor (BCF) compared to PFOA (log 2.18 vs 1.93). This is a substantial source of exposure for local fishermen. HFPO-TA was also found in the blood of nearby residents (median 2.93 ng/mL). There is very little available information about the potential toxicity of HFPO-TA to aquatic or mammalian organisms, including humans (Pan *et al* 2017).

- Perfluoroalkyl carboxylates (PFCAs) are ubiquitously distributed around the world and have been found in ng/mL levels in human blood. PFCAs with longer carbon chain lengths (C6 and above) are PPARα agonists and show developmental, hormonal, immunotoxic and tumorigenic responses in rodents, much like similar PFAS. The available toxicological information on PFCAs has been reviewed, noting that, in addition to exposure sources such as food, drinking water and

34

house dusts, an additional exposure route can be indirect, via breakdown of fluorotelomers. Some of these metabolites of fluorotelomers may be more toxic via intermediary electrophilic metabolites that can bind to DNA and proteins, and require detoxification via antioxidants such as glutathione Rand *et al* (2017).

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