

FSANZ assessment of PFOA

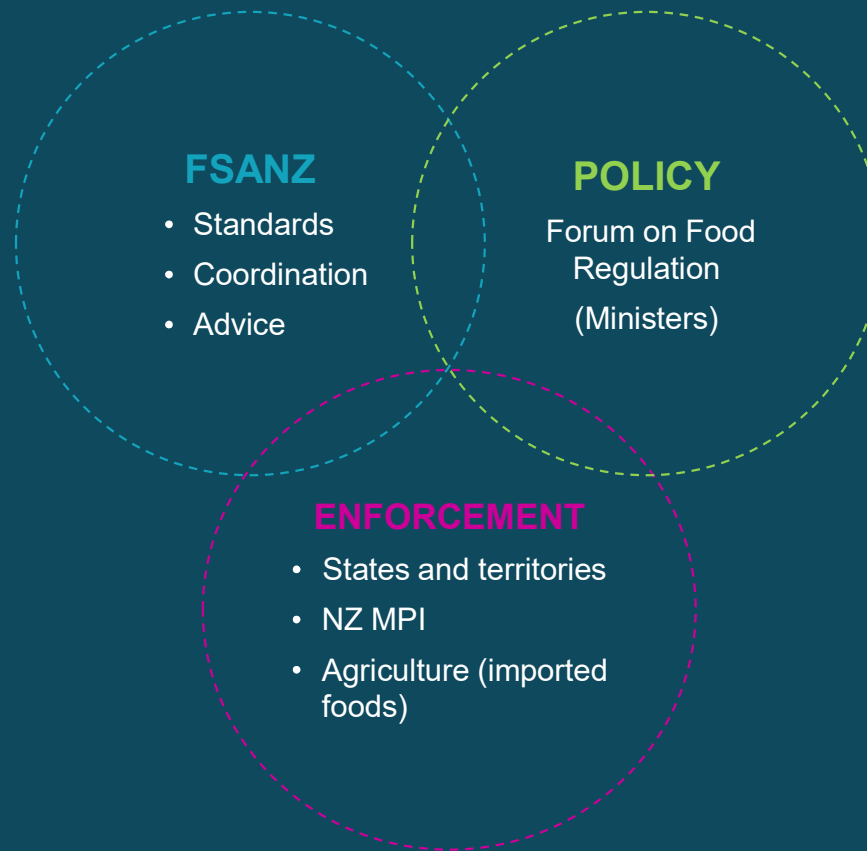
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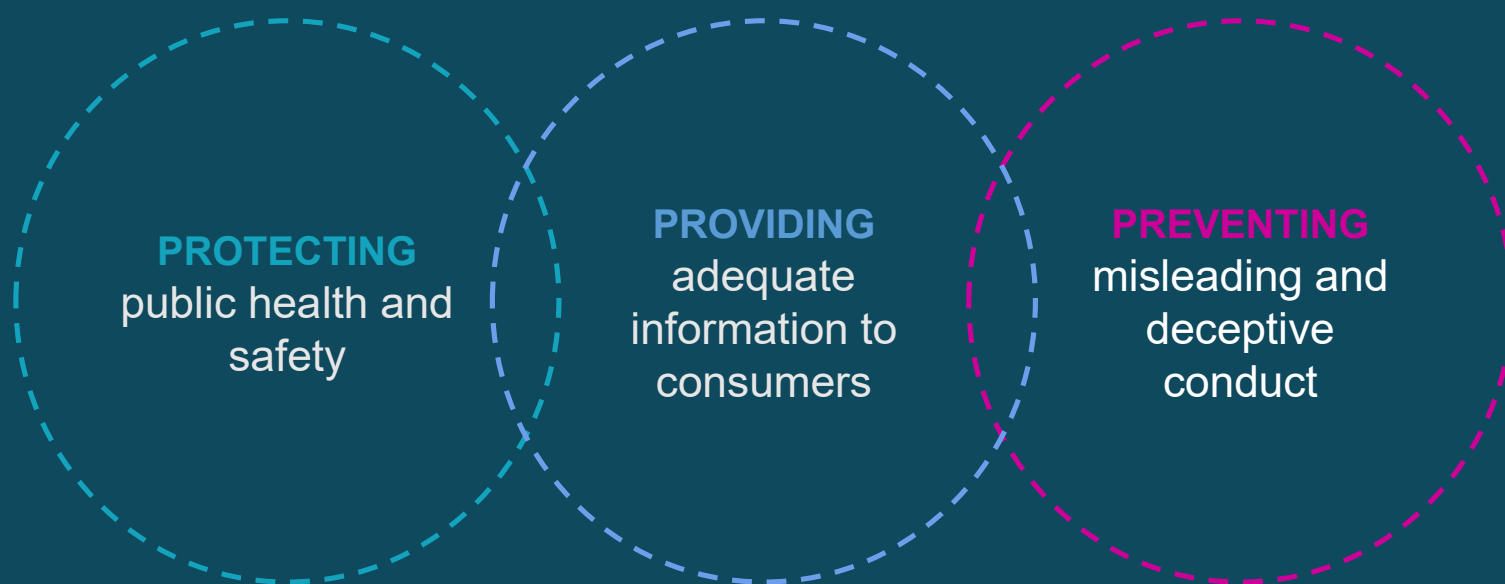
About FSANZ

- We are an Australian statutory agency within the Australian Government Health portfolio
- Our main function is to develop and administer the Australia New Zealand Food Standards Code (the Code)
- The Code is a legislative instrument, that is given effect by state and territory or New Zealand laws
- FSANZ is not responsible for enforcement

Food regulatory framework



When developing measures we consider



Hazard assessment for PFOS, PFOA and PFHxS

- Request from Department of Health to recommend HBGVs for PFOS, PFOA and PFHxS in June 2016
- Mammalian toxicology previously had been reviewed by a number of international agencies.
- FSANZ used information in these assessments as a starting point to establish Australian HBGVs.
- Justified on the basis that the evaluations had to a large extent considered the same or similar toxicological databases.

FSANZ reports on PFAS (2017-2022)

- **2017**
 - *Hazard assessment for PFOS, PFOA and PFHxS*
 - *Review of the US EPA PBPK model and independent assessment*
 - *Report on the immunomodulation potential*
 - *Assessment of dietary exposure to PFOS, PFOA and PFHxS*
 - *Interim trigger levels for PFAS in food*
- **2021**
 - *Australian Total Diet Study on PFAS*
- **2021**
 - *Updated review of immunomodulation studies on PFAS*
- **Not currently under review; assessments represent a point in time**

Existing HBGVs for PFOA in 2016

Agency, year	Type of HBGV	PoD	UF	HBGV
UKCOT, 2006	Tolerable Daily Intake (provisional)	0.3 mg/kg bw/day	200	1.5 µg/kg bw/day
EFSA, 2008	Tolerable Daily Intake	0.3 mg/kg bw/day	200	1.5 µg/kg bw/day
Swedish EPA, 2012	Derived No Effect Level	150 ng per mL serum	75	2.0 ng/mL serum
Danish EPA, 2015	Tolerable Daily Intake	0.003 mg/kg bw/day ^a	30	100 ng/kg/day
ATSDR, 2015	Minimal Risk Level	1.54 x 10 ⁻³ mg/kg bw/day ^b	90	20 ng/kg/day
US EPA 2016	Reference Dose	0.0053 mg/kg bw/day ^b	300	20 ng/kg/day

Review of the pharmacokinetics of PFOA

- PFOA is readily absorbed (>90%) and distributed throughout the body by noncovalent binding to plasma proteins.
- Transporters include organic anion transporters (OATs), organic anion transporting peptides (OATps), multidrug resistance-associated proteins (MRPs), and urate transporters
- Tissue distribution: Liver; kidney > other organs
- At low doses, kinetics are consistent with first order processes, and serum levels are proportional to administered dose
- Mainly excreted in urine, biliary and faecal excretion also contributes to the elimination of PFOA, which may be subject to extensive enterohepatic recirculation
- Slow elimination from the human body (in the order of years) with much shorter half-lives (in the order of days) in animals

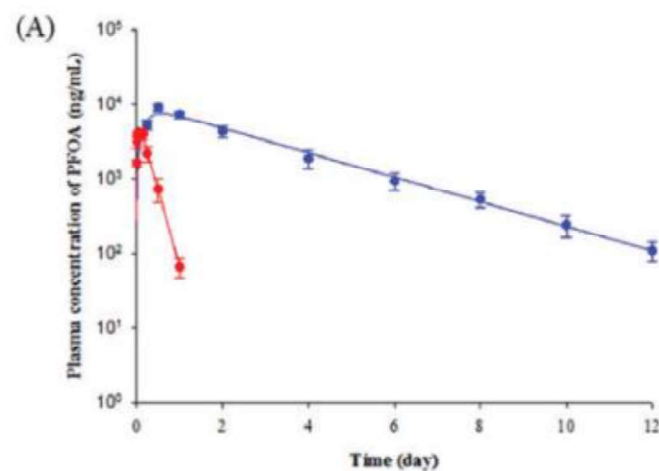
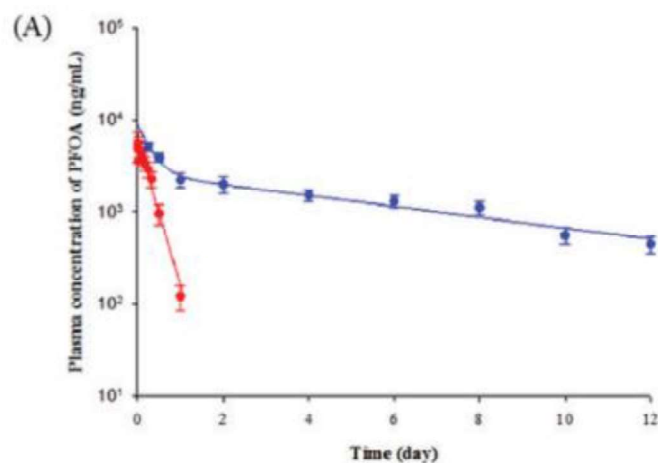
Effects of species and gender on PFOA half life

Table 6. Effect of species and gender on PFOA and PFOS half-lives.

Compound	Species	Gender	Administration route	Dose	Half-life	References
PFOA	Human (retired workers)	24 M, 2 F	Fluorochemical production workers over 5 years	N/A*	3.8 yr	Olsen <i>et al.</i> 2007 (66)
	Human (adults)	Combined M, F	Contaminated drinking water	N/A	2.3 yr	Bartell <i>et al.</i> 2010 (67)
	Human (adults and children)	Combined M, F	Contaminated drinking water	N/A	3.3 yr	Brede <i>et al.</i> 2010 (68)
	Human (adults and children)	Combined M, F	Contaminated drinking water	Highly exposed	2.9 yr	Seals <i>et al.</i> 2011 (61)
				Less exposed	8.5 yr	
	Monkey	M	i.v.	10 mg/kg	21 days	Butenhoff <i>et al.</i> 2004 (69)
		F			30 days	
	Rabbit	M	Oral gavage	10 mg/kg	5.5 hrs	Hundley <i>et al.</i> 2006 (70)
		F			7 hrs	
	Rat	M	N/A	N/A	6-8 days	Kemper. 2003 (71)
		F			3-16 hrs	
	Rat	M	Single dose i.v. or oral	1 mg/kg	1.6-1.8 days	Kim <i>et al.</i> 2016 (45)
		F			0.15-0.19 days	
	Mouse	M	Single oral gavage	1 mg/kg or 10 mg/kg	21.7 days	Lou <i>et al.</i> 2009 (72)
		F			15.6 days	

Sex differences in male and female rats

Figure 5. Mean plasma concentration-time profile of (A) PFOA, (B) PFOS after IV (left hand side) and oral (right hand side) administration of PFOA (1 mg/kg), PFOS (2 mg/kg) in male (●) and female (●) rats (mean $\pm$ SEM, n = 5) [Kim *et al.* (2016)(45)].



Reviewed EPA model and generated own estimates

Table 22. HEDs Derived from the Modelled Animal Average Serum Values - PFOA

Study	Dosing dur'n (days)	NOAEL (mg/kg/day)	NOAEL (Av Serum Conc. µg/mL)			HED (mg/kg/day)		
			EPA parameter	Our parameter	% change	EPA parameter	Our parameter	% change
Butenhoff <i>et al.</i> , 2002: monkey	182	10	101	92.2	-8.71	0.014	0.013	-7.14
Perkins <i>et al.</i> , 2004: rat, dec'd weight gain	91	1.94	93.9	-		0.013	-	
Lau <i>et al.</i> , 2006: mice, fetotoxicity	17	1	35.1	56.1	59.8	0.0049	0.0078	59.2
Lau <i>et al.</i> , 2006: mice, maternal	17	10	197	353	79.2	0.0276	0.0494	79.0

Conclusions on PBPK modelling

- Using our best parameter estimates and commercial simulation software package, the EPA estimates for the PBPK of a range of studies could be replicated with an error of less than 80%.
- Our analysis suggests
 - that there is substantial secretion of these compounds into bile with effective enterohepatic recirculation, as seen by significant amounts of material detected in faeces many days after a single dose given orally or IV.
 - there is an upregulation of active secretory transporters for PFOA at the glomerulus basement membrane and this accounts for the gender differences in the excretion of PFOA.
 - the serum concentrations of PFOS and PFOA reach steady state relatively quickly despite a long half-life
- In comparison to the application of uncertainty factors which may be 30-100 fold this is only a small component of total uncertainty.

Toxicological assessment of PFOA

- Substantial toxicological database includes
 - acute and short term toxicity studies in mice, rats and monkeys
 - subchronic studies in monkeys
 - chronic studies in mice, rats and monkeys, and
 - developmental and reproduction studies in mice and rats.
- Rodents
 - Consistent effect of PFOA in laboratory rodents is peroxisome proliferation-mediated hepatomegaly.
 - Reproductive and developmental effects: Increased full-litter resorptions, developmental skeletal defects, reduced birthweight, decreased postnatal growth rate, delayed postnatal eye-opening and hair growth, delayed puberty, decreased postweaning survival, and effects on mammogenesis.
 - Increased incidence of hepatocellular tumours and Leydig cell tumours.
- Non-human primates
 - Weight loss, increased clotting times, decreased heart and brain weights, hypoglycaemia, hypoproteinaemia, bone marrow hypocellularity, lymphoid follicle depletion and lipid depletion in the adrenal glands. Clinical signs in monkeys that were terminated moribund during a subchronic oral gavage study included anorexia, emesis, decreased activity, facial swelling, black stools, prostration and tremor.

Oral toxicity studies reviewed by FSANZ

- **Subchronic studies**
 - **90 day dietary study in rats (Palazzolo, 1993; Perkins et al 2004)**
 - Reduced body weight gain at 6.5 mg/kg bw/day. NOAEL: 1.94 mg/kg bw/day
 - **90 day study in Rhesus monkeys (Goldenthal 1978b)**
 - Decreased weights of heart (absolute and relative) and brain (absolute) in females at 10 mg/kg bw/day. NOAEL/LOAEL: not assigned because there were only 2 animals/sex/dose group
 - **180 day capsule study in male Cynomolgus monkeys (Butenhoff et al 2002)**
 - Mortality, clinical signs, body weight effects at 30/20 mg/kg bw/day. NOAEL: 10 mg/kg bw/day
- **Chronic toxicity/carcinogenicity studies**
 - **24-month dietary study in male rats (Biegel et al 2001)**
 - Single dose study, 14 mg/kg bw/day. Increased liver weights and β -oxidation activity in treated groups.
 - Significant increases in Leydig cell adenomas, hepatocellular adenomas
 - **104 week dietary study in rats (Sibinski, 1987 (with histopathology re-evaluation by Mann and Frame, 2004.))**
 - Increased liver weight, clinical chemistry and hepatocellular pathology in males at both doses. LOAEL: 1.3 mg/kg bw/day.

Oral toxicity studies reviewed by FSANZ, continued

- **Developmental/reproductive studies**

- **Two-generation oral gavage study in rats (Butenhoff et al 2004)**
 - Paternal toxicity LOAEL: 1 mg/kg bw/day. Reproductive toxicity: NOAEL: 30 mg/kg bw/day. Offspring toxicity: NOAEL: 10 mg/kg bw/day; LOAEL: 30 mg/kg bw/day
- **Oral gavage developmental study in mouse (Lau et al 2006)**
 - Maternal toxicity: NOAEL: 10 mg/kg bw/day; LOAEL: 20 mg/kg bw/day. Fetotoxicity: NOAEL: 1 mg/kg bw/day; LOAEL: 3 mg/kg bw/day.
- **Oral gavage mouse cross-fostering study (Wolf et al 2007; White et al 2009)**
 - No NOAEL or LOAEL assigned.
- **Oral gavage mouse developmental study (White et al 2007)**
 - No NOAEL or LOAEL assigned.
- **Oral gavage + drinking water developmental study in mice (White et al 2011).**
 - No NOAEL or LOAEL assigned.
- **Oral gavage developmental study in mice (Macon et al 2011)**
 - No NOAEL or LOAEL assigned.

- **Other studies**

- **Oral gavage + drinking water immunotoxicity study in mice (De Witt et al 2008).**
 - Immunological NOAEL: 1.88 mg/kg bw/day; immunological LOAEL 3.75 mg/kg bw/day.

Derivation of the TDI for PFOA

- **Studies identified as suitable for derivation of a HBGV were the Cynomolgus monkey study of Butenhoff et al 2002, the rat study of Perkins et al 2004, and the mouse developmental study of Lau et al 2006.**
 - All of these studies included serum PFOA data, so that pharmacokinetic modelling could be conducted to derive HEDs.
 - The NOAEL for each study was identified by examination of the available data, disregarding effects considered to be adaptive (liver hypertrophy in the absence of hepatocellular degeneration or necrosis), and those for which there was no dose-response effect evident (preputial opening in pups in the Lau et al 2006 study).
 - The lowest candidate TDI, derived from the NOAEL for fetal toxicity of the Lau et al (2006) mouse developmental and reproductive study, is 160 ng/kg bw/day.

Derivation of the TDI for PFOA

HEDs (mg/kg bw/day) derived from the modelled animal average serum values

Study	Dosing duration (days)	NOAEL (mg/kg bw/day)	Av. Serum Conc. (µg/mL)	HED (mg/kg bw/day)
Butenhoff et al 2002 Monkey	182	10	101	0.014
Perkins et al 2004 Rat	91	1.94	93.9	0.013
Lau et al 2006 (fetal toxicity) Mice	17	1	35.1	0.0049
Lau et al 2006 (maternal toxicity) Mice	17	10	197	0.0276

Derivation of the TDI for PFOA

Candidate HBGVs for PFOA

POD	Value (mg/kg/day)	UF _H	UF _A	UF _L	UF _S	UF _{total}	Candidate TDI (mg/kg/day)
HED _{NOAEL} Butenhoff Monkey	0.014	10	3			30	0.00047
HED _{NOAEL} Perkins rat	0.013	10	3			30	0.00043
HED _{NOAEL} Lau Mice, fetotoxicity	0.0049	10	3			30	0.00016
HED _{NOAEL} Lau mice, maternal	0.0276	10	3			30	0.00092

UF_H=uncertainty factor for intraspecies variability

UF_A= uncertainty factor for interspecies variability

UF_L= uncertainty factor for LOAEL to NOAEL extrapolation

UF_S=uncertainty factor for extrapolation from a subchronic to a chronic exposure duration

Derivation of the TDI for PFOA

FSANZ has recommended a TDI of 160 ng/kg bw/day on the basis of a NOAEL for fetal toxicity in a developmental and reproductive study in mice.

- Pharmacokinetic modelling was applied to the serum concentrations at the NOAEL and above to calculate the HED.
- An uncertainty factor of 30 was applied to the HED, which comprised a default factor of 3 to account for interspecies differences in toxicodynamics and a default factor of 10 for intraspecies differences in the human population.
- Outcome was peer reviewed domestically and internationally (Sweden)
- Considered by various Australian Committees charged with public health protection prior to publishing.

Immunomodulation review (2017)

- At high enough doses, for long enough, PFOA causes atrophy and changed cellularity of immune system organs in mice but not in rats.
- At lower doses, and presumably lower PFOA serum concentrations in mice, PFOA is reported to suppress humoral responses to inoculated antigens. The dose required to do this is about 4 mg/kg/d (LOEL) over a period of 15 days via drinking water.
- Serum concentrations associated with various changes of the immune system is sparse. Nevertheless the available information clearly indicates high serum concentrations, around 70 mg PFOA/L, are required for antibody production suppression.
- There are both positive and negative epidemiology studies showing associations for increasing PFOS and PFOA serum concentrations to compromise antibody production in children and adults.
- To date *there is no compelling evidence for increased incidence of infective disease associated with PFOS or PFOA effects on immune function*. It is difficult to envisage how the available epidemiology information can be used quantitatively in risk assessment.

Epidemiological evidence (2017)

- No agency had established a HBGV based on epidemiological evidence in 2017
- Observed that associations between exposure and several health effects have been reported in epidemiological studies, although a number of findings are inconsistent between studies and the biological significance of a number of the observed effects is questionable.
- The US EPA (2016) concluded that associations that appear to be reasonably consistent and repeatable are those with increased serum cholesterol and decreased body weights at birth.
- FSANZ updated the meta-analysis for low birth weight and serum cholesterol

Association with cholesterol and birth weight

- Studies in both adults and children suggest a positive association between total cholesterol (total-C) and low density lipoprotein cholesterol (LDL-C) and PFOA concentration at very low concentrations of PFOA but not at higher concentrations.
- At around 25 ng/mL blood concentration, total-C is about 0.2 - 0.3 mmol/ higher than total-C in the lowest PFOA blood concentration groups in the studies, above this the association plateaus.
- Overall the studies with numerical data report an association between PFOA or and birthweight at low concentrations. However, missing quantitative data from studies reporting no effect raises the possibility of selective reporting or publication bias affecting the body of evidence. The shape of the association is not clear; that is whether it is linear or nonlinear.
- Overall we could not determine whether **PFOA causes the changes**, or whether other factors are involved.
- As these are **observational** studies, FSANZ considers that the meaning and clinical significance of the associations for PFOS and PFOA for decreased birth weight and increased cholesterol in humans are uncertain and should be interpreted with **caution**.

Other actors in the Australian regulatory system

- Government Expert Health Panel Independent Health Advice (2018)
 - “concluded there is mostly limited, or in some cases no evidence, that human exposure to per- and poly-fluoroalkyl substances (PFAS) is linked with human disease.”
 - “It also concluded there was insufficient evidence of causation between PFAS exposure and any adverse health outcomes.”
 - “decisions to minimise exposure to PFAS chemicals should be largely based on their known ability to persist and accumulate in the body.”
- The ANU Health Study systematic literature review (Kirk et al 2018)
 - While there have been many studies into the health effects of PFAS it is uncertain whether or not PFAS are harmful to human health. In the few areas in which there is evidence for a possibly causal association of PFAS with an effect on human health the association is either uncertain or apparently weak.

Immunomodulation update review

- In 2021, FSANZ undertook an update of the review of potential immunomodulation by PFAS.
- Available new studies in humans primarily investigated three different potential immunomodulatory effects of PFAS:
 - decreased circulating antibody titres to vaccine-preventable diseases (4 studies)
 - increased incidence of infectious diseases (8 studies)
 - altered prevalence of hypersensitivity diseases such as asthma and allergies (5 studies)
- The review updated the systematic literature review of Kirk et al (2018) and the expert advisory panel established by the Australian government

Impaired response to vaccinations (Kirk et al, 2018)

Health Effect	PFAS exposure measured	Evaluation of evidence	Papers evaluated
Impaired response to vaccinations			
Diphtheria	PFOA, PFOS, PFHxS, PFNA, PFDA, PFHPA, PFUnDA, PFDoDA	Limited evidence for PFOA, PFOS, PFHxs, PFDA	Grandjean et al (2012, 2016, Mogensen et al 2015 (same cohort as Grandjean et al). Kielsen et al (2016)
Tetanus	PFOA, PFOS, PFHxS, PFNA, PFDA, PFHPA, PFUnDA, PFDoDA	Inadequate evidence	Grandjean et al (2012, 2016)) Mogensen et al (2015) (same cohort as Grandjean et al) Granum et al (2013) Kielsen et al (2016)
Measles	PFOA, PFOS, PFHxS, PFNA	Inadequate evidence	Granum et al (2013) Stein et al (2016a)
Mumps	PFOA, PFOS, PFHxS, PFNA	Inadequate evidence	Granum et al (2013) Stein et al 2016a)
Rubella	PFOA, PFOS, PFHxS, PFNA	Limited evidence for PFOA and PFOS; inadequate for PFHxS and PFNA	Granum et al (2013) Stein et al 2016a)
Influenza	PFOA, PFOS, PFHxS, PFNA	Inadequate evidence	Looker et al (2014) Stein et al (2016b)

Limited evidence of a health effect: A positive (direct) or negative (inverse) association has been observed between exposure to PFAS and the health effect in humans for which a causal interpretation is considered to be possible or probable, but chance, bias or confounding could not be ruled out with reasonable confidence

Inadequate evidence of a health effect: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between PFAS exposure and the health effect in humans.

Increased susceptibility to infectious disease (Kirk et al 2018)

<i>Increased susceptibility to infectious disease</i>			
Hospitalization due to infection	PFOA, PFOS	Inadequate evidence	Fei et al (2010)
Middle ear infection	PFOA, PFOS, PFHxS, PFNA	Inadequate evidence	Okada et al (2012) Granum et al (2013)
Gastroenteritis	PFOA, PFOS, PFHxS, PFNA	Inadequate evidence	Granum et al (2013)
Colds and influenza	PFOA, PFOS, PFHxS, PFNA	Inadequate evidence	Granum et al (2013) Looker et al (255)

Associations with asthma/allergic/autoimmune disease (Kirk et al 2018)

PFAS, PFNS		Evidence (2018)	
Asthma and allergic diseases			
Asthma	PFOA, PFOS, PFHxS, PFNA, PFDA, PFTrDA, PFDoDA, PFHxA, PFHpA, PFBS	Inadequate evidence	Dong et al (2013) Zhu et al (2011) Humblet et al (2014) Stein et al (2016) Steenland et al (2015)
Total allergies	PFOA, PFOS, PFHxS, PFNA, PFDA, PFDoDA, PFTrDA, PFUnDA	Inadequate evidence	Goudarzi et al (2016) Okada et al (2012, 2014) Stein et al (2016)
Total food allergies	PFOA, PFOS	Inadequate evidence	Okada et al (2012)
Shrimp allergy	PFOA, PFOS, PFNA	Inadequate evidence	Stein et al (2016a)
Plant sensitivity	PFOA, PFOS, PFNA	Inadequate evidence	Stein et al (2016a)
Cockroach sensitivity	PFOA, PFOS, PFNA	Inadequate evidence	Stein et al (2016a)
Mould sensitivity	PFOA, PFOS, PFNA	Inadequate evidence	Stein et al (2016a)
Allergic rhinoconjunctivitis	PFOA, PFOS, PFHxS, PFNA, PFDA, PFDoDA, PFTrDA, PFUnDA	Inadequate evidence	Goudarzi et al (2016)
Wheezing	PFOA, PFOS, PFHxS, PFNA, PFDA, PFDoDA, PFTrDA, PFUnDA	Inadequate evidence	Granum et al (2013) Okada et al (2012) Goudarzi et al (2016) Humblet et al (2014)
Eczema	PFOA, PFOS, PFHxS, PFNA, PFDA, PFDoDA, PFTrDA, PFUnDA	Inadequate evidence	(Goudarzi et al (2016) Okada et al (2012) Okada et al (2014) Granum et al (2013)
Autoimmune diseases			
Crohn's disease	PFOA	Inadequate evidence	Steenland et al (2013, 2015)
Multiple sclerosis	PFOA	Inadequate evidence	Steenland et al (2013, 2015)
Lupus	PFOA	Inadequate evidence	Steenland et al (2013, 2015)
Rheumatoid arthritis	PFOA	Inadequate evidence	Steenland et al (2013, 2015)
Ulcerative colitis	PFOA	Inadequate evidence	Steenland et al (2013, 2015)

FSANZ update report (2021)

- Consistent with earlier observations, the associations between increased PFAS blood levels and antibody titres in these studies were generally weak, and partially inconsistent findings were observed for PFOS, PFOA and other PFAS chemicals for the same antigen
- The evidence for an association between increasing PFAS blood levels and impaired vaccine response is insufficient for quantitative risk assessment on the basis of substantial uncertainties and limitations including:
 - the small number of studies and participants, and mostly cross-sectional design of studies such that conclusions around causality should be drawn with caution.
 - limited dose-response information with most studies investigating a narrow range of blood levels associated with background levels of PFAS exposure.
 - inconsistency in antibody response to vaccines between different PFAS congeners which cannot explained by study design.
 - potential for confounding by other known environmental immunotoxicants such as PCBs
 - uncertainty about the clinical relevance, if any, of the observed statistical associations to susceptibility to infectious disease.

FSANZ update report 2021

- Eight new studies investigated whether blood levels of PFAS are associated with increased susceptibility to infectious diseases in children.
- Five new studies examined the association between blood PFAS levels and hypersensitivity responses including atopic dermatitis (eczema), allergies and asthma.
- Some numerical associations were observed, however the evidence was often inconsistent and contradictory for different PFAS congeners.
- On the basis of the available information it cannot be ruled out with reasonable confidence that any statistical associations may have been due to confounding, bias or chance

Australian Total Diet Study on PFAS

- The 27th ATDS investigated levels of per- and poly-fluoroalkyl (PFAS) in a range of foods and beverages common to the Australian diet.
- The study tested for 30 different types PFAS, in 1,336 composite samples, representing 112 commonly eaten foods sourced from all Australian states and territories. Samples were taken across two seasons (Autumn and Summer) to account for seasonal variations.
- Only one type of PFAS - perfluorooctane sulfonic acid (PFOS) - was detected at low levels in less than 2% of all foods sampled.
- PFAS levels were well below Australian guidance values, including FSANZ trigger points for site investigation and National Health and Medical Research Council (NHMRC) drinking water guidelines.
- The overall dietary exposure to PFOS/PFOA for the general Australian population is lower than the Tolerable Daily Intake indicating no public health and safety concerns.

What's next for FSANZ and PFOA

- The best available evidence indicates that PFOA is not presently a concern in the general food supply in Australia.
- At this time FSANZ does not intend to establish MLs for PFOA in food.
- Codex Committee on Food Contaminants (CCCF) has referred PFAS to the Joint Expert Committee on Food Additives (JECFA) as a priority contaminant.
- FSANZ will continue to monitor the emerging science and consider the need to adjust the TDI for PFOA following the JECFA review.
- We will monitor an ongoing review PFAS in Australian drinking water being conducted by the National Health and Medical Research Council.
- We will also continue to provide technical assistance to jurisdictions to support site specific risk assessment.

Thank you!



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