Per- and poly-fluoroalkyl substances (PFAS)

CAS NUMBERS 335-67-1 (PFOA), 1763-23-1 (PFOS), 355-46-4 (PFHxS), 375-73-5 (PFBS), 62037-80-3 and 13252-13-6 (GenX Chemicals)

(Public Consultation draft October 2024)

GUIDELINE

Based on human health considerations, the concentration of perfluorooctanoic acid (PFOA) in drinking water should not exceed 200 ng/L (0.2 µg/L).

Based on human health considerations, the concentration of perfluorooctane sulfonic acid (PFOS) in drinking water should not exceed 4 ng/L (0.004 µg/L).

Based on human health considerations, the concentration of perfluorohexane sulfonic acid (PFHxS) in drinking water should not exceed 30 ng/L (0.03 µg/L).

Based on human health considerations, the concentration of perfluorobutane sulfonic acid (PFBS) in drinking water should not exceed 1000 ng/L (1 µg/L).

No health-based guideline value can be derived for hexafluoropropylene oxide dimer acid and its ammonium salt (GenX chemicals) at this time.

GENERAL DESCRIPTION

Per- and poly-fluoroalkyl substances (PFAS) are manufactured chemicals that do not occur naturally in the environment. PFAS include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), perfluorobutane sulfonic acid (PFBS) and hexafluoropropylene oxide dimer acid and its ammonium salt (GenX chemicals), amongst a large group of other compounds. Some PFAS are persistent in the environment, show the potential for bioaccumulation and biomagnification, and adverse health effects are observed in animal studies (e.g. potential developmental, reproductive and systemic toxicity) (HEPA 2020).

Due to PFAS being hydrophobic and heat resistant, they have been used in a wide range of consumer products including surface treatments such as non-stick cookware and in aqueous film-forming foams that are used to extinguish fires. The importation of PFAS in Australia has been reduced since 2002 (enHealth 2024), and PFOA, PFOS and PFHxS will be prohibited from import, manufacture and export under the Industrial Chemicals Environmental Management Standard (IChEMS) from 1 July 2025 (DCCEEW 2023). Historical use in firefighting foams has resulted in detection of PFAS at a number of sites including airports, firefighting training facilities and federal government sites. PFAS have also been found in groundwater, surface water, sewage effluents and landfill leachates in Australian and international studies (Ahrens *et al*. 2016; Banzhaf *et al.* 2017; Gallen *et al.* 2017; Gallen *et al.* 2018; Nguyen *et al*. 2024). The increased concentration of PFAS in biosolids from wastewater treatment processes is becoming a concern in the context of biosolid application in agriculture and the potential pathways to continued human and environmental PFAS exposure (Health Canada 2024; HEPA 2020; US EPA 2024g). PFAS can end up in drinking water directly from contaminated runoff and groundwater infiltration (Boone *et al.* 2019). The main factor

to consider for contamination of PFAS in drinking water sources is whether drinking water infrastructure or the catchment is located in the vicinity of potentially contaminating activities (NJDEP 2019b; OEHHA 2023a).

Humans can be exposed to PFAS present in sources such as food, consumer products, dust and drinking water (Health Canada 2024). The major sources of PFAS in the general population are expected to be food and consumer products, particularly in areas not impacted by heavy contamination of PFAS (Tittlemier *et al*. 2007); however, the proportion of exposure from drinking water can increase in individuals living in areas where drinking water sources are contaminated by PFAS (Health Canada 2024; OEHHA 2023). For example, estimates of exposure to PFOS and PFOA via drinking water in 2011 ranged from 2-3% for a non-exposed community (i.e. not impacted by a point source) up to an estimated maximum of 22% and 24% respectively from contaminated water supplies (Thompson *et al*. 2011a). Oral ingestion is considered to be the main exposure route (USEPA 2023). Exposure to PFOA, PFOS, PFHxS and PFBS in tap water from both inhalation and dermal routes during household use such as showering and bathing is considered negligible (OEHHA 2019).

LEVELS DETECTED IN AUSTRALIAN DRINKING WATER

In Australia, water quality data for PFAS have been collected to date on an *ad hoc* (as needed) basis in areas with contaminated PFAS sites. Some water utilities carry out regular monitoring due to the proximity of their raw water to PFAS contamination sites. Some other water utilities now include PFAS in monitoring programs, even when there is no identified source of contamination.

Concentrations of PFAS in bores surrounding contaminated sites can be very high (SLR 2024a, b), while low concentrations of PFAS have been detected in some water supplies not impacted by contaminated sites. Some drinking water source waters do not have detectable levels of PFOA, PFOS and PFHxS.

The following information on typical levels reported in Australia is provided below for PFOA, PFOS, PFHxS, PFBS and GenX chemicals. Other species of PFAS may be present in Australian drinking water supplies. Information on levels of other PFAS may be reviewed as further evidence becomes available.

PFOA

PFOA has been detected at concentrations ranging from below detection to 9.7 ng/L in Australian raw and/or reticulated drinking water supplies (Hunter Water 2024; Power and Water n,d.; QAEHS 2018a, 2018b; Sydney Water 2024; WCWA 2023;), including in a study of 33 Australian drinking water samples (Thompson *et al.* 2011a). Maximum concentrations of PFOA in contaminated residential and private bores has been detected between 20 – 10,500 ng/L (AECOM 2017a, 2017b; BSC 2021; GHD 2018).

PFOS

PFOS has been detected at concentrations ranging from below detection to 16.4 ng/L in Australian raw and/or reticulated drinking water supplies (Hunter Water 2024; QAEHS 2018a, 2018b; Sydney Water 2024), including in a study of 33 Australian drinking water samples (Thompson *et al*. 2011a). Maximum concentrations of PFOS in contaminated residential and private bores has been detected between 80 – 136,000 ng/L (AECOM 2017, 2017b; Bräunig *et al.* 2017; BSC 2021; GHD 2018).

PFHxS

PFHxS has been detected at concentrations ranging from below detection to 19.1 ng/L in Australian raw and/or reticulated drinking water supplies (QAEHS 2018a, 2018b; Sydney Water 2024; WCWA 2023), including in a study of 33 Australian drinking water samples (Thompson *et al*. 2011a). Maximum concentrations of PFHxS in contaminated residential and private bores have been detected between 130 – 54,300 ng/L (AECOM 2017a, 2017b; Bräunig *et al.* 2017; BSC 2021; GHD 2018).

PFBS

PFBS has been detected at concentrations up to 2.2 ng/L in Australian raw and/or reticulated drinking water supplies (QAEHS 2018a, 2018b). Maximum concentrations of PFBS in contaminated residential and private bores has been detected between 40 – 6,520 ng/L (AECOM 2017a, 2017b; GHD 2018).

GenX Chemicals

Hexafluoropropylene oxide dimer acid (HFPO-DA) and its ammonium salt are labelled as "GenX" chemicals because they are the primary chemicals used in the GenX processing aid technology. This technology was developed as a replacement for perfluorooctanoic acid (PFOA). The name "GenX" reflects the next generation of fluoropolymer manufacturing processes that aim to be safer and more sustainable. GenX chemicals are used in the United States to manufacture fluoropolymers which have many industrial applications including in medical, automotive, electronics, aerospace, energy, and semiconductor industries. Since GenX chemicals are substitutes for PFOA, products (e.g. some nonstick coatings) made in the United States that were previously made using PFOA may now rely on GenX chemicals (US EPA 2022).

While there are no authorised introductions of GenX chemicals for industrial use in Australia (other than small quantities (<25 kilograms (kg)) for Research and Development), it is possible that these chemicals may be present in Australia as trace residues in/on imported products that may end up in landfill which can leach into water supplies at very low levels.

No information about the concentration of GenX chemicals in Australian reticulated drinking water supplies has been identified (SLR 2024a, b). GenX chemicals are not routinely measured by Australian laboratories and have only recently been added to analytical schedules offered by some commercial laboratories in Australia (SLR 2024a, b). Further research may be needed to determine whether GenX chemicals are found in any Australian drinking waters, which would also inform whether a health-based guideline value is required.

TREATMENT OF DRINKING WATER

A preventive approach is the best way to manage risks of PFAS contamination of drinking water supplies and reduce the level of treatment needed. Focus should be maintained on measures such as selecting the best quality source water, catchment protection, multiple barriers and management of critical control points (see Chapter 3 of the Guidelines).

Standard drinking water treatment technologies including coagulation followed by physical separation, aeration, chemical oxidation, UV irradiation, and disinfection are mostly ineffective in

removing PFOA, PFOS, PFHxS, PFBS or GenX chemicals in source waters (Dickenson and Higgins 2016; Health Canada 2016; SLR 2024a, b; USEPA 2024h).

Granular activated carbon (GAC), anion exchange (AIX), and high-pressure membrane systems are commonly used techniques to remove PFAS from drinking water, but these treatment options have different strengths and weaknesses (SLR 2024a, b, USEPA 2024h). These should be considered when determining the most appropriate treatment approach depending on what is known about the specific PFAS identified in the drinking water supply.

For example, GAC and AIX can result in significant removal of some PFAS but are less effective at removing short chain PFAS (i.e. PFAS with less than 8 carbon atoms in their structure). Reverse osmosis is likely to remove shorter chain PFAS (such as PFHxS and PFBS) and is able to achieve up to >99% removal of longer chain PFAS (such as PFOA and PFOS) (Pontius 2019; Thompson *et al.* 2011b; USEPA 2024h). Safe disposal or treatment of the concentrate waste streams containing PFAS needs to be considered for all of these approaches (WRF 2016; Dickenson and Higgins 2016; US EPA 2024a). Replacing contaminated source waters with an alternative uncontaminated source water could be considered, noting risks to this approach should be assessed and discussed with relevant health authority and/or drinking water regulator.

Given the public concern about PFAS in drinking water, there may be interest in options for water treatment at home to reduce exposure to PFAS from drinking water. However, it is important to note that households with a reticulated drinking water supply with levels below the health-based guideline values do not need additional home water treatment. It should also be noted the use of home water filters can potentially reduce the concentrations of beneficial chemicals that are present in drinking water to protect public health (including chlorine residuals to prevent bacterial contamination, fluoride to protect oral health).

If there are still concerns about water quality, some in-premises water treatment units, such as home filtration or reverse osmosis units, may be effective at removing some (but not all) PFAS from drinking water (US EPA 2018, 2024a, f). However, it is noted that these methods will likely be difficult and expensive to undertake effectively at home with limited assurance of PFAS removal. If homeowners choose to proceed, care should be taken as not all commercially available water filters will be effective to the same standard. In addition, as water treatment units require regular maintenance and replacement, they should not be viewed as a permanent solution to managing PFAS. Manufacturers' instructions regarding installation, operation, maintenance and replacement should be followed to ensure the treatment units remain effective. Advice from a water treatment expert, relevant health authority and/or drinking water regulator should be sought to determine if water treatment units are appropriate for the given context, including whether they are necessary in the first place.

MEASUREMENT

PFAS can be measured in water samples by solid phase extraction followed by high-performance liquid chromatography (HPLC) coupled to electrospray ionisation tandem mass spectrometry (MS/MS) operated in negative ion mode (NMI 2017; Health Canada 2024; NMI 2023). Other methods are available to measure and detect PFAS in water (e.g. high-resolution mass spectrometry, quadrupole time-of-flight mass spectrometry and gas chromatography-mass spectrometry) (SLR 2024a, b). Complementary techniques, such as the oxidative conversion in the total oxidisable precursor assay (TOPA), may be used to determine the presence of PFAS

precursor compounds, which can be bio-transformed in the environment to form stable PFAS (e.g. PFOS and PFOA) (Houtz and Sedlak 2012).

As with all analytical chemistry, it is essential to use a method where the limit of quantification (LoQ) is sensitive enough for the level at which the guideline value is set. In drinking water, the typical limits of quantification for the methods described above are suitable for PFOA, PFOS, PFHxS and PFBS (NMI 2017; NMI 2023). The availability of these methods has been confirmed with several commercial laboratories in Australia (SLR 2024a, b).

Appropriate sampling, storage and transportation are also critical for analysis. PFAS can adsorb to materials used for sampling and analysis, so appropriate materials should be used. The potential for sample contamination during both sample collection and analysis is very high due to PFAS being used in other products, including waterproof sample labels, and therefore PFAS sample collection and analysis should be carried out by trained personnel in line with accepted guidance, using NATA-accredited laboratories and with appropriate quality control samples.

National Measurement Institute (NMI) proficiency testing of PFAS in water has indicated a wide range of measurement uncertainty (MU) between the laboratories. The wide range indicates that uncertainties should be considered carefully when reporting results. Laboratories should be reporting uncertainties in accordance with *ISO 17025 (2018): General requirements of testing and calibration laboratories* (NMI 2022).

HEALTH CONSIDERATIONS

There is limited information about the health effects of PFAS in the Australian population. An Australian Expert Health Panel concluded that there was international evidence for associations between PFAS exposure and a number of health effects (DoHAC 2018). These included: increased blood cholesterol; increased blood uric acid; reduced kidney function; some alterations in immune response; altered levels of thyroid and sex hormones; later onset of menstruation and earlier menopause; and lower birth weight in babies (DoHAC 2018). However, the Panel found that the reported differences were small with no evidence of substantial impacts on the health of individuals. The Panel found limited evidence of a potential association of PFAS with two uncommon cancers (testicular and kidney).

An epidemiological study (the ANU PFAS Health Study, ANU 2021), examining the potential health effects from high levels of PFAS exposure in three Australian communities (Katherine (NT), Oakey (QLD) and Williamtown (NSW)), found that blood levels of PFOS and PFHxS (the main components of fire-fighting foams used in those areas) were higher in exposed communities than in comparison communities except for PFOA where concentrations were similar (ANU 2021, Smurthwaite *et al*. 2021). The study also found that there were higher levels of psychological distress among people in exposed communities and an association between higher PFAS blood levels and serum cholesterol concentrations but the evidence for other adverse effects was limited and inconsistent and did not establish conclusive links between PFAS and adverse health outcomes (ANU 2021, Lazarevic *et al.* 2021).

Concerns have been raised about the potential carcinogenicity of PFOA and PFOS (US EPA 2024b, c, d; Zahm *et al.* 2024). The International Agency for Research on Cancer (IARC) has classified PFOA as 'carcinogenic to humans' (Group 1) based on 'sufficient' evidence for cancer in experimental animals and 'strong' mechanistic evidence in exposed humans (Zahm *et al*. 2024). The IARC evaluation found that there was limited evidence for cancer in humans (renal cell carcinoma and testicular cancer) and strong

mechanistic evidence in exposed humans and experimental systems. IARC has also classified PFOS as 'possibly carcinogenic to humans' (Group 2B) based on 'strong' mechanistic evidence across test systems, including in exposed humans. The IARC evaluation found that there was also limited evidence for cancer in experimental animals, and inadequate evidence regarding cancer in humans (Zahm *et al*. 2024). Full details of the IARC evaluation were not published at the time of this review and will be considered when they are made publicly available.

It should be noted that the rates of cancers examined in the ANU PFAS Health Study (i.e. results from communities exposed to high levels of PFAS) were similar across the exposed and comparison populations, or too uncertain to draw conclusions due to a small number of diagnoses. Small but apparent associations to prostate, larynx, kidney, and lung cancers were found in individual communities but not in all communities (Law *et al*. 2021). However, except for kidney and testicular cancer, there was previously only limited evidence linking these cancers and PFAS. The study could not establish whether these findings were due to chance or other contributing factors, such as a higher prevalence of smoking and other disease risk factors such as family history (ANU 2021).

International jurisdictions have developed health advice for individual PFAS based on different critical health effects in animal studies and human epidemiological studies with different weighting given to human and animal studies producing substantially different outcomes. There continues to be varying opinions about the methods and assumptions used to calculate guidance values, the approaches/policies on how to manage risks from PFAS and ongoing uncertainty about emerging PFAS of concern. A number of international jurisdictions[1] have also either considered or taken the approach of assessing mixtures of PFAS to derive sum/total values of PFAS (SLR 2024c). There are a number of different approaches that rely either on the available toxicological database for PFAS or otherwise take a non-health-based approach that considers practical achievability for monitoring, measurement and treatment capabilities (SLR 2024c).

In 2024, SLR Consulting Australia (SLR) reviewed available public health advice (such as assessments used in guidelines and standards) from national and international agencies for PFOA, PFOS, PFHxS, PFBS and GenX chemicals in drinking water (SLR 2024a, b, c). The review focused on the critical evaluation of studies that underpinned the available PFAS guidance values from other jurisdictions that were not previously considered by Food Standards Australia New Zealand (FSANZ) (2017) (the review that underpinned NHMRC's 2018 PFAS guidance). Where there was confidence that the underpinning studies were of high quality[2], the corresponding guideline values were considered for adoption/adaptation in the Australian context. This included consideration of methods to derive total/sum values of PFAS mixtures proposed by several international assessments (SLR 2024c). The information below summarises the relevant human, animal and carcinogenicity studies considered by SLR (2024a, b, c) for each chemical where information is available.

[1] EC 2022; EU 2020; Health Canada 2024; Maine DHHS 2021; Mass DEP 2022; US EPA 2024d, e; WHO 2022.

[2] SLR Consulting Australia evaluated key studies using expert judgement of study design parameters that can indicate whether a study was well-conducted and therefore considered 'high quality' or suitable/appropriate to use in guideline derivation. This included assessing whether parameters such as sample size, controls and dose groups, dose timing and delivery, observational methods and data reporting were appropriate and indicative of a high-quality study. Where possible, compliance or alignment with best practice testing standards that indicate that a study was well-conducted, such as Organisation for Economic Co-operation and Development (OECD) Test Guidelines (TG) or Good Laboratory Practices (GLP) were noted if available.

While it is acknowledged that other species of PFAS may be present in Australian drinking water supplies, the following information on health considerations is provided for PFOA, PFOS, PFHxS, PFBS and GenX chemicals. Information on other PFAS will be reviewed as further evidence becomes available.

PFOA

Epidemiological studies: Some international assessments[3] have derived benchmarks for PFOA using benchmark doses calculated from low levels of PFAS (as a mixture including PFOA) in serum associated with decreased vaccine antibody formation in children (Abraham *et al*. 2020; Budtz-Jorgensen and Grandjean 2018; Grandjean *et al.* 2012; Timmerman *et al*. 2022). Based on a critical evaluation of these studies (SLR 2024a, b, c), and consistent with the conclusions reached by FSANZ (2021), it was concluded that a causal relationship between increased PFAS serum levels (as a mixture including PFOA) and impaired vaccine response cannot be established with reasonable confidence from the available human epidemiological information. A number of limitations of the studies (such as small sample size, limited dose-response information and potential confounding by other known environmental immunotoxicants) were identified. The evidence for an association between increasing PFAS serum levels and impaired vaccine response was found to be insufficient for the endpoint to be used for derivation of a PFOA health-based guideline value. Although the reduced antibody response following vaccination has been considered by some international assessments[3] as a robust end point to derive a guidance value, it is unclear whether this correlation results in increased rates of infection and hence the clinical implications are uncertain (SLR 2024a, b; FSANZ 2021).

Guideline values have also been derived from associations between low PFOA serum levels in humans and effects on cholesterol or liver biomarkers (Darrow *et al*. 2016; Dong *et al*. 2019; Eriksen *et al*. 2013; Gallo *et al*. 2012; Nelson *et al.* 2010; Nian *et al.* 2019; Steenland *et al*. 2009) and low infant birth weight (Sagiv *et al*. 2018; Wikström *et al.* 2020).[4] Reviews of the epidemiological literature identified several study limitations that have lowered the certainty in the findings, including potential confounding, lack of clinical relevance, small sample sizes or a lack of clear, reliable dose-response relationships that are supported by similar findings in the available experimental animal literature (Burgoon *et al*. 2023; SLR 2024a, b, c).

Animal toxicity studies: Some international assessments[5] have found the data from human epidemiological studies to be of insufficient quality to derive guidance values for PFOA and instead have used findings from animal toxicological studies. Non-cancer health endpoints in animals considered by these assessments have included: developmental effects in mice (Koskela *et al*. 2016; Lau *et al*. 2006; Onishchenko *et al*. 2011); decreased pup survival in mice (Abbott *et al*. 2007; Song *et al.* 2018); increased liver weight in mice (Lau *et al*. 2006; Li *et al.* 2017; Loveless *et al.* 2006); hepatocellular hypertrophy in rats (Perkins *et al*. 2004); hepatocellular necrosis in rats (NTP 2023) and; effects on immune system markers in mice administered PFOA in drinking water (Dewitt *et al*. 2008, 2016).

Most of the animal studies underpinning these critical health effects were found to have several limitations that decreased the certainty in the findings (FSANZ 2017; SLR 2024a, b, c). These

[3] BfR 2019; EFSA 2020; RIVM 2021; US EPA 2022c, d, 2024b

[4] OEHHA 2023; US EPA 2024b

[5] ATSDR 2018, 2021; Burgoon *et al.* 2023; FSANZ 2017; MDH 2022f; MPART 2019; NJDEP 2019a; OEHHA 2019; WSDH 2019, 2022, 2023

limitations included uncertainty surrounding the clinical relevance of the observed health effects in humans versus animals, small sample sizes and a lack of clear dose-response relationships or serum PFOA data (SLR 2024a, b, c). While Dewitt *et al*. 2008 was found to be a well-conducted study with a clear dose-response for immune system effects (SLR 2024c), there was higher confidence in the Lau *et al.* (2006) prenatal developmental toxicity study and the NTP (2023) carcinogenicity and toxicity rat study[2] (SLR 2024c). Lau *et al.* (2006) appears to have been conducted using a protocol similar to best practice standards (i.e. OECD TG 414) and examined a large number of standard endpoints in a sufficiently large number of treatment groups and sample sizes (SLR 2024a, b). The 2-year NTP (2023) study reported non-neoplastic hepatocellular necrosis in rats exposed to PFOA (SLR 2024c).

Carcinogenicity: Identification of the potential carcinogenicity of PFOA has informed the development of health advice and guidance values in two international assessments.[6] Similar to non-cancer health effects, potential associations with carcinogenicity have been reported from human and animal studies. Two epidemiological studies (Shearer *et al.* 2021; Vieira *et al*. 2013), have reported associations between elevated PFOA serum levels and incidences of renal and testicular cancers. The US EPA (2024b) used the results from Shearer *et al.* (2021) to derive a non-threshold linear cancer slope factor of 0.0293 nanogram per kilogram of bodyweight per day (ng/kg bw/day) for PFOA. In comparison, IARC (Zahm *et al*. 2024) found that there was limited evidence for an association with renal and testicular cancers and it was not consistent.

An evaluation of Shearer *et al.* (2021) and Vieira *et al*. (2013) found that there were several study limitations that made these epidemiological studies unsuitable for deriving guidance values (SLR 2024c). These limitations included a lack of accounting for potential confounders (such as exposure to chemicals other than PFAS) and a lack of similar effects (e.g. kidney effects) in the available experimental animal literature that would increase the certainty in these findings. In addition, thresholds for the reported associations of PFOA exposure and renal/testicular cancers could not be readily discerned from the data available in the studies (SLR 2024c).

In addition to the epidemiological studies, potential carcinogenicity of PFOA has been reported from animal studies. Two-year chronic/carcinogenicity studies by NTP (2023)[7] and Butenhoff *et al*. (2012a) found increased incidences of neoplastic effects such as Leydig cell, pancreatic and hepatocellular tumours in male rats that were exposed to PFOA in their diet (from 1 to 1.3 milligram PFOA/kg bw/day respectively). The US EPA (2024b) identified NTP (2023) and Butenhoff *et al.* (2012a) as key animal carcinogenicity studies in their final toxicity assessment of PFOA. The NTP (2023) findings of increased incidence of pancreatic and hepatocellular tumours were rated as being from high confidence studies. The Butenhoff *et al.* (2012a) findings of increased incidences of Leydig cell tumours were rated as being from a medium confidence study. IARC cited the NTP (2023) findings of increased incidences of pancreatic and hepatocellular tumours in reaching a decision that there was sufficient evidence for cancer in experimental animals (Zahm *et al.* 2024).

The evaluation by SLR (2024c) found that Butenhoff *et al*. (2012a) and NTP (2023) were well-conducted studies (SLR 2024c), although it was noted that Butenhoff *et al*. (2012a) did not report the associated serum PFOA levels in rats that would allow a more accurate extrapolation of the

[6] Zahm *et al*. 2023; US EPA 2024d

[7] Note that NTP (2023) is also occasionally cited as NTP (2020) in SLR (2024 a,b,c) and reports from other agencies. The 2020 NTP report has been revised and updated in 2023 (NTP 2023). Minor revisions were made in NTP (2023) from the 2020 report version, all of which are marked up and identified in the NTP (2023) report. The 2023 version of the NTP report was the only version considered in the SLR evaluation.

observed findings to humans. The NTP (2023) 2-year carcinogenicity study finding increased incidences of pancreatic and hepatocellular tumours was considered to be higher quality study that was conducted appropriately and assessed effects across all developmental life stages (SLR 2024c). The use of the data associated with the increased incidence of hepatocellular tumours was considered but would have resulted in less conservative health-based guideline values than the data from the pancreatic tumours. SLR (2024c) noted that it is unlikely that the pancreatic tumours observed in male rats exposed to PFOA in NTP (2023) are relevant to humans due to their probable formation through the rat-specific peroxisome proliferator-activated receptor alpha (PPARα) pathway (SLR 2024c). However, it was also noted that the formation of the observed pancreatic effects may occur through modes of action other than the PPARα pathway (currently demonstrated in vitro but not in vivo) and so human relevance could not be discounted (SLR 2024c).

On the balance of information, taking into account the classification of PFOA as a Group 1 carcinogen by IARC (Zahm *et al.* 2024) and the rating by US EPA (2024b) that the NTP (2023) findings were from high confidence studies, the neoplastic pancreatic effects were considered to be an appropriately conservative point of departure to derive a health-based guideline value for PFOA in Australian drinking water at this time.

In regard to the approach applied to developing a guideline value for PFOA, the US EPA (2024b) derived non-threshold values from both the epidemiological and animal studies. However, as described in Chapter 6.3.3., development of non-threshold values is an approach normally applied to genotoxic carcinogens in these guidelines. The World Health Organization (WHO) adopts a similar approach. The US EPA (2024b) acknowledged a lack of information to support a mutagenic mode of action for PFOA. In addition, no evidence of genotoxicity was provided by IARC (Zahm *et al.* 2024). This is supported by experimental animal data (Butenhoff *et al*. 2012a) and data showing a lack of genotoxicity at non-cytotoxic concentrations (ATSDR 2021). Taken together, these studies support the conclusion that PFOA is a non-genotoxic carcinogen, and the use of a threshold method to derive a guideline value for PFOA (SLR 2024c).

PFOS

Epidemiological studies: Several international assessments[8] have derived guidance values using benchmark doses calculated from low PFOS serum levels associated with increased levels of total blood cholesterol reported in humans (Steenland *et al*. 2009; Eriksen *et al*. 2013; Nelson *et al.* 2010). FSANZ reviewed these studies in 2017 and concluded that while there is evidence of this association, it is not possible to determine whether PFAS causes the changes, or whether other factors are involved (FSANZ 2017). Kirk *et al.* (2018) found sufficient evidence of an association between elevated PFOS concentrations in blood and increased blood total cholesterol concentrations; however, it was noted that the observed increases in concentration were quite small and likely to have limited effects on health (Kirk *et al.* 2018). Other more recent studies examining associations between low PFOS serum levels and effects on cholesterol or liver biomarkers in humans (Dong *et al.* 2019; Gallo *et al*. 2012; Nian *et al.* 2019) cited in US EPA 2024c; however, these studies were found to have potential confounding and/or a lack of reliability in dose-response data that lowered the certainty in the reported associations (SLR 2024c).

[8] BfR 2019; OEHHA 2023

While there appears to be an association between low PFOS serum levels and low birth weights in humans (Darrow *et al*. 2013; Sagiv *et al*. 2018; Wikström *et al*. 2020), the certainty in these findings is decreased by a number of factors including potential confounding and a lack of statistically significant or reliable dose-response data (SLR 2024c). There is also a lack of similar findings at the same low serum levels in well-conducted animal studies (e.g. Luebker *et al.* 2005) which would increase the certainty in these associations in humans (SLR 2024c).

Other international assessments[9] have considered benchmark doses calculated from low levels of PFOS in serum associated with decreased antibody formation following administration of certain vaccines in humans (Abraham *et al*. 2020; Budtz-Jorgensen and Grandjean 2018; Grandjean *et al.* 2012; Timmermann *et al*. 2022; Zhang *et al*. 2023). Based on a critical evaluation of these studies and consistent with the conclusions made by FSANZ (2021), it was concluded that a causal relationship between increased PFAS serum levels (as a mixture including PFOS) and impaired vaccine response cannot be established with reasonable confidence from the available human epidemiological information (SLR 2024a, b, c). A number of limitations of the studies, such as small sample size, limited dose-response information and potential confounding by other known environmental immunotoxicants, were identified. The evidence for an association between increasing PFAS serum levels and impaired vaccine response was found to be insufficient for that endpoint to be used for derivation of a PFOS health-based guideline value. Although the reduced antibody response following vaccination has been considered by some international assessments[9] as the most robust end point to derive a guidance value, it is unclear whether this correlation results in increased rates of infection and hence the clinical implications are uncertain (SLR 2024a, b; FSANZ 2021).

Animal toxicity studies: A number of international assessments[10] have considered findings from animal toxicological studies to derive guidance values for PFOS. These have included developmental toxicity in rodents such as delayed eye opening and decreased pup body weight (Luebker *et al*. 2005), liver effects in mice and rats (Dong *et al*. 2009; Butenhoff *et al*. 2012b), increased interleukin-4 (IL-4) and decreased sheep red blood cell specific Immunoglobulin M levels in mice (Dong *et al*. 2011), suppression of plaque forming cell response (Dong *et al.* 2009; Zhong *et al.* 2016), extramedullary haematopoiesis and bone marrow hypocellularity in rats (NTP 2022)[11].

Reviews have found that some of these animal studies have study limitations that decreased the certainty in the findings and made them less suitable for deriving guidance values compared to other studies (FSANZ 2017; SLR 2024a, b, c). These limitations included factors such as uncertainty surrounding the clinical relevance of the observed health effects in humans versus animals and inconsistency of effects at low doses across similar animal studies. Zhong *et al.* (2016) was assessed as medium confidence, noting that although it was a pilot study it appears to have been conducted appropriately[2], evaluated a large number of immune system markers (as well as hormone levels and clinical parameters) and demonstrated a clear dose-response in male mice (SLR 2024c). The Luebker *et al*. (2005) and NTP (2022) studies were both assessed as high confidence as they were found to be comprehensive, high-quality[2] studies that had been

[9] EFSA 2020; RIVM 2021; US EPA 2022c, e; US EPA 2024c

[10] ATSDR 2018, 2021; FSANZ 2017; MDH 2020a; MPART 2019; NJDEP 2019b; OEHHA 2019, 2023; US EPA 2024c; WSDH 2019, 2022, 2023

[11] Note that NTP (2022) is also occasionally cited at NTP (2019) in SLR (2024 a,b,c) and reports from other agencies. The NTP (2019) report has been revised since initial publication and updated in 2022 (NTP 2022). Minor revisions were made in NTP (2022) from the 2019 report version, all of which are marked up and identified in Appendix F of the NTP (2022) report. The 2022 version of the NTP report was the only version considered in the SLR evaluation.

conducted appropriately and investigated a large number of endpoints (SLR 2024a, b, c). However, the bone marrow effects (i.e. extramedullary haematopoiesis and bone marrow hypocellularity) observed in NTP (2022) were considered to be the most critical health effects and the best point of departure to derive a guideline value for PFOS in drinking water.

Carcinogenicity: Some international assessments[12] have derived benchmarks for PFOS based on associations of liver tumours in rats in a 2-year chronic toxicity/carcinogenicity study by Butenhoff *et al*. (2012b), although it has been noted that these effects were reported to occur at the highest doses tested (1.144 and 1.385 mg PFOS/kg bw/day in male and female rats, respectively) (FSANZ 2017). As noted earlier, IARC has classified PFOS as 'possibly carcinogenic to humans' (Group 2B) based on 'strong' mechanistic evidence across test systems, including in exposed humans (for epigenetic alterations and immunosuppression, as well as several other key characteristics of carcinogenic mechanisms of action). The IARC evaluation found that there was also limited evidence for cancer in experimental animals (citing Butenhoff *et al*. 2012b), and inadequate evidence regarding cancer in humans (Zahm *et al*. 2024).

PFHxS

Epidemiological studies: Some international assessments[13] have used benchmark doses calculated from low levels of PFHxS in serum associated with decreased antibody formation following administration of tetanus vaccines in children with low levels of PFHxS in serum (Abraham *et al*. 2020; Grandjean *et al.* 2012; Budtz-Jorgensen and Grandjean 2018). Based on a critical evaluation of these studies and consistent with the conclusions made by FSANZ (2021), it was concluded that a causal relationship between increased PFAS serum levels (as a mixture including PFHxS) and impaired vaccine response cannot be established with reasonable confidence from the available human epidemiological information. A number of limitations of the studies, such as small sample size, limited dose-response information and potential confounding by other known environmental immunotoxicants, were identified. The evidence for an association between increasing PFAS serum levels and impaired vaccine response was found to be insufficient for the endpoint to be used for derivation of a PFHxS health-based guideline value. Although the reduced antibody response following vaccination has been considered by some other international assessments[13] as the most robust end point to derive a guidance value, it is unclear whether this correlation results in increased rates of infection and hence the clinical implications are uncertain (SLR 2024a, b; FSANZ 2021).

Animal toxicity studies: Other international assessments[14] have used findings from animal toxicological studies to derive guidance values for PFHxS. Reported health effects include thyroid follicular epithelial hypertrophy/hyperplasia in rats (Butenhoff *et al.* 2009), decreased thyroxine (T4) levels in rats (NTP 2022), increased relative liver weights in female rats (NTP 2022), and decreased litter size in mice (Chang *et al.* 2018).

NTP (2022) was found to be the best available study from which to derive a guideline value for PFHxS in Australian drinking water (SLR 2024a, b). It examined oral exposure by male and female rats to PFHxS and evaluated clinical pathology, thyroid hormones and liver enzymes. NTP (2022)

[12] OEHHA 2019, 2023; US EPA 2024c

[13] EFSA 2020; US EPA 2023

[14] ATSDR 2018, 2021; FSANZ 2017; MPART 2019; OEHHA 2022; WSDH 2019, 2022, 2023

was found to be conducted in accordance with relevant standardised testing guidelines[2], evaluated a large number of endpoints, and provided serum PFHxS concentrations (SLR 2024a, b).

It is noted that decreases in thyroid hormones in rodent toxicology studies are generally not considered clinically relevant to humans without a compensatory increase in thyroid-stimulating hormone (TSH) or changes to the pituitary gland observed (SLR 2024a, b). However, evidence of effects of thyroid histopathology in rats was observed by Butenhoff *et al.* (2009) at higher serum PFHxS concentrations. Associations between PFAS exposure and thyroid hormone status were also observed in some human epidemiological studies (e.g. Ballesteros *et al*. 2017; Boesen *et al*. 2020; Coperchini *et al.* 2021). On this basis it is concluded that consideration of the potential human relevancy of the thyroid hormone changes observed in the 28-day NTP (2022) study with PFHxS is appropriate.

PFBS

Animal toxicity studies: As there are limited epidemiological data, some international assessments[15] have developed health advice for PFBS based on a critical health effect of thyroid hormone disruption (decreased total thyroxine (T4)) from findings of studies in rats (NTP 2022) and in mice (Feng *et al*. 2017) (SLR 2024a, b). Both of these key studies examined oral exposure of rodents to PFBS and evaluated various endpoints, including developmental, reproductive, hepatic, renal and thyroid effects.

While NTP (2022) was found by SLR (2024a, b) to have been conducted in accordance with relevant standardised testing guidelines[2] and evaluated a large number of endpoints, Feng *et al.* (2017) was considered to be the best available study from which to derive a guideline value for PFBS in Australian drinking water (SLR 2024a, b). This is because it was considered to have been conducted appropriately[2] and evaluated more sensitive endpoints (i.e. female reproductive performance and developmental effects) over a longer timeframe than NTP (2022) (SLR 2024a, b). In addition, the clinical relevance of the observed decreases in thyroid hormones to humans were supported by these effects being accompanied by a small but statistically significant increase in TSH in mice exposed to PFBS in Feng *et al.* (2017) (SLR 2024a, b).

GenX chemicals

A review by SLR (2024a, b) found that where international assessments[16] have developed health advice for GenX chemicals, any benchmark values have been based on a critical health effect of liver effects (increased absolute and relative weight and histopathologic findings, i.e. liver single cell necrosis in parental mice) from an unpublished, industry-funded reproduction/developmental toxicity study in mice by DuPont (2010) which was reported to have been conducted according to OECD TG 421 and followed Good Laboratory Practices (SLR 2024a, b). This unpublished study without peer review was considered inappropriate for the derivation of a guideline value in Australian drinking water.

[15] MDH 2022; MPART 2019; OEHHA 2021; US EPA 2021c, 2022c; WSDH 2019, 2022, 2023

[16] MPART 2019; NJDEP 2023; US EPA 2021e, 2022c, j; WSDH 2022, 2023

DERIVATION OF GUIDELINE

Guideline values were derived for PFOA, PFOS, PFHxS and PFBS using a threshold approach consistent with guidance provided in Chapter 6 and approaches used by enHealth and WHO (enHealth 2012; WHO 2022). No guideline value was derived for GenX chemicals. A guideline value for total or sum of PFAS was not considered feasible or appropriate at this time without further research on the potential grouping of surrogates, the available toxicological evidence and the practical achievability and utility of this approach in the Australian context.

PFOA

NTP (2023), cited by the US EPA (2024b) and Zahm *et al*. (2024), was considered to be the best available study to establish a health-based guideline value for PFOA in Australian drinking water. The choice of study was based on an assessment by SLR (2024c) that found that NTP (2023) was a comprehensive, high quality (high confidence) study that was considered to have been conducted appropriately[2] and investigated a large number of endpoints (SLR 2024c). It was considered that the most critical health effect in NTP (2023) for PFOA was carcinogenicity, with neoplastic effects such as pancreatic acinar adenomas and adenocarcinomas considered to be more critical than non-neoplastic effects (e.g. hepatocellular necrosis) that occur at higher concentrations in rats (SLR 2024c). While noted that there are uncertainties about the clinical relevance to humans, these findings could not be completely dismissed in light of in vitro studies that may support a relevant mode of action in humans (SLR (2024c). As a genotoxic mode of action was not demonstrated (SLR 2024a, b, c), a guideline value for PFOA was derived using a threshold approach.

The health-based guideline value of 200 ng/L (rounded) for PFOA was determined from NTP (2023) as follows:

$$\text{200 ng/L (equivalent to 0.2 µg/L)} = \frac{\text{1946 ng/kg bw/day x 70 kg x 0.1}}{\text{2 L/day x 30}}$$

where:

- 1946 ng/kg bw/day (0.001946 mg/kg bw/day) is the acceptable daily intake of PFOA in humans determined from a benchmark dose level derived on the basis of neoplastic effects (i.e. pancreatic acinar adenomas and adenocarcinomas) observed in a two-year carcinogenicity and toxicity study in male rats (NTP 2023; SLR 2024c).
- Because of the large differences observed in the half-lives of PFOA in humans compared to animals, pharmacokinetic modelling was applied to the serum PFOA concentrations measured in experimental animals at the benchmark dose level for the observed neoplastic effects to calculate the human equivalent dose (a dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose) (SLR 2024c).
- 30 is the uncertainty factor applied to the human equivalent dose derived from an animal study. The uncertainty factor incorporates a factor of 3 to account for the uncertainty of extrapolating from animals to humans and a factor of 10 to account for human variability (SLR 2024c).
- 70 kg is taken as the average weight of an adult.
- 0.1 is a proportionality factor based on the conservative assumption that drinking water accounts for 10% of the acceptable daily intake.
- 2 L/day is the reference value of water consumed by an adult.
- The calculated value of 227 ng/L is rounded to a health-based guideline value of 200 ng/L as per the rounding conventions described in Chapter 6.

PFOS

NTP (2022), cited by the US EPA (2024c), was considered to be the best available study to establish a health-based guideline value for PFOS in Australian drinking water. The choice of study was based on an assessment by SLR (2024a, b, c) that found that NTP (2022) was a comprehensive, high quality (high confidence) study that was considered to have been conducted appropriately[2] and investigated a large number of endpoints (SLR 2024a, b, c). It was considered that the critical health effect in rats in NTP (2022) for PFOS was bone marrow effects (extramedullary haematopoiesis and bone marrow hypocellularity) (SLR 2024c).

The health-based guideline value of 4 ng/L (rounded) for PFOS was determined from NTP (2022) as follows:

$$4 \text{ ng/L (equivalent to 0.004 µg/L)} = \frac{294 \text{ ng/kg bw/day} \times 70 \text{ kg} \times 0.1}{2 \text{ L/day} \times 300}$$

where:

- 294 ng/kg bw/day (0.000294 mg/kg bw/day) is the acceptable daily intake of PFOS in humans determined from a benchmark dose level (BMDL) derived on the basis of bone marrow effects (extramedullary haematopoiesis and bone marrow hypocellularity) from a sub-chronic (28-day) toxicity study in female rats (NTP 2022; SLR 2024c).
- Although there were substantial differences between the modelled BMDLs and measured no observed adverse effect levels (NOAELs) (i.e. 29-fold difference in female rats and 5-fold difference in male rats), the former was considered to be a more statistically robust approach and was adopted in this guideline derivation for PFOS. This is consistent with the US EPA (2024c), which also applied the BMDL approach when assessing the data from this study.
- Because of the large differences observed in the half-lives of PFOS in humans compared to animals, pharmacokinetic modelling was applied to the serum PFOS concentrations measured in experimental animals at the benchmark dose level for the observed effects to calculate the human equivalent dose (a dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose) (SLR 2024c).
- 300 is the uncertainty factor applied to the human equivalent dose derived from an animal study. The uncertainty factor incorporates a factor of 3 to account for the uncertainty of extrapolating from animals to humans, a factor of 10 to account for human variability and a factor of 10 for use of a short-term study (SLR 2024c).
- 70 kg is taken as the average weight of an adult.
- 0.1 is a proportionality factor based on the conservative assumption that drinking water accounts for 10% of the acceptable daily intake.
- 2 L/day is the reference value of water consumed by an adult.
- The calculated value of 3.4 ng/L is rounded to a health-based guideline value of 4 ng/L as per the rounding conventions described in Chapter 6.

PFHxS

NTP (2022), used in several international assessments,[17] was considered to be the best available study to establish a health-based guideline value for PFHxS in Australian drinking water. The

[17] MDH 2020b; MPART 2019; OEHHA 2022

choice of study was based on an assessment by SLR (2024a, b) that found NTP (2022) was conducted in accordance with relevant standardised testing guidelines[2], evaluated a large number of endpoints, and provided serum PFHxS concentrations (SLR 2024a, b). It was considered that the critical health effect in NTP (2022) for PFHxS was thyroid effects (i.e. decreased thyroxine (T4) levels) in male rats (SLR 2024a, b), although it is noted that there are some uncertainties about human clinical relevance of this endpoint.

The health-based guideline value of 30 ng/L (rounded) for PFHxS was determined from NTP (2022) as follows:

$$30 \text{ ng/L (equivalent to 0.03 µg/L)} = \frac{2916 \text{ ng/kg bw/day} \times 70 \text{ kg} \times 0.1}{2 \text{ L/day} \times 300}$$

where:

- 2916 ng/kg bw/day (0.002916 mg/kg bw/day) is the acceptable daily intake of PFHxS in humans determined from a benchmark dose level derived on the basis of decreased thyroxine (T4) levels from a sub-chronic (28-day) toxicity study in male rats (NTP 2022; SLR 2024a, b).
- Because of the large differences observed in the half-lives of PFHxS in humans compared to animals, pharmacokinetic modelling was applied to the serum PFHxS concentrations measured in experimental animals at the benchmark dose level for the observed thyroid effects to calculate the human equivalent dose (a dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose) (SLR 2024a, b).
- 300 is the uncertainty factor applied to the human equivalent dose derived from an animal study. The uncertainty factor incorporates a factor of 3 to account for the uncertainty of extrapolating from animals to humans, a factor of 10 to account for human variability and a factor of 10 to account for the limited database of toxicological studies (e.g. no two-generation or immunotoxicity studies) (SLR 2024a, b).
- No uncertainty factor was applied for the use of a sub-chronic study as the serum PFHxS levels in rats in NTP (2022) were considered likely to be at steady state (SLR 2024a, b). The database uncertainty factor is likely to already account for use of a sub-chronic study since it is applied for a lack of chronic toxicity studies; the composite uncertainty factor of 300 was therefore considered to be sufficiently health protective (SLR 2024a, b).
- 70 kg is taken as the average weight of an adult.
- 0.1 is a proportionality factor based on the conservative assumption that drinking water accounts for 10% of the acceptable daily intake.
- 2 L/day is the reference value of water consumed by an adult.
- The calculated value of 34 ng/L is rounded to a health-based guideline value of 30 ng/L as per the rounding conventions described in Chapter 6.

PFBS

The study by Feng *et al.* (2017), used in several international assessments[18] was considered to be the best available study to establish a health-based guideline value for PFBS in Australian drinking water (SLR 2024a, b). This is based on an assessment by SLR (2024a, b) that Feng *et al.* (2017) had been well-conducted[2] with adequate reporting and consideration of appropriate study design and methods for more sensitive endpoints of interest (i.e. female reproductive performance and

[18] MPART 2019; OEHHA 2021; US EPA 2022; WSDH 2019, 2022, 2023

developmental effects) compared to NTP (2022) (SLR 2024a, b). It was considered that the critical health effect in Feng *et al.* (2017) for PFBS was thyroid effects (i.e. decreased thyroxine (T4) levels) in mice (SLR 2024a, b). It is noted that while changes in thyroid hormones in rodents are not always considered clinically relevant to humans, there was evidence in Feng *et al.* (2017) that the pituitary gland was affected in PFBS-exposed mice, indicating a mechanism of action for secondary hypothyroidism.

The health-based guideline value of 1000 ng/L (rounded) for PFBS was determined from Feng *et al.* (2017) as follows:

$$1000 \text{ ng/L (equivalent to 1 µg/L)} = \frac{94{,}849 \text{ ng/kg bw/day} \times 70 \text{ kg} \times 0.1}{2 \text{ L/day} \times 300}$$

where:

- 94,849 ng/kg bw/day (0.09489 mg/kg bw/day) is the acceptable daily intake of PFBS in humans determined from a benchmark dose level derived on the basis of decreased thyroxine (T4) levels from a 60-day toxicity study in mice (Feng *et al*. 2017; SLR 2024a, b).
- Because of the large differences observed in the half-lives of PFBS in humans compared to animals, pharmacokinetic modelling was applied to the serum PFBS concentrations measured in experimental animals at the benchmark dose level for the observed thyroid effects to calculate the human equivalent dose (a dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose) (SLR 2024a, b).
- 300 is the uncertainty factor applied to the human equivalent dose derived from an animal study. The uncertainty factor incorporates a factor of 3 to account for the uncertainty of extrapolating from animals to humans, a factor of 10 to account for human variability and a factor of 10 to account for the limited database of toxicological studies (e.g. no two-generation or immunotoxicity studies) (SLR 2024a, b).
- 70 kg is taken as the average weight of an adult.
- 0.1 is a proportionality factor based on the conservative assumption that drinking water accounts for 10% of the acceptable daily intake.
- 2 L/day is the reference value of water consumed by an adult.
- The calculated value of 1107 ng/L is rounded to a health-based guideline value of 1000 ng/L as per the rounding conventions described in Chapter 6.

GenX chemicals

There is currently insufficient information, both from toxicity and occurrence viewpoints, to determine the risk that GenX chemicals pose to health from drinking water in Australia.

A review of existing sources of national/ international guidance found that there is currently insufficient health evidence to derive a health-based guideline value for GenX chemicals in drinking water (SLR 2024a, b). Most jurisdictions that were reviewed have not set a guideline value for GenX chemicals in drinking water. Jurisdictions that have set a guideline value were informed by a single industry-funded study (Dupont 2010), which is considered inappropriate to derive an Australian health-based guideline value for drinking water due to potential conflict of interest and risk of bias.

No information on levels of GenX chemicals in Australian water supplies was identified in the review (SLR 2024a, b). Additional research is needed to determine if GenX chemicals are present in Australian drinking waters and, if they are present, at what concentrations.

REVIEW HISTORY

The fact sheet was initially published in 2018. This update of the fact sheet was based on reviews completed by SLR Consulting Australia in February 2024 (SLR 2024a, b) and August 2024 (SLR 2024c), with corrections actioned in October 2024 (refer to the Administrative Report for more information).

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