1. Approaches to testing and retesting individuals for human blood levels of PFAS

1.1 Introduction

Concentrations of various PFAS have been measured in plasma, serum, and whole blood, although serum is the most common choice for PFAS testing.[1] Serum PFAS levels are generally about twofold higher than in whole blood whereas plasma and serum levels are very similar.[2] Measured PFAS concentrations in human serum vary across different populations, from single- or double-digit nanograms per millilitre in the general population to thousands of nanograms per millilitre (ng/mL) in occupationally exposed workers and residents near contaminated sites.[1] In this section the focus is primarily on PFOS, PFOA and PFHxS as they are the PFAS commonly associated with AFFF contamination. There have been a large number (many hundreds) of studies testing PFAS levels in human serum worldwide and it is not necessary to review all those studies in detail here. There have already been several excellent reviews on PFAS serum levels in the general population and in highly exposed populations. [1, 3, 4] Other reviews specifically focused on occupational exposure to PFAS.[5, 6]

Testing of chemical contaminants in humans is a mature discipline and a book was written by the National Research Council of the National Academies (NRCNA) on the subject already in 2006.[7] Specific guidance on PFAS testing has also been published by the NRCNA more recently in 2022.[8] Regarding PFAS testing, the NRCNA 2022 report [8] recommends that "discussions about PFAS testing should always include information about how PFAS exposure occurs, potential health effects of PFAS, limitations of PFAS testing, and the benefits and harms of the testing". Clinicians would usually follow the principle that they only order testing when they know how to interpret and act on the results. However, as we will conclude below, in contaminated communities PFAS testing of serum is seldom done for clinical management purposes, but rather to understand the PFAS exposure and effects for research or for legal purposes.

1.2. Testing and retesting in populations with elevated levels of PFAS

As mentioned above, a review published in 2015 already covered testing in populations with elevated levels of PFAS.[3] The findings of that review will be briefly summarized here. Interestingly, the 2014 review totally neglected exposure related to the use of AFFF at commercial airports and military bases. The reason for this omission was that studies reporting elevated exposures related to AFFF use have all been published in the last decade, i.e. after 2015. Considering that to date there is no review on the elevated PFAS serum levels related to AFFF use, the known studies are summarized below.

1.2.1. Testing and retesting in non-AFFF related exposure scenarios

In addition to releases from use of AFFF, several other environmental releases of PFAS have reached surface and/or groundwater sources for drinking water. Depending on location, these other types of environmental releases can be described as: (1) industrial emissions from nearby PFAS manufacturing plants; (2) landfill leachate releases; and (3) run-off from sewage-sludge amended agricultural fields. Testing for PFAS in each affected community demonstrated concentrations above levels reported in the general population. [3]

Emissions of PFAS from the 3M Cottage Grove manufacturing facility as well as leaching from several local landfills resulted in elevated levels of PFAS in public and private wells in the East Metro communities of the Minneapolis-St. Paul metropolitan area.[3] A random sample of East Metro citizens in the affected areas had their serum tested for PFAS. In 2008, the geometric mean serum concentrations for PFOS (35.1 ng/mL), PFOA (15.1 ng/mL), and PFHxS (8.2 ng/mL) were

approximately three to four times higher than the 2007–2008 National Health and Nutrition Examination Survey (NHANES) data for the general population. [3] In a retesting of this population 2 years later, the geometric mean serum concentrations for the East Metro area declined in line with the serum elimination half-lives for these substances. [3] Based on these percentage declines, it was concluded that the exposure reduction efforts appeared to be working but continued serum testing was warranted to ensure further declines occurred. [3]

PFAS-contaminated wastewater from the 3M manufacturing plant in Decatur, Alabama was treated at a wastewater treatment facility which resulted in the generation of PFAS-contaminated sewage sludge.[9] Subsequent application of the PFAS-contaminated sewage sludge to agricultural land resulted in PFAS contamination of surface waters and private wells. [9] The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a human exposure investigation in which a total of 85 households participated (153 people volunteered from these households) in serum testing for PFAS. [10] Geometric mean serum PFAS concentrations in the contaminated area were approximately two to five times higher than in the reference group. [10] The range of serum PFOS concentrations for those people consuming private well water were (in parentheses): PFOS (38.6–472 ng/mL), and PFOA (7.6–144 ng/mL) and PFOS (6.1–59.1 ng/mL), which is much higher than the general population. [10] An epidemiological study was also performed on the population. [10] Retesting of some members of same population (n=45 volunteers) in 2016 showed a decline in serum concentrations.[11]

Elevated PFOA serum concentrations were found in the population living in proximity to the DuPont Washington Works fluoropolymer (i.e. Teflon) manufacturing plant (near Parkersburg, West Virginia).[12] Serum testing was originally conducted by Emmett et al. [12] on a limited scale before a large-scale serum testing effort (69,030 individuals tested over a 13-month period) was undertaken as part of a class-action lawsuit.[13] The overall geometric mean PFOA concentration was 32.9 ng/ml compared to 3.9 ng/L for NHANES at the time (2003-2004). [13] One of the six water districts sampled (Little Hocking) had a much higher PFOA mean concentration of 227.6 ng/ml (>50 times higher than NHANES). [13] This large-scale serum testing was part of a set of well-known epidemiological studies (C8 Panel). Bartell et al.[14] retested the blood of 200 residents of the Little Hocking and Lubeck water districts over an 18-month time frame to monitor potential declines in serum levels after water filtration was implemented. They estimated the average serum PFOA decline was 26 % per year resulting in a median serum PFOA half-life of 2.3 years. A number of other research projects were also set up by the C8 Science Panel and involved retesting on individuals in the contaminated area,[15] but these are not connected to clinical management. Furthermore, the C8 Medical Monitoring Program (http://www.c-8medicalmonitoringprogram.com/index) was created as part of the settlement of the class action lawsuit by DuPont. Settlement Class Members were entitled to medical monitoring paid for by DuPont. The C8 Medical Monitoring Program recommended medical screening every 3 years following the initial medical screening. In the initial screening they underwent a medical examination and provided a serum or urine sample for PFAS testing. Retesting of PFAS levels in serum or urine was offered as part of the 3-yearly follow-up medical screenings. As the C8 Medical Monitoring Program is linked to a class action lawsuit, the motivation for retesting is different compared to other contaminated communities managed by local health authorities.

Levels of fluoroethers (e.g. hexafluoropropylene oxide dimer acid, HFPO-DA or GenX) and “other PFAS” were tested in serum samples (289 adults and 55 children) of Wilmington, North Carolina residents who live downstream of a fluoropolymer manufacturing plant.[16] It was believed that the primary drinking water source of Wilmington was contaminated by the plant. Here, only the results

of the “other PFAS” are summarized as they are most relevant for Jersey. Concentrations of PFHxS, PFOA, PFOS and PFNA were detected in most (≥97%) participants and their levels were higher than U.S. national levels for the 2015–2016 National Health and Nutrition Examination Survey. [16] Median levels of the sum of 5 PFAS (PFOS, PFOA, PFHxS, PFNA and PFHpA) in the adults were 20.8 ng/ml. Retesting was done on 44 participants and the median percentage decrease for the four legacy PFAS (PFOA, PFOS, PFHxS, and PFNA) ranged between 0% and 13%.[17]

Application of sewage sludge to agricultural land near Arnsberg, Germany led the large-scale contamination of a drinking water reservoir.[18, 19] Disposal of contaminated sludge from the paper industry was identified as the source of the contamination. A serum testing study was conducted of a sample of residents from Arnsberg (men and mothers/children) with reference populations selected from nearby populations. Blood samples were tested in 2006 [18] and blood was retested in 2007 [19] and 2008 [20]. In 2006, the geometric mean PFOA plasma concentrations (in parentheses) were: children (23.4 ng/mL); mothers (23.6 ng/mL); and men (30.3 ng/mL). [18] These geometric mean and concentrations were approximately five times higher than in the reference populations. Two years later after the remediation efforts, the geometric mean PFOA plasma levels declined by 39 % (children and mothers) and 26 % (men) in the Arnsberg population compared to 13–15 % in the reference groups.[20]

Elevated serum concentrations of PFAS were reported in the serum from commercial fishermen on the Tangxun Lake in Wuhan China.[21] The fishermen ate the fish they caught on a regular basis. Fluorochemical manufacturing plants in an industrial park upstream from the wastewater treatment plant situated on the upper reaches of the lake were identified as the PFAS contamination source. PFOS serum concentrations (for 37 Tangxun Lake fishermen, 7 family members, and 9 reference individuals) were 10,400 ng/mL, 3,540 ng/mL, and 19 ng/mL, respectively. [21] The highest serum PFOS concentration measured was 31,400 ng/mL in a commercial fisherman,[21] which is the world record PFOS serum concentration, and three times higher than the next highest value reported, in a 3M production worker.

In Belgium, a first investigation that tested blood levels (800 participants) of PFAS in people living within a 3 km radius of the 3M Chemicals factory in Zwijndrecht (Antwerp Province) was undertaken and revealed elevated levels of PFAS (especially PFOS) in 9 of 10 people sampled. The results of the 2021 blood tests will be further investigated and linked with medical data. In the summer of 2022, an additional 5 km population study started where 40,000 blood samples were taken in an area up to 5 km from 3M. In addition, the Youth Study on Human Biomonitoring was also started near 3M, in which more data on lifestyle, eating habits and health were measured and monitored in a selected group of young people. All of the abovementioned studies in Belgium will allow building new knowledge on the health risks of PFAS exposure in this region. In this case the initial testing within 3 km of the factory led to a follow up testing programme which was larger (40,000 instead of 800 participants) and more widespread geographically (5 km from the factory instead of 3 km).

In Veneto, Italy high levels of PFAS contamination have been found and associated with the activity of an industrial plant located in Trissino, in the province of Vicenza. The Miteni Group (formerly called Rimar), a fluorochemical manufacturer which has produced PFAS since 1968, was identified as being responsible for the pollution. [22] The human population in the region had been exposed to elevated levels of PFAS through the consumption of PFAS contaminated drinking water. In 2016, a biomonitoring study was conducted [22] on two randomly selected groups of people 20–51 years of age: 257 subjects living in the contaminated area and 250 living in a background area not affected by the contamination incident. The results showed that those living in the contaminated area had significantly higher serum PFAS concentrations than the control group had and that participants

residing in municipalities served by contaminated waterworks had the highest serum PFAS concentrations. To address public concerns about exposure to PFAS, a health surveillance program started in January 2017 and continues for the prevention, early diagnosis and treatment of chronic disorders possibly associated with PFAS. Blood (and urine) testing for 12 PFAS was offered to the entire highly exposed population of 105,000 people, which makes this study unique. Data were also collected through a structured interview on socio-demographic characteristics, personal health history and lifestyle habits. A preliminary study of 18,345 participants born between 1978 and 2002, 14–39 years of age at recruitment was published in 2020,[23] but recruitment continued. The population is being recruited for a second round, including retesting of blood and urine for PFAS, which started in September 2020. By February 2022, 55,597 individuals were recruited (60,5% of invited) in the 1st round, and 2,623 in the 2nd round. The median PFAS serum concentrations for PFOA, PFOS and PFHxS were recently reported to be 36.8 ng/mL, 3.8 ng/mL and 3.7 ng/mL, respectively.[24] The program includes a thorough assessment of individual exposure as well as behavioural and clinical risk factors for cardiometabolic disorders, providing tailored counselling for exposure and risk reduction, and the referral of subjects with altered biomarkers for subsequent diagnostic and therapeutic evaluation.

1.2.2 Testing and retesting in AFFF-related exposure scenarios

In addition to Jersey, elevated human serum levels related to AFFF use have been observed at 11 locations in the US,[25, 26] 1 location in Sweden,[27] 3 locations in Australia [28] and 1 location in Denmark. (ref) Here we briefly review the different serum testing strategies used in these 16 known locations that have elevated PFAS serum levels related to historical AFFF use.

In Jersey, a programme of free-of-charge serum testing was arranged in 2022 for people who had lived in the affected areas between 1991 and 2006, regularly consumed contaminated borehole water from the affected areas, and had symptoms consistent with conditions that have been associated with PFAS exposure. (ref) A total of 88 results was obtained. The geometric means for serum PFHxS, PFOS and PFOA were 13, 11 and 3 ng/mL.

In Ronneby, Sweden, in 2014, i.e. six months after provision of clean water, all residents in the municipality were invited to free-of-charge serum testing. In total 3507 participants were recruited, which was about 13% of the entire Ronneby population at the time.[27] The participation rates from contaminated and minimally contaminated areas were approximately 30% and 5%, respectively. [27] In Ronneby the mains water was the main historical PFAS exposure source. The geometric means for serum PFHxS, PFOS and PFOA were 114, 135 and 6.8 ng/mL for all Ronneby residents.[27] In Ronneby serum was retested to determine if PFAS levels were declining and to determine serum half-lives. [29, 30]

In Australia, between 2016 and 2019, 2392 adults and 195 children were recruited from the PFAS Management Areas in Katherine, Oakey and Williamtown to participate in free-of-charge serum testing. In total, 32% (817/2587) of participants from the exposed communities were current residents of one of the PFAS Management Areas at the time of blood collection. Not all of these participants consumed contaminated borehole water while living in the PFAS Management Areas. The geometric means for serum PFOS, PFHxS and PFOA were 4.9–6.6 ng/mL, 2.9–3.7 ng/mL and 1.3–1.8 ng/mL, respectively. [28] These levels are notably lower than in many of the other studies because the sampling mixed participants who consumed contaminated borehole water with those who did not.

In the United States, The Centers for Disease Control and Prevention (CDC) and the ATSDR conducted free-of-charge serum testing in 10 communities (Westhampton Beach and Quogue Area, New York; Montgomery and Bucks Counties, Pennsylvania; Hampden County, Massachusetts; Berkeley County, West Virginia; New Castle County, Delaware; Spokane County, Washington; Lubbock County, Texas; Fairbanks North Star Borough, Alaska; El Paso County, Colorado and Orange County, New York) that are near current or former military bases and were found to contain PFAS levels in the past exceeding the Environmental Protection Agency's 2016 health advisory of 70 parts per trillion (ppt) for PFOA and PFOS combined. [25] These studies assessed PFAS levels in the serum of some residents in each community living near the current or former military bases where public water systems or private wells had PFAS levels above EPA's health advisories. Participants were selected based on specified criteria with the aim of collecting data that were generalizable to each sampling frame (areas within the site communities where known or expected PFAS exposure occurred). Tap water and indoor dust samples from a subset of participating households were also analyzed. The primary aim was to understand and control exposure rather than to relate exposure to health effect (i.e. epidemiology). Between September 2019 and October 2020, 1988 eligible people (1791 adults and 197 children) from 1094 households participated in the sampling across the 10 locations. The highest age-adjusting geometric means of serum levels across the 10 studies for PFHxS, PFOS and PFOA were 65.6, 39.1 and 8.9 ng/mL. [25]

Also, in the United States, in Pease New Hampshire, a total of 1578 eligible individuals provided serum samples for serum testing in 2015. [26] Many members of this community situated near Pease Airforce Base had consumer water from a contaminated well, which had been contaminated due to historical AFFF use at the base. Eligible participants were those who consumed contaminated drinking water while working on, living on, or attending childcare at the former Air Force base, while it was an active base or in the civilian community of Pease after the base closure. The aim of the study was to understand PFAS exposure. The geometric means for serum PFHxS, PFOS and PFOA were 8.59, 4.12 and 3.09 ng/mL. [26]

In Denmark in 2020, high levels of PFOS and PFHxS were detected in a wastewater treatment plant in Korsør, Denmark, and the source of contamination was found to be a firefighting training facility where AFFF had been regularly used. (ref) In 2021, analyses of the meat from four calves, who had grazed in a field near the firefighting training facility also revealed high levels of PFOS and PFHxS indicative of AFFF contamination. The cattle were the main source of beef intake for members of a local Cow Grazing Association since 1999. Analysis of PFAS in the serum of the Cow Grazing Association (187 individuals) showed particularly high levels of PFOS (mean 43 ng/ml), which is more bioaccumulative in cows than PFHxS and PFOA. (ref) A randomized clinical trial was performed on the exposed population to determine if treatment reduced PFOS serum levels. Despite the treatment effectively decreasing PFOS serum levels in the clinical trial, the Danish authorities decided to not make the treatment generally available. This decision was because they could not conclude that treating individuals to lower PFOS serum levels would provide any health benefits. An exception was made for highly exposed women, who planned a pregnancy. They also decided not to provide retesting to the exposed population as the PFAS levels tested cannot be used to inform on health effects on an individual basis. (ref)

In summary, only the Swedish and Australian studies aimed to relate PFAS serum levels to health effects (as summarized in Report 2). While health data are available for Jersey, this study has too low a number of participants to be used for epidemiological studies. The primary aim of the US studies was to better understand exposure so that it could be effectively reduced going forward.[25] Only

the Swedish study has to date retested a subset of the original participants. The purpose of this retesting was to determine if exposure in the population had declined. [29, 30]

1.3. Testing and retesting in the general population

Exposure to PFAS has been estimated from the concentrations of the target PFAS in serum, plasma, or whole blood in numerous studies conducted around the world since the early 2000s (see multiple references Kato et al.[4]). Observed PFAS serum concentrations vary by geographical location, PFAS type, sex, and age. [1]

NHANES is the most extensive and well-known national serum testing programme and has measured PFAS-levels in blood in the U.S. population since 1999.[31] NHANES PFAS data have been publicly released in 2-year cycles. NHANES is principally designed to assess the health and nutritional status of U.S. adults and children. The survey is unique in that it combines interviews, physical examinations, and analysis of biological samples for contaminants, including PFAS for Americans of 12 years of age and older. The NHANES survey examines a nationally representative sample of about 5,000 persons each year. However, NHANES included a subset of around 2,000 individuals in each cycle for PFAS measurements. In studies such as NHANES that aim is to get a representation sample of the general population the following considerations are required; stratifying your target population by relevant demographics like age, sex, socioeconomic status, region, etc., to capture population diversity; having a sample size that provides sufficient statistical power; and using a random sampling method to avoid selection bias.

Even if NHANES is considered a good representation of the PFAS exposure in the U.S. general population, Wisconsin have initiated their own state-wide survey (The Survey of the Health of Wisconsin (SHOW)) which using similar methodology to NHANES.[32] The aim is to characterize the variability of PFAS exposure in a statewide representative cohort in the US. It can also be used to identify high risk populations and inform state public health standards and interventions, especially among those not living near known contamination sites.

For the majority of the generally-exposed populations examined around the world, the four most commonly studied PFAS have been PFOS, PFOA, PFHxS and PFNA). PFOS usually has the highest serum concentrations followed by PFOA, while other PFAS are detected both at lower concentrations and frequencies. [4] In hot spot contamination areas and occupational settings, the concentration patterns observed often differ from those reported among the general population (e.g. PFHxS is higher than PFOA in serum in an AFFF-impacted population). Interestingly, the ranges of blood concentrations of PFOS, PFOA, PFHxS, and PFNA in the general population are remarkably similar worldwide among many countries, suggesting a common historical exposure source. Higher concentrations of PFOS, PFOA, and PFHxS are found in males compared to females and this has been mainly attributed to monthly blood loss from menstruation in women.

In many of the studies reviewed in the above sections of the report, the contaminated population was often compared to a nearby reference population which in turn was compared to a well-known testing programme for the general population (often NHANES is used). The aim of this comparison exercise is to confirm that the contaminated population is in an isolated region only.

Temporal trend studies of PFOS, PFOA and PFHxS have been undertaken in several countries through retesting a representative sample of the general population at regular intervals.[1, 4] The temporal trend studies are typically “cross-sectional” in design whereby a similar representative cross-section of the population is sampled at each time point (as in NHANES) [31] rather than retesting the same individuals (known as a longitudinal testing design). In NHANES a cross-section of

the US population is sampled every two years since 1999 and the serum analyzed for PFAS. Similar temporal trends have been observed between studies and countries despite some differences in sampling design among studies, pools vs individual specimens, plasma vs serum, sample size, time period and potential regional differences in exposure.[4] The concentrations of these PFAS in blood followed similar increasing trends from the 1970s to the mid-1990s due to the increasing production volumes in this period (e.g. PFOS peaked at about 30 ng/L in the US general population at the turn of the millennium) and then have declined since the early 2000s following their industrial phase out by 3M in 2000-2002. [4] China and some other Asian countries are an exception to these otherwise general time trends because these countries increased production of PFOS and PFOA when 3M phased out their industrial production of long-chain perfluoroalkyl chemistries in 2000-2002,[33] and have only recently announced that they too will cease production of some long-chain perfluoroalkyl chemistries. PFAS are still today ubiquitously detected in people around the world in single digit ng/L levels and declining trends in blood may be plateauing off as serum levels approach a steady-state with background environmental exposure intakes.[1]

1.4. Testing and retesting in occupationally exposed populations, especially firefighters

Christensen and Calkins [5] reviewed occupational exposure studies and identified 92 individual studies for PFAS. Most occupational studies reviewed (~60%) evaluated PFAS exposure in fluorochemical production workers or first responders (mostly firefighters). In addition, occupational studies focused on ski wax technicians, fishermen, textile manufacturing, a metal plating workshop, a powder coating shop, a metalworking shop, a plastic production facility, a pesticide packing plant, outdoor clothing (and gear) shops, offices, college lecture halls, school laboratories, computer rooms, primary/secondary classrooms, furniture shops, printing shops, autobody shops, a mechanical shop, an electrotechnical shop, carpet shops, a car selling store, electronic stores, a sports equipment shop, coffee shops, internet cafes, restaurants, libraries, movie theaters, and hotels. [5] The highest serum levels were reported in fluorochemical workers, but, in comparison to reference populations, one or more PFAS were elevated in most workers and in most workplaces that were assessed in the review. [5] Here we provide a summary only of the research done on occupation exposure of PFAS for firefighters as it is most relevant occupational exposure for Jersey.

Serum testing of PFAS in firefighters was reviewed by Rosenfeld et al. [6]. The 10 studies that were reviewed by Rosenfeld et al. in the US and Australia showed that firefighters have elevated serum levels of certain PFAS such as PFOS and PFHxS [5]. In Australia, Rotander et al. [34] studied 149 firefighters working with AFFF at training facilities in Australia's Airservices Aviation Rescue Fire Fighting Service and reported that firefighter PFOS and PFHxS serum levels were 6–10 times and 10–15 times higher, respectively, than in the general population. A larger study followed on 799 current and former Airservices staff, with 130 staff from the earlier study.[35] Although PFAS were still elevated, the geometric mean dropped between 2015 and 2018, suggesting that levels continued to decline since the 2005 phase-out of 3M Lightwater AFFF in Australia. Nilsson et al.[35] further found that PFOS and PFHxS serum levels were positively correlated with length of employment working with AFFF. Firefighters who started work in Australia before 2005 had serum concentrations of PFHxS and PFOS higher than the general population, while those who started working after 2005 had levels similar to the general population. In the US, eight additional studies reported elevated levels of PFAS in the serum of both fulltime and volunteer firefighters.[35]

Dermal and inhalation exposure from PFAS-impregnated turnout gear have both been suggested to be exposure pathways for firefighters, but these pathways are considered of lesser importance compared to exposure from the use of AFFF during training and firefighting.[6] The fact that Australian firefighters who commenced worked after 2005, and still wore PFAS impregnated turnout

gear, had similar levels to the general population provides supporting evidence that AFFF-derived exposure is much more important than exposure related to turnout gear.[35] Modern fluorotelomer-based AFFF is based on short-chain C6 PFAS chemistry. No exposure to PFOS or PFHxS is possible from the use of modern fluorotelomer-based AFFF as it does not contain these substances.[36]

1.5. Discussion on strategies for testing and retesting serum for PFAS

In the 2006 NRCNA book[7] on testing of contaminants in humans, it recommended that it is first necessary to determine the purpose of retesting, which can be several:

- Tracking exposure over time: These studies monitor the levels of PFAS or biomarkers in individuals over extended periods. The aim is primarily to understand how exposure to PFAS changes over time and can be used e.g. to derive serum half-lives.
- Assessing health outcomes: By correlating test data with health outcomes, researchers can identify potential links between exposure to certain chemicals and the development of diseases or health conditions over time.
- Evaluating public health interventions: To assess the effectiveness of public health policies and interventions aimed at reducing exposure to harmful substances. This helps in determining whether these measures are successful and where improvements might be needed.
- Identifying at-risk populations: These studies can highlight specific groups within the population that are more vulnerable to certain exposures, such as children, pregnant women, or occupational groups. This information is crucial for targeted public health strategies.
- Understanding environmental changes: To reveal how changes in environmental levels impact human exposure over time.
- Supporting regulatory decisions: The data from these studies provide evidence that can inform regulatory bodies in setting safety standards and guidelines for exposure to various chemicals.

When it comes to retesting of individuals with elevated PFAS exposures, the following guidance is given in the NRCNA 2022 report,[8] which provides specific guidance on PFAS testing:

- For individual tests, consider confirmatory retesting when the result is much higher or lower than anticipated given exposure history;
- Consider retesting to understand exposure changes due to:
    - public health actions (such as drinking water treatment programs or site cleanup are taken to reduce exposure);
    - patients take actions to reduce exposure (such as installing water filters, moving from a community with known high levels of PFAS in drinking water, or modifying occupational exposures); or
    - the patient moves into a community with known high levels of PFAS or otherwise has a suspected increase in exposure risk.
- If there is interest in follow-up testing of PFAS to determine declines in exposure and determination of serum half-lives, allow at least a year between each retesting.
- Retesting is of no or limited value if initial serum levels are low and exposure does not change.

This guidance given above taken from the NRCNA 2022 report[8] is purely related to retesting for the purpose of understanding exposure. Also, no guidance is given above as to what is considered "low" serum levels. However, it is further recommended in the NRCNA 2022 report[8] that clinicians should use serum or plasma concentrations of the sum of PFAS to inform clinical care of exposed patients, using the following guidelines for interpretation:

- Adverse health effects related to PFAS exposure are not expected at less than 2 ng/mL.
- There is a potential for adverse effects, especially in sensitive populations, between 2 and 20 ng/mL.
- There is an increased risk of adverse effects above 20 ng/mL.

Therefore "low" serum levels can be concluded to be less than 2 ng/L. However, the above advice may lead some individuals to believe that if they have serum levels above 2 ng/L they are at a higher risk of certain health effects related to PFAS exposure. However, it is impossible to predict health outcomes for *individuals* based on their PFAS serum levels. The authors presumably mean that there is a potential increased risk of adverse effects *on the population level* at exposure levels above 20 ng/L. It is nevertheless precautionary guidance because everyone in an industrialized country had levels of at least 20 ng/L 20 years ago and levels of 2 ng/L are fairly typical for the general population at the time of writing in 2024.

In practice, retesting for clinical management purposes in contaminated communities has not been undertaken often and is not recommended by some health authorities. For example, in Denmark retesting is not recommended in contaminated communities for the following reasons (ref):

- PFAS-levels cannot be used to predict health outcomes;
- Testing of blood samples need to be actionable, i.e. guide medical decisions and treatments;
- Counseling for highly exposed individuals does not differ from that of the background population.

At Ronneby in Sweden, the authorities follow the same general approach as in Denmark and do not offer retesting of serum levels to those individuals who took part in the initial broad testing of PFAS in the contaminated community. (ref) They also do not offer testing, or recommend individuals to test themselves, for PFAS serum levels if they live in the contaminated area but have previously been tested. Similar to in Denmark, they argue that there are no medical reasons for testing serum levels of PFAS because the test result cannot be used to predict anything about the individual's health or risk of future illness. (ref) In Ronneby, there is, however, serum retesting ongoing within various research projects focused on understanding serum half-lives of PFAS,[29, 30] but there is no clinical management connected to this retesting.

In the cases where retesting in contaminated communities has been done, reviewed above, it is clear that retesting was done largely for understanding changes of exposure, e.g. in order to improve understanding of the half life of PFAS moieties in the community, or for other research purposes, rather than to monitor the patient's wellbeing (i.e. clinical management). It can also be concluded that Jersey is unique in only testing PFAS in the serum of individuals with symptoms consistent with conditions that have been associated with PFAS exposure. All other studies tested individuals asymptomatically in the first testing timepoint and then typically retested a subsample of the original population at a later timepoint to determine if exposure had declined. Health data are usually collected from the sampled population for epidemiological research, and rarely for clinical management purposed. A few research studies have resampled PFAS levels in order to ascertain if there is a relationship with the course of a particular illness or biomarker related to PFAS

exposure,[37-39] and other studies have retested in order to assess suitability to enter or to remain in programmes of clinical intervention seeking to lower PFAS body burden.[40, 41] In one identified case, regular retesting of serum was performed in conjunction with regular health monitoring, but this was connected to a class action lawsuit and the motivation for retesting is very different compared to other contaminated communities managed by local health authorities. There is limited guidance provided for when retesting should be ceased, although in the NRCNA 2022 report it is suggested that adverse health effects related to PFAS exposure are not expected at serum levels less than 2 ng/mL. [8] If one accepts the conclusion regarding lack of adverse health effects below this level, it would be unnecessary to retest individuals once serum levels were below 2 ng/mL.

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