Review of the published literature on phlebotomy to manage PFAS exposure

Introduction

An initial search of the published literature to assess the impacts on health of therapeutic phlebotomy in populations exposed to per- and polyfluoroalkyl substances (PFAS) found no studies. A further review, on the effects of phlebotomy on the concentration of PFAS compounds in serum found three intervention studies. The context and findings of these studies are outlined below.

Findings from the literature

In the summaries below, we have reported the findings from the studies and also tried to contextualise those findings on the basis of other characteristics such as nature of exposure and baseline PFAS levels. These are important in evaluating the studies and also their applicability to the affected population in Jersey.

Genuis et al in 2014 (Genuis, et al. 2014) reported on a family who had accumulated high levels of perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA); in particular from repeated and large-scale use of PFAS-containing carpet treatments in their home. Once they realised they had been exposed and had high serum levels, they ceased using the treatments and discarded most of their carpets, replacing them with wooden flooring. Thus, ongoing exposure largely stopped. Although some measurements of household dust revealed some measurable level of PFAS, such ongoing exposure was low compared to their past exposure.

In the paper they estimate and provide a graph with half lives in the family. These half-lives are about 2.1, 1.2 and 2.1 years for PFHxS, PFOS and PFOA respectively. From their repeated phlebotomy, the average amount of blood given was 1802 ml/year in this family. They compare these results to a population who had had occupational exposure to PFAS and were retired at the time of study, but a more comparable population, particularly because of age and gender mix, would be the Swedish population followed up with multiple testing after ending exposure to drinking water contaminated with high PFOS and PFHxS firefighting foam (Li, et al. 2018). For the Swedish population reported half-lives were 5.3, 3.4 and 2.7 years, for PFHxS, PFOS and PFOA respectively. For ease of comparison these have been converted into the expected percentage fall per year. The difference is the % drop due to the intervention (average blood donation 1802 ml/y). This can be converted to the expected benefit % drop for one phlebotomy donation of 470ml. This is summarised in Figure 1, below.

Figure 1 Percentage reduction in PFAS, Canadian family

	PFHxS	PFOS	PFOA
% fall per year in Genuis et al 2014	29.4	47.7	28.5
Expected % fall per year in comparison population (Li et al, 2018)	12.2	18.1	22.9
% fall from Genuis minus expected	17.2	29.6	5.6
% fall predicted for one phlebotomy	4.48	7.72	1.47

Source: (Genuis, et al. 2014), (Li, et al. 2018)

In an Australian study of firefighters (Gasiorowski, et al. 2022) with occupational exposure to PFAS-containing firefighting foams they were randomised into three groups (one offered up to 5 phlebotomy interventions, one plasma donation, and a control just observed with no intervention). To allow for any ongoing exposure for the whole population, the impact of the phlebotomy is estimated from the difference between those giving blood and those with no intervention. On average they gave 4.3 blood donations; so the impact per blood draw can be estimated directly. Please note, the results for PFOA are a little more approximate as they are presented in less detail in the data tables and had to be read from the graph in the paper. The baseline concentrations, and absolute and relative reductions from phlebotomy are summarised in Figure 2, below.

Figure 2 Reduction in serum PFAS, Australian firefighters

	PFHxS	PFOS	PFOA (approx.)
Baseline serum concentration (ng/ml)	3.6	10.9	1.2
Drop attributed to intervention (ng/ml)	0.6	1.1	0.3
% fall attributed to intervention	16.67	10.09	25.00
% fall predicted from one phlebotomy	3.88	2.35	5.81

Source: (Gasiorowski, et al. 2022)

One of the intervention arms in the Gasiorowski study was plasma donation. While this intervention is beyond the scope of this review and will be considered in detail as part of our third report, a similar analysis on plasma donation is included for completeness at this stage.

In the plasma donation group in the Gasiorowski 2022 study (Gasiorowski, et al. 2022) they had an average of 6.4 plasma donations; each one “up to 800 ml”. For these calculations we assume that the plasma is 55% of the blood volume and each donation was 800 ml, thus the total average donation was 800*6.3 ml of plasma, equivalent to 800*6.3/0.55 = 9163 ml of whole blood. As the paper states up to 800 ml, the true total plasma drawn will be less so the predicted fall per phlebotomy will be a little higher. This is presented in Figure 3, below.

Figure 3 Impact on serum PFAS of plasma donation in Australian firefighters

	PFHxS	PFOS	PFOA (approx.)
Baseline serum concentration ng/ml	5.2	11.7	1.1
Drop attributed to intervention (ng/ml)	1.5	3.1	0.8
% fall attributed to intervention	28.9	26.5	72.7
% fall predicted from one phlebotomy	1.47	1.35	3.7

Source: (Gasiorowski, et al. 2022)

An Italian intervention study provides some data on a small population with a high body burden of PFOA in particular (https://www.quotidianosanita.it/ 2017). They report that “The average drop after four phlebotomy procedures from a starting serum median concentration of 113.6 ng/ml, of 40.1 ng/ml corresponds to a 35% drop from the initial value”. Each procedure removes 616 ml of plasma so we can estimate that 4*616 ml is equivalent to 4*616/0.55 = 4480 ml of blood and so one normal phlebotomy would be predicted to have led to a reduction of 35*470/4480 = 3.7% reduction in serum concentration, consistent with the prediction from the Gasiorowski study for PFOA (Gasiorowski, et al. 2022).

Models of likely benefit

Another approach is to model the likely benefit. In pharmacology there is the concept of the volume of distribution (Vd). This is the apparent volume into which the total amount of a drug or chemical would need to be distributed to provide the same concentration as it currently is measured in blood plasma. For example, if you consume 200 micrograms of a compound and you measure the concentration in plasma as 0.025 micrograms/ml, then the Vd, the theoretical volume that gives you that concentration is 200/0.025 = 8000 ml or 8 litres. More usually Vd is expressed as ml per kg body weight: given that it is increases with the size of the person. For an adult weighing 70 kg that would be 8000/70 = 114 ml/kg body weight (bwt). The volume of distribution varies between chemical substances depending on how they distribute around the body.

For PFAS there are several different Vd estimates published. Widely used are estimates made a few years ago: 170 ml/kg for PFOA, 230 ml/kg for PFOS, and the same value as PFOS is assumed for PFHxS (Thompson, et al. 2010). A recent review drawing on several studies, however, concluded their best estimates were 430 ml/kg for PFOA, 320 ml/kg for PFOS and 290 ml/kg for PFHxS (Chiu, et al. 2022). Conversely, work in Sweden, in the population studied for estimating half life (Li, et al. 2018), has measured rates of total excretion from urine and faeces, this work, as yet unpublished suggested lower values for Vd close to 100 ml/kg.

Applying these various Vd values from 100 to 420 to a 70 kg adult, we can estimate the expected reduction in measured PFAS from normal phlebotomy. Firstly the concentration in plasma needs to converted to whole blood. Most but not all PFAS is stored in the plasma and the ratio of PFAS measured in serum or plasma to PFAS measured in whole blood averages 1.7 (Poothong, et al. 2017). Thus for a Vd of 420 ml/kg, removing 470 ml of whole blood would be expected to reduce the concentration measured in serum, by (470/1.7)/(420*70)= 0.9%. If the Vd is estimated to be 100 ml/kg the serum would drop by 4%. This range of estimates 1 to 4% is broadly in line with the observed findings.

Further analysis and discussion

The findings from the various intervention studies are summarised in Figure 4, below.

Figure 4 Summary of the intervention studies

	PFHxS		PFOS		PFOA	
Study location:	Serum med. conc. ng/ml at baseline	% reduction from 1 phlebotomy	Serum med. conc. ng/ml at baseline	% reduction from 1 phlebotomy	Serum med. conc. ng/ml at baseline	% reduction from 1 phlebotomy
Canada (phlebotomy)	109.3		39.5		5.7	
		4.48		7.72		1.47
Australia (phlebotomy)	3.6		10.9		1.2	
		3.88		2.35		5.81
Australia (plasma)	5.2		11.7		1.1	
		1.47		1.35		3.7
Italy (phlebotomy)					114	
						3.7

Source: (Genuis, et al. 2014), (Gasiorowski, et al. 2022), (https://www.quotidianosanita.it/ 2017)

From these three intervention studies the estimated benefit per phlebotomy procedure in terms of reductions in measured serum PFAS concentrations, ranged from 1.5% to 7.7%. Given that three independent studies of people with raised past exposure all showed a clear reduction related to blood (or plasma) donation, there is surely no doubt that a reduction, over and above that from normal body elimination, would be expected for individuals with raised PFAS in Jersey, but there is uncertainty of the exact magnitude of the fall. It is also unclear how average reductions across a population might apply to a given individual, as there is considerable variation in half-life from person to person. There is also uncertainty about the potential health benefits of such a fall. Finally, as the ranking of impact between different PFAS is not consistent between the studies, it is hard to be confident in estimating which PFAS compound is likely to be reduced more, so it is reasonable to take a central average as the likely reduction for all of them. We would suggest a reduction of 4% per phlebotomy treatment as a reasonable estimate of the benefit from one treatment, and if one undertook 6 procedures in a year, the maximum benefit would be accumulated impact of six 4% reductions, a total reduction of approximately 22%. This would be in addition to any background reduction over time (which would be up to 12, 18 and 23% for PFHxS, PFOS and PFOA respectively)

To illustrate this in actual concentration terms, we can estimate based on average trends in the studies summarised above, what that would mean for someone with a body burden for PFHxS associated with a serum concentration of 20 ng/ml over the course of a year. If they did nothing it would fall by 12% ie 2.4 ng/ml, to 17.6 ng/ml. If they had a phlebotomy procedure it would fall by a further 4% to 16.8 ng/ml. If they had 6 phlebotomy procedures it would fall by 12% plus 22%, to 13.2 ng/ml.

It is important to note that everyone has some PFAS in their blood from various exposures, and the expected benefit is not so great if serum levels are close to the general background serum levels. If one's PFAS is only slightly raised above general population averages, then it would not fall by as much as 22%, as the PFAS is potentially being topped up again to some extent, from the general environmental and dietary exposure. This can be estimated by measuring PFAS in blood of people not next to a local source of contamination. Such a background average would be the likely final level reached, not zero concentration, if one had many phlebotomy procedures. Such figures for background levels are not available in Jersey directly, but one can get an estimate of the likely average background from other studies. A recent Europe-wide blood contaminants study (European Environment Agency and the European Commission 2023) included PFAS, and the data can be openly consulted. Recent average background serum levels of PFAS are for PFHxS mainly in the range 0.2 – 0.5 ng/ml, for PFOA 0.5 – 1.5 ng/ml, and for PFOS 1 to 3 ng/ml. Therefore, for people with serum levels only a little higher than those values the phlebotomy would give proportionately less benefit. The percent benefit would apply to the difference between the measured level and the background level. So for example assuming a background of 3 ng/ml for PFOS, if someone's measured level was 9 ng/ml, the percent reduction would apply to the 6 ng/ml more than background that they have, so a 22% reduction would be 22% of 6 ng/ml (about 1.3 ng/ml), not 22% of 9ng/ml (about 2 ng/ml).

In conclusion the likely benefit of phlebotomy would be a 4% fall in serum levels for one procedure, 22% fall for six procedures, but less of a fall if the starting concentration was low and virtually no reduction expected as the concentration reaches the population background level.

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