

Body burden and disease risk

By the term “body burden” of PFAS is meant the cumulative amount of these substances accumulated in an individual over time. Part of this is in the blood, mainly the serum or plasma rather than the cells, part of this is spread around other organs in the body. The proportion of the total body burden residing in other parts of the body is at least as much as in the blood, but we use the serum concentration as the measure of body burden. The rate of excretion (through bladder, gut and menstrual blood loss) is proportional to the serum concentration or body burden. Therefore, with steady intake (from diet and water) the body burden increases, until the rate of excretion equals intake and the serum concentration reaches a steady state.

Epidemiological studies seek to relate the risk of disease to PFAS exposure. The exposure can be in terms of comparing an exposed population with a non exposed one, or comparing degree of body burden i.e. serum concentration, with the risk of disease. Disease can be directly characterised, such as having a diagnosed cancer or thyroid disease, or a clinical marker which may lead to clinical disease may be affected. Examples of these clinical markers include blood pressure, cholesterol levels, antibody reactions to vaccination, hormone levels usually measured in blood like the PFAS.

For understanding and preventing disease in populations exposed to potential toxins, both the nature of the relationship the dose-response relationship, and the reversibility of these associations are important and we discuss them here.

Dose-Response Relationship

The dose-response relationship (or strictly speaking the exposure-response, as the exposure may be concentration or the dose or the accumulated intake) describes how the magnitude of exposure to a chemical relates to the severity or frequency of associated adverse health effects (Eaton & Klaassen, 2008). The shape can be a simple straight line where the effect proportionally increases with dose, though even this is not straightforward to interpret as in some papers, the exposure or the outcome, or both can be log-transformed. Such straight line relationships are very helpful for assessing risk as one can extrapolate the risk from one study to estimate the risk at higher or lower exposure levels. Or it may be that in the low exposure range there may be evidence of a threshold, an exposure level below which no effect is evident compared to a true no exposure. At the other end of the exposure range, the effect may flatten off: further exposure does not incrementally increase the risk further. Rarer still are non-monotonic dose response curves, where the risk may go down and then up again as the exposure changes, or even suggest a beneficial effect at low doses but harmful at high doses (hormesis) (Vandenberg et al., 2012).

Studies have demonstrated a dose-dependent relationship between PFAS exposure and immunotoxic effects. Higher serum concentrations of PFAS have been associated with reduced antibody responses to vaccines in children (Bline et al., 2024). Grandjean et al. found that a doubling of PFAS concentration corresponded to a significant decrease in antibody levels, indicating a linear dose-response relationship in this case between antibody levels and the logarithm of serum PFAS (Grandjean et al., 2012).

Several studies have demonstrated a positive dose-response relationship between serum PFAS levels and plasma cholesterol. Higher concentrations of PFAS compounds like perfluorooctanoic acid

(PFOA) and perfluorooctane sulfonate (PFOS) are associated with increased total and LDL cholesterol levels. For instance, (Nelson et al., 2010) found that elevated serum PFAS concentrations correlated with higher cholesterol in a U.S. population sample. Several studies spanning large ranges of concentration show a pattern of steep increase in relation to PFAS at lower serum concentration ranges and a levelling of the dose response relationship at higher levels. Other studies, however, seem to show a nonlinear dose response (Canova et al., 2020; Steenland et al 2009; Li et al 2020).

Several studies have demonstrated a positive dose-response relationship between serum levels of perfluorooctanoic acid (PFOA), a type of PFAS, and the risk of cancer. For example, Barry et al. found that individuals living near a chemical plant with higher serum PFOA concentrations had increased incidences of kidney and testicular cancers (Barry et al., 2013). Specifically, those with the highest exposure measured as cumulative dose, showed significantly elevated risks compared to those with the lowest exposure, suggesting a dose-dependent effect.

Overall, there does seem to be evidence that higher body burdens of PFAS may be associated with greater risk, although the relationship between dose and risk doesn't always seem to be a linear one.

Evidence for Risk Reduction Through Body Burden Decrease

Past PFAS exposure has been associated with adverse health effects such as cancers. Cross sectional studies show adverse effects on clinical markers, such as raised cholesterol. Whether these disease risks disappear if exposure falls to zero is not certain. As the maternal body burden goes down this would directly benefit the unborn child and infants, but for people with past exposure there is a concern that the risks may persist for them. Firstly, it takes some time for the body burden to go down, given the long half life of these PFAS. Secondly, while reducing the body burden of PFAS may reasonably be considered to reduce disease risk, but there is not yet much direct evidence on the reduction of risk following the reduction of PFAS exposure.

We know from studies of other exposures that have reduced that the associated risks do fall.

The increased cancer risk resulting from exposure to certain toxins can sometimes be reduced by eliminating or minimizing the exposure, but complete reversibility is not always possible. For example, smoking cessation significantly decreases the risk of lung cancer over time; former smokers experience a gradual risk reduction, approaching that of never-smokers after about 15 years (Peto et al., 2000). Similarly, reducing exposure to ultraviolet (UV) radiation can lower the risk of skin cancer, as DNA repair mechanisms may correct some of the damage caused by prior exposure (Armstrong & Krickler, 2001). However, for carcinogens like asbestos, the risk of mesothelioma remains elevated even after exposure stops due to irreversible changes in mesothelial cells (Stayner et al., 2013). Therefore, while reducing exposure to certain toxins can decrease future cancer risk, the extent of reversibility depends on the type of toxin, the duration of exposure, and the timing of intervention. It is plausible this also applies to PFAS.

It has been demonstrated that air pollution mortality falls following improvements in general air pollution levels [expand and add ref].

For immune effects, reversibility of immunotoxic effects depends on factors such as the type of toxin, exposure duration, and individual health status. For instance, immunosuppression caused by heavy metals like lead and mercury can be partially reversible upon cessation of exposure and with appropriate medical intervention (Lawrence & McCabe, 2002). Similarly, exposure to certain pesticides has been linked to immune system impairments that may

improve over time after the exposure ends (Corsini et al., 2013). However, the extent of recovery can vary, and in some cases, prolonged or high-level exposure may lead to lasting immune dysfunction. Overall, reducing exposure to immunotoxic substances can facilitate the partial or full restoration of immune function. It is plausible that this also applies to PFAS.

The only direct evidence of the impact of reducing PFAS exposure are some studies of the association of cholesterol in populations where exposure had fallen and serum levels were going down. In the C8 study of a US population exposed to PFOA a group of 700 people had repeated measurements of both PFAS and cholesterol four years apart (Fitz-Simon et al 2013). Both PFOA and PFOS declined over the period and they found that there was a tendency for people with greater declines in serum PFOA or PFOS to have greater total cholesterol and LDL decrease. For a person whose serum PFOA fell by half, the predicted fall in LDL cholesterol was 3.6% (95% confidence interval = 1.5–5.7%). The association with a decline in PFOS was even stronger, with a 5% decrease in LDL (2.5–7.4%) per halving in PFOS. A larger study in Italy also included repeat measurements of both lipids and PFAS, averaging 4 years apart, with the same direction of association but smaller decreases in cholesterol (Batzella et al 2014). Declines in PFAS concentrations were associated with decreases in all lipids. For a natural log-decrease in PFOA HDL-C decreased by 1.99 % (95 % CI: 1.28, 2.70), TC by 1.49 % (95 % CI: 0.88, 2.10), and LDL-C by 1.40 % (95 % CI: 0.45, 2.37). A natural log decrease is a reduction by a little more than a half. Overall there was not a decrease in cholesterol in the two population, but the individual correlations of changes in PFAS to changes in lipids is reassuring that the association of cholesterol with PFAS is reversible.

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Risks and wider benefits of haemodialysis

Haemodialysis is a life-sustaining treatment for patients with end-stage renal disease (ESRD) or acute kidney injury (AKI), where the kidneys can no longer perform their essential functions of filtering waste products and excess fluids from the blood. During haemodialysis, blood is diverted from the patient's body to a machine called a dialysis machine, where it passes through semi-permeable membranes. These membranes allow waste products and excess electrolytes to diffuse into a dialysis solution while retaining larger molecules like proteins and blood cells (Daugirdas et al., 2012). The purified blood is then returned to the patient's circulation. Typically, haemodialysis sessions occur three times per week, lasting about 3 to 5 hours each (Johansen et al., 2021).

Safety and Tolerability of haemodialysis

Haemodialysis necessitates frequent, lengthy sessions that can disrupt daily activities. It requires some form of surgical intervention to make vascular access easier and also limitations on fluid and certain nutrients may affect enjoyment of food. Fatigue and weakness are common post-dialysis and can hinder social and occupational functioning. Prevalence of depression is high among dialysis patients, affecting quality of life, as well as adherence and outcomes (Palmer et al., 2013). Overall, haemodialysis is poorly tolerated.

Common Side Effects

- **Hypotension:** Hypotension is the most frequent intradialytic complication, affecting up to 20-30% of sessions (Henrich, 1986). It can result in dizziness, nausea, vomiting, and loss of consciousness. This may be less common in people with normal kidney function.
- **Muscle Cramps:** Fluid and electrolyte shifts during dialysis may cause cramps. Muscle cramps occur in approximately 5-20% of patients (Hossli, 2005). This may be less common in people with normal kidney function.
- **Pruritus (Itching):** It is not clear what the cause of the itching is; it may involve uremic toxins, dry skin, and inflammation. Pruritus affects up to 50-90% of haemodialysis patients (Mathur et al., 2010). This may be less common in people with normal kidney function.
- **Vascular Access Infections:** Infections can occur in arteriovenous (AV) fistulas, grafts, or central venous catheters. Catheter-related bloodstream infections range from 0.5 to 5.5 episodes per 1,000 catheter-days (Lok & Mokrzycki, 2011).
- **Arrhythmias:** Cardiac arrhythmias occur in up to 25% of patients during dialysis (Mavrakanas & Charytan, 2016). They are caused by electrolyte shifts, particularly potassium and calcium levels. This may be less common in people with normal kidney function.

Rare Side Effects

- **Sudden Cardiac Death:** People with underlying cardiac disease, electrolyte imbalances or hypotension are at risk of sudden cardiac death. This accounts for approximately 25% of all deaths in dialysis patients (Mavrakanas & Charytan, 2016). This may be less common in people with normal kidney function.
- **Dialysis Disequilibrium Syndrome:** This results from the rapid removal of urea leading to cerebral oedema. It is characterised by neurological symptoms ranging from headache to seizures and coma (Murdeswar HN, 2023). This may be less common in people with normal kidney function.

- **Haemolysis:** Mechanical stress from dialysis equipment or contamination with disinfectants can lead to haemolysis; the breakdown of red blood cells (Tharmaraj & Kerr, 2017). This may present with back pain, chest pain or dark urine and can have serious sequelae (Murdeswar HN, 2023).
- **Anaphylactic Reactions:** These are rare, severe allergic reactions to dialysis membranes or sterilising agents (potentially also some of the medicines given alongside dialysis). This is a medical emergency.

In addition to this, people receiving haemodialysis are at risk of vitamin and mineral depletion and are likely to require regular blood testing and vitamin and mineral supplementation, particularly iron.

Capital and revenue requirements for establishing and running a haemodialysis service

Necessary Equipment

There are several items needed to deliver dialysis itself (NICE, 2018) and to ensure appropriate water quality for the delivery of dialysis (Coulliette & Arduino, 2013).

- **Haemodialysis Machines:** These are advanced devices that remove waste products and excess fluids from the blood. They are equipped with features like volumetric control, ultrafiltration, and safety alarms. They must be MHRA-approved and capable of performing haemodialysis efficiently and safely.
- **Water Treatment Systems:** These are essential for producing ultrapure water required for dialysis. They include reverse osmosis units, deionizers, and ultrafilters to remove contaminants and toxins.
- **Artificial Kidneys (Dialyzers):** These are disposable units containing semi-permeable membranes for blood purification. They are available in different sizes and membrane types to suit patient needs.
- **Other consumable equipment:** Sterile single-use tubing, fistula needles, personal protective equipment and waste disposal supplies.
- **Dialysate Concentrates:** Acid and bicarbonate solutions mixed with purified water to create dialysate. These allow customised electrolyte composition to match patient requirements.
- **Anticoagulants:** Typically, heparin, administered to prevent blood clotting during dialysis.
- **Saline Solutions:** Used for priming the extracorporeal circuit and managing hypotension.
- **Patient Monitoring Equipment:** Devices to monitor vital signs like blood pressure, heart rate, and oxygen saturation. Scales are also required for pre- and post-dialysis weight measurement to assess fluid removal.
- **Emergency Equipment:** Includes defibrillators, oxygen supplies, and resuscitation kits for immediate response to emergencies.
- **Water Testing Supplies:** Kits and devices to regularly test water quality for contaminants and bacteria.
- **Imaging equipment:** To facilitate vascular access

In addition to this equipment, vascular access would be required, either through a long term indwelling cannula or through the surgical creation of an arteriovenous fistula. Catheters require care and maintenance and both catheters and fistulae are prone to failure.

Required Personnel

- **Lead clinician:** Probably a consultant nephrologist with expertise in haemodialysis. Role includes oversight of medical procedures, assessing patient therapeutic and diagnostic needs, and compliance with medical standards.
- **Specialist nurses:** To perform vein punctures, operate dialysis machines, and monitor patients during the procedure. They need to be certified in the delivery of dialysis and trained in the use of specific dialysis equipment.
- **Dialysis Technicians:** To prepare machines and monitor equipment
- **Surgical staff:** To obtain vascular access
- **Maintenance and Cleaning Personnel:** To ensure cleanliness of the facility and proper functioning of equipment. This is critical for infection control and meeting health standards.

Maintenance and Regulatory Compliance

- **Regular Servicing of Equipment:** Haemodialysis machines and water purification units require routine checks and servicing by qualified technicians.
- **Calibration of Equipment:** Medical devices must be calibrated regularly to ensure accuracy (ISO, 2022).
- **Facility Cleaning Protocols:** Adherence to strict cleaning schedules for donor areas, equipment, and common spaces.
- **Infection Control:** Implementation of standard precautions to prevent cross-contamination
- **Licensing and Accreditation:** Obtain necessary licenses from health regulatory organisations.
- **Standard Operating Procedures (SOPs):** Develop and maintain SOPs for all processes, aligning with MHRA, FDA and European Medicines Agency (EMA) guidelines.
- **Staff Training and Certification:** Ongoing education to keep staff updated on best practices and regulatory changes.
- **Audits and Inspections:** Regular internal audits and readiness for external inspections.
- **Documentation:** Comprehensive record-keeping for patient care and adverse event tracking (Lundin et al., 2008).

Offering a haemodialysis service involves more than just cleansing blood; it requires a robust infrastructure of specialised equipment, skilled personnel, and stringent maintenance protocols.

Cost of a Haemodialysis Service for Human Use

Capital cost

The cost of a new haemodialysis machine in the UK ranges from approximately **£15,000 to £30,000** per unit, depending on the manufacturer, model, and features (Roberts et al., 2022). Advanced models with additional capabilities such as online hemodiafiltration or biofeedback systems may be at the higher end of the price range. It should be noted that, in order to maintain continuity of service, at least two machines would be required. Because the potential use here is for the removal of PFAS, rather than to replace renal function, it is difficult to predict how many treatments might be needed. It is unlikely that it would be anywhere near the number needed to offer renal replacement therapy in Jersey.

In addition, a Water Treatment System is essential to provide ultrapure water for dialysis. Costs range from **£10,000 to £20,000**, depending on capacity and technology (ISO, 2024). Installing such a system may require modifications to existing facilities to accommodate the machine, including water supply, drainage, and dedicated electrical circuits. Estimated cost: **£5,000 to £10,000**.

Additional Costs to Consider

- **Maintenance and Service Contracts:** Essential for the safe and effective operation of the machine and the water treatment system, there will be regular maintenance and calibration, carried out by facility staff. In addition to that there would be a requirement for a service contract with the manufacturers. These can be of the order of **£10,000-£20,000** per annum (assuming two dialysis machines and one water treatment system).
- **Consumables:** Artificial kidneys cost approximately **£10 to £20**. Assuming ten treatments required, that equates to **£100 to £200** per patient per year, or **£5,000 - £10,000** overall. Tubing sets cost **£5 to £10**, so calculating on a similar basis, the total cost would be **£2,500 - £5,000** overall. Dialysate solutions cost approximately **£3** per treatment, or **£1,500** overall. Vascular access costs, if using a tunnelled cannula, would be approximately **£800** per cannula, cannulae last up to six months, so the cost is **£1,600** per patient per year. Cannula care, blood testing and vitamin/electrolyte replacement can be reasonably estimated to cost around **£5,000** per patient per year. Taking all those together, consumable costs would potentially be up to **£23,100** per annum.
- **Training and Staffing:** In addition, the salary costs of the staff described above, staff must be trained to operate the machine safely. Some manufacturers offer training programs, which may be included or charged separately. Assuming the consultant nephrologist is half time, the surgical staff are 0.1 WTE and all other staff are full time, staff costs (excluding on costs) are likely to be between **£200,000 and £250,000** per annum.
- **Regulatory Compliance:** Compliance with the Medicines and Healthcare products Regulatory Agency (MHRA) regulations may involve fees and/or modifications to the facility.

In summary

Bring all this together, a haemodialysis service would have set up costs, assuming two machines, and the necessary water treatment infrastructure and installation, of the order of

£100, 000. Running the service for one year, assuming 50 patients receiving 10 sessions each, would cost around **£1,380,000 per annum.**

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