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 & Kricker, 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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