The Guest That Cannot Finish

Why PFAS stays in the body, why it raises cancer risk without leaving a trace, and what follows for treatment and for measurement

J. Konstapel — Constable Research, Leiden
Version 2.0 — 19 November 2026
© 2026 J. Konstapel, Constable Research, Leiden. All rights reserved.

Abstract. This essay makes three claims about the fluorinated compounds known as PFAS, and explains each of them from the beginning, assuming no prior acquaintance with the chemistry, the epidemiology, or the theoretical framework used. The first claim is that PFAS does not remain in the body because it cannot be destroyed. Compounds that cannot be destroyed are, as a rule, excreted without difficulty. PFAS remains because the body actively retrieves it, using the same machinery that conserves bile acids. Retention is a conservation mechanism working correctly on a guest it cannot tell apart from the molecules it was built to save. The second claim is that PFAS does not cause cancer in the way the word usually implies. It does not damage DNA, and the official classification of PFOA as carcinogenic to humans does not say that it does. What the evidence supports is that PFAS slows the pathways that would otherwise have cleared a damaged cell. The third claim is that both of these follow from one structural point: certain properties of a living system are properties of a whole course of events and cannot be read off a single measurement, however precise. Three measurements that have not been made follow directly from the argument, and all three are described in enough detail to be carried out.

1. Introduction

1.1 What this essay is about

Per- and polyfluoroalkyl substances, abbreviated PFAS, are a family of several thousand synthetic compounds that have been manufactured since the 1940s. They are used wherever a surface must repel both water and oil: non-stick cookware, waterproof fabric, food packaging, cosmetics, and above all fire-fighting foam. They are popularly called forever chemicals.

The name points at the feature that makes them useful and the feature that makes them a problem, which are the same feature. A PFAS molecule consists of a chain of carbon atoms in which the hydrogen atoms have been replaced by fluorine. The bond between carbon and fluorine is the strongest single bond in organic chemistry. Nothing in the environment breaks it easily, and nothing in the human body breaks it at all. The compounds therefore accumulate: in soil, in water, in the blood of essentially every person who has been tested anywhere in the world.

Two questions follow, and this essay is about both. Why does PFAS do harm, and what can be done about the harm once the compound is already in the body? And why, when investigators go looking for the harm around a factory that emitted PFAS for decades, do they so often find nothing?

The answers offered here are not the usual ones, and they are reached by applying a particular way of looking, which must be explained first.

1.2 The framework: what closure means

This essay uses the Vacuum.Net theory, a framework the author has developed over a number of years and applied to problems in physics, chemistry, biology and medicine. Only one part of it is needed here, and that part can be stated without any mathematics.

The framework describes processes as paths. A system does not merely have states; it moves through a sequence of positions, and that sequence has a shape. Some paths come back to where they started, or to a place from which the system can continue; others do not. The word used for the first kind is closure. A path closes when the process it describes completes: the thing that was begun is finished, the position that was taken is released, and the system is free for whatever comes next.

Three consequences of this way of looking matter for what follows, and they are the whole of the theoretical apparatus used in this essay.

First, closure is a property of a whole path and never of a point on it. If you stop a process at one moment and measure it exhaustively, you cannot tell from that measurement whether the process was going to close. A fever at its peak looks the same whether it is about to subside or about to kill. To see closure you need at least two observations separated in time, because what you are measuring is a return, and a return has no meaning at a single instant. This sounds obvious when stated, and it is routinely violated in practice, as section 10 will show.

Second, closure can be defined operationally, so that it is measurable rather than merely descriptive. Deliver a defined disturbance to a system at a known moment. Then watch two things. One is whatever rises in response and ought to subside: call it the transient part. The other is whatever is permanently altered by the episode and ought to stay altered: call it the registering part. The path has closed when the transient part has returned to its prior value within some characteristic time, and the registering part carries a stable change. Two numbers come out of this: how much of the disturbance was recovered, and how long the recovery took. Neither can be obtained from a single blood sample, a single scan, or a single count. Both require at least two moments.

Third, closure belongs to a pair and not to either member of the pair alone. Whether a path closes depends on the host and on the guest together. The same organism closes one encounter and fails to close another; the same agent is resolved by one host and not by another. It is therefore an error to speak of the closure properties of a substance as though they were properties of the substance, in the way that molecular weight is. They are properties of a relation.

1.3 Why bring this to PFAS

The reason for bringing this framework to PFAS is that the PFAS literature contains two statements that are repeated constantly and that do not survive examination. Each of them, it will be argued, is a case of attributing to a substance what is in fact a property of a relation, or of looking for at a point what exists only along a path.

Sections 2 to 7 deal with the first: why PFAS stays in the body. Sections 8 and 9 deal with the second: what PFAS has to do with cancer. Section 10 applies the result to the best-documented European case, the Chemours works at Dordrecht in the Netherlands, and explains why three separate investigations there found nothing and could not have found anything. Section 11 sets out three measurements that follow, all of which can be made now.

2. Two statements that do not fit their answers

The first statement is that PFAS persists in the human body for years because the carbon-fluorine bond cannot be broken. The elimination half-life of perfluorooctanoic acid, PFOA, the most studied member of the family, is given in years. Half-life here means the time it takes for half of what is present to leave the body; a half-life of three years means that if nothing further is taken in, half of the current burden will still be there three years from now. For perfluorohexane sulfonate the figure is longer still. The explanation offered is indestructibility.

The difficulty is that indestructibility does not by itself produce retention. Consider what the kidney does. It filters blood, allowing small dissolved molecules through into what will become urine, and then selectively reclaims the ones worth keeping: glucose, amino acids, salts. Everything not reclaimed leaves the body. The kidney does not need to destroy anything, and it does not require a molecule to be chemically altered before disposing of it. A small, water-soluble, chemically inert molecule is in principle the easiest thing a kidney ever handles. Many such compounds are cleared within hours.

So if PFAS remains for years, something must be holding it. Chemical inertness is not that something. Inertness explains why PFAS is not converted into something else; it does not explain why it is not excreted unchanged. The explanation that is universally given answers a question that was not asked.

The second statement is that PFAS causes cancer. In 2023 the International Agency for Research on Cancer, the arm of the World Health Organization that classifies carcinogens, placed PFOA in Group 1, its highest category, defined as carcinogenic to humans.[1] Yet where this has been tested in a residential population living around a European factory that emitted the compound for decades, no excess of cancer was found: not in total, and not in any of the three specific cancers the investigators went looking for.[2]

These two findings are usually treated as a puzzle to be resolved by more data. The argument of this essay is that each marks a place where the standard picture has the wrong shape, and that the right shape makes both of them unsurprising.

3. Where the body actually puts it

PFAS is routinely grouped with the classical persistent pollutants, such as dioxins and polychlorinated biphenyls, and the grouping carries an assumption about where in the body the compound ends up. Those compounds are fat-soluble and collect in adipose tissue. PFAS does not behave this way. More than ninety-nine per cent of what is present in blood is bound to proteins: to albumin, the most abundant protein in plasma and the body general-purpose carrier, for the shorter chains; and increasingly to the globulins, a heavier class of plasma proteins, for chains of seven carbon atoms and longer. The longer members also associate with the phospholipids that make up cell membranes.[3]

There is a standard laboratory measure of fat solubility, the octanol-water partition coefficient, which records how a substance distributes itself between an oily solvent and water. For PFAS this measure predicts behaviour in the body poorly. Partitioning between protein and water, and between membrane and water, predicts it well.

This is not a technical footnote to be passed over. A compound sitting in fat is sequestered: it is out of circulation and relatively inert where it sits. A compound bound to albumin is in circulation permanently, carried past every receptor, every transport protein and every membrane that blood reaches, continuously, for years. The same body burden means something entirely different in the two cases. The first is a store; the second is an occupation.

4. A path that ends, and a path that does not

To see what kind of occupation it is, consider first how the body handles a molecule that PFAS closely resembles.

A fatty acid is a chain of carbon atoms with an acid group at one end. It is the basic unit of dietary fat and one of the body main fuels. When a fatty acid enters a cell it is taken up, recognised by the proteins that handle lipids, carried into the mitochondria, and there dismantled two carbon atoms at a time in a process called beta-oxidation. The fragments are fed into the reactions that supply the cell, and what is left over leaves as carbon dioxide and water. The path has an end, and it is the end that matters: when the molecule is consumed, the position it occupied is released, and the handling machinery is free for the next one.

Now look at PFAS. Chemically it is a chain of carbon atoms with an acid group at one end, and the handling machinery recognises it accordingly; it has, in addition, the behaviour of a bile acid, of which more in the next section. So it is taken up, bound, carried, and presented to the machinery that would dismantle a fatty acid.

---

[1] IARC Monographs evaluate the carcinogenicity of PFOA and PFOS. IARC announcement, 30 November 2023. Annotated reference 5.

[2] Incidentie van kanker in het gebied rond chemische fabriek Chemours, Dordrecht (1989-2013). Dienst Gezondheid & Jeugd. Annotated reference 8.

[3] Forever Chemicals, Finite Defenses: PFAS Burden the Liver, Break Mitochondria, and Outpace Modern Regulation. International Journal of Molecular Sciences, 2026. Annotated reference 1.

What it cannot do is be dismantled. Beta-oxidation works by attacking the carbon chain at specific positions, and in a perfluorinated chain every one of those positions is occupied by fluorine, bound to carbon by the strongest single bond available. No enzyme in any mammal cleaves it. PFOA and PFOS are what chemists call terminal: other fluorinated compounds are broken down into them, and they are broken down into nothing.

The position is therefore occupied, and for its occupant the path has no end. This is the structural statement from which everything else in this essay follows. In the vocabulary of section 1.2: a path has been entered that cannot close.

This immediately reorganises the inventory of harms. The toxicological literature records a long list of effects: PFAS binds the nuclear receptors that govern how cells handle lipids and bile acids, among them PPAR-alpha, PPAR-gamma, CAR, PXR, FXR and LXR, which are the molecular switches controlling those systems; it impairs mitochondrial beta-oxidation, which is the best-supported of its mitochondrial effects; it uncouples oxidative phosphorylation, meaning that mitochondria continue to burn fuel while producing less usable energy from it; it generates reactive oxygen species faster than the cell antioxidant defences can neutralise them, with damage to membrane lipids and to mitochondrial DNA following; and it disturbs bile acid synthesis and transport.[4]

Presented as a list, these look like a series of separate attacks delivered by one aggressive agent. They are better read as one condition seen at successive positions along a single path. At each of those positions, the agent is not doing something. It is failing to leave.

5. Why the body keeps it

5.1 What bile acids are, and why they are recycled

The second displacement in the standard account concerns how PFAS is retained, and it requires a short account of a system that has nothing to do with pollutants.

Bile acids are molecules the liver makes from cholesterol and secretes into the intestine with the bile. Their function is to emulsify dietary fat, breaking it into droplets small enough to be absorbed. They are metabolically expensive to produce, and the body does not make a fresh supply for each meal. Instead it recovers them. In the last part of the small intestine, the ileum, specialised proteins in the wall of the gut capture bile acids from the intestinal contents and return them to the bloodstream, which carries them back to the liver, which secretes them into the bile again. The great majority of the bile acid pool goes around this circuit several times in the course of a single meal. The arrangement is called the enterohepatic circulation, and it is a conservation device of considerable elegance.

The proteins that perform the capture are called transporters. A transporter is a protein embedded in a cell membrane whose job is to move a specific class of molecule across that membrane, often against a concentration gradient and at the cost of energy. They are not filters; they are selective pumps, and what they select is determined by molecular shape and charge.

5.2 The circuit, and what happens when the wrong guest enters it

Three organs operate transporters that recapture PFAS from fluids that would otherwise carry it out of the body.[5]

In the kidney, the organic anion transporters OAT1, OAT3 and OAT4, together with the urate transporter URAT1, reabsorb PFAS from the filtrate after it has been filtered out of the blood, returning it to the circulation. The consequence is extreme: less than one tenth of one per cent of the protein-bound fraction is excreted in urine.

---

[4] Forever Chemicals, Finite Defenses: PFAS Burden the Liver, Break Mitochondria, and Outpace Modern Regulation. International Journal of Molecular Sciences, 2026. Annotated reference 1.

[5] A state-of-the-science review of interactions of PFAS with renal transporters in health and disease. Annotated reference 2.

In the liver, the transporters OATP1B1 and OATP1B3, together with NTCP, the sodium-taurocholate cotransporting polypeptide, take PFAS up from the blood arriving from the gut.[6] In the intestine, ASBT, the apical sodium-dependent bile acid transporter, together with OATP2B1, returns PFAS that reached the gut in the bile back into the circulation.

In the PFAS literature this activity is described as reabsorption, and the word carries an implication of leakage: a barrier that is failing to hold. That implication is wrong, and correcting it is the first main result of this essay.

These transporters are not a failing defence. They are the return limbs of the conservation circuit described above, and they are doing exactly what they evolved to do. For a genuine bile acid the arrangement is sound, and it is sound for a specific reason: there is a forward limb with an end. What is recaptured is eventually used, altered and voided. The circuit drains, because the path through it closes.

Place in that circuit a guest that cannot complete the forward limb, and the identical machinery becomes a trap. The kidney reclaims it from the filtrate. The liver reclaims it from the portal blood. The intestine reclaims it from the bile. Each organ performs its function correctly. Nothing terminates, so nothing drains.

The inversion is worth stating plainly, because it changes what the numbers mean. The half-life of years does not measure how tough the molecule is. It measures how efficient the conservation machinery is. Retention is not a defence failing. It is a conservation mechanism succeeding, on the wrong guest.

6. The proof from treatment

An argument of this kind would remain speculative if it rested only on the plausibility of the picture. It does not, and the strongest evidence for it is not observational but interventional.

Consider what the two accounts predict. If retention were a property of the compound, as indestructibility implies, then interfering with the body own bile acid handling should do nothing to it. If retention is produced by the recapture circuit, then removing one limb of that circuit should open a route out, and the burden should begin to drain.

A bile acid sequestrant is a drug that does precisely this. Cholestyramine is a resin that is not absorbed; it passes down the gut binding bile acids to itself, so that the ileal transporters cannot capture them and they leave in the stool. It has been in clinical use for decades to lower cholesterol, on the principle that a liver forced to make new bile acids consumes cholesterol doing so.

In a randomised crossover trial in Denmark, forty-five participants took cholestyramine at three doses of four grams daily for twelve weeks. Serum PFOS fell by sixty-three per cent. Reductions were smaller but clear for the other members of the family: around forty-four per cent for PFDA, thirty-nine for PFNA, twenty for PFOA, fifteen for PFHxS. Side effects were mild and gastrointestinal.[7] A smaller crossover study in Ronneby, Sweden, in a population exposed through contaminated drinking water, used cholestyramine and colesevelam in ten participants and found reductions of up to forty per cent.[8]

The significance of this result is easy to miss. The drug does not touch the PFAS molecule. It does not break it, bind it, or alter it chemically in any way. It removes one of the three return limbs, and sixty-three per cent of the body burden of PFOS leaves within twelve weeks. That number is a direct

---

[6] Roles of Organic Anion Transporters in the Renal Excretion of Perfluorooctanoic Acid. Basic & Clinical Pharmacology & Toxicology. Annotated reference 3.

[7] Substantial decrease of PFAS with anion exchange resin treatment: a randomised crossover trial. Environment International, 2024. Annotated reference 13.

[8] University of Gothenburg study of cholestyramine and colesevelam in Ronneby residents, Environment International. Annotated reference 14.

measurement of what the intestinal limb was contributing to retention, and it is not a number that the indestructibility account has any way to produce.

A second line of evidence comes at the problem from the opposite direction. In a randomised trial of 285 firefighters in Victoria, Australia, plasma donation every six weeks reduced PFAS levels by approximately thirty per cent over twelve months, an effect still measurable three months after the donations stopped; blood donation every twelve weeks also produced levels significantly below control.[9] No transporter is blocked here. Donation simply creates a fourth exit, an artificial one, which the body cannot reverse because the material physically leaves. That it works at all, and works slowly, is what one would expect of a slow external tap operating alongside three functioning return limbs.

7. The half-life belongs to the pair

Section 1.2 stated that closure is a property of a host-guest pair rather than of either member. Applied here the consequence is immediate, and it is testable.

The elimination half-life of PFOA is not a property of PFOA. It is a property of a compound-host pair, determined by how many return limbs that particular host operates, and how vigorously.

This is already half-confirmed in data that has been read a different way. Mice clear PFOA in hours; humans take years. Male and female rats differ by more than an order of magnitude, and the difference tracks the expression of renal transporters.[10] Within the human population the variation is wide. A review of the field identified nine human and eight rat kidney transporters already studied for PFAS handling and proposed seven further untested candidates, and linked the documented sex and species differences in half-life to transporter activity. In a modelling exercise, the glomerular filtration rate, which is the rate at which the kidney filters blood in the first place, influenced serum half-life more than transporter expression did.[11]

The field calls this population variability. The word treats the variation as noise scattered around a true value belonging to the compound. The reading offered here is that there is no such true value to be scattered around. The host-specific return capacity is the quantity itself, and quoting a single human half-life for PFOA is a category error, in the way that quoting a single incubation period for a pathogen without reference to the host would be.

This matters practically, not just conceptually. If half-life is a property of the pair, then the same environmental exposure produces materially different burdens in different people, and the people who retain most are not those who were exposed most. Regulatory limits set on exposure rather than on retention will protect some populations and not others, and will have no way of telling which is which.

8. What the cancer classification actually says

The second of the two statements can now be taken up.

The standard account of chemical carcinogenesis runs as follows. An agent reaches the DNA of a cell and damages it. A mutation results. If the mutation falls in the wrong place, the cell escapes the controls on its growth, and a tumour develops from its descendants. Agents that work this way are called genotoxic. For benzene or aflatoxin this is the mechanism, and it has two convenient properties: the damage leaves a recognisable signature in the tumour, and there is a dose below which the probability of the initiating event becomes negligible.

---

[9] Effect of Plasma and Blood Donations on Levels of PFAS in Firefighters in Australia: A Randomized Clinical Trial. JAMA Network Open, 2022. Annotated reference 15.

[10] Roles of Organic Anion Transporters in the Renal Excretion of Perfluorooctanoic Acid. Basic & Clinical Pharmacology & Toxicology. Annotated reference 3.

[11] A state-of-the-science review of interactions of PFAS with renal transporters in health and disease. Annotated reference 2.

For PFOA, neither property is available, because PFOA is not genotoxic. This is not a dissenting view; it is what the classification itself rests on, and the grounds repay reading closely. IARC rated the evidence from human studies of specific cancers as limited, for kidney cancer and testicular cancer. It rated the evidence in experimental animals as sufficient. The Group 1 placement, carcinogenic to humans, comes from combining that animal evidence with strong mechanistic evidence in exposed humans, and the mechanistic evidence rated strong concerned two characteristics: epigenetic alteration and immunosuppression.[12]

Genotoxicity is not among them. The classification does not assert that PFOA damages DNA, and no part of the case for it depends on the claim.

The two characteristics that are rated strong deserve explanation, since the terms are not self-explanatory.

Epigenetic alteration refers to changes in how genes are read rather than to changes in the genes themselves. The DNA sequence is unaltered; what changes is the pattern of chemical marks that determine which genes are switched on, how strongly, and in which cells. These settings normally adjust in response to circumstances and then return.

Immunosuppression refers to a reduction in the capacity of the immune system to mount and complete a response. In the PFAS literature the best-documented human instance is a reduced antibody response to vaccination.

In the vocabulary of section 1.2, these two are the same thing. Epigenetic alteration means that reading settings do not return to their prior values after a disturbance. Immunosuppression means that an immune response does not run to completion. Both are statements about return and not about damage: the transient part fails to subside within its characteristic time, and the registering part carries an offset it should not carry. That is precisely the operational definition of a failure of closure.

9. Cancer without a signature

From this the role of PFAS in cancer follows, and it is not the role usually assumed.

Cells with damaged or deranged genomes arise continually in every person, through copying errors, background radiation, ordinary chemistry. The great majority are detected and dealt with: arrested, repaired, induced to die, or cleared by immune cells. What determines whether a tumour develops is not primarily whether a damaged cell appears, but whether the pathway that deals with it runs to completion.

PFAS does not produce the damaged cell. It lengthens the return time of the pathway that would have closed on it.

Three consequences follow, and they correspond closely to what the epidemiological record actually looks like.

There is no signature. A general slowing of clearance leaves no mark in the tumour that eventually appears. There is no PFAS mutation to find, no characteristic histology, nothing that examination of the tumour could reveal. The tumour is an ordinary tumour that was not cleared.

There is no threshold. An agent that multiplies an existing rate acts at every level of exposure, scaled down as exposure falls but never switching off. The regulatory apparatus is built to find a dose below which an effect does not occur. For this mode of action there is no such dose, only a progressively smaller multiplier. This is why PFAS limits keep being revised downwards without ever reaching a level at which the question is settled.

There is no individual attribution. A raised probability cannot be traced back to a particular case. The question a resident near a contaminated site asks, which is whether the factory caused the cancer, has

---

[12] Carcinogenicity of perfluorooctanoic acid and perfluorooctanesulfonic acid. IARC Monographs evaluation, The Lancet Oncology, 2023. Annotated reference 4.

no answer in principle. This is not a gap that further research will fill. It is a consequence of the mechanism.

10. Why Dordrecht found nothing

10.1 What was measured

The DuPont works at Dordrecht, later Chemours, emitted PFOA for decades. The Dutch National Institute for Public Health and the Environment, RIVM, estimated that residents were exposed through the air at levels above the chronic exposure limit, in the worst case for twenty-five years, with the limit no longer exceeded after 2002. Drinking water was not elevated. Effects on the liver could not be excluded. The additional cancer risk was assessed, on the basis of animal data, as limited.[13] Blood PFOA concentrations in residents were measured in 2017.[14]

Cancer incidence was then counted. For the postcode areas Dordrecht-Noord, Sliedrecht-Zuid-West and Papendrecht-Oost, all new cancer diagnoses between 1989 and 2013 were tallied and compared with the number the national rates would predict for a population of that size and age structure. Kidney, testis and liver were singled out because of the PFOA literature. No site was elevated in any of the three areas. The total for Dordrecht-Noord fell below expectation.[15] A comparable study in Molenwaard in 2018 reached the same conclusion.[16] In Sliedrecht for 1998 to 2017 the total was raised, but through skin cancer, which has no connection to PFOA; kidney and testicular cancer were not elevated.[17]

10.2 Why that design could not have worked

This is a count. It asks one question: is there an excess here. It produces one number per area, compared against one expected number.

What is being looked for, on the account given above, is a multiplier applied to a background rate that is dominated by smoking, age and chance. In a total of roughly two thousand cases accumulated over twenty-five years, a modest multiplier is not distinguishable from the ordinary variation of that background. The design has almost no power to detect the thing it was deployed to detect.

A null result from such a design is therefore close to uninformative. It does not show that there was no effect; it shows that this instrument could not have seen one. And this is precisely the point at which both parties to the public dispute go wrong, in opposite directions: the company treats the null as evidence of safety, and the residents treat it as evidence of concealment, when in fact it is evidence of very little.

This is the structural point of section 1.2 in its most concrete form. A single incidence figure for an area is a point measurement. The quantity sought is a slope. A slope is not readable at a point, however carefully the point is measured.

10.3 What the American studies did differently

---

[13] Risicoschatting emissie PFOA voor omwonenden locatie DuPont/Chemours, Dordrecht. RIVM. Annotated reference 6.

[14] Betekenis resultaten bloedonderzoek PFOA omwonenden DuPont/Chemours. RIVM report 2017-0101. Annotated reference 7.

[15] Incidentie van kanker in het gebied rond chemische fabriek Chemours, Dordrecht (1989-2013). Dienst Gezondheid & Jeugd. Annotated reference 8.

[16] PFAS en kanker. GGD Zuid-Holland Zuid. Annotated reference 10.

[17] Het optreden van kanker in Sliedrecht (1998-2017). Dienst Gezondheid & Jeugd, 2019. Annotated reference 9.

The contrast with the investigations in the Mid-Ohio Valley, around the DuPont Washington Works plant in West Virginia, is instructive. It is often said that those studies succeeded because they were larger. That is not the main reason, and the numbers are worth setting out correctly, because they are frequently misreported.

The C8 Health Project of 2005 and 2006 enrolled approximately sixty-nine thousand people. This is the figure usually quoted, but it was a single cross-sectional health survey with blood sampling, not a cohort followed over time. The cohort assembled for cancer follow-up was considerably smaller: 32,254 individuals, of whom 28,541 were community members and 3,713 plant workers. Median follow-up from age twenty was 32.9 years, but only 4.4 years following the survey itself.[18]

The study that produced the clearest cancer signal was a third design again. It was a case-control study, meaning that instead of following a population forward in time, it took people who already had a given cancer and compared their exposure histories with those of people who did not. It covered 25,107 cancer registrations across thirteen counties for the years 1995 to 2005. For testicular cancer it reported an adjusted odds ratio of 5.1 with a confidence interval from 1.6 to 15.6. An odds ratio of 5.1 means the odds of the disease were about five times higher in the most exposed group; the confidence interval gives the range within which the true value is likely to lie. That interval is very wide, and it is wide because the estimate rests on six cases in the highest serum exposure category. Kidney cancer odds were roughly doubled in the high and very high categories.[19]

Six cases. That fragility is part of why IARC rated the human evidence limited, and it should be stated rather than glossed. But the relevant observation here is that a signal was obtained at all, from six cases, where three Dutch studies working with far larger total counts obtained nothing.

Two things differ between the two settings. The first is the size of the exposure contrast: at Washington Works the route was drinking water over decades, with serum concentrations in some water districts two orders of magnitude above background, whereas at Dordrecht the route was air and the drinking water was not elevated.

The second, and the decisive one, is that the American studies had a dose axis. Individual cumulative exposure was reconstructed for each participant from modelled water concentrations, residential history and measured serum levels, and the analysis asked whether risk rose with the amount received. The Dutch studies asked whether a geographic area had more cases than the country as a whole.

For a rate multiplier these two questions are not equivalent, and the second is far the weaker. The signal of a multiplier lies in the ordering, in the fact that more exposure goes with more disease, and not in the total. An analysis along a dose gradient can recover that ordering from a handful of cases. A geographic count can miss it in thousands.

11. Three measurements that have not been made

11.1 Block two return limbs at once

Every intervention tested to date removes one limb of the recapture circuit. Cholestyramine and colesevelam remove the intestinal limb, and they work.

Probenecid is a long-established drug that inhibits the organic anion transporters in the kidney, and therefore removes the renal limb. It was examined within the C8 Health Project, in an observational analysis comparing twenty-three adults taking probenecid and thirty-six taking cholestyramine among 56,175 participants. Cholestyramine lowered serum PFAS significantly. Probenecid produced modest

---

[18] Winquist, A. et al. Design, methods, and population for a study of PFOA health effects among highly exposed Mid-Ohio Valley residents and workers, 2013. Annotated reference 11.

[19] Vieira, V. et al. PFOA exposure and cancer outcomes in a contaminated community: a geographic analysis, 2013. Annotated reference 12.

increases that did not reach statistical significance.[20] On that basis the independent PFAS Scientific Advisory Panel for Jersey advises against probenecid and makes bile acid sequestrants the first-line intervention, with donation of blood or plasma second.[21]

On the reading developed here, the probenecid result is exactly what should have been expected, and it carries no verdict on the drug.

Closing one of three limbs while the other two run does not evacuate the burden. It redistributes it. What the kidney declines to reclaim is still taken up by the liver and the intestine and returned to the circulation; and serum concentrations may even rise, because material mobilised from tissue stores enters a compartment that still has no exit. A modest, non-significant increase is what that would look like, and it is what was observed.

The prediction is therefore specific, and it is the most actionable item in this essay. Probenecid combined with a bile acid sequestrant should contribute more than its effect alone, and more than the two effects added together. The sequestrant supplies the exit; the transport inhibitor stops the system from routing around it. Neither alone constitutes a way out.

No study has blocked two limbs at once. The Danish, Swedish and Australian trials each address a single one. Given that the single-limb intervention already achieves sixty-three per cent, and that both drugs are old, cheap and well characterised, a small crossover trial stands between the current standard of care and a materially better one.

11.2 Link the 2017 serum data to the national cancer registry

Serum PFOA was measured in residents around the Dordrecht plant in 2017. The Netherlands maintains a complete national cancer registry. These two datasets have not been joined.

Joining them converts the Dutch question from a count into a gradient, which is the only form in which the quantity is detectable at all. Individual serum values, supplemented where possible by residential history to reconstruct cumulative exposure, would permit exactly the analysis that produced a signal in the Mid-Ohio Valley from six cases. It requires no new sampling, no new consent for collection, and no further waiting: only record linkage and the governance arrangements to permit it.

Until that is done the dispute cannot resolve, and it is worth being explicit about why. The company is correct that no excess has been demonstrated. The residents are correct that exposure above the limit occurred for up to twenty-five years. Both are correct, because they are describing different quantities, and the measurement that would adjudicate between them has not been performed on data that already exists.

11.3 Measure return, not burden

The third proposal follows from section 8 and is the most general.

PFAS produces no acute illness. There is no fever, no crisis, no moment at which the body visibly responds. In the terms of section 1.2, the transient part is to a first approximation empty. There is only register.

That is why a single serum concentration correlates so weakly with outcome, and why the epidemiology has been so unrewarding relative to the effort invested in it. A failure of closure is not present in a single measurement. What is measurable is return: deliver a defined disturbance, record how long the system takes to come back, and record what offset it keeps.

The notable thing is that the field has already done this once without describing it that way. Vaccination is a defined disturbance delivered at a known moment. Antibody titre over the following

---

[20] Perfluoroalkyl substance excretion: effects of organic anion-inhibiting and resin-binding drugs in a community setting. Annotated reference 16.

[21] Third Report of the Independent PFAS Scientific Advisory Panel for Jersey, 2025. Annotated reference 17.

weeks is a return measure. And reduced vaccine response is the one effect of PFAS in humans at ordinary exposure levels that is found reliably and accepted as a valid endpoint. That is not a fact about immunology. It is the only endpoint that happens to have been measured in the right form.

The prediction that generalises it: PFAS burden lengthens return time across multiple systems and not immunity alone, and does so at burdens where cross-sectional measures show nothing. Any system that admits a defined, ethically deliverable disturbance with a measurable recovery trajectory is a candidate: glucose tolerance after a standard load, resolution of inflammation after a standardised challenge, closure of a small wound. Each requires at least two timepoints, and none of them is a blood level.

12. What this is and is not

This essay does not claim that PFAS is harmless, nor that the residents of Dordrecht were wrong to be concerned. Exposure above the chronic limit for up to twenty-five years is established by the national institute; effects on the liver could not be excluded; and the Group 1 classification stands on grounds that this essay accepts and reinterprets rather than disputes.

Nor does it claim that the Dutch cancer studies were incompetently performed. They answered the question they posed, and answered it correctly. The argument is that the question posed could not have revealed the quantity at issue, and that treating the null result as evidence of absence is an error made by both sides of the dispute.

What the essay does claim is structural, and it can fail at three identifiable points. If a combined sequestrant and transport-inhibitor regimen proves merely additive rather than more than additive, the recapture-circuit account is weakened. If an individual-level dose-gradient analysis of the Dordrecht population shows no relation between cumulative serum PFOA and cancer incidence across a genuine range of exposure, the multiplier account is weakened. If return measures in non-immune systems show no dependence on body burden in populations where cross-sectional measures also show none, the generalisation of section 11.3 fails.

One wider point is worth stating separately, because it does not depend on PFAS at all. The regulatory and epidemiological apparatus of environmental health was built to detect agents that do something: that bind a receptor, damage a base, cross a threshold. It is correspondingly poor at detecting agents that fail to leave, or that slow a return. For that second kind, every instrument in routine use is a point measurement: the body burden, the incidence count, the threshold dose. The quantity is not located at a point.

PFAS is unlikely to be the only member of that second class. It is simply the one whose production volume made it impossible to overlook.

Annotated references

Each footnote in the text names the reference it draws on; the numbers below are those names. A reference used at more than one point in the argument carries a footnote at each of them.

1. Forever Chemicals, Finite Defenses: PFAS Burden the Liver, Break Mitochondria, and Outpace Modern Regulation. International Journal of Molecular Sciences, 2026. https://www.mdpi.com/1422-0067/27/6/2723

   The source for section 3 and for the inventory of mechanisms in section 4. Establishes that more than ninety-nine per cent of serum PFAS is protein-bound, that albumin carries the shorter chains and globulins those of seven carbons and longer, and that protein-water and membrane-water partitioning predict distribution where octanol-water partitioning fails. Also the source for impaired beta-oxidation as the best-supported mitochondrial effect, and for the receptor, oxidative-stress and bile-acid findings.

2. A state-of-the-science review of interactions of per- and polyfluoroalkyl substances with renal transporters in health and disease: implications for population variability in PFAS toxicokinetics. https://pfascentral.org/science/a-state-of-the-science-review-of-interactions-of-per-and-

polyfluoroalkyl-substances-pfas-with-renal-transporters-in-health-and-disease-implications-for-population-variability-in-pfas-toxicokinetics

The transporter inventory used in section 5.2 and the variability data in section 7. Identifies nine human and eight rat kidney transporters already studied for PFAS and proposes seven untested candidates; attributes sex and species differences in half-life to transporter activity; reports that glomerular filtration rate influenced modelled serum half-life more than transporter expression did. The review own framing of this as population variability is the framing contested in section 7.

3. Roles of Organic Anion Transporters in the Renal Excretion of Perfluorooctanoic Acid. Basic & Clinical Pharmacology & Toxicology. https://pure.fujita-hu.ac.jp/en/publications/roles-of-organic-anion-transporters-in-the-renal-excretion-of-per/

   Primary experimental source for renal OAT-mediated reabsorption of PFOA and for the sex difference in elimination in rats. Supports the renal limb of the circuit described in section 5.2 and the pair-dependence argument of section 7.

4. Carcinogenicity of perfluorooctanoic acid and perfluorooctanesulfonic acid. IARC Monographs evaluation, summarised in The Lancet Oncology, 2023. https://pfascentral.org/science/carcinogenicity-of-perfluorooctanoic-acid-and-perfluorooctanesulfonic-acid

   The basis of section 8, and the single most important reference in this essay. Establishes that the Group 1 classification rests on sufficient evidence in experimental animals combined with strong mechanistic evidence in exposed humans for two characteristics, epigenetic alteration and immunosuppression; that human cancer evidence was rated limited, for renal cell and testicular carcinoma; and that genotoxicity is not among the strongly evidenced characteristics. The whole of sections 8 and 9 depends on reading these grounds correctly.

5. IARC Monographs evaluate the carcinogenicity of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). International Agency for Research on Cancer, 30 November 2023. https://www.iarc.who.int/news-events/iarc-monographs-evaluate-the-carcinogenicity-of-perfluorooctanoic-acid-pfoa-and-perfluorooctanesulfonic-acid

   The agency own announcement, used to confirm the Group 1 placement for PFOA and Group 2B for PFOS directly from the source rather than from secondary reporting.

6. Risicoschatting emissie PFOA voor omwonenden locatie DuPont/Chemours, Dordrecht, Nederland. RIVM. https://www.rivm.nl/publicaties/risicoschatting-emissie-pfoa-voor-omwonenden-locatie-dupontchemours-dordrecht-nederland

   The exposure assessment underlying section 10.1: air exposure above the chronic limit for up to twenty-five years in the worst case, drinking water not elevated, the limit no longer exceeded after 2002, liver effects not excludable, additional cancer risk assessed as limited on animal data. The document that establishes the exposure was real, which section 12 takes as given.

7. Betekenis resultaten bloedonderzoek PFOA omwonenden DuPont/Chemours. RIVM report 2017-0101. https://www.rivm.nl/bibliotheek/rapporten/2017-0101.pdf

   The 2017 serum measurements in residents. This is the dataset whose linkage to the national cancer registry is proposed in section 11.2, and the reason that proposal requires no new fieldwork.

8. Incidentie van kanker in het gebied rond chemische fabriek Chemours, Dordrecht (1989-2013). Dienst Gezondheid & Jeugd Zuid-Holland Zuid. https://www.dienstgezondheidjeugd.nl/assets/uploads/2016-03-23-Rapportage-incidentie-kanker-rondom-Chemours.pdf

   The principal Dutch incidence study, and the design analysed in section 10.2. Observed against expected counts for kidney, testis and liver in three postcode areas, with no site elevated in any area and the Dordrecht-Noord total below expectation. Worth reading in full by anyone who wishes to judge whether the criticism made here is fair: the report is careful about its own limits, and the overreach is in how it has been used rather than in what it says.

9. Het optreden van kanker in Sliedrecht (1998-2017). Dienst Gezondheid & Jeugd Zuid-Holland Zuid, 2019. https://www.dienstgezondheidjeugd.nl/assets/uploads/2019-11-25-Rapport-Het-optreden-van-kanker-in-Sliedrecht-in-de-periode-1998-2017.pdf

The later Sliedrecht analysis, in which total incidence was raised through skin cancer while kidney and testicular cancer were not. Included because it is sometimes cited as a positive finding; it is not one for PFOA.

10. PFAS en kanker. GGD Zuid-Holland Zuid. https://www.ggdzhz.nl/gezondheid-en-milieu/pfas-en-gezondheidsadviezen/veelgestelde-vragen/kanker

    The regional public health summary. Confirms the Molenwaard 2018 result and states the official position that cancer risk from recent emissions for residents is negligibly small. Useful as the clearest statement of what residents are currently told.

11. Winquist, A. et al. Design, methods, and population for a study of PFOA health effects among highly exposed Mid-Ohio Valley community residents and workers. Environmental Health Perspectives, 2013. https://escholarship.org/content/qt54q143pp/qt54q143pp.pdf

    The source for the cohort figures in section 10.3: 32,254 participants, 28,541 community members and 3,713 workers, median follow-up from age twenty of 32.9 years and 4.4 years after the 2005-2006 survey. Read this before quoting the familiar sixty-nine thousand figure, which belongs to the health survey and not to the cancer follow-up. The two are routinely conflated, including in earlier drafts of this essay.

12. Vieira, V. et al. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environmental Health Perspectives, 2013. Summarised at https://foodpackagingforum.org/news/high-exposure-to-perfluorinated-compound-linked-to-kidney-testicular-cancer-in-humans

    The case-control analysis of 25,107 cancer registrations across thirteen counties for 1995 to 2005. Source for the testicular cancer odds ratio of 5.1 with confidence interval 1.6 to 15.6, resting on six cases in the highest serum exposure category, and for the approximate doubling of kidney cancer odds in the high and very high categories. The decisive example in section 10.3 of a gradient design recovering a signal that a count design cannot.

13. Substantial decrease of per- and polyfluoroalkyl substances with anion exchange resin treatment: a randomised crossover trial. Environment International, 2024. https://www.sciencedirect.com/science/article/pii/S0160412024000837

    The Danish cholestyramine trial: forty-five participants, twelve weeks, sixty-three per cent reduction in serum PFOS with smaller reductions for the other compounds. The central interventional evidence for the whole argument of sections 5 and 6, and the baseline against which the combination trial proposed in section 11.1 would be judged.

14. Certain medicines accelerate elimination of PFAS from the body. University of Gothenburg, published in Environment International. https://manufacturingchemist.com/certain-medicines-accelerate-elimination-of-pfas-from-the

    The Ronneby crossover study of cholestyramine and colesevelam in ten participants, with reductions up to forty per cent, each participant serving as their own control. A second, smaller, independent confirmation of the intestinal-limb result. The report is a secondary account; the underlying paper in Environment International should be consulted for the primary figures.

15. Effect of Plasma and Blood Donations on Levels of Perfluoroalkyl and Polyfluoroalkyl Substances in Firefighters in Australia: A Randomized Clinical Trial. JAMA Network Open, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8994130/

    The Victorian firefighter trial, 285 participants with ninety-four per cent retention. Source for the approximately thirty per cent reduction over twelve months with six-weekly plasma donation and for the persistence of the effect three months after the intervention ended. Read in section 6 as the creation of a fourth, external exit rather than the blocking of a return limb.

16. Perfluoroalkyl substance excretion: effects of organic anion-inhibiting and resin-binding drugs in a community setting. https://pfascentral.org/science/perfluoroalkyl-substance-excretion-effects-of-organic-anion-inhibiting-and-resin-binding-drugs-in-a-community-setting

    The observational analysis within the C8 Health Project of twenty-three probenecid users and thirty-six cholestyramine users among 56,175 participants. The source of the probenecid null result reinterpreted in section 11.1, and the confirmation that the two agents were analysed separately and never used in

combination. Note that this is observational and small, which is a further reason not to treat the probenecid finding as settled.

17. Third Report of the Independent PFAS Scientific Advisory Panel for Jersey. Government of Jersey, 2025. https://www.gov.je/SiteCollectionDocuments/Health%20and%20wellbeing/Draft%20Third%20Report%20of%20the%20Independent%20PFAS%20Scientific%20Advisory%20Panel%20for%20Jersey.pdf

    The most developed clinical guidance currently in existence: bile acid sequestrants as the single best intervention, colesevelam recommended from defined serum thresholds, phlebotomy second-line, probenecid advised against, treatment to median background followed by monitoring. Section 11.1 proposes that the probenecid recommendation be tested in combination rather than accepted as settled. These are prescription medicines and the clinical decision belongs with a physician; nothing in this essay is medical advice.

Named and not read

18. Barry, V. et al. (2013), Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant, Environmental Health Perspectives. Repeated attempts to retrieve the full text failed at the host. This reference is listed because it is central to the literature and a reader following this subject will meet it; it is placed here, separately, because it was not read. No figure from it is cited anywhere in this essay, and the cohort numbers in section 10.3 are taken from the Winquist design paper instead.

© 2026 J. Konstapel, Constable Research, Leiden. All rights reserved.