Minutes of public meeting of the PFAS Scientific Advisory Panel on Teams
10am on 17 April 2024

Panel Members present:	Dr Steve Hajioff – Independent Chair Dr Tony Fletcher – PFAS and Health member Professor Ian Cousins – PFAS and Environment member
In attendance:	Grace Norman – Deputy Director of Public Health (until 11.30) Sarah Tyler – Senior Policy Officer Julia Head – Senior Policy Officer Anita De La Cour – Executive Assistant

Welcome:
The Chair welcomed everyone to the 17 April meeting of the Scientific Advisory Panel, and reminded people the meeting was being recorded.

Introductions:
The Chair and Panel members introduced themselves.

Dr Steve Hajioff, Independent Panel Chair: A background as a GP for 25 years and a retired Director of Public Health from an area of London with two major international airports and a variety of other environmental hazards and challenges. Not a PFAS expert but has done lots of work with National Institute of Care Excellence and other groups about translating science into policy. Dr Hajioff has also worked a lot in the pharmaceutical industry.

Dr Tony Fletcher, PFAS and Health Panel Member: Environmental Epidemiologist at the London School of Hygiene and Tropical Medicine, working on PFAS since 2006 and member of the panel with experience of epidemiological studies on the health effects of PFAS in contaminated communities in West Virginia in the United States, in the Veneto region, in Italy, and in Ronneby, and is the health expert on the panel.

Professor Ian Cousins, PFAS and Environment Panel Member: A Professor in Environmental Chemistry at Stockholm University, an expert on PFAS, appointed as the environmental expert on this Panel and whose expertise on PFAS is on the sources, transport, fate, and exposure of PFAS.

Grace Norman, Deputy Director of Public Health for the Government of Jersey, the commissioner of this work, and a standing observer at these meetings.

Support staff for programme management and administration were also in attendance.
Dr Hajioff mentioned Sarah Tyler who has been coordinating this programme of work since the beginning and has done an amazing job. This will be Sarah's last meeting and Dr Hajioff thanked her for all the support she has given the Panel, it has been invaluable. Sarah has been wonderful to work with.

Julia Head will be taking over from Sarah and we are looking forward to working with her. Julia has a background in toxicology which may be useful for the panel over and above broader public health experience which her and Sarah shared.

Anita was thanked for minuting the meetings.

Members of the public were also in attendance. The Chair reminded people that the meeting is being recorded and a copy of the recording can be requested by emailing publichealth@gov.je.

Declarations of Interest
No additional declarations.

Minutes of last meeting

January meeting minutes were discussed and agreed by the Panel to be a true and accurate record of the meeting.

February meeting minutes were shared on screen as they were not sent in advance of the meeting. The Chair apologised that they were not available sooner. The Panel reviewed the minutes in the meeting. Following a question from Tony, the Chair confirmed that the subject matter experts who presented in February meeting have reviewed the minutes and have both agreed they are an accurate representation of the meeting and their presentations. Dr Fletcher suggested that both presentations should be referred to as "fascinating" and the Chair agreed as they both were fascinating. This change will be made in the minutes.

The minutes were agreed by the Panel to be a true and accurate record of the meeting and very well presented. Dr Fletcher congratulated Sarah on the minutes and the Chair agreed. The fact these minutes were not circulated ahead of the meeting was again apologised for by the Chair, indicating that they needed to be reviewed by the subject matter experts for accuracy ahead of sharing which sometimes takes some time.

Additional findings since the last meeting

There has been some media around ground water and PFAS levels in water supplies and food internationally. These are interesting and important and will be incorporated into the work in Report 4 on PFAS in the environment but are not directly relevant to this particular report. Therefore, they will not be discussed at present.

The Environmental Protection Agency (EPA) in the United States have released new guidance on PFAS. Prof Ian Cousins noted that the EPA have concluded that there are no safe levels of PFOS and PFOA and set the target values for both at 0 based on them probably causing cancer. The EPA set the drinking water guidelines based on a socioeconomic analysis of what is feasible to achieve, and the levels are set in the low nanogram/L levels. This is very similar to the levels which have been set in Sweden and Denmark, indicating some international agreement on drinking water guidelines with the most stringent ones being set in the low nanogram/L level. Prof. Cousins noted a difference however, as in Sweden the sum of 4 PFAS is set at 4ng/L, but in Denmark the limit is 2ng/L for the sum of 4 PFAS. Sweden and Denmark derive the limits from EFSA guidelines and is based on immunotoxicity endpoint. The US EPA is using a different endpoint, using cancer as a basis of their 0 level. This can be confusing that there are lots of different guidelines using different endpoints.

The Chair reminded the audience that there are lots of things that we come across in our daily lives which are associated with an increased risk of cancer. For example, the nitrites in smoked and processed meats such as sausages. These are not removed from the food chain completely. A factor being associated with an increased risk of cancer doesn't necessarily mean that that risk of cancer is high.

Dr Fletcher indicated that those are health advisory levels, and that the ideal target concentration would be below the regulatory level and are calculated based on the vaccine data endpoints. But whether it is to protect the risk of cancer or impact on the immune system, the target level is a practicable level which is set as a judgement on the feasibility and practicability for measurement. The same applies to regulations in the UK by the Health and Safety Executive or the Environment Agency. At some point the regulatory level is set at a level which is practicable after considering the costs and benefits of reaching that level.

Prof Cousins noted that very low levels of pg/L (picograms per Litre) is totally unachievable from a treatment viewpoint and would be financially and practically unavailable. All the tap water in Stokholm is about 4ng/L (nanograms per Litre) and therefore residents are exposed at levels in the low ng/L all the time. Rain is also at the same level. 80% of exposure comes from food, so even if the water was made to be PFAS-free, most people would continue to have exposure from fish and meat. Prof Cousins commented that it is a difficult message to communicate to the public.

The Chair clarified that the levels of PFAS that the EPA has concluded are safe water levels at 0 PFAS and therefore eliminated in the water are aspirational, and they can only be an aspirational, for several reasons:

1. It is technically not possible to measure absence of PFAS in water
2. It is financially not possible to totally eliminate PFAS from water
3. It would be not cost effective because at very low levels it is assumed that it will not have a significant impact on health outcomes
4. It would make a minimal difference to daily intake of PFAS because exposure from drinking water is typically lower than other routes of exposure, such as food (although this does not apply in places where there has been significant contamination of water supplies)

The Panel agreed to focus on the regulatory levels for now as they apply to Report 2 but will consider the aspirational levels further in Report 4.

The EPA have now set the regulatory level in the USA as 4ng/L (4ppt) (parts per trillion) for either PFOS or PFOA and 10ng/ml for PFHxS and 3 other PFAS. Then there is a risk calculation applied if there are multiple PFAS to result in a maximum risk factor.

Dr Fletcher explained how to calculate the limits for several PFAS in water. He described GenX which is a substitute for PFOA in situations such as manufacturing Teflon and has appeared in recent years. A level has been set at 10ppt for PFHxS and also GenX. The sum should not be more than 10ppt where they have the same limit. A framework has been developed to assess multiple PFAS. As new chemicals are identified which may have different limits, the sums are added together in relation to their limits. For example, PFBS is much less toxic and the limit is 2000ppt. Instead of adding together the individual concentrations, they must be added together relative to their target limits. For example, add together the level of PFHxS / 10ppt, GenX / 10ppt and PFBS / 2000ppt and if each of those percentage fractions doesn't add up to more than 100%, you are within the limit. But if the sum of those percentage fractions exceeds 100% then the limit has been exceeded.

The Chair reminded the Panel that the three compounds which are of particular interest for Jersey are PFOS, PFOA and PFHxS. GenX does not need to be considered as it was not in the firefighting foam used at the airport.

This will be covered in much more detail in Report 4.

As previously noted, the new EPA set limits for the USA are similar to the Swedish and Danish values and are lower than the UK values which has a tiered system of 10 and 100. It is expected that the UK limits will reduce, and this is being discussed by UK Government. These new EPA set levels in the USA are only slightly stricter than the level of concern of the first tier of UK regulation.

The Chair indicated that this is very helpful and it will have an impact on what we consider in Report 4, but important to have this discussion now as the EPA guidance will be seen by the public and is not easy to understand. This discussion has added clarity.

The Chair congratulated Prof Ian Cousins on two award winning papers recently.

Update on progress of literature reviews for Report 2 – Health impact of PFAS

Prof Ian Cousins talked the Panel through his paper about how PFAS gets in and out of the body and is distributed around the body. This will help the Panel to understand where the opportunities and risks are. The paper has been shared in advance of the meeting.

Prof Cousins has looked at different routes for uptake of PFAS and focused on relevant PFAS for Jersey PFOS, PFHxS and PFOA. It has been known that people have had organofluorine [PFAS] in the blood since 1960s but it was not well known until early 2000s. Everyone on the planet is assumed to have PFAS in their blood.

There are 3 main routes for all chemicals entering the body:
- Ingestion (eating food or drinking water, ingesting dust)
- Inhalation (breathing into lungs)
- Dermal (shower products through the skin)

The importance of these routes is studied using animal studies, mostly using rodents and monkeys, although the scientific community have tried to not use animals in recent years. There are lots of historical animal studies with PFAS in 1990s and early 2000s so the relative importance of these routes for uptake is quite well known. For example, if a rat ingests PFAS there is close to 100% absorption into the body through the ingestion route, which is unusual. For other substances such as Polychlorinated biphenyls (PCBs), hydrophobic substances, the absorption through the gut is quite poor.

The studies on absorption through the skin have shown poor absorption for both animals and humans. A study was conducted where PFAS was added to a suntan lotion which was applied on skin and blood levels were measured after exposure. PFAS was recorded in the blood and absorption was calculated as approximately 1% or less, which was very low. This was a very extreme exposure scenario and still resulted in this low exposure. Rat and mice studies also show that dermal is not an efficient route of uptake.

The Chair commented that 100% absorption by inhalation is common based on his experience in the pharmaceutical industry but 100% absorption through ingestion is very unusual though.

Prof Cousins noted that PFAS are quite water soluble compared to PCBs, this is why they get into ground and drinking water. This may be how they are getting through in water from the gut, but the mechanism is not fully defined yet.

Dr Fletcher indicated that there is a theory that they are actively transported via a family of active transporters called OATs – organic anion transporter proteins. The body mistakes PFAS for a nutrient and so absorbs it efficiently because the body treats it as though it is useful for the body. PFAS is efficiently absorbed through the kidney as well.

There are many pathways for ingestion. Humans eat various foods, drink water, and ingest dust. These have been modelled as well as the inhalation and dermal pathways to work out which are the dominant pathways. Which pathway is dominant depends on the population. For the general population who are not affected by contamination events, normal background exposure is from protein rich foods like fish, meat, eggs, milk, cheese because chemicals like PFOS accumulate in the food chains. For the general public, for PFOS, PFOA and PFHxS, ingestion from food is the dominant pathway, although recognising that there is also exposure from water and dust ingestion. This varies if this is broadened if other PFAS are considered - short chain are more dominated by water, long chain more governed by food.

For those who are affected by specific contamination, (e.g. AFFF exposure in areas like Jersey), then drinking water is the predominant route of exposure. This is the same for people who live near the Teflon plant in North America. There are also occupational sources.

The Chair posed a question regarding occupational exposure and queried whether it would be through other routes other than drinking water such as inhalation? Prof Cousins confirmed it would be via routes other than drinking water ingestion. Therefore, the Chair commented that occupational exposures, while important are not the best comparators where the prime route of exposure is drinking water. Dr Fletcher commented that if one is interested in the systemic effects, then the route of exposure is not significant, it does not matter once PFAS is inside the body because blood and fluids are in contact with everything in the body. The advantage of occupational studies is that typically a group of workers would have exposure to one particular chemical dominating exposure which would then be able to help concentrate on effects of one particular chemical. The downside is that the doses and exposure are usually much higher than the general population. It is part of the evidence base of linking particular diseases with health effects though.

The Chair commented that because as there is 100% absorption through ingestion, the other exposure routes do not make a large difference to a person's overall exposure. This is unusual for there to be 100% oral absorption. Additionally, often in pharmacology, there is a first pass metabolism conducted by the liver which can change a compound into something else or break it down. This does not happen with PFAS.

Prof Cousins indicated that for people living in contaminated areas where AFFF has contaminated drinking water supplies, there is evidence that contaminated produce can be an additional exposure. Where contaminated borehole water is used on farms to water crops and animals, there is evidence that there is additional exposure from this use. This is mentioned in the section Prof Cousins has prepared for the report.

There has been a study which reports a distribution of PFAS in human organs in Demark. This study design is rare due to ethical challenges. The findings confirm the theories about how PFAS is distributed in the body and organs. It indicates that PFAS is mostly distributed to the liver, kidney and blood. This confirms the hypotheses regarding the distributions among the organs in the body. PFAS binds quite strongly to the serum albumin protein in the body, among others.

The Chair questioned whether the high levels in the liver and kidney could be related to reabsorption loops with PFAS coming in via the blood supply to the liver and the kidney, and also being reabsorbed. Prof Cousins confirmed this theory could be correct and indicated that slow elimination plays a part in this too. PFAS have long half-lives as a result of this circulation and reabsorption.

There is no evidence that PFOS, PFHxS or PFOA are metabolised in any way to form other compounds and break down within the body.

There are precursors, small fragments of chemicals which can be brought together within the body to potentially form these PFAS compounds. This is another source of exposure to PFAS compounds, by people being exposed to these precursors which are then metabolised in the body to make the PFAS compounds. This complicates matters.

Elimination (also referred to as excretion) is mostly through urine. There is also some evidence of elimination through faeces but urination is thought to be the dominant route. Women have additional elimination pathways through monthly menstruation because PFAS bind strongly to blood proteins. This becomes an important elimination pathway for women. There can also be minor reductions in PFAS due to birth and breastfeeding. Elimination half-lives vary between different PFAS but also between studies and individuals. There is research ongoing to attempt to understand this but at this present time it is not known why this is although one hypothesis is that it might be due to kidney function.

PFAS can also be transferred in-utero through the placenta. An unborn baby will have PFAS in their blood, and a newborn will have similar concentration of PFAS in their body to their mother. Babies receive a high dose of PFAS from breastfeeding, meaning that breastfed babies get a strong exposure to PFAS in their early life. Body burden can be high when breastfeeding ends. There are longitudinal studies showing levels in blood increasing in early months, peaks around 1 year old. As breastfeeding ends and they grow, body burden drops with growth dilution.

The Chair commented that there is lots of evidence that breastfeeding is very helpful, it makes children healthier, and in some cases saves children's lives. There is no evidence yet that that there are any risks from breastfeeding with PFAS exposure which would in any way outweigh those benefits. The studies which have researched the association between PFAS and breastfeeding have still advised breastfeeding as the safer option even where there is a potential risk from PFAS being passed on to the breastfeeding baby. The Chair commented that it is important people are not scared away from breastfeeding which is incredibly beneficial on the basis of the evidence.

Prof Cousins commented that the section could be much longer, but that he feels it is an appropriate length for this report.

Comments were invited, and Dr Fletcher commented that on the issue of excretion, a number of authors, mostly animal toxicologists, claim that the kidney excretion is dominant compared to liver* and gut excretion but there are others that argue the opposite. A Japanese study quoted 20%excretion by the kidney. New data from Dr Fletcher's group examined urinary and faecal samples from Sweden in participants whose exposure has been stopped. The findings were that there is net excretion, and that for PFOS, 80% of excretion is through faeces and the gut, and only 20% for the urine. It's more balanced for PFHxS. Because there are conflicting statements in the literature, the report should reflect that both routes are significant and should

not overemphasise renal excretion. *[* Dr Fletcher mis-spoke and said 'kidney' in the meeting, but he meant liver and apologises for any confusion caused.]*

The Chair agreed that it was a useful point to make because for Report 3, looking at potential treatments, this could include treatments which limit reuptake in the kidney and liver. When considering the specific PFAS molecules, we need to understand which is the most important.

Dr Fletcher also commented on the long half-lives and said that there is lots of variability in individual levels, but most average between 3 and 5 years. PFBS and GenX both have half lives in range of 2-3 months and so they are much more rapidly excreted. The amount of active reabsorption is much less because it is thought that, unlike more well studied PFAS, they are not recognised as potentially good nutrients by the body and so are treated as redundant chemicals, excreted, and not reabsorbed. This mechanism is quite specific to the chemical and the chain length. The consequence of that is that if you ingest complex mixtures of PFAS e.g. AFFF, the ones which are measurable in the serum are the ones with long half-lives. Some will get excreted within a couple of weeks. For situations where exposure is controlled, only the ones with long half-lives will remain. This is why the literature is dominated by these compounds, because the ones in samples are seen after the rapidly excreted ones have gone. Therefore, the literature picture of exposure is primarily of these long half-life chemicals. This is important because your body has them for longer time which is important if they are toxic because they are present for a longer period of time.

The Chair commented that if the short chain, short half-lives ones are more biologically active, then they could be responsible for damage which is being attributed to the ones which have a longer half-life and therefore remain. This is a concern. Dr Fletcher agreed and commented that GenX is just as toxic as PFOA when given in the same concentrations to animals but is presumed to be much less toxic to humans because it has a much more rapid rate of excretion.

Grace noted that the results from the Islanders showed that PFHxS was the compound that was most prevalent at levels above the threshold that we set. She proposed that the potential reason for this is that the half-life is much longer and asked for clarification that this was the case.

Dr Fletcher agreed. If the water had contained PFOA, PFOS and PFHxS at the same concentration, then you would expect to see PFHxS at the highest concentrations in blood because it has the longest half-life. You would expect them to end up at steady state as having the highest concentration in the blood.

The chair asked for additional questions or comments. Dr Fletcher pointed out that this is a challenge because Prof Cousins has gone into a lot of detail which sets a high bar for the level of detail we should be presenting in every section. This is interesting, and Dr Fletcher indicated that he would think about it. The Chair thinks it is not too detailed and indicated that although each of these reports are a standalone piece of work, it is also part of a body of work and this level of detail will be extremely helpful in Report 3 and Report 4. It does not necessarily mean that we need to think about exposure pathways in every potential health effect or biodistribution in ever health effect, but it is useful as a context and it will be very useful when we consider potential treatments and exposure reduction approaches going forward.

Dr Fletcher indicated that studies conducted on individual PFAS compounds to study the different excretion patterns between different PFASs gives a different pattern in the serum than from environmental exposure. This is because the environmental exposure is a mixture of types

of PFAS. In studies which look at individual PFAS, the results could be less meaningful in mixtures exposure context such as in Jersey. This clarification is required to be added between this section and the one on health effects. The Chair agreed entirely and said it would also be important when looking at treatments.

The Chair thanked Prof Cousins for the paper, he considers it great and the right level of detail to inform this report and the next two. It has been a useful discussion.

Agenda item – Health effects data – Dr Tony Fletcher

Dr Fletcher commented that he is not so advanced in preparing text as Prof Cousins, and so has no document to share. However, Dr Fletcher has been reviewing and preparing sections. He commented that he had spoken previously about the evidence for cancer and that today he will talk about two other outcomes of particular interest which have the strongest evidence:

1. Effects on vaccine efficiency
2. Cholesterol

<u>Vaccine efficiency reduction in children</u>
This was the lead effect which was used to determine a tolerable weekly intake by the EFSA (European Food Safety Authority) review of evidence and it was for the provisional target value for EPA (American Environmental Protection Agency). The final target value set by the EPA in drinking water was 0 because the cancer effect took over, but the provisional one was based on vaccine data.

Data on children's immunisation to common vaccines including diphtheria and typhoid shows that antibody levels are not as high in people with higher levels of PFAS. In other words, the routine titre levels have gone up a bit less as they have been hampered by the presence of PFAS. Not all studies have shown this, but many have repeated this apparent effect which is judged by the scientific community to be a real association. However, there is not evidence which shows that this reduction in individual level immunity is resulting in increases in disease. Diphtheria is a rare disease so even if the population protection against diphtheria was reduced for everyone because of PFAS in the body, it would not be expected to lose the herd immunity.

Dr Fletcher commented that the expectation would be that if reduced vaccine efficacy was a generic effect across vaccines, that it would be also reflected in common infections. There have been a number of studies trying to establish if upper respiratory infections have gone up in populations in relation to contrasting levels of PFAS. A few years ago it seemed there was not much evidence of that but recently the balance of evidence has been shifting somewhat as there are now several studies that are indicating that there is an increased risk of common infections in relation to contrasting levels of PFAS exposure. The evidence is still not overwhelming, but there is more of a coherent patten that both the childhood vaccines which have been studied (diptheria and typhoid) are consistent with a reduced protection against common infections in children.

In adults, a marginal effect was found, a borderline significance, on the protection from flu vaccination for seasonal flu in the PFOA study in the US. Recent work in Sweden looking at whether the antibody levels in response to COVID were affected by quite high PFOA exposure did not find an effect. This is for adults and is a different type of vaccine and antibody so that doesn't necessarily conflict with the childhood data. It might be that the childhood immune system is inherently more vulnerable. The evidence is still that there is an interference with the immune system and there is consistent data on childhood infections.

Dr Fletcher commented that the animal data that one of the previous subject matter experts talked about is convincing in that you can show experimentally that the immune system in animals is compromised by experimental exposure to individual PFAS chemicals.

The Chair indicated that the immune system is quite important in cancer protection, noting that his experience is in the pharmaceutical industry rather than environmental hazards. There are two ways in which drugs are associated with a risk in cancer. 1) Some drugs cause changes in the DNA, they cause mutations which turn into cancerous cells, and 2) some drugs suppress the immune response which otherwise normally eliminates gets rid of with the lots of small cancers which people get all the time. He questioned whether there had been any thought about whether this immune modulation could be part of, or all of the mechanism to the increased risk of cancers?

Dr Fletcher considered it a good question and indicated that he didn't know at present. There is some indication that the endocrine system affects cell proliferation which affects the later stage of transition from a mutated cell to a cancer cell. This is in addition to the immune protection about cancer cells. Particularly in testicular cancer, the discussion is hinged on whether or not PFAS are endocrine-disrupting chemicals, and would be on a pathway affecting the development of cancer. This would not necessarily apply in kidney cancer. Dr Fletcher agreed and would consider the impact of immune modulation when looking for evidence on kidney cancer.

On epidemiology, there is a quantitative story between childhood vaccines which has been used for setting target values for no affect levels or low affect levels for regulatory purposes and to some extent is reflected in infections. There is supportive toxicological data to underpin that as a real association. This will be summarised quite reasonably for chemicals which are of concern – there is data on PFOS and PFOA. The evidence is a little stronger for PFOS and immune effects but there is not much data on PFHxS.

Dr Fletcher moved on to discussing autoimmune conditions such as Lupus and ulcerative colitis. He described how he found in the C8 analysis of a PFOA-exposed population, ulcerative colitis showed a significant dose response relationship. This is considered to be a rogue result because several autoimmune conditions were considered and that was the only one which came out as significant; there was not a pattern of several other pathway related conditions also being associated. Subsequently, Dr Fletcher looked in some detail whether or not that would also be apparent in the Ronneby (which has an exposure profile more comparable to Jersey because it is an AFFF exposed population) and no effect was found; there was not an increased risk of either colitis generally or ulcerative colitis in particular. Dr Fletcher noted that he will check on the other autoimmune responses. The findings in the C8 analysis was either a false positive or very specific to PFOA at high concentrations, so it is probably not relevant for an AFFF exposed population.

The Chair commented that we have receptors on the surface of our cells called Human Histocompatibility Antigens, HLA types. Some of these are associated with autoimmune disease. Ulcerative colitis is associated with a particular HLA called B27, as is Crohn's disease and ankylosing spondylitis and Systemic Lupus Erythematosus. Rheumatoid arthritis is associated with something completely different. The Chair suggested Dr Fletcher looks at autoimmune diseases to see if it is associated with that particular HLA, but noted that it wouldn't form part of this current report as it is a large area of study.

Cholesterol

Dr Fletcher continued feeding back his findings. There are multiple cross-sectional studies which have looked at whether there is an association between PFAS in the blood and cholesterol levels. Most indicate there is a consistent association for PFOA, PFOS and especially PFNA comes out very strongly associated with total cholesterol and sometimes HDL and LDL subtypes of cholesterol. The discussion in the literature is divided between those who think that is a real association which is probably causal, and some who think it is not causal and that instead it could be entirely caused by confounding factors or even reverse causality.

Dr Fletcher commented that there are several ways to look at this. One is to look at the potential mechanisms associated with this effect. Dr Fletcher was recently involved in a paper with some toxicologists and looked at a number of different pathways. These included PPAR, CAR, PxR, CYP7 receptors which are affected by PFAS, involved in cholesterol synthesis, metabolism, transport, conversion of bile acids into cholesterol. This could plausibly explain the positive association but it is complicated because in animal tests it looks like the opposite happens- that high exposure to PFAS reduces cholesterol. This is why some researchers do not believe that PFAS causes high cholesterol, because the human findings are contrary to the animal study findings. Dr Fletcher commented that he prefers to focus on the consistency of the epidemiology evidence.

Cross-sectional studies are a weak study design because it is not known whether the change in cholesterol levels or PFAS levels came first. Comparing different water districts in the C8 study where you can see there is an objective ecological difference in average exposure where you can see a difference in cholesterol. The district which has highest exposure of PFAS in the water and the blood also has the highest cholesterol levels. In a follow up study where people had no further major exposure to PFAS and measurements were repeated of PFOA and cholesterol, the ones whose PFAS levels had fallen the most also showed the biggest falls in their cholesterol levels.

All different study designs, cross-sectional, ecological, and longitudinal, suggest that there is a real association between PFAS levels and cholesterol. This is triangulation, using different methods with different vulnerability to bias. If findings show a consistent result across different study designs then there is a more convincing evidence base for causality. Dr Fletcher commented that without knowing the mechanisms, the pattern seems to be that there is a real causal association across multiple studies. The cross-sectional data is partly confounded so it probably overestimates that association.

Dr Fletcher moved on to explaining the consequences of higher cholesterol and noted that the general assumption is that cardiovascular disease could go up. However, he noted that the interesting finding here is that the evidence for increased disease risk is not strong. There is one mortality study which showed an excess of cardiovascular disease in the Italian data. In the follow up analysis with very large numbers in the C8 study, no association was found with any category of cardiovascular disease. Therefore, it looks like the increase in cholesterol is not reflected by an increase in cardiovascular disease. Dr Fletcher noted that this is why some researchers believe that the apparent relationship must be due to confounding and it’s not a real association.

American data suggests that part of the explanation for the lack of cardiovascular disease in spite of increases in cholesterol may be because PFAS also increases HDL (i.e. 'good’ cholesterol which is protective for cardiovascular disease). It suggests that overall, the LDL to HDL percentage or ratio doesn’t change.

Another phenomenon the Panel noted that is CRP (C reactive protein) which is an indicator of general inflammatory response, seems to be inversely correlated to PFAS in the American C8 population. The people with higher PFAS have in general slightly lower levels of CRP and this finding is also present in the cross-section analysis and this between area analysis. This would be indicative of some kind of protective mechanism relative to cardiovascular disease.

The Chair commented that CRP is also a measure of inflammation and infection in the body. That indicator could also relate to the immune modulation discussed earlier. When someone has an infection their CRP goes up, but if their immune system is underactive, then their CRP will be lower than someone with a more active immune system. The Chair commented that you would expect to have an elevated CRP in ulcerative colitis and rheumatoid arthritis.

Dr Fletcher commented that there are not many studies reported on CRP. He went on to comment that the starting point of a review was to summarise the evidence which indicates that there are associations with cholesterol. The different study designs show consistency underpinning the association being causal. The Panel has observed that it is not just total cholesterol but that there are LDL, HDL and potentially CRP factors which are complicating the interpretation of that increased cholesterol also being reflected with increased mortality, which the evidence suggests it doesn't seem to be.

Dr Fletcher commented that there is a mechanistic discussion including relevant pathways which would help support the theory that these are real associations. This could be covered by referencing the paper which discusses that, as it would not be proportionate to go into mechanistic information for every outcome. The Chair commented that mechanisms are interesting for the Panel to discuss and may speak to biological plausibility where in areas where the evidence is really weak. The Chair agreed that for the purposes of this report, detail around mechanisms is not necessary. This report is about the Panel understanding what the potential health impacts are which are caused by PFAS, and communicating those risks to doctors and other healthcare professionals, and people who may be potentially affected. Knowing the roles of individual mechanisms is not relevant for this purpose as that would be for academic study, not for this report.

Dr Fletcher summarised that PFAS does affect cholesterol and that should be worrying, but it also has other parallel effects which does not increase chance of dying as a result of increasing this cholesterol, and he therefore draws a nuanced conclusion.

The Chair agreed that it is complicated because the relationship between cholesterol and information and cardiovascular disease is not as clear as may be assumed. To an extent, elevated cholesterol could be a marker of inflammation in the vessels for some people, not necessarily just people exposed to PFAS through AFFF. Dr Fletcher noted that he would ensure his written submissions for the Panel are available for the next meeting, and to the rest of the Panel.

The Chair indicated that on the immune side it is almost that we see contradictory findings. Reduced vaccine response suggests a reduced activity in the immune system and the reduced ability of the immune system to respond to antigens, hostile biological compounds or chemicals. If the increase in ulcerative colitis is real or some of the other suggested increases around autoimmune diseases, they are usually associated with an increased response to antigens or things within the body's own make up that we shouldn't normally react to. He questioned how do we interpret a simultaneous increase and decrease in immune response?

Dr Fletcher commented that it relies on whether the ulcerative colitis effect is real, and that has only been found in one study and not supported by other studies. For that reason, he considers this to be a chance finding. Multiple different disease categories were looked at and there is always a risk that things are found by chance and other findings which are real are not found. There is always a risk to under or over report findings, and that is why it is very important to look at the breadth of evidence from different studies. If there is a new apparent outcome without a strong biological basis to explain it, it could be a chance finding. Chance findings do happen, and we need to be mindful that in the C8 work, 44 different disease categories were considered and just by chance alone, a statistically significant result would be expected, just caused by change, for at least 2 of the disease categories. The C8 group concluded that there should be more than one different study design or different studies to support it. For kidney cancer for example, C8 had a significant finding in the study, and a study with a different design in workers also found a finding. For ulcerative colitis, there was only one study that showed a statistically significant association, so it seemed convincing, but this finding hasn't been found in other studies so Dr Fletcher is comfortable considering that it is a false positive caused by chance.

The Chair summarised that there is some evidence around reduction of immune response which could have some broader implications and is up for discussion. Dr Fletcher agreed with this comment and noted that multiple bigger expert panels have concluded that this is a real effect. However, the Chair noted that the Panel hasn't seen convincing evidence at this point around the impact of PFAS on autoimmune diseases, such as rheumatoid arthritis, Crohn's, ulcerative colitis, and Lupus. The evidence is not there at this point. Dr Fletcher also agreed with this summation.

Prof Cousins noted that he presumes there will be some discussion about the weight of evidence with these effects, and that if there are multiple epidemiological studies, multiple panels agreeing, with dose response and animal studies then all of this can be taken together as strong evidence of this effect. But one epidemiological study on its own linking PFAS exposure with a random disease, even if they do show a statistical association, should not be considered on their own. Methodologically, it would not be appropriate to review single studies in isolation and draw conclusions from them; the evidence needs to be looked at in totality. Dr Fletcher noted that there are scientists taking publicly available NHANES data to look at multiple associations and picking out the significant ones, which is methodologically flawed.

The Chair commented that in epidemiology, 1 in 20 times you will find a chance association at the 95% centile. But finding the true association is much more complicated.

There is an EFSA panel which is producing a guidance document on how to evaluate epidemiology and synthesising evidence in support of determining causality. It was pointed out that in this area of work, it used to be difficult to get an academic paper published if it did not have strong results, meaning that small studies were more likely to be published, and this resulted in publication bias. Now it is much easier to get papers published as there are many more journals. The only barrier is funding, meaning that random findings are more likely to be published if the group can pay the journal fees which makes things harder and introduces a systematic bias. Therefore, the non-positive studies are more likely to be published which means the evidence base should become more robust.

The Chair commented that this problem demonstrates the importance of the approach that the Panel is taking whereby we triangulate results using multiple studies and multiple study types before drawing any conclusions about health effects. That risk of finding one paper which

confirms something you already believe continues, and is why it is important to assess all of the available evidence.

Dr Fletcher thanked the panel for their thoughts.

The Chair thanked Prof Cousins and Dr Fletcher for their presentations and thoughts.

Agenda item – Next steps

The Chair noted that the next steps are about completing all these reviews as we go through this process of developing this report.

Dr Fletcher questioned timings. The Chair commented that for the next meeting on May 16th we will need draft sections for the report to allow editing into the report. In the June meeting there will be a broader discussion bringing the whole process together and considering recommendations.

Any other questions
None.

Any other business
None.

Date of next meeting

16th May 10am – 1pm by Teams as usual

The Chair thanked the panel members and observers and particularly Sarah, Anita and Julia and the members of the public who have been observing the meeting.

There being no further business, the meeting was closed.

To note that the Panel can be emailed via PFASpanel@gov.je.

Details of meeting dates and times can be found at PFAS in Jersey (gov.je)