Minutes of public meeting of the PFAS Scientific Advisory Panel

10am on 16 May 2024 on Microsoft Teams

Panel Members present:

- Dr Steve Hajioff – Independent Chair
- Dr Tony Fletcher – PFAS and Health member
- Professor Ian Cousins – PFAS and Environment member

In attendance:

- Julia Head – Senior Policy Officer

Welcome:

The Chair welcomed everyone to the 16 May 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. Grace was not able to be present at this meeting. Julia Head will step in with some comments from her which she has prepared.

Support staff for programme management and administration were also in attendance.

Dr Hajioff thanked Julia Head for being present. Julia has a professional background in toxicology which will be useful for us. Julia will raise any important toxicological comments if appropriate.

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

Dr Hajioff apologised for the lack of April minutes which are taking longer to prepare due to the complicated nature. March minutes are available to discuss and were shared in advance of the meeting.

Dr Hajioff asked for feedback on each page of the minutes. Edits were made where appropriate.

Prof Cousins noted some small inaccuracies in the chemistry section. Prof Cousins took an action to correct the notes after the meeting.

On page 5:

- Grace asked for clarification around PFAS not being major surfactants in firefighting foam. Prof Cousins clarified the point which was recorded in the minutes.
- The current definition of fingerprinting in the minutes was questioned and changed to be an accurate statement. Dr Hajioff asked if fingerprinting can give a time course as well? Prof Cousins indicated that it is possible, but very complicated due to too much uncertainty and so is not used for this purpose.
- Clarification was provided on the point regarding cross-contamination during storage of AFFF. This will be expanded on in Report 4

On page 7:

- Grace questioned the use of the word “explained” and this was considered to be clear and accepted.
- The sentences regarding brain and bone cancers found in Ronneby vs other studies were clarified by Dr Fletcher.
- The point regarding risk of cancer from AFFF is lower than PFOA in other studies was clarified by Dr Fletcher.

Matters arising

Dr Hajioff noted that the panel should plan to have a discussion about how the difference in serum levels in Ronneby vs Jersey is interpreted because there is potentially a different time interval between exposure and assessment. This is to be considered when looking at the data at a later date. Dr Fletcher asked how long the exposure had been going on in Jersey. It was agreed that this topic was not discussed further at this present time but recorded as a point for discussion in the next meeting when discussing interpretation of findings from the literature and subject matter experts.

Dr Fletcher noted that most of the toxicity discussion is around perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) because that is what is measured in blood and they are stable and they bioaccumulate. There is some animal toxicological data on precursors to these acids. The European Chemicals Agency (ECHA) report on AFFF mentions a lot of the other components which have been identified and what toxicological data there is. Dr

Fletcher noted that reviewing each of the precursors individually would be very time consuming and asks how we should engage with and summarise data available on other compounds in AFFF. Dr Hajioff noted that precursors is an important matter arising which the Panel will need to consider and have as a key part of discussion regarding the "unknown unknowns". This will allow a communication of uncertainty.

Dr Fletcher notes that precursors also relate to exposure. Prof Cousins mentioned that it would be possible to do a Total Oxidizable Precursor Assay (TOP assay) to get an understanding of the level of precursors. A TOP assay involves analysing the water sample to achieve a concentration of the different acids, then the water sample is oxidised and analysed again. The difference between the two figures is the precursor contribution. Prof Cousins indicated that this would be an interesting assay to perform on water from Jersey to give an idea of precursor contribution, however it does not indicate which precursors are present and that would require additional analysis.

Dr Hajioff noted that understanding the decay curve of precursors would also be useful in Report 4 when environmental clean up is considered by the panel which Prof Cousins agreed with in principle.

Dr Fletcher noted that precursors may be associated with health concerns too, but as Ronneby has similar exposure scenario this will be covered in the epidemiology assessment as the Ronneby population had precursors in their blood.

Prof Cousins noted that TOP assays can theoretically be conducted on blood samples of exposed populations but to his knowledge this analysis has not yet occurred.

Dr Hajioff commented that for the common health conditions, looking at precursors separately probably is not materially meaningful, because the impact of pre-cursors will already be included in the epidemiology evidence that the Panel has reviewed already. But there are two scenarios where it might be useful to look at precursors:

- rare consequences which have not been demonstrated epidemiologically because the disease is so rare and it is difficult to have found it
- if the disease is so common it becomes a rounding error because there are so many other causes that it is difficult to attribute it to any particular cause

Dr Hajioff commented that he does not believe it is necessary to do a deep dive into the literature on precursors in general, but rather the panel should look at them in the context of some of the specific conditions under consideration, the ones highlighted by experts by experience. The panel agreed.

Dr Fletcher noted that since the last meeting he has been made aware of a book published around the Italian experience of PFAS contamination in Veneto by a group of social scientists in Italy. The book is in Italian. Dr Fletcher considers that this book may be relevant as one of the chapters is on the mental effects of the contamination in the area. The details of the book have not been reviewed. There may have been a review and projected what they think might be the stress related hazards in the community, or whether there is some local evidence of that having been demonstrated. There is a full PDF which Dr Fletcher will share with the panel.

Dr Hajioff thanked Dr Fletcher and agreed that there may well be useful information in that book.

Additional findings since the last meeting

Prof Cousins noted that there has been a lot of concern recently around trifluoroacetic acid (TFC) – an ultra short chain perfluroalkylacetate (PFA). This compound is being closely considered because the levels of this substance have been going up significantly in the environment. It is a very short version of PFOA with only 2 carbons, a carboxylic group and one carbon which is fully fluorinated. PFA is not very toxic compared to longer chain PFASs, but many researchers are concerned because levels are rising over time and people are flagging it as a concern because eventually everything is toxic if it crosses a threshold. PFA is very persistent, the behaviour of PFA shows what happens when a chemical is persistently released into the environment.

Dr Hajioff asked if trifluoracetic acid is in 3M AFFF? Prof Cousins confirmed that it is, but that it is not the major source. The major source in any substance (for example rain water, surface water, blood, etc) are fluorinated refrigerants. Dr Fletcher asked if it is a metabolic product of breakdown of other PFAS materials? Prof Cousins answered that it may be, because when destroying or breaking down PFAS, you don't always mineralise them [i.e. *convert them to inorganic product*] then they don't break fully down to fluoride, they break down to shorter chain PFA. This breakdown would be a physical process and would not happen naturally in the environment or human body. Prof Cousins noted that PFA is in micrograms per litre levels whereas we are usually talking about nanograms per litre levels, so PFA is present at much, much higher levels. Dr Hajioff asked due to it's short chain, does PFA have any other behaviours? Dr Fletcher commented that it is rapidly excreted, and Prof Cousins added that there is no way to remove it from water except at extremely high cost so in effect it is there forever. Prof Cousins predicts that PFA will be mentioned in the news in the future.

Health impact of PFAS – Dr Tony Fletcher

Dr Fletcher presented a verbal report without slides. He gave an overall picture of the health effects of PFAS and noted that the literature on PFAS is enormous.

<u>Exposure</u>

AFFF is a complex exposure dominated in the serum measurements by PFOS and PFHxS and to a lesser extent, PFOA. There is always an inherent mixture and also the possible mixture of precursors which are no longer present when taking and analysing blood serum later. The Ronneby situation in Sweden where there are over 10,000 people exposed to AFFF is different to the Jersey exposure is still comparable and in fact is a more suitable comparison than evidence on single types of PFAS or background exposure to mixed PFAS which much of the literature is reflecting.

<u>Sources of information for the paper:</u>

Dr Fletcher's paper will start with the 20 papers published by Ronneby research teams and summarise the results. This will be supplemented by review papers including those from:

- International Agency for Research on Cancer (IARC) - reviews looking at carcinogenicity of PFOA and PFOS specifically.
- United States Environmental Protection Agency (EPA) – report on PFHxS

- European Chemicals Agency (ECHA) – reviews forming the supporting documents for the banning of AFFF across Europe
- The European Food Safety Authority (EFSA) – summary of 4 most prevalent PFASs, PFOA, PFHxS, PFOS and PFNA and recommended limit for exposure to the sum of those
- Subject Matter Experts – detailed specific studies they have been involved with

Dr Fletcher is writing a report which will be shared ahead of the next meeting.

The overall picture is that there are clear effects on cholesterol, although reassuringly, there does not seem to be an associated cardiovascular disease risk. IARC considers cardiovascular risk as sufficient for PFOA, and possible for PFOS. The EPA are considering PFOA and PFOS as "likely carcinogens" for their risk assessment and Standard setting purposes. There are a number of other health conditions which have been linked to health effects in one or more studies. For example, in the Ronneby studies, they found effects in diabetes, language development in children and polycystic ovarian syndrome (PCOS). Those have not been replicated in other studies and are therefore considered "possible". Replication is very important, as is systematic review. The various reports by IARC, ECHA etc have been prepared using a systematic review process.

When looking at systematic reviews, Dr Fletcher cautioned that the reader must understand the criteria for authors inclusion or rejection of studies due to quality. For example, the EPA have done an in-depth synthesis of the literature on PFHxS and during study of this review, Dr Fletcher noticed that the Ronneby study was classified as low quality in this review and rejected by the authors for synthesis for evidence. This is because the Ronneby study is deemed to be 'uninformative' for PFHxS (even though it has the highest serum levels) because it is a mixed exposure which includes PFOS and PFOA therefore the effect of PFHxS solely cannot be picked out and so the study was excluded from the EPA's review.

Dr Hajioff explained that, on that basis, every epidemiology study would be considered low quality, and yet this is probably the most important data in helping understand the health risks for the population in Jersey.

Dr Fletcher reported that the EPA believe the studies are more reliable where there are individual measurements of serum levels so that they can be simultaneously statistically adjusted for in the analysis, but that excludes some of the most important studies where there is clear contrast of exposure between people who are drinking differing water sources. This is because drinking water sources have mixed PFAS exposures and the studies are reliant on exposure classification based on the water subjects are drinking rather than the serum levels at an individual level.

Dr Hajioff discussed the fact that addressing chemicals individually is also problematic in the light of the point which Professor Kristina Jakobsson brought up in Report 1 around the imperfect dose response for cholesterol. Increasing PFOS beyond a certain level is not associated with a further increase in cholesterol, so how do you correct where it is a non-linear dose response?

Dr Fletcher commented that the panel will come back to non-linear dose response when looking at the general principles of systematic reviews later in the meeting. He continued to note that it is a reviewer's judgement call as to whether the precision of biomarker measurement is believed. If this is ranked as more believable than having a clear contrast of exposure related to mixed exposures, valuable information useful for assessing exposure will

be lost. The exposure contrast and the associated results revealed in the Swedish studies are of more value than the individual studies or the systematic reviews trying to separate out individual substances.

Dr Hajioff commented that this really interesting as someone with a background in pharmacology. When trialling a new drug, biomarkers are the lowest value outcome measures. Even though they are easy to measure and are reliable, their real-world implication is seen as irrelevant. Some countries wouldn't register a drug with only biomarker data and without real-world measurements.

Dr Fletcher gave another example. A systematic review of the effect of PFOA on birthweight was conducted showing a significant negative effect of PFOA on birthweight. Associate Professor Christel Neilson, (who previously presented to the Panel) showed there is overall no effect in Ronneby, but this hides a more complex picture. There was a significant increase in the proportion of babies born at low birth weight for one sex, and a decrease for the other. This effect may be real or may be a chance finding because other researchers have not found a sex-specific difference. One of the systematic reviews which concluded there *was* a significant effect of PFAS on birthweight did a quality check on all of the studies.

One of the studies done on the C8 population was rejected as being low quality because they didn't have measured serum levels, they had modelled serum levels because there was a model available which applied across the whole population. The systematic review authors considered measurement more credible than modelling. Dr Fletcher pointed out, however, that measurement can be subject to a bias, for example, where if you have a big baby and a big increase in weight during pregnancy, there is a dilution in the blood levels of PFAS which can confound the association between exposure and effect. There is a tendency to believe the biomarker results as being the measurable and most precise, and due this belief, the authors of this systematic review discounted the largest study which turned out to be non-positive. Therefore, this decision had a big effect on the results of the meta-analysis. This complication forms part of the discussion in the report.

Dr Hajioff noted that Dr Fletcher makes an important point which is about reliability (i.e. getting the same answer repeatedly when the conditions are the same) vs validity (i.e. getting the answer which is technically accurate). Cholesterol is measured because it is important in heart attacks and strokes. This is the only reason we measure it. With PFAS, evidence suggests that there is an increase in cholesterol but there is not a commensurate increase in heart attacks and strokes. This means that the cholesterol measurement is reliable (because it is giving the same answer each time), but it is not valid because it doesn't tell us anything about real world experience. Therefore, it is thought, therefore, to be less relevant to the lives of people who are affected because of not leading to poorer health outcomes.

Dr Fletcher agrees. He is not persuaded that a change in birthweight has strong evidence in relation to PFAS, but others take the opposite view. It is a contested area of discussion. Both sides of the argument will be addressed in the summary prepared by Dr Fletcher.

There are a number of adverse health effects of PFAS which are 'probable', 'possible', and 'definite', and clearly PFAS is an exposure that one would want to avoid. The implications for the situation in Jersey, where there is a small population, is that it will be almost impossible to demonstrate either the presence or absence of a risk caused by PFAS. If the population of exposure is 100 people, then a rare condition such as kidney cancer would not be expected to

appear in such a small population, even if the risk is dramatically increased. If the risk went up 10% (comparing the situation to Ronneby), then you would still not expect to find any evidence of harm in such a small population.

Dr Hajioff commented that if there is an unexpected cluster of disease within the small population, for example 8 cases of kidney cancer in an area of PFAS exposure within this population, then the opposite conclusion can be drawn, that there is a clear indication of risk of exposure is related to disease. But because it is likely there will be none, or maybe one, then it will be difficult to draw that conclusion.

Dr Fletcher commented that if there was one case of kidney cancer within this population and an estimated relative risk of 1.1 was defined by comparing with other similar populations, then it would be hard to say whether that particular case is caused by the exposure. Realistically there is unlikely to be a major attributable health impact in a population because the population is small, and the increased risk identified in other populations are relatively modest. Also, the heath impact would be unlikely to be able to be shown in any health survey within the population. Therefore, we must rely on benchmark standards in systematic reviews. The EPA has documented their estimate of acceptable drinking water levels which is as low as technically feasible rather than based on a quantitative risk assessment. The EFSA recommendations and the target serum levels of sum of 4 PFAS or equivalent tolerable weekly intake would be a suitable benchmark to use. It is not possible to give an estimate of the relative risk of a disease, or say that the effect has gone up by x% in relation to exposure. Instead, the conventional risk assessment approach can be used to compare likely exposure to an established benchmark of exposure. The EFSA benchmark is sufficiently robust to use in this situation.

Dr Fletcher summarised by noting the panel cannot estimate risk quantitively for this population, but the exposure profile can be compared to the EFSA benchmark.

Dr Hajioff agreed that this is a good approach provided we are using the correct benchmarks. Very different exposures could be argued to be not appropriate benchmarks. For example, using a benchmark derived from near the DuPont factory where the mixed exposure is very different to the mixed exposure in Jersey. This would be less valid than AFFF studies like Ronneby. Dr Fletcher commented that the DuPont factory is only releasing PFOA, resulting in an exposure greater than background.

The Ronneby team have had some discussions about whether it is possible to form a quantitative assessment of risk, but there is not yet sufficient evidence to do this. The exposures are reliant on ecological contrasts between high, medium and low exposure areas. These contrasts are not good enough to be able to convert into risk per nanogram per ml blood. The studies which have provided that metric are the studies on childhood vaccination in relation to maternal exposures. These are at low, background population levels.

Dr Hajioff noted that we have seen a difference in antibody responses to childhood vaccination. He questioned as to whether a meta analysis has been done across multiple studies to look at any change in the incidence of the diseases which are vaccinated against, for example, measles, mumps, rubella, pertussis? Is a change in incidence of disease a marker of immune dysfunction, or is it clinically important because it is increasing the risk of these nasty diseases?

Dr Fletcher answered that the diseases which come out strongest are diphtheria and tetanus and these are so rare such that a reduction in the antibody titres is not reflected in a change in the population data on those particular diseases. Epidemiologists assume that if it is a general depression of childhood immune response to those vaccinations then that should be reflected in a general reduction in immunological defence against common infections. The literature is a little unclear. Some studies show no evidence of an increase, some do show an increase in common childhood infections in relation to PFAS exposure. There is some evidence which is not overwhelming, but not absent either. There is no formal meta analysis of this area.

Dr Hajioff commented that some studies will be on common cold coronaviruses where antibody immunity is much less important. It is a complicated mixture of studies. Dr Fletcher agreed for common cold coronaviruses but not COVID.

Dr Hajioff asked for any comments or questions for Tony but none were received. He thanked Dr Fletcher for his presentation. Dr Fletcher will bring together his findings in a report.

Draft document on groups at potential increased risk from PFAS exposure

The panel discussed the document prepared by Dr Hajioff.

Dr Hajioff commented that is important to identify the groups of people who are potentially more vulnerable and potentially might need preferential monitoring or intervention due to the reason why they are more vulnerable. This is work which has been done elsewhere in the world.

Dr Hajioff has summarised the factors in the literature:

- Age – people who are either very old or very young could be at increased risk from PFAS exposure. The very young particularly due to long half-life in the body and because children are in a developmental phase, the potential for a lifelong adverse outcome might be higher. Some of the studies seem to suggest this is the case.
- Those who have greater exposure through occupation or other additional exposure source. This will be investigated in Report 4
- Socioeconomic disadvantage can be a factor. Areas of greater deprivation are more likely to become contaminated, and they may also have poorer access to healthcare
- Pregnancy – if a pregnant person is exposed, then the PFAS will pass through the placenta resulting in higher risk for the foetus
- People with certain diseases and comorbidities. This is complicated and potentially problematic.

Factors do not exist in isolation – someone can have multiple risk factors which makes overall risk higher e.g. a child living in disadvantaged environment and have an illness which makes them more susceptible.

Dr Hajioff asked for comment and suggestions.

Julia requested on behalf of Grace that the panel takes into account multiple exposures and discusses this aspect.

Dr Fletcher questioned why it was important we understood the vulnerable groups and what impact it has on the recommendations we will give? If the main exposure has stopped and there

is a population with a body burden related to past exposure, why would we recommend different activities for those who fall into different vulnerability groups?

Dr Hajioff agreed with the point, and indicated that we will talk about this again in Report 3 when considering wider testing and treatment. He countered by saying that if someone has a co-morbidity, for example, they have an illness that is associated with PFAS exposure, it might be reasonable to recommended to the health care professionals who look after them should be aware of the increased risk, and so take the PFAS increased risk into consideration during treatment of the patient. If we are concerned about low birth weight for other reasons, we could provide additional advice to those who are pregnant and those who care for them about what can be done to mitigate risk of reduced birthweight.

Dr Fletcher still holds the opinion that everyone should be aware of the increased risk situations, and that there shouldn't be extra advice or surveillance advice given to those who are vulnerable. These are general principals about groups at risk, but they don't necessarily translate into advice in a given population. Dr Fletcher considers the co-morbidity is the most important aspect and more care should be taken in the screening and identification of other potential risks. The effect on children, the risk of reduce effectiveness of vaccination, is thought to be related to perinatal or in-utero developing immune system. This is an important reason for protecting everybody, including those individuals.

Dr Hajioff agreed that the Panel shouldn't let the targeted approach undermine the universal approach in terms of advice and support, due to the effect being marginal. There are a couple of caveats and that is additional exposure e.g. working with PFAS and living in a plume area. In this case, there may be a consideration when reporting about testing in Report 3 for additional monitoring.

Dr Fletcher agreed, saying that thinking about multiple routes of exposure is important as these are groups at extra risk of exposure. This should be deferred to Report 3 where the panel are considering exposure. Dr Hajioff agreed.

Socioeconomic disadvantage is a known explanation for comorbidities; usually poorer health is an indicator for disadvantaged socioeconomic status. However, in some cases, higher wealth is actually associated with higher exposure to PFAS, e.g. carpet treatments, waterproofing treated garments, food packaging and more household goods. The more general poverty-related exposure scenarios may not be true in this case, because some of the more PFAS treated products are more expensive. There is some American evidence showing a correlation of higher wealth, more disposable income being positively associated with higher exposure to PFAS compounds. It is not a simple correlation for PFAS.

Dr Hajioff commented that this paper will also be useful for Report 3 and Report 4, and is included in this report as background. This paper will be used to inform later work as well.

Draft document on key concepts of environmental epidemiology

Dr Hajioff presented the paper, and explained that measurement of exposure is important, either a direct measurement if possible or modelled exposure in the absence of measurement. There are different pros and cons for those different approaches. It is necessary to have an assessment of exposure before potential outcomes can be evaluated.

Different study designs were noted in the paper, and they were also touched upon in Report 1. The key point is that experimental studies cannot be used in environmental epidemiology due to it not being ethical to expose people to a risk and measure the outcome. Therefore, randomised controlled trials is not an option for measuring the impact of PFAS on humans.

There are 4 basic study types described in the paper. Yellow highlight are words to go into the PFAS glossary.

Outcome measures was discussed reflecting a discussion about biomarkers vs clinical endpoints vs demographic endpoints. For example, is measuring cholesterol or survival the right outcome measure to look at? How is the meaning of these biomarkers assessed? There are different concepts related to risk which have been outlined in the document, including how potential risk from an exposure is measured.

Bias is discussed in the paper including confounding and ecological fallacy. Dr Hajioff reminded the panel that just because factors are associated with each other, does not mean they are causal. An assessment must be done to look at causality. The paper concludes with a note on how to deal with challenges such as confounding and how to correct for ecological fallacy.

Dr Hajioff invited comments and questions on this paper which is designed to help readers understand why the conclusions and recommendations to be drawn in Report 2 have been formed.

Dr Fletcher noted a couple of comments. He considered the paper to be a good summary of a lot of the concepts and language which is used when describing the studies, but thought it may be a bit abstract for the audience. Dr Fletcher suggested illustrating this paper with tangible examples from the PFAS literature of the sorts of studies which are done to help the reader understand. Typically, the two main types of cohort study in PFAS research are 1) linking general population classified by exposure to health outcomes (e.g. Ronneby) or 2) studies using available registers of biomarker databases containing blood measurements and have been followed up over time (e.g. Danish database or NHANES where there is baseline exposure measurement and follow up). He also referred to case control studies, for example looking at cancer cases and linking them to historical exposures, and cross-sectional studies which mainly look at biomarkers. These general descriptions of studies would be made more accessible by providing specific examples. Dr Fletcher would be happy to provide a number of these.

Dr Fletcher continued by speaking about ecological studies. There are studies which the outcome data may not be ecological data, there may be individual data including confounding data on smoking for example, which means it is semi-ecological. He requests that this distinction is made in the paper. For many of the studies in PFAS literature this distinction is not a problem, because there is individual data to do with outcome. However there is a concern that there is some residual ecological confounding in the general socioeconomic status which varies between areas. Dr Fletcher will provide more examples to make the paper more accessible. Dr Hajioff thanked Dr Fletcher for this offer.

Dr Hajioff asked a clarification question. He noted that it is not uncommon in randomised control studies that there is a unit of randomisation which is not a person, it might be a hospital or a GP surgery. There is a statistical correction to apply to deal with how those groups or

clusters behave as a single entity rather than as a group of people. Is there a similar process in ecological studies with intra-cluster correlation correction?

Dr Fletcher said yes, it is generally called multi-layer modelling, which is a statistical tool. There may be individual data but then there would be an area classification for say, deprivation index for that area and that allows statistically to cluster for health and/or effect at that level. Dr Fletcher does not recommend getting into that level of detail for this paper.

Prof Cousins noted that epidemiology has not always been accepted for risk assessment in certain jurisdictions, and animal model data has been more important. The combination of animal model data and epidemiological data is quite powerful. For example, if an effect is seen in an animal model, and also in a human population, then the combined evidence is powerful. In her presentation, Jamie DeWitt [previous Subject Matter Expert] often pointed out the different effects that have both epidemiological evidence and data from animal studies and this is powerful evidence.

Dr Hajioff agreed, and noted that the animal data speaks to biological plausibility and helps to triangulate in that way.

Dr Fletcher noted that he has recently been part of an EFSA panel which has drawn up a guidance document on the systematic assessment of epidemiological data and the features to look for and the strengths and weaknesses of different study designs which should be considered when doing a systematic review. The quality of individual studies and how they are judged, and in particular triangulation across several different epidemiological designs to make that more confident assessment of causality going beyond just association is reflected in that EFSA document. Dr Fletcher will share this document with Dr Hajioff. He noted that this overlaps with the next document on critical appraisal which Dr Hajioff agreed with.

Draft document on Understanding risk

Dr Hajioff noted that this document is quite important as a broader primer and will be of particular relevance in Report 4. It has been developed to be used across different reports.

The way humans perceive risk is often fundamentally different to the size of the hazard that they face. Dr Hajioff illustrated this using people who smoke (high risk activity) but are afraid of air travel (a much lower risk activity). There is a literature and reason about why the way people perceive risk is different to the magnitude of the hazard itself. It is important to understand this concept. Dr Hajioff explained the concept of locus of control to explain this phenomenon. For example, you are in control as to whether you light a cigarette or not, but you are not in control of flying the aircraft. This is one of the reasons why there is a mismatch between perceived risk and hazard magnitude. The technique to understand the hazard magnitude nature is called risk assessment. There are various approaches to assessing risk.

The overall risk of something happening, for example, developing kidney cancer, is called ‘total risk’ or ‘absolute risk’. ‘Attributable risk’ is the part of that risk that is directly caused by a certain exposure, for example PFAS. There is often a difference in risk between the overall total risk and the extra part of the risk caused by the exposure. Conceptually, Dr Hajioff considers this quite difficult.

He continued to explain about absolute vs relative risk. Absolute risk is the likelihood of developing a condition, but relative risk is how much more likely someone is to develop a condition because of their exposure. Dr Hajioff explained using an example from the smoking literature. People who smoke are twice as likely to have a serious heart event and 13 times more likely to develop lung cancer than people who do not smoke. This is smokers' 'relative risk'.

In the total population, heart disease is more common than lung cancer, so it is said that the absolute risk of heart disease is much greater than the absolute risk of lung cancer. Consequently, a small increase to the absolute risk of heart disease will result in much more disease than a small change to the absolute risk of lung cancer. This remains true even though the relative risk for lung cancer (for people who smoking compared to those who don't) is much higher (13:1) than relative risk for heart disease (2:1). These are difficult concepts to understand. Even a small increase in risk that is quite common can be more burdensome on a population than a large relative risk increase in something that is very, very rare.

The ecological fallacy is an important concept in epidemiology and was touched upon in the last section. Ecological studies are those which measure health risk and outcome at a whole population level, and one of the issues with this type of study is that some things which are true at a population level are not true at the individual level, which means that generalising from a population to an individual is very difficult and imprecise.

Dr Hajioff continued by highlighting the difference between risk *factors* and risk *markers*. A risk marker is something that doesn't necessarily *cause* the negative outcome, but is *indicative* of the negative outcome. For example, is elevated serum cholesterol a risk factor for heart disease and stroke, or is it a marker of inflammation and a risk marker for heart disease and stroke? Those aspects often need to be unpacked in risk analysis.

The paper introduces uncertainty and risk communication. Dr Hajioff commented that most of the time people do not absolutely understand what risks are. There is a human tendency to want to create certainty for some sort of reassurance when certainty doesn't in fact exist. The Panel recognises the need, when assessing risk properly, to be honest about what is unknown and communicating risk clearly, which is very challenging. The panel spoke previously about the psychological impacts of environmental contamination. One of the impacts which became clear in the Australian qualitative study is that simply the act of instigating a population testing programme increased people's anxiety rather than decreasing it. This was because the nature of risk was not communicated appropriately. People make the connection in their minds that if testing is being provided, it must be important and it must be dangerous. This issue around communication needs to be considered in this work and ensure that risks are communicated in a way that doesn't increase anxiety and worry, and that does provide clarity and a proportional understanding of what that risk is.

Finally, Dr Hajioff introduced risk management as a series of approaches to minimise or optimise risk across a wide range of factors. That can vary from mitigation, transferring risk, avoidance, and other factors, and this will be conditional on how big the actual risk is and the nature of what that risk is. He illustrated by noting that if there is a big risk of a problem with your fingernails, that might be less important than a small risk of someone dying. All of these considerations need to be thought through in the approach to risk management.

Dr Hajioff invited comments on this document.

Prof Cousins considered it a good general overview. He questioned whether the panel introduce the specific examples we have in PFAS, noting that this is not in his professional background. The US EPA have set a maximum contaminant level goal of 0 for various PFAS. He explained that the definition of this is "the level at which no known or anticipated adverse effect on health or persons occur which allows for an adequate margin of safety. Anything above 0 can be a possibility of an effect." However, he questioned what this definition actually means in practical purposes, and noted that he has difficulty understanding it himself. He continued by noting that this level of 0 is based on the fact that they're carcinogenic and that last year it was extremely low levels in the picograms/litre level which were unachievable. This situation is difficult to communicate. He questioned if there is a real risk there if a human is always being exposed to much higher levels than 0 or picograms level; is there a risk of developing cancer or having an immune response? Prof Cousins questioned the panel about whether there is the need to discuss what being exposed to these higher levels and the achievability of 0 means.

Dr Hajioff noted that he deliberately steered away from that in this paper because that's what the panel should be discussing in Report 4, this section is just to introduce the concepts. He agrees that this is very challenging, when thinking about the unintended consequences of what the US EPA has done in terms of community anxiety. This is because the EPA have not taken the traditional, risk management approach of conducting a low as reasonably practicable risk assessment.

Prof Cousins noted that the EPA did conduct this type of risk assessment afterwards, as they set enforceable limits on a feasibility and economic study resulting in detailing what are the levels which are achievable and enforceable. These levels are much higher. They also set health based limits which are extremely low. For a member of the public, if you see that they are only doing it to the levels which are achievable rather than the health levels, then that will increase anxiety.

Dr Hajioff noted that he is also considering risk shifting. He explained that the more stringent the EPA sets a target in the US, the more manufacturers of certain PFAS requiring processes will move offshore, and people will be exposed in riskier environments like in East or South Asia. More people end up having their health affected because one place has made the rules stricter. Prof Cousins agreed and said that this situation has happened, not just with PFAS but with lots of other chemicals as well.

Dr Fletcher asked for clarification on the fact that the US EPA recommendation is considered technically feasible. Prof Cousins said he was not 100% sure. The enforceable levels are feasible to the point that it is possible to measure those levels and it is possible to treat down to those levels within a reasonable cost. Dr Fletcher asked if they had done a socioeconomic assessment and decided it was a reasonable cost? Prof Cousins answered by indicating that there has been lots of kick back saying these levels set by the US EPA are too high. In this case, the health assessment was done and then the feasibility assessment was done. This is the way it works in lots of jurisdictions.

Dr Hajioff noted that in Europe, the assessment is conducted together to come up with a balanced approach, but Prof Cousins was not sure and needs to look into it. There are so many different levels around the world which are considered to be safe which is very confusing for the public.

Dr Fletcher notes that the UK levels are set at levels using the ALARP principle (As Low As Reasonably Practicable), which takes into account the judgement of whether the cost is proportionate. This is difficult because it depends on who pays. If the polluter pays, then the public actually pay more to reimburse the polluter, so the clean up is still paid for by the public either through water bills or taxes. But that should be taken into account. He cannot confirm off hand whether who pays has been considered.

Prof Cousins read the definition as being "what is the MCL (maximum contaminant level) for the treatment technique which may be achieved with the use of best available technologies taking cost into consideration." Dr Fletcher noted that for the purposes of this report, he would suggest that the panel is very general about the principles of risk management and not get into a level of detail. Dr Hajioff agreed and said that we will need that level of detail in Report 4, but not this one. The panel agreed that this was reasonable.

Dr Fletcher had additional comments on the section on risk factors and risk markers. Dr Fletcher explained that he was expecting a risk marker to be something like a clinical sign that was a predictor of disease like antibody or cholesterol levels. However, Dr Hajioff has introduced risk markers as risk indicators which are more signs of disease, e.g. weight loss. He considers this scenario confusing and suggests deleting that idea, and stick to risk markers being intermediate steps which are predictors of disease in general, like antibody reduction or cholesterol.

Dr Hajioff noted that Dr Fletcher made a good point, and that he had used those examples because he was using previous knowledge on diagnostic risk markers in cancer, and because they are risk markers when the person comes to see a doctor. They are markers which contribute to the predictive risk of that person's health state being as a result of cancer, that is how they are used in diagnostics.

Dr Fletcher considers the terminology to be a clinical doctor definition, in that it sounds more like a symptom, for example, a high temperature is a risk factor for an infection, but an infection is not the only reason for a high temperature.

Dr Hajioff explained that this situation is how risk markers are used diagnostically, with the exception of smoking which is both a risk marker and a risk factor, or asbestos exposure.

Dr Fletcher answered, noting that you would look at DNA damage or epigenetic markers which are considered on the causal pathway of disease, whereas weight loss or high temperature is not on the causal pathway, it's a sign of being sick. He considers it misleading to call it a risk marker, even though in your context of individual diagnosis it is used. He notes that it is a completely different use of the terminology in the context of the rest of this document and requests that it is not used.

Dr Hajioff said he would find different examples to fit Dr Fletcher's definition rather than the clinical diagnostic definition, and thanked Dr Fletcher for his input, noting that it was very helpful.

Dr Fletcher said in terms of general background and context the summary document is good.

Dr Hajioff explained that the idea is that the documents discussed today would all form part of the introduction as a conceptual framework under which decisions and judgements on evidence are made in future reports. He noted that the panel are used to working in this manner

in their professional lives, however the general public are not used to this way of working and this not necessarily how most people might understand the literature.

Dr Hajioff thanked the panel for their comments and will edit accordingly.

Draft document on Critical appraisal and systematic review

Dr Hajioff introduced this paper explaining that critical appraisal and systematic review are the key tools used in evaluating scientific literature and understanding what that means in the real world. There are many steps in making that assessment. The sorts of questions to ask oneself are:

- Is the study the best sort of study to demonstrate what we are looking at?
- What sort of evidence does it present in terms of outcomes?
- How many people included in the study?
- Is it in a setting which can be generalised to another setting?
- Confounding, has it been thought about and controlled for?
- Reliability vs validity outcome measures
    - Has the study just used something easy to measure (reliability) or have they used something which is really useful (validity)? In the context of PFAS, cholesterol is easy to measure but does it matter in terms of increase heart attacks or strokes, as this would be the impact on someone's quality of life.
- Is it set in an environment that is comparable?
    - E.g. studies done in America under a different health care organisation may be different so studies affected by types of healthcare systems may not be applicable to Europe. Another example is that lung diseases in Spain are defined differently to the UK and so cannot be compared.
- Setting applicability
- Statistical significance – this is basically a measure that we're looking at two different groups, are they really different? Could it be a chance finding? How certain can we be that this increase in this particular problem in one group over another is actually real?
- Clinical importance when we're assessing medicines or risk (not currently mentioned in the document). The size of the impact to the person is very important, and some interventions can have minimal impact. For example, a medication which improves a health outcome by 1% is less clinically important than one which improves health by 20%.

Dr Hajioff concluded by explaining that these are the key points to highlight so that the process of doing the reviews that are elsewhere in the reports can be understood a bit better by readers who don't do that professionally. He opened the floor for comments and questions.

Prof Cousins noted that there is a journal which only publishes systematic reviews called the Journal of Environmental Evidence. He explained the process of getting a systematic review published in that journal, which is long and extremely thorough. This process involves publishing the protocol first, including the criteria used for assessing the various studies that we were looking into, the statistical methods, the search terms etc. The protocol is assessed by a big panel. Researchers all look at the same studies independently and input findings using an online tool and someone evaluated to see if everyone came to same consensus by using pre-

determined criteria. He explained that in his experience, for every study, data had to be input into a spreadsheet and it took 3-4 years to do this one assessment. It is well established, but there are strict protocols.

Dr Hajioff said that that process is gold standard, and there are other ways to do it. Every systematic review that he has been involved with has one evaluator and was less onerous. He agreed that the research question must be defined first, the approach and methodology is defined, and what "good" looks like. It is important to note what will be of value in a study and what you will not use. There will always be censorship of study and exclusion of studies which don't meet the criteria. This all needs to be set up *a priori*. This explanation may need to be strengthened in the document.

Prof Cousins described the gold standard systematic review process:

- The methodology must be made very clear beforehand and the team should stick to it, and work in a very methodical way
- The search terms for how the literature would be searched and which search engines would be used should be defined
- Capture all the papers, document all the papers then systematically go through determining whether the paper is relevant
- Once got the final group of papers, assign to different experts who would determine against previously determined criteria
- Cross checked by an independent expert

Dr Hajioff said there are different standards within this, and that a meta analysis as described by Prof Cousins is at the top. These are the principles and it is important to be overt where this has been differed from. This does not mean that the review is not valid, but that there are practical considerations, such as this project at Government of Jersey is time limited and does not have 3 years available to conduct a systematic review. He indicated that the National Institute of Health and Care Excellence (NICE) doesn't go into that level of detail and it is one of the biggest systematic review delivering organisations in Europe. Dr Hajioff noted that the feedback from the panel is really useful and will be used to clarify the text in this report.

Dr Fletcher pointed out that the Panel isn't carrying out a full systematic review of published literature, as the methods are more pragmatic, and it is important that the report is clear about the methodology the Panel have employed so that it is clear.

The Panel had a discussion about how to best describe the methodology of their work and Dr Hajioff confirmed that he would amend the report to be clear about what the Panel has done, and ensure that it does not erroneously suggest that the Panel have undertaken a systematic review of the whole literature.

Next steps

Dr Hajioff asked if there was anything outstanding to pick up. The panel indicated that there was not.

Any other questions

None.

Any other business

Dr Hajioff informed the panel, observers and members of the public that there may need to be an additional panel meeting in June. We are committed to being able to have a public consultation event on a full draft as soon as possible to not delay reports.

Dr Hajioff asked Julia to ensure the technical difficulties is addressed in the video recording to maintain confidentiality.

Date of next meeting

6 June 10am – 1pm by Teams as usual.

The Chair thanked the panel members and observers and particularly 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)

Actions from the meeting

Action	Action given by	Action taken by	Date for delivery
Correct chemistry section notes in April minutes	Dr Hajioff	Prof Cousins	By next meeting 6 June
Bring together health effect findings in a report	Dr Hajioff	Dr Fletcher	By next meeting 6 June
Provide tangible examples from PFAS literature to illustrate key concepts of environmental epidemiology paper	Dr Fletcher	Dr Fletcher	By next meeting 6 June
Make the distinction between ecological data and semi-ecological data	Dr Fletcher	Dr Hajioff	By next meeting 6 June
Share recent EFSA document on systematic	Dr Fletcher	Dr Fletcher	By next meeting 6 June

assessment of epidemiological data			
Edit re risk factors in Understanding risk paper	Dr Fletcher	Dr Hajioff	By next meeting 6 June
Re-write Critical appraisal and systematic reviews paper as discussed	Dr Hajioff	Dr Hajioff	To be circulated on email
Maintain confidentiality in video processing	Dr Hajioff	Julia	Before sending out recording to Islanders