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EDITORIAL REVIEW

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Evolving appreciation of risk associated with environmental per- and polyfluoroalkyl compounds (PFAS)

J A Millar PhD FRACP FRCP (Glasg.)

Editor, Tasman Medical Journal, PO Box 499, Denmark WA 6333 Australia

Abstract
Polyfluoroalkyl compounds have existed since 1939. As a group they are causing increasing concern over adverse effects on human health and biological systems generally, based on th lack of clearance if they escape into the environment. This article summarises the current attitudes, regulation and science of environmental PFAS. *Tasman Medical Journal 2023; 5(2): 6-9*

Regrettably, we now have a modern counterpart of the fictitious chemical that dissolves everything (that is, nothing can contain it). The new compound (actually, thousands of related compounds) does not degrade, and the question is how can they be prevented from accumulating in the environment and causing adverse consequences for human health and damage to biological systems generally? The molecules in question are carbon chain compounds in which all mid-chain carbon atoms are bonded to two fluorine atoms, with the carbon valence of 4 saturated throughout. The result of this structural element is extraordinary chemically stability and resistance to physical or biological degradation. The energy content of carbon single bonds[1] with fluorine and other common atoms present in organic molecules (Table 1) demonstrates why polyfluorinated alkyl substances (PFAS) are resistant to degradation and hence potentially hazardous or toxic. In addition, fluorine atoms are large compared to oxygen and hydrogen and impose steric hindrance on potential substitution.

Chemical bond	Bond energy (KJ/mol*)
C – C	347
C – O	358
C – H	413
C – F	**485**

Table 1. Energies of bonds with carbon in organic compounds. The bond energy is the energy required to break the bond. Note: 1 KJ is the energy required to boil about 3ml water from room temperature.

Note especially the difference in the energies of carbon/fluorine and carbon/oxygen bonds. These data demonstrate why polyfluoalkys in the environment cannot degrade by oxidisation except under special conditions, why they are effective flame retardants for use in bushfires and fires at military bases, and why as polytetrafluoroethylene (Teflon®) they can render cooking equipment "non-stick". The number of PFAS that could be synthesised is almost without limit, and there are currently over 9000 types including seven commonly available discrete compounds

("legacy" PFAS[2]), as shown in table 2, grouped as either "short chain" (4-6 carbon atoms) or "long chain" (6-9 carbons). Teflon is a polymer.

Category	Common abbreviation	Name	Formula
Short	PFBA	Perfluorobutanoic acid	$C_4HF_7O_2$
	PFBS	Perfluorobutane sulfonic acid	$C_4HF_9O_3S$
	GenX	2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate	$C_6HF_{11}O_3$
Long	PFNA	Perfluorononanoic acid	$C_9HF_{17}O_2$
	PFOA	Perfluorooctanoic acid	$C_8HF_{15}O_2$
	PFOS	Perfluorooctane sulfonic acid	$C_8F_{17}SO_3H$
	PFHxS	Perfluorohexane sulfonic acid	$C_6HF_{13}O_3S$
	PTFE (Teflon)	Polytetrafluoroethylene	$(-C_2F_4-)_n$

Table 2. Chemical details of current common PFAS compounds. GenX has a branched-chain structure via an ether linkage, with the branches having 3- and 2-carbon chains respectively.

An obvious question is whether these compounds are toxic, given their chemical stability, as in general they are rapidly absorbed and widely distributed after administration, and not metabolised *in vivo,* in keeping with their chemical stability. However, the *physical* properties of PFAS may affect metabolic processes indirectly. For example, would their presence in the lining of the biliary tract or renal tubules be harmless? One suspects not. The toxicology data are difficult to interpret because (a) effects differ in humans and animal models; (b) the spectrum of pathological effects varies amongst PFAS in Table 2; (c) concentration-effect (dose-response) curves cannot be compiled easily; (d) prospective controlled studies are not possible; and (e) typical human exposure is often to more than one PFAS but the potential for combined toxicology is not known. Most toxicology data is for PFOA and PFOS.

Organ System	Detail
Hepatic and metabolic	Increased transaminases and decreased blirubin Increased total and LDL cholesterol
Reproduction and development	Decreased fertility Pregnancy-induced hypertension and re-eclampsia Lower birthweight
Immune	Reduced responses to vaccines
Endocrine	Thyroid disease
Oncology	Testicular and renal cancers
Skeletal[5]	Abnormal mineralisation: osteoporosis

Table 3. Reported associations between environmental PFAS exposure and health effects by organ system.

The associations shown in Table 3 do not amount to proven cause and effect, and some remain qualitative or even vague. For this reason, chemical or drug authorities and health equivalents tend to to play down possible PFAS environmental toxicology. For example, in Australian Government PFAS Taskforce website rather inconsistently states: "*The Australian Government's Expert Health Panel for PFAS found that although the scientific evidence in humans is limited, reviews and scientific research to date have provided fairly consistent reports of an association with several health effects. The health effects reported in these associations are generally small and within normal ranges for the whole population. There is also limited to no evidence of human disease or other clinically significant harm resulting from PFAS exposure at this time."*[3] The Victorian Environmental Protection Agency states:[4] *"Most of us are exposed to low levels of PFAS. This is mostly from eating food or drinking water with PFAS in it. This is unlikely to be harmful to our health. Recent studies show people's exposure to PFAS in the general environment is reducing"*. These quotations agree that PFAS are common environmental contaminants and that proof of substantial health effects is lacking, but may be over-reassuring.

Nevertheless, scientific studies in animals have shown clear links between PFAS exposure and health effects. The most reliable epidemiological evidence comes from the USA. The literature is vast and it is helpful to refer to authoritative summary papers.[5,6] Human toxicology cannot be inferred directly from animal data and has to include objective criteria for assigning confidence that any association indicates cause and effect. Using these criteria, the

US National Center for Biotechnology Information has published[7] "sufficient" evidence of an association between PFAS exposure and decreased antibody response (in adults and children), dyslipidemia (in adults and children), decreased infant and fetal growth, and increased risk of kidney cancer (in adults). In contrast, the often quoted relationship in laboratory animals between PFAS and increased liver enzymes was assigned the lower category of *"limited or suggestive"* evidence. We note that even the strongest category above the report does not include a claim that the link with PFAS is causal. Thus, unlikely as it seems, even the strongest associations in this field may turn out to be non-causal, and this may justify the temperate language used in the Australian websites.

On the other hand the ubiquity of environmental PFAS is undeniable. Friends of the Earth Australia provide 2,424 geographical site entries or other references in the pages accompanying the Australian PFAS Map,[8] with comment that PFAS are "ubiquitous" across Australia and accompanying emotive text (*"PFAS chemicals have been linked to a number of diseases, yet the Australian Government stubbornly refuses to end the use of PFAS chemicals in Australia, even after they have been banned overseas").* FOEA also call PFAS *"the new asbestos",* though at present, in spite of evidence of increased mortality according to tertiles of PFAS exposure,[9] this appears to be an exaggeration. We note that only a few countries or US states have banned PFAS.

The efects of PFAS are not limited to health. In Australia, compensatory payments have been made by the government in settlement of individiual and class action claims by citizens living close to high use areas such as defence bases.[10] The settlement was for reductions in property values in these areas, not for health effects. In the US, the 3M Company has agreed to provide funding of US$10.3bn over 13 years to *"provide funding for public water suppliers nationwide that have detected PFAS in drinking water, as well as for eligible PWS that may detect PFAS at any level in the future"*[11] Again, this enormous expenditure is not for clinical purposes. But the amount provided in relation to the likely threat of disease is eye-watering, and the reason for the lack of concordance between the cash being paid and the human consequences is uncertain.

How might the threats of PFAS be moderated? Banning PFAS is unlikely to be effective because of their economic importance. Finding ways of destroying the offending chemical species is one option. Though the bond energies suggest that such an approach with PFAS is impossible, "ball milling" using boron nitride has been shown to be successful in destroying PFAS in sediments (but not in water).[12] Nevertheless, PFAS destruction appears not to be an impossibility. So hope of a solution remains.

In summary, PFAS is a chemical class with valuable properties across any industrialised economy. At the same time, once they escape into the environment they are impossible to eradicate and toxicological effects if any are likely to become progressively more marked. Currently these effects appear modest, but current health effects on biological systems generally and humans in particular are likely to increase and may become significant. Clearly an efficient and effective system of regulation is required, but authorities in Australia have adopted a "whole of government" approach working alongside a "PFAS Task Force" whose members are not identified. Its Annual Reports are published anonymously. A formal recommendation to create the office of PFAS Co-ordinator was declined in 2017. Thus the chain of leadership in this area is uncertain. This may serve in the meantime, while the health effects are unverified, but in the long run it is likely to be inadequate.

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