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**STATE OF MINNESOTA DISTRICT COURT FOR THE COUNTY OF HENNEPIN FOURTH JUDICIAL DISTRICT**

**CIVIL ACTION NO. 27-CV-10-28862**

**STATE OF MINNESOTA, *et al.* v. 3M COMPANY**

# EXPERT REPORT OF PHILIPPE GRANDJEAN, MD, DMSc

**PREPARED ON BEHALF OF PLAINTIFF STATE OF MINNESOTA**

**22 September, 2017**

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# I. INTRODUCTION

My name is Philippe Grandjean. I have been asked by counsel for the State of Minnesota to provide, from an epidemiological perspective, an evaluation of the human health risks associated with environmental PFC[a] contamination from 3M's manufacturing and disposal operations in Minnesota.

## A. Qualifications

I earned my M.D. and D.M.Sc. degrees from the University of Copenhagen, Denmark, in 1974 and 1978, respectively.

I serve as Adjunct Professor of Environmental Health at the Harvard School of Public Health (since 2003) and as Professor and Chair of Environmental Medicine at the University of Southern Denmark (since 1982). I previously served for a brief period (1980-1982) as the Director of the Department of Occupational Medicine at the Danish National Institute of Occupational Health. Former positions in the U.S. include Research Fellow and Senior Fulbright Scholar, Mount Sinai School of Medicine in New York (1978-1979), and Adjunct Professor of Neurology and Environmental Health, Boston University Schools of Medicine and Public Health (1994-2002). As part of my employment as a civil servant in Denmark, I have served for more than 30 years as the Consultant in Toxicology to the Danish Health Authority. In the latter capacity, I have reviewed and commented on case reports, research studies, and proposed regulations on environmental chemicals. I also serve on the Scientific Committee of the European Environment Agency (EEA) and on the European Advisory Committee on Health Research of the World Health Organization (WHO).

My research in environmental epidemiology focuses on the health effects of exposures to environmental chemicals, including perfluorinated alkylate substances (PFCs or PFASs).[a] Most of my efforts have concentrated on the effects of environmental pollutants on early human development. This research has been financed by public sources, mainly the National Institutes of Health and other U.S. agencies, the European Commission, and the Danish Research Agency. I have published about 500 scientific papers, of which most are research articles in international scientific journals with peer review. My h-index in the Web of Science data base is greater than 60. Seven of my articles published in the last 10 years have earned the attribute "Highly Cited Paper," i.e., they received enough citations to place them in the top 1% of published papers in the field. This list includes an article on PFAS immunotoxicity published in the Journal of the American Medical Association (JAMA) in 2012. I have also authored or edited 20 books, including textbooks on environmental health and risk assessment.

[a] Terminology concerning perfluorinated compounds has evolved. The term PFC had been used to refer generally to perfluorinated compounds. Recently, the scientific community has with more precision started to settle on the term PFAS to refer to the narrower family of perfluorinated alkylate substances, which family includes PFOA, PFOS, PFBA and most of the other chemicals relevant in this matter. For ease of reference, and for consistency with some of the historical documentation in this case, I will, for the most part, use the term PFCs to refer to the family of PFASs, and will use more specific terms when the situation warrants. A table of the abbreviations I use in this report is attached as Exhibit A.



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I am regularly invited as speaker at international conferences and other scientific events. Regarding PFCs, I was invited to give a special presentation at the meeting of the (U.S.) National Advisory Environmental Health Sciences Council (at the National Institute of Environmental Health Sciences) in 2012, and also that year at a meeting of the Emerging Chemicals Workgroup, U.S. Environmental Protection Agency (EPA). Both presentations were on the immunotoxicity of PFCs. In the fall of 2016, I was invited to give a special presentation on PFOA at the committee meeting of the United Nations Stockholm Convention.

I am (Founding) Editor-in-Chief of the open-access scientific journal, Environmental Health (since 2002), which ranks among the upper 25% of journals in the field. I also serve or have served on editorial boards of about a dozen journals within medicine, environmental science, and toxicology. As editor and as reviewer for other major journals, I frequently evaluate manuscripts on environmental epidemiology and toxicology.

I have served on, sometimes chaired, or acted as rapporteur for, expert committees under the auspices of the WHO, the International Agency for Research on Cancer (IARC), EPA, the European Commission, the European Food Safety Authority (EFSA), and other organizations. During my six-year membership of an EFSA expert panel, I participated in developing the opinion on 'Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts' [1] and the 'Guidance of the Scientific Committee on Use of the benchmark dose approach in risk assessment' [2]. EFSA is currently developing updated opinions on PFCs, and I have been recently approached by EFSA and invited to serve as ad hoc expert to help finalize these assessments.

I have previously served as an expert witness in the U.S. regarding mercury pollution. In that regard, I wrote an expert report and testified in deposition and at trial in the case Maine People's Alliance v. Holtrachem Manufacturing Co. in 2002 and again in 2014. I also wrote an expert report and testified in deposition at the request of the U.S. Department of Justice, regarding pollution from coal-fired power plants, in 2008 (United States et al., v. Cinergy Corp et al., District Court for the Southern District of Indiana, Indianapolis Division) and later contributed to an amicus statement to the appeals court. I also served as expert witness at the request by a Danish lower court (1999) and subsequently by the superior court (2007 and 2011) regarding adverse health effects of indoor use of a wood treatment product containing a pesticide.

A copy of my most recent CV is attached as Exhibit B. A list of publications which I authored or co-authored, including those of the past 10 years, is attached as Exhibit C.

**B. Materials relied upon**

For the purposes of this report, I have relied in part on my own epidemiological research and publications concerning PFCs. I also have reviewed the epidemiological literature concerning studies by others on the human health risks associated with exposure to PFCs. In this report, citations to studies are in brackets in the text, [x], with these endnote references listed in Exhibit D. Among other sources of information, such as the reports from the C8 panel [3], I have relied upon the most recent version of ATSDR's draft ToxProfile [4], the evaluation of



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immunotoxicity by the NTP [5], the assessment of carcinogenicity by IARC [6], and recent reviews [7-10].

In addition to epidemiological studies, I have considered certain supporting toxicological information from laboratory animal studies and *in vitro* models, but I do not necessarily provide a complete review of all such supporting evidence, as my focus is human health. While summarizing available documentation, I also outline the emergence over time of the knowledge on human PFC exposures and associated risks.

I have had access to reports of certain studies which were commissioned or sponsored by 3M, to documents filed by 3M with the EPA, and to documents provided in connection with the discovery phase of the court proceedings. I comment as to certain of the 3M documents, particularly those which reflect epidemiological or toxicological studies, from a scientific perspective. As part of my report, based on 3M documents available to me, I characterize how 3M's knowledge on human health effects of PFCs has evolved, so that I can assess the extent to which these risks may have been underestimated or disregarded in the past. I reference documents produced by 3M in discovery, as I had access to the discovery record, but they are exceedingly numerous and I have not personally reviewed all of them.

While preferentially citing studies published in peer-reviewed journals, and relying on my own research experience, I cite the additional sources that I consider most relevant. Published literature is referred to by numbers in square brackets, and the unpublished materials are referred to by superscript letters listed in the footnotes.

### C. Exhibits

I may use as exhibits part or all of any of the documents or papers cited in this report including this report itself; graphs or tables drawn from data in any of those documents or papers; any document helpful as foundation for or illustration of my testimony; any document considered or cited or relied upon by any other expert in this case; any document used as an exhibit or produced in discovery by any party or non-party or expert; or any document needed to respond to or rebut testimony by any witness including any other expert.

### D. Updates and reservation

The opinions expressed in this report are my own and are based on the data, documents, and facts available to me at the time of writing. Should additional relevant or pertinent information become available, I reserve the right to supplement the discussion and findings in my report. I also reserve the right to respond to any opinions on similar topics by other experts in this matter, and to respond to any criticism or comment on my opinions.

### E. Compensation

I am being compensated at the rate of $250 per hour for my time, which is my customary rate for matters of this type. My compensation does not depend in any way on the content of my opinions.



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### F. Previous service as expert at deposition or trial during last 4 years

Maine People's Alliance and Natural Resources Defense Council, Inc. v. Holtrachem Manufacturing Company, LLC and Mallinckrodt US LLC, Case No. 1:00-cv-00069-JAW, United States District Court for the District of Maine.

## II. SUMMARY OF OPINIONS

The major opinions expressed in this report, which are described below in more detail along with more minor and supportive opinions, can be generally summarized as follows:

- PFCs pose a substantial present and potential hazard to human health. In particular, it is my opinion, based on the weight of the epidemiological evidence and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to at least human immune system functions, reproductive functions including adverse effects to the next generation, endocrine functions, thyroid functions, liver functions, and cardiovascular functions, and by causing or increasing the risk of cancer. Both PFOA and PFOS show convincing associations with these outcomes.

- This opinion mainly relies on available evidence on PFOS and PFOA, with somewhat less documentation on PFHxS. To date, PFBA has been less studied than certain PFCs such as PFOA and PFOS, in part because of PFBA's short apparent elimination half-life (T½) in blood serum. However, a recent study shows that PFBA is retained significantly in human kidneys and lungs, rather than blood, and serum concentrations are therefore not reliable indicators of retention in body organs. Moreover, even early 3M-sponsored studies showed adverse effects from PFBA in laboratory animals in the liver, thyroid system, cholesterol levels, and negative developmental effects on the next generation. Given the similar structure of PFBA to other more-studied PFCs particularly at the end group of the chain, given the adverse human health effects that have been shown as to PFOA and PFOS, and given the adverse effects already shown as to PFBA, it is my opinion that PFBA too poses a substantial present and potential hazard to human health.

- Adverse health effects have been documented in epidemiological studies at background exposure levels. Recent and currently deveoping scientific insight is likely to justify more protective drinking water limits in the future. Thus, PFC contamination of drinking water within current limits may not be considered safe in the future.

- Adverse effects of PFCs were identified in animal studies commissioned by 3M as far back as the 1970s, but the company did not pursue these findings to characterize the nature of the hazards. Early studies of worker health inappropriately sought to explain away any possible associations with ill health. Minutes were edited to remove language that suggested the presence of a health hazard. Further, documentation of the transfer of PFCs via maternal milk was not revealed to the public. By 2000, when 3M announced the phase-out of PFC production, it announced that "the presence of these materials at these very low levels does not pose a human health or environmental risk," but this statement



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was at odds with the information already known to 3M. As late as 2016, a 3M Medical Director made a similar misleading statement.[b] Independent research more recently, and at a substantial delay, began to examine adverse effects of PFCs, and risks to human health have been identified at very low exposure levels.

## III. BACKGROUND ON PFC PRODUCTION AND CONTAMINATION

### A. An abbreviated history of PFC production

By way of brief background, my understanding of the history of PFC production is basically as follows.

Perfluorinated compounds (PFCs) have a wide range of applications, and they have been in use for over 60 years. PFCs were first manufactured by 3M in Cottage Grove, Washington County in Minnesota, in 1947 or shortly thereafter.

Perfluorooctane sulfonyl fluoride (POSF) was a main product for producing other PFC compounds, especially PFOA, but PFOS, PFBA and other PFCs were also produced, along with a variety of branched isomers, mostly with 4 to 9 carbons. Some of the PFC products (such as FOSA) degrade to PFOS.

Global environmental dissemination became publicly known by about 2000 (but as is mentioned below was known by 3M many years earlier). A phase-out of commercial PFOS and PFOA production from the end of 2002 was announced by 3M in 2000.

The academic research community (outside 3M) became aware of the environmental dissemination of PFCs following reports on world-wide dissemination and the legal proceedings regarding the contamination of the Upper Ohio River Valley. These experiences inspired an increased scientific interest in PFCs, especially during the most recent 10 years, as revealed by a growing number of scholarly papers published on PFC contamination, exposures and adverse effects in experimental models and epidemiological studies.

### B. Widespread, persistent environmental contamination

Also by way of background, I outline my basic understanding of PFC environmental contamination.

Major physicochemical properties of PFCs were characterized in publications as early as 1951 [11]. Standard chemical handbooks listed PFC vapor pressures and water solubilities at least by the 1970s (although they may not have been accurate). Many PFCs (or their salts or precursors) are somewhat water soluble and can potentially leach through soil to reach the groundwater, while some compounds have a sufficient vapor pressure to allow their dissemination via the atmosphere. These properties must have been known at 3M in the 1970s or earlier than that.

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[b] 3M_MN04422606. 3M plays down impact of toxic chemicals affecting Williamtown water. ABC, 15 March, 2016.



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PFCs do not occur naturally. Many PFCs show high thermal, chemical and apparent biological inertness, properties that made them useful for certain industrial purposes, though at the same time also rendering these compounds an environmental hazard due to the potential for persistence and bioaccumulation [12]. The carbon-fluorine bond is strong, thus making the PFCs virtually indestructible in the environment and in the human body. However, as a 3M-supported report claimed in late 1997, organofluorine compounds are "generally viewed as recalcitrant because of their lack of chemical reactivity" [13].

Although most PFCs are oleophobic and therefore do not accumulate in fatty tissues (in contrast to dioxin and other persistent halogenated compounds), especially PFOS is now known to bioaccumulate in aquatic and marine food chains. In collaboration with researchers at Michigan State University, 3M's Robert Howell in 1997 reported on the persistence of organofluorine compounds in the environment [13]. Accordingly, and belatedly, a 3M memo from 1998 concludes that "we must begin to capture and incinerate the waste water process streams containing residuals as soon as possible."[c]

Internal 3M reports from 1998 (apparently not published) also confirmed the occurrence of PFOS in bald eagles from Minnesota and Michigan,[d] and in marine food chains involving seals, sea lions, killer whales and porpoises.[e] As a major, and sometimes sole producer of PFCs, 3M and its products would clearly be suspected as a source of this contamination, whether close to or far from the production facilities.

Long-range aqueous transport — e.g., via the Mississippi River, groundwater and ocean currents — allows PFCs in their soluble anionic forms to reach remote locations. In addition, several precursor compounds can be metabolized to PFOA and PFOS in the environment or in humans. The global dissemination of PFCs also occurs through atmospheric transport of volatile precursors, which are metabolized into the more persistent PFCs that are then deposited. Pollution of terrestrial and aquatic food chains resulted in high concentrations of PFOS in vulnerable species even in remote ecosystems, including, for example, polar bears [14, 15].

In late 1998, 3M environmental scientist Richard Purdy wrote to his 3M colleague, Georjean Adams, and suggested that his food chain risk assessment demonstrated a significant risk that should not be kept confidential.[f] In another email, Purdy referred to a plan to examine environmental dissemination and then concluded: "For 20 years the division has been stalling the collection of data needed for evaluating the environmental impact of fluorochemicals. PFOS is the most onerous pollutant since PCB and you want to avoid collecting data that indicates that it is probably worse."[g]

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[c] 3MA00905854. Accumulation and Disposal of Waste Water at Decatur. page 3MA00905854.
[d] 3MA01402884. Occurrence of PFOS in wildlife (Part 1/ Eagles and Albatrosses), page 3ma01402885.
[e] 3MA00468422. Pioneer Food Chain Risk Assessment of PFOS, page 3MA00468422.
[f] 3M_MN00053763. Risk to the Environment Due to the Presence of POFS. page 3M_MN00053763. I have not determined if and when such reporting took place.
[g] 3MA01373218.pdf. Page 03 166322.



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On the basis of these studies and other evidence, the concerns about ignored environmental risks made Dr. Purdy seek to resign in 1999 due to his "profound disappointment in 3M's handling of the environmental risks associated with the manufacture and use of PFOS and its precursors, such as EtFOSE and MeFOSE)."[h] In his apparent letter of resignation, Dr. Purdy said: "3M told those of us working on the fluorochemical project not to write down our thoughts or have email discussions on issues because of how our speculations could be viewed in a legal discovery process. This has stymied intellectual development on the issue, and stifled discussion on the serious ethical implications of decisions."[i] Dr. Purdy had worked on PFCs at least from 1993, but apparently, none of his work was published, given that I could locate no relevant scholarly publications under his name. He did give a presentation at the SETAC 2001 conference, where he discussed environmental risks from PFCs, and notes prepared on behalf of 3M challenged his presentation and suggested ways in which 3M should counter Dr. Purdy's conclusions in regard to environmental toxicity of PFOS and PFOA.[j]

Dr. Purdy called PFOS the most "insidious pollutant since PCB" (i.e., polychlorinated biphenyls, industrial chemicals that were banned in the US in 1979 and included among the "dirty dozen" in 2001 when the Stockholm Convention was launched by the United Nations). Dr. Purdy also noted about PFOS that "it is probably more damaging than PCB because it does not degrade." He described his experience at 3M: "At almost every step, I have been assured that action will be taken – yet I see slow or no results. I am told the company is concerned, but their actions speak to different concerns than mine. I can no longer participate in the process that 3M has established for the management of PFOS and precursors. For me it is unethical to be concerned with markets, legal defensibility and image over environmental safety." A summary of 3M's food-chain findings was submitted to the EPA in 2003.[k]

### C. Environmental contamination in Minnesota

I understand that, not surprisingly, PFC contamination has occurred in the environment remotely from the production site and at particularly elevated concentrations in areas proximate to 3M's facilities and disposal sites. The PFC releases have affected not only 3M workers but also many residents, especially in the East Metro area and nearby communities. I defer to other experts for the State of Minnesota on the extent and levels of the contamination, but my working understanding is summarized in part as follows:

- For an unknown period – beginning decades ago – residents in the East Metro area and nearby communities have consumed drinking water and, quite likely, freshwater fish and farm products contaminated with PFCs. The total number of residents exposed to this pollution over time likely numbers tens of thousands.

- A systematic study from 2008 showed that serum PFOA concentrations in residents averaged about 10-fold above national averages, and individual results ranged up to 100-fold above the national average. As this study was designed to be representative of the exposed local population, a sizable number of current and past Minnesota residents in the

[h] 1999.03.28 – 3MA10065677.pdf
[i] 3MA10065677. Resignation letter from Richard Purdy to 3M. page 3MA10065678.
[j] 3MA02600383.pdf. SETAC – PFOS Report. November 15, 2001.
[k] AR226-1486. Environmental and health assessment of perfluorooctane sulfonic acid and its salts.



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East Metro area have been exposed to very substantial amounts of PFOA and related PFCs.

- Serum concentrations are known to decrease only slowly. Background serum concentrations are now decreasing, and a 2010 re-examination of residents of affected communities confirmed this trend [16]. However, the cumulated PFC burdens in past and present residents will remain above national levels for many years to come and will depend on the extent to which continued exposures are minimized.

## D. Drinking water contamination

### 1. PFC disposal practices

It is my understanding that in Minnesota, waste from the 3M production processes was disposed both at on- and off-site locations. Sources of contamination include 3M's Cottage Grove manufacturing facility. Disposal facilities used by 3M from about 1956 onward included the Oakdale Disposal Site, the Woodbury Disposal Site, and the Washington County Landfill. It is likely that some of this waste contained PFOS, PFOA and PFBA as well as precursor substances.[l]

In 1966, DuPont, which purchased PFCs from 3M to make Teflon, among other things, decided that wet Teflon scrap should no longer go to a municipal land-fill in the Upper Ohio River Valley but instead should be kept on the plant for "disposal at sea at a future date."[m] This decision appears to reflect an early recognition of the risk of environmental discharge.

### 2. PFCs discovered in drinking water sources

It is my understanding that, after the disposition of PFC waste became known at the Minnesota Pollution Control Agency (MPCA), a method for chemical analysis of water for PFOA and PFOS was established. Soon after that, PFCs were identified in samples from nearby groundwater monitoring wells and in soil samples.

Subsequently, PFC contamination was found in the groundwater further away in both Washington and Dakota Counties. In Oakdale, the average PFOA concentration in the municipal water was 0.57 µg/L (or 570 ng/L), i.e. before the special water treatment was built in 2006. Much higher levels were found close to the production facility, with maximum measured water concentrations in groundwater wells at Cottage Grove of 619 µg/L (PFOA), 318 µg/L (PFBA), 26 µg/L (PFOS), and 40 µg/L (PFHxS) [17]. One µg (microgram) is one millionth of a gram, and this unit is one thousand times greater than 1 ng (nanogram), which is one billionth of a gram. As a general tendency, lower concentrations were found at greater distances from the sources.

For comparison, the current EPA limits for PFOS and PFOA in water are 0.07 µg/L, and the 2009 MDH Health Risk Limits (HRLs) for PFOA and PFOS in water were both 0.3 µg/L. In 2011, MDH developed limits for perfluorobutane sulfonate (PFBS) and

[l] 3M_MN03521906. FC-PFOA-PFOS East Metro.
[m] AR226.1445, memo from J.E. Higginbothaim, 10/28/66, p. 00079



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perfluorobutyrate (PFBA) at 7 µg/L. In May of 2017, MDH released its updated limits of 0.027 µg/L and 0.035 µg/L for PFOS and PFOA, respectively. While still relying on the EPA risk evaluation, the lowered limits were considered to better protect the fetus and the breastfed infant.

Most efforts to date to characterize the extent of the pollution in Minnesota have focused on drinking water exceeding the MDH HRLs for PFOA and PFOS, as complemented by biomonitoring studies of PFC concentrations in serum of residents consuming this water. However, as I discuss and evaluate below in the section on exposure limits, the available information on water contamination needs to be considered in light of what can be reasonably assumed, given the current insight into the health impact from exposures to PFC contamination even at background levels.

Although some older water analyses of questionable quality have been identified [18], it is not known precisely when the groundwater contamination began, but I understand that the plume of contaminated ground water likely reached private wells and community water supplies decades ago.

The State has determined that, by now, over 100 square miles of groundwater have been contaminated by 3M's disposal of PFCs, and the source of residential drinking water for tens of thousands of Minnesotans has thus been affected by the PFC waste disposal. The area of contamination includes four major aquifers; namely, the St. Peter, Prairie du Chien, Jordan, and Franconia aquifers. These four aquifers serve as the sole source of drinking water for approximately 125,000 or more Minnesotans who reside in the Twin Cities area.

Four of eight Oakdale municipal wells were discovered to be contaminated with PFOA and PFOS above MDH 2017 Health Based Values for drinking water, thus affecting up to 6,655 households supplied with the municipal water. Also, several hundred private wells in nearby communities were found to be contaminated. In 2008, the estimated population in Oakdale was 27,249 in 10,803 households in 2006, and Lake Elmo had 7,695 inhabitants in 2,738 households [18]. Thus, a very substantial population has apparently been exposed to the PFC contamination.

As PFCs are not removed from drinking water by standard treatment processes, a large granular activated carbon system was installed on the two most contaminated wells in Oakdale, and these wells were then used preferentially. This system is known to remove long-chained PFCs, while other PFCs may be more difficult to remove [19]. After lowering the limits for PFOA and PFOS, MDH announced that approximately 120 private wells, primarily in Lake Elmo and Cottage Grove, were known to be contaminated with PFOA or PFOS above the 2017 MDH limits.[n] As the water contamination likely began many years ago, the exposed population also includes former residents. Current residents have also been exposed at levels MDH does not consider protective, because they did not have an alternative water supply provided until limits were lowered again in 2017. In short, the population exposed to hazardous water contamination is therefore larger than previously assessed.

[n] http://www health.state.mn.us/news/pressrel/2017/water052317.html



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PFBA contamination also was and is present in Minnesota drinking water sources. Indeed, it may be more widespread due to the greater mobility of this compound, and because this PFC seems to pass carbon filters more easily. PFBA water contamination has been discovered in Cottage Grove, St. Paul Park, Newport, Woodbury, Hastings and South St. Paul in 2006-2007 [18].

In a parallel setting in the Upper Ohio River Valley (West Virginia and Ohio), drinking water wells as far as 20 miles away were contaminated by releases from a Dupont industrial facility using PFCs from 3M. PFOA was detected in public water supply wells in this vicinity at levels up to 44 µg/L and in private wells up to over 13 µg/L [17]. Further in this report, the extensive health data recently collected by the C8 Panel from the Upper Ohio River Valley community [3]will feature prominently.

## E. Other contaminated sources affecting humans

### 1. Fish

I understand that effluents from the 3M Cottage Grove facility and from the off-site waste deposit sites led to discharges into the Mississippi River and some Minnesota lakes [18]. State and EPA scientists have documented PFC pollution of Lake Elmo and approximately 139 miles of the Mississippi River from St. Anthony Falls in Minneapolis (Hennepin County) downstream to the La Moille Dam (Lock and Dam No. 6), south of Winona. I have not searched the 3M documents to determine when 3M became aware of the PFC contamination of fish.

PFC-contamination of waterways results in biomagnification in aqueous food chains, with PFOS apparently causing greater accumulation than PFOA or PFHxS PFHxS [20-22]. Increased PFC concentrations have been found in fish in the greater metropolitan area and in Mississippi River Pool 2. For example, in bluegill filets from fish samples taken in Minnesota from Lake Calhoun, and from four downstream locations on the Mississippi River, median PFOS concentrations ranged between 50 and 275 ng/g [22].

In another study of fish from Mississippi Pool 2, concentrations in bluegill, freshwater drum, smallmouth bass, and white bass fillet tissue ranged from 3.2 to 757 ng/g, with an overall mean PFOS concentration for all fish fillet of 46 ng/g wet weight [23].

Consumption of a meal sized portion (200 g, or 6.5 ounces) of this fish would then lead to average exposures of 150 ng/kg body weight (BW) for an adult weighing about 60 kg. Even though such dinners might not happen daily or weekly, the magnitude of the exposure is noteworthy, particularly in light of evidence that many fish are heavily contaminated. For example, in a 2012 study of PFCs in Mississippi River Pool 2, the highest concentration of PFOS in a fish was measured at 6,160 ng/g in a carp in section 4 of Pool 2, near the 3M Cottage Grove facility.[o]

Water at the previous MDH limit of 0.3 µg/L would contribute about 10 ng/kg BW per day (assuming about 2 L of water consumption for a 60-kg adult). Thus, fish from contaminated waters can be an important additional source of intake. Based on similar

[o] https://www.pca.state mn.us/sites/default/files/c-pfc1-21.pdf



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calculations, the MDH has issued fish consumption advice for bluegill, carp, largemouth bass, northern smallmouth bass, walleye, and white bass from Mississippi pool 2 and for some species also for the Minneapolis chain of lakes [18, 24].

### 2. Breast milk

Recent data support that U.S. children have higher serum concentrations than adults [25, 26]. As a potential contributor, evidence has accumulated that PFCs are excreted in human milk [27]. Analyses of paired samples of maternal serum, cord serum, and maternal milk have demonstrated that PFCs are transferred through the human placenta and via human milk [28, 29]. During prolonged breast-feeding, the cumulated postnatal exposure to PFCs through lactation can be much higher compared to prenatal exposure, especially for PFOA [29], thereby causing additional exposures during sensitive early development. From serial blood samples in young children, a recent study showed that extended breastfeeding could increase an infant's blood concentrations of PFCs to several-fold above the mother's [30].

These observations are in accord with a 3M-sponsored study on EtFOSE and FC-95 (PFOS) carried out in goats, as indicated by an email to Dr. Larry Zobel in early 1998.[p] The first studies on transfer into milk were apparently carried out in 1993, as a document from that time states: "There is some preliminary evidence that in lactating goats PFOS is transferred to milk. It is likely that lactating human females would also transfer PFOS to milk."[q] Again, it appears that 3M decided not to publish the results of this study, and it further appears that 3M did not follow up with analyses of human milk to establish the potential implications of this discovery.

In a two-generation study involving rats published by 3M's Dr. Butenhoff and coauthors in 2004, pup weights in the highest dose group were consistently decreased throughout the lactation period [31]. This study also found a slight but statistically significant decrease in lactation index (percent viability from day 5-22 post-partum) for $F_1$ pups. It is not clear whether these observations were due directly to toxicity from PFCs in the milk, or indirectly via deficient lactation, and such concerns were apparently not of interest to the authors. The transfer of PFCs through maternal milk in animal models was finally recognized by 3M colleagues in a 2005 publication [32].

Accordingly, the recent publications on PFC transfer via human milk [27, 30] do not represent a discovery, but rather a re-discovery of a mechanism identified by 3M much earlier, in 1993, in studies that 3M did not disclose publicly. The relevance of the 3M results on PFC transfer via lactation in goats must be considered in a wider perspective. Due to growing concerns about lactational transfer of dioxins, PCBs, and some pesticides, toxicological studies began to pay attention to this pathway, and in 1976 the World Health Organization began a global monitoring program to measure persistent pollutants in human milk [33]. Since a thorough review handbook on human milk contamination and health risks was published in 1991, the

[p] 3MA00906295. Fluorochemical Projects Underway in the Environmental Laboratory. Page 3MA00906295.
[q] 3MA10037365, PFOS Disposition, custodian Reagen, William K. Page 3MA10037367.



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concern has been regularly raised [34]. Perhaps this evidence inspired studies at 3M on transfer of the non-lipophilic PFCs via milk.

Additional to PFCs in maternal milk, infants fed formula prepared with contaminated drinking water also could be substantially exposed to PFCs. Observed ratios between PFOA concentrations in drinking water and human serum and between concentrations in human serum and milk suggest that milk concentrations may approximate those occurring in contaminated drinking water [7]. Thus, Minnesota infants from contaminated communities likely had highly elevated exposures no matter they were breastfed or bottle-fed. A contributing factor is that infants and children have a higher fluid consumption compared to adults on a BW basis. Accordingly, PFC burdens will increase more rapidly than in adults, and exposures to house dust and other domestic sources can further increase this difference [17, 25].

Of related concern, several studies support that U.S. children have higher serum concentrations than adults [25, 26]. This tendency is also reflected by serum-PFC concentrations in other populations, e.g., in my own team's study of Faroese children [35]. Most of these studies did not consider the carry-over of PFCs from breastfeeding.

Given that PFCs are eliminated in human milk [27], women will decrease their own serum concentrations by each pregnancy and the duration of lactation [36]. Although advantageous to the women, children will absorb greatly increased PFC doses, and they are likely more vulnerable to toxic effects due to sensitive organ development processes at early life stages, as I shall discuss further below.

I note that the accumulated evidence on exposure via breastmilk as well as transplacental passage, in May of 2017 led the MDH to revise downward the limits for PFOA and PFOS in drinking water [37].

### 3. Consumer goods and other sources of exposure

Other PFC exposure pathways likely contribute to background exposures that affect residents of Minnesota and the U.S. population in general. For example, PFCs are used in a variety of consumer goods, including certain textiles [41]. PFCs from textiles may contribute to levels in house dust, which may be a particular source affecting children [7, 41].

Several of the exposure sources may be interrelated, as local production and point sources may contribute to human exposures via more than one pathway. Air pollution from a production facility can result in inhalation exposure, and dust deposition will contribute to freshwater and soil contamination. The latter may lead to groundwater contamination. Food may be contaminated via use of drinking water for preparation of soup, gravy, and other foods.

Due to the stability of the PFCs, releases from sources in Minnesota also contribute to global cycling of these substances, thus adding to the so-called background contamination levels, e.g., in marine fish, some of which are also marketed in Minnesota. Accordingly, at least some of the so-called background exposure in the Minnesota population likely originates from production and emissions of thousands of tons of PFCs or precursor compounds from 3M facilities.



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### 4. Summary on exposures

In conclusion, many thousands, probably tens of thousands of residents in the East Metro area and nearby communities have been exposed to PFCs from environmental pollution that has particularly affected drinking water and freshwater fish. The contamination was revealed publicly about 2005, but likely reached residents much earlier, as much as 20, 25, or more years ago. As the PFCs are excreted in human milk, infants would be at particular risk, whether they were breastfed or received substitute made with contaminated water.

## IV. HUMAN EXPOSURE TO PERFLUORINATED COMPOUNDS

### A. Early knowledge of human exposure

By way of background, I first outline the early information on human exposures to PFCs, including information in relation to 3M.

Apparently, the first public report that suggested that the general population had been exposed to fluorine-substituted organic compounds appeared in Nature in 1968 [42], where Dr. Donald Taves from the University of Rochester showed that serum proteins (from his own blood) contained an elevated amount of non-extractable fluorine that could not be ascribed to fluoride from drinking water or food. In the following years, it became clear that industrial organofluorides were a likely source.

The occurrence of PFCs in the human body was further characterized when fluoride in blood samples was found to be partially bound to organic compounds of unknown structure and that they were bound to albumin [42, 43].

As would have been predicted by the known chemical properties of the PFCs, laboratory animal studies soon confirmed that PFCs are easily absorbed, both from oral intake and inhalation [4, 17, 44]. Even some dermal absorption has been documented following cutaneous contact [45], but generally is believed to be negligible (apart from certain occupational settings), as compared to the other environmental exposure pathways.

It appears that 3M started measuring worker blood samples for organic fluorine by about 1976. In 1979, they measured five workers' serum PFOS concentrations and found the levels to be 100-fold higher than the expected level. Total organic fluorine was 4.1-10.1 ppm (or mg/L), which is equivalent to 4100-10,100 ppb (or µg/L), and PFOS represented 55% - 80% of that in the worker samples. By comparison, nine different studies published between 1972 and 1989 suggested average serum organic fluorine concentrations about 30-40 ppb (or µg/L) in the general population.[r] The latter is similar to the general background average serum-PFOS concentration of 30.4 µg/L in the NHANES samples from the general U.S. population in 1999-2000 [46].

A further report from Dr. Taves and his colleagues in 1976 extended their studies and showed that there was widespread contamination of human tissues with organofluorine

[r] AR226-0548.pdf, Perfluorooctane Sulfonate: Current Summary of Human Sera, Health and Toxicology Data, Table II.1, page 000026



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compounds which likely derived from commercial sources such as PFOA (or PFOS, as it seemed later on) [47]. Background serum concentrations of these compounds were estimated to range from about 10 µg/L to about 130 µg/L (again corresponding to the later analyses of NHANES blood samples carried out by CDC).

Dr. W.S. Guy, one of the authors of this later report, informed 3M by telephone in 1975 that the study was going to be published soon at the annual American Chemical Society conference. In this regard, 3M's J.D. LaZerte noted that the authors were "attempting to locate the source of the organic fluorocompound and thought that SCOTCHGARD might be the source." In response, J.D. LaZerte noted that he advised Dr. Guy "not to speculate."[s] In other words, when fluorocarbons similar to those produced by 3M were found to be widespread in human blood, 3M advised against assuming that 3M products could be a source. But as the major if not sole producer of such compounds, 3M and 3M products constituted an obvious and likely source. Dr. Guy's finding, reported in 1976 [47], was an important milestone. In fact, one could have expected it to have triggered an extensive examination by 3M of the fate of PFCs emitted from 3M production facilities and waste disposal sites, and from dissemination via consumer products. I have found no evidence that 3M seriously considered the potential implications of the research findings at the time or soon thereafter.

In the late 1970s, at the time when Dr. Taves and his co-workers were identifying organofluorine compounds in blood samples, landmark cases of environmental pollution were unfolding, one of them Love Canal close to the Niagara Falls in upstate New York [48]. At this site, highly stable organo*chlorine* compounds, such as hexachlorocyclohexanes and chlorinated benzenes were leaking from a chemical dump. The organo*fluorine* compounds being studied by Dr. Taves, including PFCs from 3M, shared several properties with the organochlorine compounds in Love Canal, i.e., a low vapor pressure, some solubility in water, substantial stability and resistance to break-down, and bioaccumulation. In addition, both the PFCs and the chlorinated compounds were deposited at public waste sites and were released in sewage water. Given the attention paid to chlorinated compounds already fifty years ago and onwards, a producer, like 3M, of highly stable organofluorine compounds with physicochemical properties suggesting a potential for environmental dissemination and bioaccumulation, would be expected to trigger a careful assessment of the safety of the PFCs. The 3M documents reveal that similar concerns were raised 20 years later by 3M's Dr. Richard Purdy, but that the warnings were not taken seriously, even this recently (and therefore led to Dr. Purdy's letter of intended resignation).

After the institution of regular blood testing at 3M's production facility in 1976, the 3M medical service team noticed, by September of 1984, an increasing trend in worker organic fluorine concentrations in blood and advised "we must view this present trend with serious concern [...] exposure opportunities are providing a potential uptake of fluorochemicals that exceeds excretion capabilities of the body."[t] It is not clear from the file how this

[s] 3MA01326445. Chronology - Fluorochemicals in Blood. page 3MA01326445, Confidential Information.

[t] AR226-0483.pdf, 3M Internal Correspondence re Organic Fluorine Levels, from DE Roach to PF Riehle, dated August 31, 1984. page 003586.



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recommendation was developed, nor how it was received, but health examinations apparently became part of the routine (see Section VI.B).

One action taken by 3M was to search to see if it could find any blood samples that were free of organofluorine compounds. When that was unsuccessful, the following conclusion was proposed in an internal document: "It is in the interest of 3M to strengthen the evidence of non-industrial sources of organic fluorine in nornal human blood."[u] 3M initiated efforts beginning in 1993 to show that organic fluorine in blood could be from entirely natural sources.[v] This too obviously was a futile effort.

As analytical methods became more sophisticated in the 1990s (with LC-MS instrumentation), specific compounds, such as PFOA, were identified and determined in serum samples from exposed workers.

In May of 1998, 3M reported to the EPA the finding of PFOS in blood samples from the general population.[w] In September of that year, Battelle, a 3M contractor, assessed data quality on 12 data sources provided by 3M on PFOS concentrations from non-occupationally exposed populations. Battelle concluded that in most cases there was not enough written documentation of the study design and sampling protocols to judge whether the resulting data were statistically valid, a conclusion that seems overly skeptical and judgmental. The only data source that was approved by Battelle to be statistically defensible was the data set of 1998 pooled serum from U.S. blood banks (geometric mean 28.2 ppb or µg/L).[x] These results became available via the EPA in 2003, and a follow-up study from 2000-2001 was published and showed that PFOA and other PFCs were indeed present in virtually all subjects tested [49]. This way, the suspicions raised in the 1970s by researchers from the University of Rochester were finally recognized.

Subsequently, the Centers for Disease Control found that almost all blood samples collected from a representative sample of Americans above 12 years of age during the 1999-2000 cycle of the National Health and Nutrition Examination Survey (NHANES), contained PFOA, PFOS and/or nine other long-chain PFCs [46, 50]. Subsequent NHANES studies have continued to document the wide occurrence of PFCs in the U.S. population.

Overall, it appears to have taken 3M about 25 years to accept and publicly disclose the dissemination of PFCs into the environment, thereby affecting very large populations. Still, even after PFCs were discovered in local drinking water, a 3M executive in 2007 claimed that the water was safe: "Based on science, there are no health risks from PFBA,

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[u] 3M_MN03112528.pdf. In search of non-industrial sources of organic fluorine in normal human blood from the general public.

[v] 3M_MN031125328. In search of Non-Industrial Sources of Organic Fluorine in Normal Human Blood from the General Public.

[w] AR226-0622.pdf, 12/9/98 Letter form W. Weppner (3M) to Charles Auer (EPA) re agenda for 12/14/98 meeting, page 1.

[x] AR226-0036.pdf, Working Memorandum on Data Quality Assessment. page 001728 and page 001722; and 226-1486.



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PFOA or PFOS at levels found in the environment," 3M's vice president for environmental, health and safety operations said.[y]

### B. Detection and distribution of PFCs in humans

Although most studies have relied on analyzing serum or plasma PFC concentrations (which are very similar), those measures may not accurately reflect the amounts of PFCs retained in the body overall. For example, PFCs may not show the same partition in blood, with some of them being bound to red cells, rather than serum proteins [51]. Thus, certain PFCs, such as PFOSA and PFHxA, occur only to a small extent in serum or plasma, as they bind to the red blood cells. Moreover, although PFOS and PFOA are both PFC compounds with the same length of the carbon chain, in the blood, a greater fraction of PFOS than of PFOA occurs in plasma [51].

Some PFCs are rarely detected in human blood or serum, as they accumulate in internal organs. Thus, when PFC retention in tissues was determined at 99 autopsies, PFBA was the PFC most commonly detected in kidney and lung and also showed the highest concentrations with medians of 263 and 807ng/g, respectively [52]. In liver and brain, PFHxA showed the maximum levels with medians of 68.3 and 141ng/g, respectively. These organofluorine substances are rarely detected in serum samples, yet substantial accumulation in target organs occurs. Thus, the absence of detectable amounts of these PFCs in a blood sample should not be taken as an indication that no exposure has occurred or that any uptake has been eliminated.

With this caveat, serum-PFC analyses are still useful for exposure assessments for some of the PFCs. Thus, the Centers for Disease Control and Prevention (CDC) have focused on serum samples collected in connection with the NHANES [50]. These data show that PFOS, PFOA, and PFHxS continue to be detectable in virtually all Americans. There seems to be little difference in adults associated with age, but men have higher PFC concentrations than women (likely to be due, at least in part, to pregnancies and lactation), and some ethnically-related differences also exist that are likely due to dietary differences. Median concentrations in serum about the time that PFOS production was phased-out were about 30 ng/mL (PFOS), 5 ng/mL (PFOA), and 2 ng/mL (PFHxS) [50]. The average for 2007-2008 for PFOS had decreased to 14 ng/mL, while PFOA and PFHxS had changed only little [46, 53]. The 2008 data from NHANES served as national average data for comparison with the biomonitoring study carried out by MDH in the affected area that year [54]. PFBS was mostly below the detection limit, and PFBA was not reported.

The long-chain PFCs are persistent in the human body and therefore stay in the blood and in organs for a long time. They may be excreted in urine, though only slowly, and the elimination half-lives are several years. This means that a continuing exposure results in accumulation of the PFCs in the body. The concentration in a blood sample therefore reflects exposures that happened during the last several years. On the other hand, when exposure stops, then elimination will be slow, usually with a constant fraction being excreted each month, each year. First-order toxicokinetics are usually assumed, i.e., that constant fractions of serum

[y] 3M_MN03012886. Early media reports – House Hearing.



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concentrations are eliminated over time [55, 56]. The time it takes for half the compound to be eliminated is called the (biological or elimination) half-life.

From serial analyses of serum samples from former 3M production workers after retirement, half-lives for long-chain PFCs have been estimated to be ~3years (PFOA), ~5years (PFOS), while most short-chain PFCs have a relatively short T½ in serum of ~3days (PFBA) [57]. However, the serum half-life for PFHxS is unusually long, i.e., ~9 years. If the exposure is not completely eliminated during the follow-up, the body burden will decrease more slowly (if at all). However, calculations based on serum concentrations may be erroneous, as very high PFC concentrations in various organs show that "deep" compartments, e.g., in the liver may have much longer retention times [52].

Accordingly, these half-life calculations are not precise. Also, the correlation between PFC chain length and half-life is not absolute in that, for example, the six-carbon chain (C6) PFHxS has one of the longest half-lives, while eight-carbon chain (C8) PFCs such as PFOA and PFOS have somewhat shorter half-lives (see above). Animal studies suggest that, at high exposure levels, the renal excretion may become concentration-dependent as the tubular reabsorption mediated by organic anion transporters becomes saturated [58], and variability in kidney function between subjects may also play a role. Thus, while toxicokinetic modeling may depend on the range of blood concentrations and the individual variability associated with model parameters [56], reasonable results have been obtained modeling PFC kinetics using a first-order model [55, 59]. This approach has been used by the C8 Panel to estimate serum concentrations both before and after blood sampling.

Since 1999-2000, serum PFOS concentrations in NHANES have shown a significant downward trend, presumably because of discontinuing industrial production of PFOS in the U.S. In contrast, the PFOA concentrations during 1999-2000 were higher than during any other time period examined, but then remained essentially unchanged during 2003-2008 [53]. In Red Cross blood donors, declines in geometric mean concentrations from 2000–2001 to 2010 were 76% for PFOS and 48% for PFOA (48%) [60]. The decline in PFOS suggested a population halving time of 4.3 years, which agrees with the geometric mean serum elimination T½ of 4.8 years reported in individuals [57]. However, blood donors are not ideal for population studies and for assessment of the kinetics of the PFCs that occur in the blood. At each blood donation, a fraction of the body burden of the PFCs is removed, and repeated blood donation can therefore increase the elimination of PFCs from the blood compartment. A shortened elimination half-life in blood donors was demonstrated in six family members with elevated PFC exposures [61]. Likewise, local residents classified as frequent blood donors had much lower serum concentrations of PFOS, PFOA and PFHxS than the non-donor population [16]. Similarly an Australian study showed that regular venesection treatment of hemochromatosis patients resulted in approximately 40% lower serum concentrations of PFOA, PFOS, and PFHxS [62].

Laboratory animals, especially the rat, show different retention patterns and even sex-related differences in elimination rates. Most laboratory animals have much shorter elimination half-lives than humans. In interpreting toxicology studies, the specific accumulation patterns must therefore be considered. An appropriate way of ensuring proper interspecies comparisons often relies on serum concentrations (or tissue concentrations), rather than dose levels.



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### C. Serum analyses from Minnesota residents

The first data on serum PFOA and PFOS concentrations in residents of the affected communities, beyond 3M employees, were obtained by MDH while the drinking water was substantially contaminated. They showed average serum PFOA and PFOS concentrations of 54 ng/mL and 37 ng/mL, respectively, in 75 adult residents from Oakdale, and 30 ng/mL and 16 ng/mL in 26 adults from Lake Elmo [18]. Of note is that 10 Oakdale children were included in this study, and that one of them had the highest serum concentrations of 180 ng/mL (PFOA) and 155 ng/mL (PFOS) observed among all participants. The anonymized data file did not include important parameters, such as duration of breastfeeding. Also, due to the method for selection of participants, these data are best characterized as a case series that is not necessarily representative for the residents of the affected communities.

Two years later, a follow-up study was carried out to examine changes in serum-PFCs since the first specimens were collected [54, 63]. The study covered households served by the Oakdale municipal water supply and households with contaminated private wells in Lake Elmo and Cottage Grove. Eligible subjects aged 20 years or older in the households selected had lived at their current residence prior to January 1, 2005, i.e., before the PFCs were detected in the water. The serum concentrations averaged (range in parenthesis) 15.4 (1.6-177) ng/mL for PFOA; 35.9 (3.2-448) ng/mL for PFOS; and 8.4 (0.3-316) ng/mL for PFHxS.

A total of 164 of the participants from 2008 were re-examined on this occasion, and serum concentrations had declined on average by 21% (PFOA); 26% (PFOS); and 13% (PFHxS) [63]. Assuming elimination half-lives of 3, 5, and 9 years, for the three PFCs, average reductions by 25%, 37%, and 14% would be expected if all exposures had ceased at the time of the first blood sampling. The same pattern was evident in 2014, when further follow-up was conducted [64]. Thus, although some continuing exposures to PFOA and PFOS may continue, from water and other sources, it appears that the exposure to these particular PFCs, at least as regards their presence in serum, has been significantly decreasing. The decreases are in approximate accordance with our knowledge on elimination half-lives (see previous section). However, continued exposure to contaminated drinking water with PFC concentrations below the MDH limits likely prevented serum concentrations from decreasing at the maximal rate. Thus, even several years after the drinking water was filtered, the average serum concentrations are still several-fold higher than US averages. These studies were not designed to identify and document high-level exposures, but the maximum serum concentrations found show that excesses of about 100-fold (PFOA and PFHxS) and10-fold (PFOS) above U.S. average levels remained in this community (although many residents may have moved away or died in the meantime). For confidentiality reasons, the MDH reports do not contain any further detail, e.g., whether subjects with the highest levels of exposure had resided longer in the communities, but an age-dependent increase was noted. The highest PFOA and PFOS levels are similar to findings in the Mid-Ohio Valley, see section IV.D [65].

As the publicly available summaries do not provide much detail [54, 63, 64], I have examined the MDH database from the first study to carry out some complementary statistical analyses. Thus, in the questionnaire used, the study participants were asked about the number of years of residence in their current home (they were apparently not asked about previous residences). The serum-PFOA concentration showed a stronger association with



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duration of residence than did PFOS and PFHxS (both of which may not depend as much on water intake as does PFOA). The correlation coefficient is 0.33 (a perfect correlation would have a correlation of 1, while no correlation would be 0). Although this coefficient is unlikely a matter of chance (p value below 0.001), there is much scatter. For example, the highest serum-PFOA concentration occurred in a 50-year resident (only three other subjects had been at the current residence longer). However, in another subject, resident for 46 years, the serum-PFOA was barely increased compared to the background. A range of factors must have contributed to this variability beyond the simple duration of possible exposure, such as the actual water contamination level and its possible changes over the years, the daily water consumption from the tap, and intake from other sources such as fish.

Regarding the latter, the participants were asked how often they consumed fish or shellfish caught from lakes and rivers in the local area, and only 11 of 161, who responded to the question in 2010, said yes, possibly because they were sports fishers (or from a household with one). Those who consumed local freshwater fish, had about 40% higher serum concentrations of both PFOA and PFOS, and tripled levels of PFHxS (differences in actual concentrations were more similar). Although the latter PFC has not been found to bioaccumulate in fish from the Mississippi, there may be other waters in the Twin City area that may be particularly polluted with this substance, thus possibly leading to this substantial increase in serum levels in fish consumers. Because of the long elimination half-life of PFHxS, exposures many years ago may still be reflected in elevated serum concentrations.

Otherwise, the highest reported serum-PFC concentrations have been encountered in production employees, and 3M worker concentrations of PFOA have ranged up to 100 µg/mL, or 100,000 ng/mL, with more recent values being lower [66]. Analysis for perfluorobutanoic acid (PFBA) was attempted for serum samples from 127 former employees and 50 current employees of the 3M Cottage Grove Facility, but concentrations were below the detection limit in 73% of the former employees and 68% of the current employees, and only 4% of the samples contained PFBA above 2 ng/mL, with maximum concentrations of 6.2 ng/mL for the former employees and 2.2 ng/mL for the current employees [57, 67]. Despite the short serum-based half-life, several former employees and local community residents had measurable concentrations of PFBA in their blood, although this may have been due to continuing exposure, e.g., through contaminated drinking water. In light of PFBA mainly binding to certain tissues, such as the kidney and lungs (see Section IV.B), non-detectable concentrations are not diagnostic, but measurable serum concentrations certainly suggest substantial exposures.

## D. Serum analyses from other populations

### 1. Mid-Ohio River Valley

In the similar setting in the Upper-Ohio River Valley in West Virginia, where PFOA concentrations in drinking water in affected communities averaged about 3,500 ng/mL, the median serum-PFOA concentration in exposed residents was 374 ng/mL [65], about 100-fold above concentrations normally found in Americans. Based on these data, a water-PFOA concentration of about 1000 ng/L can be assumed to result in a serum concentration of 100 ng/mL (or 100 µg/L), i.e., a ratio of approximately 1:100 during steady state [68]. However, note



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should be taken that this approximate ratio covers average numbers for residents with different histories of water consumption and with variable durations of residence in the area.

This average ratio between PFOA in drinking water and in serum of participants is consistent with the data from 98 East Metro residents with private wells [63], if the expected post-exposure decline in serum concentrations is taken into account. Thus, an average serum-PFOA level of 25 ng/mL will result from a contamination of 250 ng/L in the drinking water. Short-term residence would result in lower serum concentrations, while high daily water intakes would increase the accumulation in the body. Assuming a background level in serum of 4 ng/mL at the time, a PFOA concentration in drinking water at about 10 ng/L (or 0.01 µg/L) will contribute an average of about 20-25% of the total exposure to this compound, while a PFOA concentration in drinking water of 100 ng/L can be estimated to increase the serum PFOA concentration by 250%, with drinking water in this case contributing over 70% of the total exposure [7].

Thus, like in the Mid-Ohio River Valley, water contamination is a very substantial source of PFC exposures in Minnesota, even if the previous MDH water limit of 0.3 µg/L (300 ng/L) was not exceeded. (As discussed in Section IX, I conclude that MDH's prior values were not sufficient to protect against adverse effects, and, indeed, MDH lowered limits in 2017.)

### 2. International comparisons

Internationally, where they have been measured, average serum concentrations appear to be fairly similar to those obtained from NHANES by CDC, though with higher levels, e.g., in Inuit populations [69]. Our own studies in the Faroe Islands have shown maternal and child serum concentrations of PFOA, PFOS, and PFHxS [35] that roughly correspond to U.S. levels [53], although the Faroese (like the Greenlanders) appear to be mainly exposed to PFOS and PFHxS through their marine diet [70], rather than through drinking water. I note that caution must be applied when carrying such comparisons between different populations, as, e.g., long-term breastfeeding can cause elevated concentrations in infants and lowered levels in the mothers, and repeated blood donations can also lower blood-PFC concentrations (see Section IV.C).

## E. Conclusions on PFC exposure in Minnesota residents

PFOA and PFOS are long-chain PFCs that are very stable in the body and also have long half-lives in serum concentrations. PFHxS is shorter chain, with six carbons, but has a longer half-life in the serum than PFOA and PFOS. PFBA is more quickly eliminated from the blood but is retained in the kidneys and the lungs; the tissue half-life is unknown, but can be assumed to be fairly long. These PFCs therefore accumulate and remain in the body up to many years after cessation of the exposure.

For an unknown period that may have lasted decades, residents in the affected area have consumed drinking water contaminated with PFOA and other PFCs. Locally caught freshwater fish and, to some extent, local farm produce mostly likely added to the excess exposures. Due to the contamination of major aquifers serving East Metro and nearby communities, it is likely that tens of thousands of residents have been exposed to excess amounts



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of PFOA and related PFCs, and long-term residents may have been exposed to elevated concentrations for decades.

As recently as 2010, serum PFOA and PFHxS concentrations in residents in the affected communities show up to 100-fold excesses above national averages, and PFOS concentrations 10-fold above U.S. average levels. To the extent that residents outside East Metro have consumed drinking water, or fish, contaminated by PFCs originating from 3M facilities, the exposed population is likely substantially greater than hitherto assumed. Higher serum concentrations were seen in subjects who had resided in their present home for longer time, and in subjects who ate freshwater fish from local lakes. A small number of analyses show high concentrations in serum from children, and elevated levels may originate from breastfeeding. PFBA and PFHxA accumulate in organ tissue, and serum concentrations therefore do not reflect the exposure.

Exposure patterns change with time. Eight major producers (including 3M) participate in the phase-out of PFC emissions, through an agreement with the EPA, with the aim of reducing and then eliminating global facility emissions and product content of PFOA and related chemicals. However, even if these commitments are or have been met, environmental dissemination of and human exposure to PFCs are anticipated to continue for the foreseeable future due to the persistence of the PFCs already disseminated in the environment, their redistribution and their continued formation from precursor compounds [71].

Although serum PFC concentrations are known to be decreasing in the U.S. population, the cumulated PFC burdens of residents (past and present) of the affected communities will remain above national levels for many years to come.

## V. METHODOLOGICAL ISSUES IN RISK EVALUATION

### A. Interpretation of epidemiology studies

Because it would be unethical to conduct experimental studies in humans with substances that may cause cancer or other serious effects, the main human epidemiological evidence on the PFCs comes from observational studies of occupational cohorts and from community studies of subjects exposed at different background levels such as through contaminated drinking water.

#### 1. Occupational studies

The existing occupational studies mainly regard males and are generally cross-sectional, with only few providing follow-up over several years. In some studies, blood analyses provide information on accumulated exposure levels at the point of time where the blood was drawn.

Information from cross-sectional or prospective studies of worker populations exposed to highly increased levels of PFOA and other PFCs is useful, but can be complex to interpret. For example, follow-up studies of workers can show an overall mortality deficit [72-74], i.e., that the exposed workers lived longer than expected for the general population. Further, an easily available comparison group, e.g., the U.S. general population may not be appropriate, if



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a disease, such as prostate cancer, occurs at a different (lower) rate in the background population of Minnesota, as compared to the country as a whole. In addition, deficits in mortality or morbidity should not necessarily be interpreted as a sign that PFC exposure is beneficial to health, but rather that the exposed population, at least at the time of first hire, was in a better health condition and with better longevity prospects than the background population, which includes the non-working population, some of whom may suffer from chronic disease or otherwise have an increased mortality risk. Such selection bias is well established. Although it does not affect all health outcomes uniformly, the healthy worker effect demands critical assessment of relative risks, not just those that may show a statistically significant excess, but all outcomes [75]. A 1989 letter with detailed tables from Dr. Jack Mandel to 3M's Dr. Larry Zobel emphasized that deaths among former Chemical Division and Chemolite employees occurred in 41 states.[z] Both total cancer and prostate cancer were elevated in the two groups when compared to Minnesota rates. The findings are similar to an article by Drs. Gilliland and Mandel published in 1993 [72].

Partial adjustment may be achieved by using occupational comparison groups that have not been exposed to PFCs or other hazards. Another local occupational group might avoid "healthy worker" selection bias and geographical differences, but one must then make sure that the comparison group is not exposed to some other toxicants. Exactly this issue was relevant in regard to the control group of 3M workers from St. Paul that does not appear to have been unexposed,[aa] as further discussed below. As an optimal comparison group may not be available, it may be preferable to show the results from the exposed population in comparison with more than one reference population and to identify the strengths and weaknesses of the comparisons.

3M's Drs Geary Olsen and Larry Zobel were clearly aware of these issues when they commented, in 2006, on Dr. Bruce Alexander's draft version of a manuscript that was later published with a revised title, with Dr. Olsen as a co-author [76]. The 3M colleagues criticized the use of "non-exposed" 3M workers as a control group (with a very low cancer mortality) and emphasized the importance of the general population, although the healthy worker effects would bias the results.[bb] Tables were produced to show the impact of using different comparison groups.[cc] In the end, the published article highlighted the comparison with general population rates but also included the internal comparison group with several caveats [76].

As a further concern, mortality statistics are limited by numbers of deaths and provide little information about diseases that are rare, occur mainly in the elderly or that are not reflected well by mortality data that may not include all contributing conditions at the time of death. As an alternative, some studies use clinical pathology tests or other diagnostic means obtained at a particular point in time, to uniformly establish disease or risk markers, although such data may sometimes be complex to interpret in terms of long-term health implications.

### 2. General population studies

[z] 3MA00632313 Letter of April 6, 1989 from Dr. Jack Mandel to Dr. Larry Zobel.
[aa] 3MA00058525. Memo to Clifford W. Hanson from F.A. Ubel. April 3, 1978.
[bb] 3MA02557490. Letter to Dr. Bruce Alexander, July 14, 2006.
[cc] 3MA00632317 and 3MA00632315 prepared Dr. Jack Mandel and sent to Dr. Larry Zobel on April 6, 1989.



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Highly relevant information regarding environmental health risks often originate from prospective studies of cohorts generated within the general population. For PFCs, this can mean either local communities affected by contamination of drinking water and other emissions from production facilities or from more general (background) environmental exposures. Many studies are cross-sectional, but the validity of serum-PFC concentrations as long-term exposure biomarkers can be supported by the long elimination half-life of PFCs. Nonetheless, prospective studies often can be more useful, as changes in exposures can be better linked to changes in health. Also, birth cohorts are very important, as they can reveal impacts of exposures during early stages, but such data are often limited in numbers, and long-term follow-up studies are expensive and of course take a long time. Thus, while many human studies have focused on gainfully employed adult males, only a small number of published articles relate to developmental exposure and vulnerable subgroups such as pregnant women and children. The limited extent of prospective information on exposed birth cohorts is unfortunate, as it is not just the dose that can matter but also the timing of the dosing in regard to the developmental stage of the subjects [77]. As illustrated by laboratory animal data, developmental exposure to PFOA induces effects that are not necessarily seen in response to exposures during adulthood [78].

Many studies, also in exposed communities, are limited by uncertain chronic PFC exposure information (in part because early exposure measurements or estimates, when available, may have been inaccurate). Studies with prospective information on exposure levels are few. Again, data regarding prenatal or childhood exposures remain scant at this point. A further concern is that exposures are usually mixed, and it may be difficult to distinguish between effects attributable to particular PFCs.

### 3. Bias toward the null

In the field of epidemiology, there is a well-known and often misleading bias toward the null, of which epidemiologists (and readers of epidemiology reports) need to be careful, especially when public health is at stake. Studies that do not show a statistical significance are sometimes called "negative," although this is misleading. A better word in non-informative. Joint analyses of several such studies may well show a significant difference or trend. Table 1 highlights common causes of bias toward the null in epidemiological studies, i.e., reasons that a study might not show the existence of a risk that indeed is present, though hidden due to the bias. These are all relevant to reports by 3M authors. While biases in the opposite direction also exist, they are usually of much less significance [79].



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Table 1. Causes of bias toward the null in epidemiology studies [79].

| |
|---|
| Inadequate statistical power in small studies |
| Lost cases and inadequate follow-up for long-term effects |
| Exposed or otherwise inappropriate comparison (control) group |
| Exposure misclassification |
| Insensitive or imprecise outcome measures |
| Failure to adjust for confounders with effects in the opposite direction |
| Disregarding vulnerable subgroups |
| 5% probability level to minimize risk of false positives (Type I error) |
| 20% probability level to minimize risk of false negatives (Type II error) |
| Pressure to avoid false alarm |

The bias toward the null is particularly problematic where human health is concerned; scientists and public health officers therefore often assess and rely on the direction or weight of the evidence and not solely on statistical significance, as it may take a very long time to obtain complete and irrefutable proof. Thus, observational studies will rarely if ever provide a 100 percent proof, and it is always possible for someone critical of the weight of the evidence to raise some type of doubt seeking to require additional or improved data before a conclusion can be drawn [80, 81]. It is important to repeat that the presence of uncertainties often tends to cause underestimations of actual risks, not the opposite, and this issue is of importance especially regarding substances that have not yet been studied in the detail desired. Again, many unfortunate past errors in regard to industrial chemicals have shown that initial assessments were erroneous and led to an underestimation of the true risks [82].

In the present report, while considering the extent of possible biases, my conclusions are stated in terms of assessing whether PFCs pose a substantial present and potential hazard to human health. In many instances, the existing evidence of a hazard is much stronger than that, but I understand this to be the applicable legal standard. I shall also rely on the findings regarding the PFC contamination in WV-OH, where "probable link" assessments were requested by the court and then provided by the C8 scientific panel in its reports. My evaluation as an expert therefore considers the uncertainties involved, the plausibilities and what could possibly be known, given the study opportunities and methodologies applied.

## B. Toxicity and interpretation of data

It is partly because of potential limitations of epidemiology studies, in particular when randomized clinical trials are not possible or appropriate, that I also examine the toxicological evidence from animal studies, as is common in epidemiology, to evaluate the plausibility of the epidemiological findings and whether or not they are supported by the experimental evidence. However, the toxicology studies that would be most relevant were not necessarily carried out. As expressed in an internal 3M email exchange on a proposed



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reproductive toxicity study, the considerations whether to carry out the study should include the "possibility of finding repro effects when conducting such a study."[dd]

Regarding PFCs, one potential critique that has been leveled by 3M scientists [83], particularly against certain animal models, is that effects of PFOA may be species-dependent and contingent to, e.g., activation of a peroxisome proliferator-activated receptor (PPAR). This family of receptors consists of three isotypes (PPARα, β, and γ) that regulate cellular differentiation and metabolism of lipids and carbohydrates. Although these receptors are present in humans as well, they differ in their expression in different species, thus potentially complicating extrapolation from some rodent studies to human health [7]. However, as concluded in a recent risk assessment, both human and mouse PPAR-alpha are activated by PFOA *in vitro*, and the results do not clearly indicate that human PPAR-alpha is less sensitive than rodent PPAR-alpha in the *in vitro* systems [10]. Also, certain studies have used specially-bred rodents – some of them genetically modified not to express a particular receptor under study – to control for any such possible effect.

## VI. HEALTH EFFECTS FROM PERFLUORINATED COMPOUNDS

I outline in this section the general development over time of PFC-related research, in particular at 3M. I also touch upon key studies and reviews to outline how information was obtained over time and how knowledge was pursued (or wasn't) over time. I highlight 3M-derived information, whether from formal publications or court files.

### A. Early warning signs

Given that 3M was an innovator in PFC production and the primary if not sole manufacturer in the U.S. for many years, it is not surprising that much of the early examination of PFC properties was undertaken or sponsored by 3M. What does appear to be remarkable is how little and how late 3M's knowledge on environmental dissemination and toxicity was publicly disclosed and how little this information inspired the company to conduct in-depth studies to reveal and understand any PFC-associated risks.

As already mentioned, the first public report that suggested that the general population had been exposed to fluorine-substituted organic compounds appeared in Nature in 1968 [42], where Dr. Donald Taves from the University of Rochester showed that serum proteins contained an elevated amount of non-extractable fluorine that could not be ascribed to inorganic fluoride from drinking water or food.

As also mentioned above, it appears that 3M started measuring worker blood samples for organic fluorine by about 1976. In 1979, they measured five workers' serum PFOS concentrations and found the levels to be 100-fold higher than the level that would be expected.

At about the same time, a further report from Dr. Taves and his colleagues showed that there was widespread contamination of human tissues with organofluorine compounds which likely derived from commercial sources such as PFOA (or PFOS, as it seemed

[dd] 3M_MN03436924.pdf. Page 3M_MN03436925.



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later on) [47]. 3M's J.D. LaZerte noted that he instructed Dr. Taves's team "not to speculate" that Scotchgard was the source (see Section IV.A).

After the institution of regular blood testing at 3M's production facility in 1976, the 3M medical service team noticed, at least by September of 1984, an increasing trend in worker organic fluorine concentrations in blood.[ee] Health examinations were apparently routinely carried out at 3M, although it is not clear when formal and systematic records were kept. One additional action taken by 3M was to search for blood samples that were free of organofluorine compounds. 3M also initiated efforts beginning in 1993 to show that organic fluorine in blood could be from entirely natural sources.[ff] Both efforts were unsuccessful, but revealed a strategy to pursue studies that might benefit company interests.

Among warning signs as early as the late 1960s and 1970s of potential adverse health effects from PFCs were complaints from consumers and doctors that Scotchgard could cause adverse effects, such as bronchospasm.[gg] 3M denied any link between use of their product and toxic effects and instead referred to trichloroethane as a potential risk, although the LD50 for the latter is 2-3 orders of magnitude greater than for the fluorochemicals.

## B. Early epidemiology studies (1970s to 1990s)

As a general matter, information on adverse health effects of PFCs originated with early studies of exposed workers, as complemented by some experimental toxicology studies[7, 9, 17], I shall again mainly focus on developments at 3M to the extent that I have been able to identify relevant information.

While a published scientific article in 1980 reported on the presence of organic fluorine compounds in serum from exposed workers [84], and drinking water contamination in Ohio and West Virginia by PFOA was discovered and later publicly disclosed [71], PFC industries, such as 3M and DuPont, conducted some evaluations of potential health effects over time, but the results of these investigations were generally in the form of internal reports that were not published in the peer reviewed literature [71].

According to internal 3M documents, 3M consulted, in the late 1970s, with their external expert reviewer, Dr. Harold C. Hodge. Dr. Hodge had served as the first President of the Society of Toxicology and was department chair at the University of Rochester, NY. Among his research interests was the toxicity of inorganic fluoride [85]. At a meeting in 1978, Dr. Hodge told 3M's medical director, Dr. F.A. Ubel, that physical examination results of employees should be compared with controls. "There appears to be indications of liver change from the physical

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[ee] AR226-0483.pdf, 3M Internal Correspondence re Organic Fluorine Levels, from DE Roach to PF Riehle, dated August 31, 1984. page 003586.

[ff] 3M_MN03112538. In search of Non-Industrial Sources of Organic Fluorine in Normal Human Blood from the General Public.

[gg] 3M_MN01235364. Letter from Mrs. David Sweeney on February 22,1969 concerning SCOTCHGARD Brand Fabric Protector; 3M_MN01314621. Letter from Dr. Leo Johns to 3M company on August 14, 1967; 3M_MN01314624. Letter from Mrs. Russel H. Taber to 3M company on June 7, 1966. page 3M_MN01314625.



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examination results. In terms of indicators of liver disorder, there are [sic] a higher percentage at Chemolite than at Decatur and the organically bound fluorine level at Chemolite is correspondingly higher."[hh]

At this time, Dr. Hodge indicated that a potential hazard was present. When reviewing the data on fluorocarbons in blood the following year, Dr. Hodge commented regarding a POSF-based compound: "The study of levels of FC-807 [a PFOS precursor, PG] or its metabolites is of utmost importance in determining possible future problems. It should be determined if FC-807 or its metabolites are present in man, what level they are present, and the degree of persistence (half-life) of these materials. If the levels are high and widespread and the half-life is long, we could have a serious problem."[ii] Interestingly, in a subsequent document referring to this conversation,[jj] Dr. Hodge's comment was edited, and the last sentence from previous version was deleted, i.e., that "we could have a serious problem." It is not clear whether Dr. Hodge had agreed with the deletion of his conclusion.

A 1978 memo written by Dr. F.A. Ubel, 3M's medical director, refers to a conversation with Drs Leonard Schuman and (then) Mr. Jack Mandel, where a follow-up study of Chemolite workers was discussed. The two would act as 3M consultants without the involvement of their university. The memo says that the two researchers would respect confidentiality. I have been unable to find any records of the findings from such study.

A joint meeting was held in 1979 between 3M and DuPont, i.e., 3M's fluorochemical exposure committee and DuPont's Eugene Berman and some colleagues. The latter group had reviewed the documentation of organofluorine compounds in blood samples from workers and decided that it was not of sufficient importance to notify the EPA: "The committee reviewed the information on fluorochemicals in blood and came to the same conclusions as 3M--that since there were no adverse health effects, there was no reason for an 8E notification under TSCA."[kk] It is not clear how the committee decided that "there were no adverse health effects," and I would disagree from a medical perspective. The decision recalls the statement by Dr. R.A. Kehoe, a medical consultant to the lead industry, who adopted an approach to the hazards of lead exposure that essentially dismissed evidence of potential harm to human health or the need for action to protect the public on the basis that the harm had not been conclusively proven. Kehoe's approach later became known as the infamous "show-me" rule, according to which "it took 2 years to put lead into gasoline and 60 years to take it out" [86]. In the intervening period, exposure to lead contamination was linked to extensive harm, and the global benefit from phasing out lead additives to gasoline has been estimated to be $2.45 trillion/year [87]. As has seen on many occasions, it is easy (and often irresponsible) to raise doubts only about research results which are pointing toward a risk, and financial stakes can easily inspire such exaggerated doubt-raising [80].

Minutes from the 1979 meeting said: "DuPont was asked if they had carried out any chronic studies on fluorochemicals in the past and if they planned any in the future. In both

[hh] 3MA00967742. Minutes of meeting with H.C. Hodge (August 23, 1978). page 3MA00967744.
[ii] 3MA00967775. Meeting Minutes – Meeting with H.C. Hodge (April 26, 1979) page 3MA00967780.
[jj] 3MA00592803. Meeting Minutes – Meeting with H.C. Hodge (June 7, 1979). page 3MA00592806.
[kk] 3M_MN00050981. Meeting Minutes on July 20, 1979. page. 3M_MN00050983



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cases the answer was negative. Fluorochemicals have a low priority in their chronic testing program. They would not carry out such studies unless they were forced to by regulations. (…) 3M was asked if we had considered 8E notification. DuPont was told that we had considered it several times, but felt that since we have seen no adverse human health effects and our chemicals had no widespread potential for bioaccumulation, we did not feel we had a reportable case." [ll] 3M's conclusion of "no adverse human health effects" would obviously depend on how hard they looked, as acute toxicity would not be expected, and chronic or delayed adverse effects can only be ruled out by conducting detailed studies. Likewise, "no widespread potential for bioaccumulation" is counter to predictions from physicochemical properties, and it is not clear how 3M justified the conclusion (which was later shown to be erroneous). 3M either closed its eyes to the evidence, or chose purposefully not to find it, or being generous to 3M, it seems possible that 3M may have mistakenly relied on the absence of evidence, despite the old dictum that "the absence of evidence is not evidence of absence," which later became famous in U.S. politics.

3M had an excellent opportunity to gather evidence emanating from health surveillance of exposed workers, such as those employed at the 3M Chemolite (Cottage Grove, Minnesota) manufacturing plant. A cross-sectional study of worker health was summarized by the 3M medical officer in 1982. There was a high prevalence of high blood pressure, and elevation of cholesterol, changes that the authors believed to be more likely due to lifestyle, not occupational exposures.[mm] It is not clear how this conclusion was reached, as the fact that other factors may have contributed to the outcomes does not mean that the occupational exposure had no impact. In particular, elevated cholesterol – as an indication of liver toxicity – was soon found to be a major effect of PFC exposure and should not have been ignored in 1982.

The most extensive early epidemiology study was conducted in connection with the thesis project carried out by Frank Gilliland, MD from the University of Minnesota School of Public Health. This study provided surveillance data on employees who voluntarily participated in the program at the Chemolite plant. Although Gilliland identified several associations that suggested adverse health effects, 3M later undermined the findings from the 1990 medical examination data stating that they could not be repeated in subsequent 1993 and 1995 medical surveillance examinations. This was also the conclusion of an article with 3M's Dr. Geary W. Olsen as the first author and published in the Journal of Occupational & Environmental Medicine in 1998; Dr. Gilliland was a co-author on that paper.[nn] One potential reason for the difference between the conclusions by Dr. Gilliland and Dr. Olsen is that Dr. Olsen in the later article relied on measured PFOA concentrations, while Dr. Gilliland had access to measured total organic fluorine only, thus perhaps including other PFCs that may have contributed to the changes

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[ll] 3MA10035034Phone Conversation Report # Disclosure Of Info On Levels Of Fluorochemicals In Blood / Note Dated 19790730.

[mm] AR226-0481.pdf, 3M Internal Correspondence re 1981 Chemolite Health Evaluations, from DE Roach to PF Riehle, dated August 12, 1982. page 003581.

[nn] AR226-0474.pdf, Geary W. Olsen, et al., An Epidemiological Investigation of Reproductive Hormones in Men with Occupational Exposure to Perfluorooctanoic Acid, 40 JOEM 614-619 (July 1, 1998), with Summary of study. page 003468. Also as Olsen, Geary W., et al. "An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid." *Journal of occupational and environmental medicine* 40.7 (1998): 614-622.



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observed in the 1990 examinations.[oo] In a letter to Dr. Geary Olsen dated 23 October 1996, Dr. Gilliland (by then an Assistant Professor at the University of New Mexico) raised concerns about the follow-up study and asked that the manuscript should reflect the viewpoint of all the co-investigators: "The overall focus might best be directed toward addressing the specific research hypotheses of the study rather than refuting the preliminary 1990 study."[pp] This apparent shift in focus is concerning, as it suggests that 3M was seeking to bias the results in order to undercut the earlier study.

The letter suggests that Dr. Gilliland did not have access to the new raw data, but a memo from Dr. Geary Olsen indicates that supplementary data analyses were carried out,[qq] although it is difficult to judge the conclusions drawn by Dr. Olsen without access to the tables referred to, as they were not in the published paper [88]. The article listed Dr. Olsen as the first author, Dr. Gilliland second, followed by other 3M colleagues, including Dr. J. Mandel. It is not clear whether and how Dr. Gilliland's concerns were taken into account. The blood concentrations showed an apparent logarithmic distribution, but a log transformation, which one would normally expect, was apparently not used. Also, while there were concerns about some differences in the methods, only cross-sectional analyses were included. The two follow-up studies in 1993 and 1995 included 111 and 80 workers, 68 of them being the same, and 94 subjects examined in 1993 also participated in the 1990 study carried out by Dr. Gilliland. The published article refers to a half-life of 18-24 months for PFOA in serum as reason for not using repeated measurements methods to examine the data [88], although this reasoning does not invalidate the use of a stronger "repeated measurements" analysis.

Dr. Gilliland's supervisor at the University of Minnesota, Dr. Jack S. Mandel, had previously as a 3M consultant co-authored other articles with other 3M colleagues, and he has also coauthored publications that were supported by other industry sources. Dr. Mandel is now employed with the Exponent consulting firm. Dr. Gilliland pursued an academic career and is now a Professor at the University of Southern California.

Another early source of information relates to the registered mortality of 3M employees considered to have been exposed to PFCs (mainly PFOA). Film plant workers were used as the control group for these occupational studies, although it was known that they had at least some exposure and therefore constituted a very imperfect control group (see Section V.A.1).[rr] According to Alan De Waard, nearly all (95% plus) new employees on the Decatur site started in the chemical plant, and many started in the fluorochemicals drying jobs.[ss] This issue of exposed control groups was apparently not mentioned or taken into account in the published articles written or sponsored by 3M; the lack of an unexposed control group would tend to dilute

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[oo] AR226-0474.pdf, Geary W. Olsen, et al., An Epidemiological Investigation of Reproductive Hormones in Men with Occupational Exposure to Perfluorooctanoic Acid, 40 JOEM 614-619 (July 1, 1998), with Summary of study. page 003474

[pp] 3MA00630893. Letter from Dr. F. Gilliland to Dr. G. Olsen, 23 October 1996.

[qq] 3MA00652081. Memo to file, 15 January 1998.

[rr] 3M_MN00000789, Fluorochemical Steering Committee Minutes.

[ss] 3MA00000675, Re: FC Communications.



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the findings and bias the results toward the null. This problem is similar to control animals being exposed to contaminated feed in a toxicology test.

Many studies also suffered from selection bias. The 3M health and mortality studies focused on production plant workers exposed to PFCs. But at the time, it was already well known that workers exposed to toxic substances might erroneously appear to be in better health, with lower mortality than the background population due to the "healthy worker" effect, i.e., that the employed population is on average in better health than the population at large [75, 89]. In addition, a cohort mortality study was not carried out in 3M's Antwerp plant due to "its recent construction in the 1970s,"[tt] and former employees that were not covered by 3M insurance were also not part of the study.[uu] Also the explanatory power of the statistical models was low, only 2% - 30%.[vv]

Systematic evidence from 3M's occupational medicine records was analyzed only from the 1990s and then reached the public at a delay, and only in parts, and without detailed reference to the caveats. Such studies were apparently not a matter of priority. Again, discussions were held at 3M whether Dr. Gilliland's data constituted a TSCA 8(e) submission, i.e., whether they referred to a human health hazard.[ww] It appears no such report was ever submitted.

### C. Early toxicology studies (1970s to 1990s)

Despite being known and in commercial use since about 1950, little was published in scientific journals on PFC toxicology until the 1980s. Internal 3M documents show that company scientists had been aware of the health risks of PFOA as early as the 1960s [90]. Publications on the solubility of PFOA salts were publicly available in the 1960s (although they may not have been accurate). Immunotoxicity was documented in a study available to the EPA in the late 1970s, but this outcome was apparently not further pursued for many years. One difficulty was that analytical chemistry did not reliably determine organic fluorides in organic matrices until the late 1970s.

When the magnitude of worker exposure to and absorption of PFOA became evident and impossible to ignore any longer, a series of studies were initiated by 3M, including an *in vitro* mutagenicity assay, 28-day oral studies in rats and mice, and 90-day oral studies in rats and monkeys.[xx]

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[tt] 3MA01407039. An Epidemiology Investigation of Clinical Chemistries, Hematology and Hormones in Relation to Serum Levels of Perfluorooctane Sulfonate among Male Fluorochemical Production Employees. page 3MA01407050.

[uu] 3MA00514877. Appendix III Robust Summaries of Toxicology, Epidemiology, and Health Studies. Appendix III, III-65. page 3MA00514877

[vv] 3MA01407039. An Epidemiology Investigation of Clinical Chemistries, Hematology and Hormones in Relation to Serum Levels of Perfluorooctane Sulfonate among Male Fluorochemical Production Employees. page 3MA01407103.

[ww] 3M_MN00000789, Fluorochemical Steering Committee Minutes.

[xx] 3MA02512309. Animal Toxicity Studies with Ammonium Perfluorooctanoate.



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In a review of 3M-sponsored subacute toxicity studies by 1979, a conclusion on PFOS was that "FC-95 was the most toxic of the three compounds studied and certainly more toxic than anticipated. [...] Unless there are adequate data through human epidemiological evaluations that can reasonably assure relative safety of these compounds following long term exposure, lifetime rodent studies should be undertaken as soon as possible."[yy] However, 3M apparently did not submit any study to the EPA until 1987, which was a two-year chronic study in rats; several pre-1976 studies were submitted to the EPA only in 2000.[zz] Likewise, epidemiology information, for example of 3M workers, was slow to emerge publicly. Of note, 3M and Dupont agreed in 1979 about the low priority of toxicology studies and the lack of a TSCA requirement to report findings to EPA.

Early PFOA toxicology studies commissioned by 3M were summarized in 1980 [44], and the liver was highlighted as a target organ, while effects on the immune (or reticuloendothelial) system were also reported. The studies reviewed had been conducted in two stages, first with a focus on skin and eye irritation, acute oral toxicity, and one-hour inhalation studies. The study reports were not submitted to the EPA until 2000.[aaa]

Later on, a 1988 pilot feeding study in rats for 28 days revealed that "[t]he primary lesion consisted of focal to multifocal cytoplasmic enlargement (hypertrophy) of hepatocytes among animals fed 300 ppm or less, and multifocal to diffuse enlargement of hepatocytes among animals fed 1,000 ppm or more."[bbb] Subsequently, in 1997, it was reported that the rat feed contained PFCs, and control groups showed the presence of PFOS in livers of control rats used in toxicology studies; the source was traced to fishmeal in the feed.[ccc] With PFOS present in the rodent feed, the control animals were not free of PFC exposure, as should have been intended.[ddd] For interpretation of low-dose toxicity, the presence of a true (unexposed) control group is crucial, as an underestimation of dose-related effects may otherwise occur.

Effects on lipid metabolism and thyroid function were among those studied at non-3M research institutions in the 1980s [91, 92]. Induction of peroxisome proliferation in the liver was well established by 1990 and resulted in a substantial number of publications on mechanistic aspects.

### D. Further 3M-influenced research (1990s to early 2000s)

Scientists working with the 3M company began to publish studies on PFC toxicology from the late 1990s [88], although far from all studies at 3M were published, and often with a delay. In 1998, a 3M report to the EPA reported the widespread occurrence of PFCs in serum samples from blood banks, and environmental contamination and the persistence of the

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[yy] 3MA00593073. FC-95, FC-143 and FM-3422 - 90 Day Subacute Toxicity Studies Conducted at IRDC - Review of Final Reports and Summary.

[zz] 3MA00016315. September 8 2000.

[aaa] 3MA00016315. September 8 2000.

[bbb] 3M_MN00433331(FC-143). September 29 1988.

[ccc] 3MA01470049. Email attachment found in Custodian Olsen, Geary W. (CB429_1208981).

[ddd] 3MA00176550. Post-pioneer Risk Assessment of Adverse Effects in Marine Mammals from PFOS in the Food Chain, #1. page 3MA00176550.



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PFCs in the human body became an increasing concern [71]. In April 2000, 3M submitted to the EPA a study that showed deaths among monkeys exposed to fairly low levels of PFOS.[eee] Soon after that, 3M announced that it was phasing out the production of PFOS, stating that the chemical had been "detected broadly at extremely low levels in the environment and people." Yet 3M qualified the findings by stating: "All existing scientific knowledge indicates that the presence of these materials at these very low levels does not pose a human health or environmental risk" (http://www.chemicalindustryarchives.org/dirtysecrets/scotchgard/4.asp).

Dr. Geary W. Olsen from 3M was an author of more than 30 articles published in 1998 and onward. However, the influence of 3M on PFC research goes beyond in-house studies and authoring original reports and reviews. The company also funded or supported research elsewhere, whether by contract laboratories or academic institutions. A total of eight such studies were published in 2010-2012. Thus, 3M scientists and their collaborators contributed a substantial proportion of recent scientific articles available on the PFCs, especially in the early years of this millennium. This support and influence has some troublesome aspects.

The most comprehensive mortality study of 3M workers compared deaths at Cottage Grpve with those at the unexposed St. Paul plant from 1947 to 2002. In the thesis report by Dr. Raleigh,[fff] exposure estimates were generated from air measurements, and dividing the workers into six different levels of exposures, a dose-dependent risk appeared for prostate cancer, although not statistically significant. The author concluded that the results supported previous findings of a prostate cancer risk. However, in the published report [93] that was co-authored by Dr. Olsen from 3M, emphasis was on comparisons with the general population, the absence of a trend in quartile (not sextile) exposure groups, and the lack of apparent association of prostate cancer was said to be in agreement with findings in other studies. The Discussion section of the published article notes that family history of prostate cancer may play a role. Indeed, a study published the same year [94] showed a PFAS-associated prostate cancer risk in subjects from the general population who had a family history of the disease. This issue has apparently not been considered in 3M-supported research.

We have previously seen that 3M had a clear interest in depicting its products as toxic only at very high doses and that any findings that suggested adverse effects at lower exposures were challenged and mostly kept away from the public. While this type of bias is probably common in the chemical industry [95], it is a problem that 3M support or sponsorship of published research may not always have been disclosed, but rather seems to have been downplayed and perhaps hidden. A note from a meeting in 2008 suggests that the findings by a consulting company "should be published, probably by a ghost writer."[ggg] It is of course difficult to determine the extent to which this approach was used by 3M.

A report from July 2012 mentions "3M perfluorochemical studies in progress," supported by research contracts. One contract for "Danish birth outcome study" was awarded to a private entity named International Epidemiology Institute, jointly with UCLA and Aarhus

[eee] AR226-0145. 26-Week capsule toxicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in cynomolgus monkeys, p. 002636.
[fff] 3M MN03059185.pdf. Cancer mortality in 3M chemical workers. December 2013.
[ggg] 3M_MN00863024. Plastics Europe Fluoropolymers Committee / 081009 Ad-hoc Tox WG Minutes. page 3M_MN00863026.



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University in Denmark (most of the results from these studies did not lead to firm conclusions). One of the publications listed by 3M provides the following information on indirect support: "The original study was supported by the International Epidemiology Institute (IEI), which received funding from the 3M Company" [96]. Of further interest, the blood samples were analyzed for PFOS and PFOA by 3M's laboratory in St.Paul.

A Danish cancer case-control study was also funded by a 3M contract to the participating institutions, including the IEI [97], and it provided the following statement: "The 3M Company had no role in the design of the study, interpretation of the results, or writing of the paper. The authors declare they have no competing financial interests." Nonetheless, the study questionably concluded that serum-PFC concentrations appeared not to be related to a cancer risk – despite signs of elevated risk for prostate cancer despite the short follow-up time.

Among 3M-supported studies mentioned in a 2008 report is a study from Stockholm, where PFOS immunotoxicity surprisingly could not be replicated by oral dosage [98]. The article, published in 2010, refers to 3M support by an unrestricted research grant and also thanks Dave J. Ehresman from 3M for serum analyses (there is no 3M co-authorship). But the published article only superficially mentions possible limitations that could explain the apparent absence of immunotoxicity. As another example, 3M authors [83] cited a publication to support their view that cellular receptors vary between animal species and PFC toxicity. Two of the 3M authors are acknowledged in the publication referred to [99] for "critical review and helpful suggestions," but there is no information on funding or conficts of interest.

Analytical quality is essential in these types of research, and most publications in the field report quality assurance data. However, in regard to the 3M-supported Danish national birth cohort, where blood samples were sent by regular mail, those that were collected in the winter showed very substantial differences between paired samples ranging from -77 to +38% for individual PFC analyses; in most cases concentrations were lower in the delayed and transported samples[100]. Such substantial imprecision, assumed to be random apart from varying with season, will likely cause a bias toward the null, thereby underestimating the PFC impact on the outcomes [101]. The study authors have apparently not reported on the implications of this serious analytical imprecision and their interpretation of the problem in regard to their published reports on lacking or minimal exposure-related adverse effects.

In my view, it is clear that 3M inspired and influenced PFC research and that publications on 3M-supported projects sometimes disclosed 3M authors, sometimes not. Analyses of research bias have documented that publications reporting on industry-supported studies tend to be biased toward conclusions beneficial to the sponsor's interests, even if a potential conflict of interest is declared. This has been found in regard to pharmaceuticals [102], nutrients [103], tobacco [104], and toxicants [105]. There are indications that such bias is present here in regard to studies sponsored by 3M. Part of the bias is that only selected reports, if any, have been made available to the public. An additional source of bias could be due to the choice of control groups and reference populations as well as the statistical approach to data analysis.

In 2004, the EPA filed a suit against DuPont alleging that "DuPont had – over a 20 year period – repeatedly failed to submit information on adverse effects (including information on liver enzyme alterations and birth defects in offspring of female DuPont



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workers)" [90]. Although no systematic study has been carried out by the EPA regarding 3M and PFCs, the evidence available suggests that 3M aimed at concealing or explaining away, or delaying unwelcome conclusions, and that 3M-commissioned or 3M-sponsored research was less likely to provide results that would be against the company's interests. In 2006, the U.S. EPA reached a settlement agreement with 3M to resolve 3M's reporting violations under the Toxic Substances Control Act, according to which 3M did not admit to a violation, but agreed to pay a penalty in excess of $1.5 million for 244 separate violations.[hhh]

## E. Growth of PFC research

Even though PFCs have been produced for over 60 years, independent publication on PFC toxicity only began in earnest about 10 years ago [106]. The broader scientific community, therefore, is still at an early stage of understanding about how human exposure to these compounds affects health. For example, chronic toxicity studies have been published only based on rats [7]. A formal cancer bioassay is also missing. In addition, insufficient attention had been paid to exposures during sensitive developmental stages. I note in particular that few epidemiology studies have focused on exposures during infancy or prenatally, although early development must be considered a highly vulnerable period that must be taken into regard when determining exposure limits [107]. It is remarkable that such studies were apparently not carried out under industry auspices in the several decades of commercial production.

Since the first reports in scholarly journals that revealed widespread global occurrence of PFOS in wildlife [108] and the detection of PFCs in blood from the general population [109] were published about 2000, the scientific literature on the environmental and toxicological aspects of PFCs has increased, and the annual number of publications on the PFCs is said to exceed 400 [110]. Still, by comparison, the quantity is less than for many other chemicals for which there are human health concerns.

The Web of Science lists a total of more than 34,000 publications when searching for titles using the words 'perfluorinated' or 'perfluoro*'. However, only about 10% of these publications relate to environmental sciences, toxicology, or public, environmental, and occupational health. Only 60 articles were published before 1990 and 179 during the 1990s. Many of the early studies focused on PFCs other than those relevant to this report, many of them mainly related to chemical research. Thus, most of the published articles on human health risks from PFCs are fairly recent.

To understand the growth of health-related knowledge on PFCs in further detail, I examined the coverage of the main substances in 78 major journals within the fields of environmental science, toxicology and public health during the first 10 years of this millennium [106]. These are the journals in which my colleagues and I would most frequently publish our findings, and they also prominently figure in the reference list of this report. I used the unique Chemical Abstracts Service (CAS) number for PFOS and PFOA and extracted the articles from the SciFinder data base. The 120,000 journal articles published in these journals during 2000-2009 included a total of 271 articles that, at least to some extent, covered PFOS and a slightly

[hhh] https://www.epa.gov/enforcement/3m-company-settlement;
https://www.epa.gov/sites/production/files/documents/3m-consentagr.pdf;
https://www.epa.gov/sites/production/files/documents/3m-auditagreement.pdf.



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higher number (363) on PFOA (most of the articles being the same). More than half of these articles were from 2008 and 2009, thus indicating a recent and substantial increase in research activity. Of the 120,000 articles published in these journals during 2000-2009, only 37 referred to PFBA.

For comparison, the twenty most mentioned environmental chemicals (e.g., toxic metals, PCBs, and PAHs) were each covered in over 2,000 articles during this period, and lead alone was dealt with by close to 1,000 articles each year. Thus, in comparison, PFCs were not priority compounds for publicly-published environmental and toxicology research, at least up to 2007. As an indication of increased attention, the Web of Science lists a total of 2,310 PFC publications for the years 2010-2016 in the same relevant fields, i.e., an average of 370 per year, a substantial increase.

When using the National Library of Medicine database (PubMed), the search items 'perfluorinated' or 'perfluoro*' return about 10,000 articles for all years, of which one out of four is retained when limiting to 'humans'. Of these, 450 are classified as referring to children and 181 to infants, as of March, 2017. Again, most of these publications relate to medical technology uses, or are merely descriptive, thus only to a limited extent dealing with adverse human health effects from long-term environmental exposures.

Accordingly, the intensive focus on PFCs in scientific publications happened during the most recent 10 years, thus slowly emerging decades after the first discoveries of PFC toxicity at 3M. Also, the reports from the court-mandated C8 studies, described below, are also very recent and mainly relied on cross-sectional study designs, although fortunately on large population groups.

The evidence at hand is therefore fairly recent and unlikely to represent the full toxicological perspective, such as those that may occur at a delay, and some adverse effects and vulnerable subpopulations may not yet have been identified. The occurrence of adverse effects at chronic exposure to low PFC levels still needs to be explored in greater detail, especially regarding the long-term effects of developmental exposures. As has been seen on numerous occasions [82], the evidence available today may therefore underestimate the true extent of the PFC toxicity.

## F. Public knowledge on PFCs

Even though PFCs had been produced for over 60 years, little was published on adverse health effects of PFCs before 1990. As reviewed above, early scientific studies carried out under 3M auspices were in some cases not published (such as the study of the transfer into milk[iii]) or only published after a delay of up to about 25 years (as in the case of some of the toxicology studies). Some of the findings led to apparent internal controversies that may have prolonged the delay in publication or the decision not to publish, such as Dr. Gilliland's study of worker's immune functions.[iii] Some reports were held back and not submitted to the EPA after

[iii] 3MA10037365, PFOS Disposition, custodian Reagen, William K, page 3MA10037367.
[iii] CB429_1167824, Custodian: DiPasquale, Thomas J., Peripheral Blood Lymphocyte Count in Men Occupationally Exposed to Perfluorooctanoic Acid. page 3MA00323876 to 3MA00323890.



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3M internally, but without proper evidence, decided to conclude that "there were no adverse health effects."[kkk]

At least one medical report on adverse health effects in 3M workers was never published. Thus, Dr. Frank Gilliland sought to publish his results on immune dysfunctions in 3M workers. In December 1993, Dr. Jeff Mandel, Dr. Gilliland's adviser from 3M's Medical Department, provided 3M's FCSC with a copy of Dr. Gilliland's draft manuscript entitled "Peripheral Blood Lymphocyte Paper."[lll] Dr. Mandel indicated, "We're working with [Dr. Gilliland] regarding some of the wording." After the FCSC reviewed the Gilliland lymphocyte paper, it was not published, and the results were not shared with the EPA, or with state regulators at the time.[mmm] I have not identified any other relevant studies that were carried out, although I have been unable to identify systematically any additional unpublished reports of medical interest in addition to the cases of delayed or incomplete reporting. Overall, 3M appeared to set overly strict requirements before allowing conclusions on the existence of adverse effects, and it seemed that 3M used outside experts to elicit uncertainty about conclusions considered unwanted.

Some of the exposure patterns and adverse health issues that have been recently reported can be seen as a consequence of the physicochemical properties of the PFCs that were known already in the 1950s [11]. I have been able to locate only few documents from 3M that clarify how the knowledge on environmental fate and human exposures developed over time. However, that a substantial risk to human health was present must have been realized at 3M long before Dr. Purdy summarized his concerns in the 1990s.

Certainly, very substantial information must have been available to 3M by the time of the announcement in 2000 that a phase-out of commercial PFC production would be completed by 2002. The company reported two years later that environmental contamination in Minnesota had occurred.

Although an increased number of biomedical articles on PFCs has appeared during the most recent decade or so, the adverse effects at low exposure levels have probably not been fully characterized, especially regarding vulnerable populations and developmental exposures. Prudent conclusions therefore must consider that the evidence so far is not completely developed, especially where the existing evidence is pointing toward probable harm. An expert group appointed by the National Research Council (NRC) refers to this erroneous conclusion as the "untested chemicals assumption" [111]. From reviewing the background evidence, it is clear to me that this consideration was not considered by 3M, but that the company in fact attempted to weaken evidence that was unwelcome.

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[kkk] 3MA10035034. Phone Conversation Report # Disclosure Of Info On Levels Of Fluorochemicals In Blood / Note Dated 19790730.

[lll] 3MA00323875-890.

[mmm] CONT003896. Plaintiffs' memorandum in support of their motion to amend their complaint to add a claim of punitive damages. page CONT003912.



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## G. Recent key reviews, studies and resources

I mention here certain recent key reviews and studies. In my discussion of particular endpoints, in the next section, additional reviews and studies are referred to.

### 1. C8 Science Panel

General population studies addressing PFCs mainly have been cross-sectional, but important research data have emerged from the Mid-Ohio River Valley population, where PFC contamination of drinking water occurred. The final conclusions of the C8 Science Panel, as submitted to the Court, refer to the probable links of the PFC contamination and plausible adverse effects regarding cancer and several other important health conditions. The C8 Panel carried out several large-scale studies, although most of them focused on PFOA. The Panel concluded that PFOA exposure was probably linked to six important health conditions, including two types of cancer [8].

In somewhat greater detail, the West Virginia Circuit Court in 2005 approved a class action Settlement Agreement in a lawsuit about releases of PFOA from DuPont's production facility in Wood County, West Virginia. The Settlement created a Science Panel of three epidemiologists that was to conduct research in the community to evaluate probable links between PFOA exposure and human disease.

In addition, a C8 Health Project was established to collect data from Class Members through questionnaires and blood testing. This community health study includes approximately 70,000 Ohio and West Virginia residents with at least one year of exposure to drinking water contaminated with PFOA from about 50 ng/L to over 3000 ng/L. Data on serum PFOA concentrations provide information on the relationships between external dose from drinking water and the internal dose, i.e., the serum concentration, and a variety of biological changes. The median serum-PFOA concentration for all participants was 28 ng/mL, and the median in the highest decile (the subjects with the highest 10% of exposures) was 482 ng/mL.

These data, and the conclusions released by the Science Panel constitute an important basis for the present report. Based on the results from these studies and an evaluation of the literature, the Science Panel delivered reports on 'probable links,' as summarized in the final report from 2012. The C8 Panel determined that exposure to PFOA had Probable Links to adverse effects on the following human health conditions (Table 2).

Table 2. Adverse human health conditions, where 'probable links' to PFOA exposure was identified by the C8 Panel [112].

- Ulcerative Colitis
- Pregnancy-Induced Hypertension/Preeclampsia
- Thyroid Disease
- High Cholesterol
- Kidney Cancer
- Testicular Cancer



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Although the reports to the Court were not peer-reviewed at the time and only provide a brief summary of the new study results, most of the evidence has since then appeared in peer-reviewed scientific journals, which will be referred to below.

### 2. Other major assessments

The PFCs have been the focus of a variety of evaluations carried out by regulatory agencies, such as the Agency for Toxic Substances and Disease Registry (ATSDR) and the U.S. Environmental Protection Agency (EPA). In addition, reviews on particular aspects have been generated by the National Toxicology Program (NTP) on immunotoxicity and by the World Health Organization's International Agency for Research on Cancer (IARC) on cancer risks. These sources refer to a wider range of studies than the present report, where the focus is on human health regarding exposures occurring in Minnesota.

Human epidemiological studies have certain inherent limitations, as the evidence by nature is observational and often without well-characterized exposures over time and without unexposed control groups, as is possible in toxicological laboratory studies. This means that each subject's exposure must be characterized from, say, a chemical analysis of a blood sample, which then acts as a proxy variable and reflection of the true exposure, though without indicating the exact daily intake. Likewise, the human epidemiology studies can document only correlations between exposure measurements and particular outcomes, and such correlations may not always be causal.[nnn]

A more common complexity is that exposures usually are mixed, i.e., that we are exposed to more than one PFC at a time. For example, subjects with high PFOS exposures usually have elevated exposures also to other PFCs. Even if serum-PFOS concentrations show clear associations with some adverse effects, then it is difficult to rule out any causative role contributed by other PFCs that may or may not show statistically significant associations with the outcome. However, due to the contamination in the Upper Ohio River Valley, a unique situation occurred, where PFOA was the main PFC in the exposure, and strong evidence on PFOA effects could therefore be extracted. In addition, some populations may be exposed to PFCs to variable degrees and in different relative proportions, and statistical methods can then help separating the likely impacts linked to individual PFCs.

In the absence of human experiments on PFC toxicity, which would of course be unethical, agencies often choose to rely on experimental studies in laboratory animals to generate risk assessments and to reach conclusions on safe exposure limits for single PFCs. While this has been a long-term tradition for these purposes, the present report evaluates the weight of the epidemiological evidence on adverse effects of PFC exposures in the light of supporting toxicity evidence to determine whether these particular PFCs pose a substantial present and potential hazard.

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[nnn] Dr. Deanna Luebker of 3M acknowledged that the determination that epidemiological findings demonstrate a causal relationship between the presence of a PFC in a subject and an adverse effect involves a degree of judgment and is supported by various factors, including evidence of "enough data so the numbers are strong enough," statistical evaluation, data comparison, sufficient sample sizes and evidence of the incidence and commonality of a given effect, evidence of an increase in effect at higher exposure. Luebker Dep. Tr. (Aug. 29, 2017) 49:9-50:15.



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# VII. ADVERSE HEALTH EFFECTS AT INDIVIDUAL ENDPOINTS

As stated above, it is my opinion that PFCs pose a substantial present and potential hazard to at least human immune system functions, reproductive functions including adverse effects to the next generation, endocrine functions, thyroid functions, liver functions, cardiovascular functions, and by causing or increasing the risk of cancer. Below, I discuss the different human health hazards one by one. The first section is on immune system dysfunctions, as much evidence is now available and because these effects have not been dealt with in detail in reviews by regulatory agencies. To some degree, this is true also in regard to reproductive toxicity and endocrine disruption, while other organ systems and cancer have been dealt with in substantial detail elsewhere, so that my coverage can be briefer.

In each of the following subsections, I discuss the epidemiological evidence that I rely on, summarize the supporting toxicological evidence, and lastly discuss possible mechanisms, and additional studies or potential criticisms relating to the endpoint in question. I have made a reasonably comprehensive review of the epidemiological evidence, and have employed a weight of the evidence approach, as is commonly accepted in the scientific community in reviewing studies on a particular topic.

## A. Immunotoxicity and autoimmunity

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to human immune system functions.

The immune system is crucial in fighting communicable diseases. It is also crucial in detecting and eliminating cancer cells. In addition, the immune system is involved in allergic disease and in autoimmunity. As the adaptive immune system is programmed during early development, immunotoxicity assessment is particularly relevant in subjects with PFC exposures during early life [113]. As discussed above, PFCs are excreted in human milk, and breastfed children may thus be particularly at risk.

The immune system is a sensitive target for PFC toxicity, perhaps the most sensitive, as illustrated by studies of deficient antibody responses to routine vaccinations in children exposed to PFCs. This approach was recommended by an international symposium in 1999 [114] and has been used to characterize immunotoxic effects of, e.g., polychlorinated biphenyls (PCBs) and dioxins [115-118]. Children who are highly exposed to immunotoxicants may be unable to generate enough antibodies to provide protection against the infectious diseases against which they are vaccinated. Responses to vaccinations in terms of concentrations of specific antibodies can therefore be used to assess immune dysfunctions.

The National Toxicology Program (NTP) concluded in 2016 that PFOA and PFOS are likely, or "presumed to be," human immunotoxicants [5]. NTP uses the term "presumed" to denote the level of evidence just below "known," and stronger than "suspected." In addition, autoimmunity, including ulcerous colitis, is a documented adverse effect [119]. Taken as a whole, PFC exposure at levels similar to or below those reported from the East Metro area are associated with a range of immunotoxic effects.



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As I discuss further below, prospective studies of birth cohorts have shown dramatic negative effects of PFCs regarding children's response to routine immunizations, thus demonstrating that these substances can adversely impact the development of the adaptive immune system in early childhood. A reduced or flat antibody concentration response to vaccinations has been observed even in adults of the general population at elevated serum-PFC levels. Such effects are linked to an increased occurrence of infectious diseases. Thus, the implications can be substantial. The mechanism of action is not yet clear in terms of how PFCs may affect allergy, autoimmune disease (such as ulcerative colitis, as suggested by the C8 Panel), and other immune functions, e.g., eliminating cancer cells.

**1. Epidemiological evidence**

My review of available epidemiological studies demonstrates a strong link between PFC exposure and adverse effects on human immune system functions.

a. I was the principal investigator of a study that found significant adverse impacts of PFC exposure on indicators of vaccination efficacy in children. The first study, which was based on 656 births in the Faroe Islands followed 587 of the children through to age 7 years and found that a doubling in exposure to PFOS and PFOA was associated with an overall decrease by about 50% in the antibody concentration [35, 120]. At the same time, a substantial number of children at age 7 had such a low antibody concentration that they had no long-term protection against the targeted diseases despite a total of four vaccinations.

To understand the significance of this finding, a brief explanation of routine immunizations is helpful. By inoculating an antigenic component of a pathogenic organism, the body develops a defense in terms of antibodies. The aim is to protect against future development of the disease. Vaccination is considered one of the cornerstones of modern disease prevention. When a child receives the scheduled Td (tetanus-diphtheria) vaccinations, for example, he or she will generate sufficient capacity for antibody production to avoid getting infected by tetanus and diphtheria. If a person's antibody concentration is too low, his or her immune system will likely be unable to fight off the disease.

The antibody response to childhood immunizations is of clinical relevance and reflects major immune system functions, and in addition is a feasible parameter to use in population studies [121]. Thus, study subjects have all received the same doses of antigen (in the form of the vaccines) at the same ages, and examinations can then be scheduled at similar ages, i.e., at similar intervals after the most recent vaccination [114]. Our particular study focused on the fishing community of the Faroe Islands, where residents with frequent intake of marine food have increased exposures to marine contaminants, such as the PFCs [70]. A major advantage of these studies is that the population is fairly homogeneous and that participation rates at follow-up remain high.

We have followed a Faroese birth cohort of 656 singleton births through to adolescence [122]. Among PFCs in maternal pregnancy serum, PFOS showed the strongest negative correlations with antibody concentrations in their children at age 5 years (after three vaccinations within the first year after birth), where a doubling in exposure was associated with a difference of -41% ($p = 0.0003$) in the diphtheria antibody concentration. PFCs in the child's



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serum at age 5 likewise showed clear, negative associations with antibody levels, especially at age 7 (two years after a booster vaccination at age 5 years), and a doubling in PFOS and PFOA concentrations was associated with differences in antibody levels between -24 and -36% (joint effect of -49%, p = 0.001, in a structural equation model) in the overall antibody concentration. For doubled concentrations at age 5, PFOS and PFOA showed odds ratios (ORs) between 2.4 and 4.2 for falling below a clinically protective antibody level of 0.1 IU/mL for tetanus and diphtheria at age 7. We concluded that developmental exposure to PFCs is associated with humoral immune system deficits in humans [35]. It is worth noting that the PFOS and PFOA levels in maternal pregnancy serum and the child's serum at age 5 that were measured in this study showed concentrations similar to, or lower than, those documented in prior studies in the U.S. [46].

Of particular concern is the finding that several children at age 7 years (two years after the age-5 diphtheria and tetanus vaccination booster) had antibody levels against diphtheria and/or tetanus below the clinically protective level of 0.1 IU/mL [35, 123]. This means that the children had no long-term protection against the diseases – despite a total of four vaccinations. We calculated the ORs for a doubling in the child's age-5 serum-PFOA concentration as a predictor of having an antibody concentration below 0.1 IU/mL at age 7 years. The ORs for tetanus was 4.2 (95% CI, 1.5-11.4) and for diphtheria was 3.3 (95% CI, 1.4-5.5). Both were significant at a $p$ level <0.01. PFOS showed lower ORs (marginal significance), and certain other measured PFCs, such as PFHxS, had ORs below 2 and non-significant (we determined serum concentrations only of the major PFCs in this study). Our regression analyses also showed PFOA to be a strong predictor of lowered antibody concentrations. When we used a structural equation model that allowed us to combine the two serum-PFOA measurements at ages 5 and 7 years [120], we find that a doubled serum-PFOA concentration was associated with a change in the age-7 antibody concentration of -38.2% (95% CI: -56.1; -13.0) for tetanus and -34.7% (95% CI, -52.5; -10.2) for diphtheria. When we adjusted for the other PFCs, the regression coefficients were -29.6% and -26.9 %, respectively, i.e., virtually unchanged [120]. Likewise, adjustment for the elevated PCB exposure in the Faroes did not materially affect the calculations, as would be expected due to the poor correlation between the two [35].

b. The findings of our above study are consistent with a smaller study carried out in Norway on a subgroup from the national birth cohort. In 50 3-year-old children, inverse correlations were found between the mother's PFC exposure during early pregnancy and decreased antibody levels in their children against four different childhood vaccinations, with rubella showing a statistically significant decrease at higher exposures to PFHxS, PFOA, PFOS, and PFNA [35]. This study also found that increased concentrations of PFOA, PFNA, and PFHxS were linked to statistically significant increases in the incidence of their children suffering from common cold and from gastroenteritis. Of importance, in these children, elevated PFC exposures were linked to both lower antibody concentrations and more frequent infections.

c. In a more recent Faroese birth cohort, serum-PFAS concentration profiles during infancy were estimated based on the duration of breastfeeding, and the calculations were validated by comparison with measured serum-PFC concentrations at age 18 months. At the lower PFC exposures, inverse associations with age-5 serum concentrations of antibodies against tetanus and diphtheria vaccines were similar to those seen in the previous cohort. Concentrations estimated for ages 3 and 6 months showed strong inverse associations with antibody



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concentrations at age 5 years, i.e., more than four years later. particularly for tetanus. These associations were stronger than those seen for PFC concentrations at ages 18 months and 5 years and therefore support the notion that the developing adaptive immune system is particularly vulnerable to immunotoxic exposures during infancy. This finding also means that studies relying on serum concentrations that do not reflect ages at peak vulnerability will likely underestimate the true effects.

d. U.S. colleagues relied on the NHANES to extract data on a total of 1,831 adolescents aged 12-19 years between 1999 and 2006 [124]. In cross-sectional comparisons, a doubling of the concomitant serum-PFOS concentration showed a 13% decrease in rubella and 6% in mumps antibody concentrations, while measles did not show a clear association. In the authors' wording, the findings suggest a less robust response to vaccination or greater waning of vaccine-derived immunity over time. This study is of interest, as it focused on childhood vaccines other than the diphtheria and tetanus toxoids.

e. In addition to routine childhood immunizations, many people receive immunizations for the flu, often on an annual basis and for a specific flu variant, such as the Avian flu or the Swine flu. PFC exposure has been shown to be linked to decreased flu vaccine effectiveness. Thus, a study carried out in connection with the C8 studies encompassed 411 adults, whose serum samples were analyzed before and about three weeks after flu (A/H3N2) vaccination [125]. Thus, the elevated serum-PFOA concentrations were associated with a weakened vaccine antibody response also in adults.

f. PFC exposure has also been shown to be linked to decreased effectiveness of boosters of vaccines first received in childhood. In a study of 12 healthy adult volunteers, increased PFC exposure was associated with flatter changes in the serum concentrations of tetanus and diphtheria antibodies. Following the booster vaccination, antibody responses widely differed during the first 10 days, with two subjects appearing not to respond at all, and the steepness of the antibody concentration increase was inversely associated with the concomitant serum PFC concentrations, especially for PFOS and PFHxS[126].

g. This decreased short-term response to vaccines is in agreement with the similar PFC-associated decreased responses seen in 419 of the Faroese children at age 5 years [35, 123]. When re-examined about a month after the booster vaccination against diphtheria and tetanus, lower antibody responses were found at increased concurrent exposures to PFOS, PFOA, and PFHxS, while prenatal exposures appeared to play a lesser role in regard to the response to the booster. Although past exposures were unknown, the results suggest that adverse effects on short-term vaccine responses in adults may be primarily determined by the current exposure, independent of age.

h. Other studies have also linked PFC exposure to adverse impacts on the body's ability to fight off various common diseases including colds, fevers and gastroenteritis. Thus, a study of 359 Danish children from the Odense Child Cohort found that increased maternal serum concentrations of PFOA and PFOS at the end of the first trimester was significantly associated with a higher frequency of fever and symptoms in their children. The study followed the cohort of 359 children at ages 1-3 years by monitoring the frequency of fever and associated symptoms every 2 weeks for a year (via text messages). The number of days with



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fever >38.5ºC (>101.3ºF), and also in combination with nasal discharge or cough, was significantly increased in association with increases in the maternal serum concentrations of PFOA and PFOS [127]. These findings are in accordance with the much smaller Norwegian study already mentioned [128].

i. As part of the studies of the Danish National Birth Cohort, maternal early pregnancy serum from randomly selected 1400 women and their offspring were analyzed by 3M for PFOS and PFOA [129]. Hospitalizations for infection of the offspring were identified by the linkage to the National Hospital Discharge Register, through to age 11 years. Diagnoses, such as airway infection, appendicitis, middle ear infection were merged, and no clear pattern was observed when results were stratified by child's age at infection. In addition to relying only on exposures during early gestation, a recent study raised doubt about the validity of the chemical analyses [100]. Nonetheless, this study was highlighted by 3M authors who criticized our 2012 JAMA article [83], as commented on below.

j. Most recently, a study of a large Japanese birth cohort recorded physicians' diagnosis of common infectious diseases – including otitis media, pneumonia, respiratory syncytial virus infection, and varicella – up to 4 years and reported higher incidence rates at elevated prenatal exposures to PFOS and PFHxS [130]. Like the Odense Birth Cohort study, it focused on the most relevant preschool ages, did not exclude cases that were not hospitalized, and relied on valid prenatal exposure measurements.

k. In adults, a study conducted by the C8 Science Panel based on the health examinations concluded in an interim report that increased PFOA exposure was associated with lower serum concentrations of total IgA, IgE (in females only), though not IgG [112]. Thus, using total and non-specific immunoglobulin concentrations, this study is at least partially supportive of adverse immune effects from PFOA exposure. The result concerning IgG concentrations should be interpreted with some caution because the C8 study examined total IgG immunoglobulins (whereas our study, A.1.a. above, focused on concentrations of specific IgG antibodies directed against vaccine antigens), thus substantially limiting the sensitivity of the C8 study.

l. PFCs also have been found to be linked to certain forms of autoimmune disease, in which the body's immune system attacks its own tissues. This link is demonstrated by two studies conducted by C8 Science Panel epidemiologists, the first being an occupational study of 3,713 workers, whose PFOA exposures were evaluated. Using a ten-year lag, the occurrence of ulcerous colitis and, without a lag, rheumatoid arthritis showed significant associations by greater disease frequencies at elevated PFOA exposures [131]. These results were also reflected by the C8 Panel conclusions, where the C8 Panel stressed a probable link between PFOA exposures and ulcerative colitis.

m. The second study concerned the general population in the Mid-Ohio River Valley, where 151 cases of ulcerous colitis were identified in connection with the medical examinations. With a p value less than 0.0001, higher serum-PFOA concentrations predicted a greater risk of developing the disease [119].



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n. Similarly, in the C8 Panel's study of the >50,000 residents of the Mid-Ohio River Valley, certain immune function parameters were measured. Specifically, antinuclear antibody (ANA) concentrations in serum were used as a screening parameter for autoimmune disease, such as rheumatoid arthritis. There was an increasing trend with serum-PFOA concentrations. In contrast, the inflammation marker, C-reactive protein, fell with increasing PFOA. In each case the pattern was repeated in the same way for males and females [112]. Although summarized in the reports from the Panel, no peer-reviewed article has been located.

o. Allergies may also be related to PFC immunotoxicity, as reported by studies linking PFC exposure to increased development of allergies in children [132]. First, a study of 244 Taiwanese children found that increased cord-blood concentrations of PFOA and PFOS correlated with elevated cord-blood IgE in boys [133]. The immunoglobulin IgE is usually increased in allergic subjects, but the predictive value of elevated cord-blood IgA in regard to subsequent development of allergy or atopy is limited [134]. Further, a study of 343 Japanese births reported an inverse association between PFC concentrations and cord serum IgE concentrations [135], thus revealing opposite tendencies in the two studies.

p. Using more reliable clinical data, a study of the Faroese birth cohort born in 1997-2000 included data on allergy and asthma at ages 5 to 13 years [136]. Twenty-two of the 559 children had not been vaccinated against MMR, and among those, higher serum concentrations of the five PFASs at age 5 years (but not prenatally) were associated with increased odds of asthma at ages 5 and 13. However, the associations were reversed among MMR-vaccinated children. While PFAS exposure may impact immune system functions, this study suggests that MMR vaccination might be a potential effect modifier.

q. A recent study from China assessed pulmonary function parameters in children with and without asthma [137]. Children with asthma had higher PFC exposures, and their pulmonary functions were poorer the higher the PFC exposure. It therefore seems that PFC exposure may contribute to the development and worsening of asthma.

r. When white blood cell populations are affected by exposure to an immunotoxicant, differential counts of the peripheral blood cells may be a useful measure. In about 50 5-year-old Faroese children, the current serum-PFASs concentrations were associated with higher basophil counts [138]. Although clear associations were otherwise not seen with PFAS exposures in this small sample, the exposure-related changes in lymphocyte subpopulations suggest cellular immunity effects and dysregulation of T-cell mediated immunity.

s. To further explore the mechanisms, a study was carried out in Norway to characterize gene expression in cord blood and its association with PFAS concentrations, antibody concentrations, and infectious disease incidence. Several immunomodulatory genes, especially the C17 gene, were linked to all three parameters, and these findings therefore supported a PFAS-linked genetic mechanism underlying both the lowered antibody response and the increased susceptibility to infectious disease [139].

t. Regarding occupational exposures, a study of 3M workers found clear associations between increased PFC exposure and decreased leukocyte counts, a sign of adverse



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impact on the human immune system. These immunotoxicity appeared to be in agreement with experimental data, especially those in monkeys. The results were reported by Frank Gilliland, MD, as an outcome of his thesis work at 3M about 1990. In his thesis, Dr. Gilliland concluded: "Total serum fluorine was negatively associated with all peripheral leukocyte counts except PMNs [PolyMorphonuclear Neutrophils] and MONOs [Monocytes], which were positively associated."[ooo] Of note, the basophil count at elevated exposures was lower in the adults, while a recent study showed that they were higher in highly-exposed children [138].

Regarding this study, it is worth noting that 3M was aware of Dr. Gilliland's findings of immune system abnormalities, but, unlike certain other findings in Dr. Gilliland's thesis, no report of the immune system findings was publicly disclosed. Thus, in articles published after submission of Dr. Gilliland's thesis, and jointly authored with 3M's Dr. Geary Olsen, nothing was mentioned about leukocyte counts, despite Dr. Gilliland's thesis results that showed clear suggestions of immunotoxic effects. In June of 1993, Dr. Gilliland forwarded to Dr. Jack Mandel, his thesis adviser who was part of the 3M medical service, three manuscripts concerning PFOA-exposed Chemolite employees; the manuscripts were to be submitted for publication that summer.[ppp] Dr. Gilliland and Dr. Mandel co-authored three papers in the public record, one of them on mortality and only two on clinical findings,[qqq, rrr, sss] but none of them includes the results on PFOA immunotoxicity. However, the files produced by 3M contain a manuscript entitled "Peripheral Blood Lymphocyte Count in Men Occupationally Exposed to Perfluorooctanoic Acid."[ttt] It is likely that this manuscript was part of the package sent to Dr. Mandel in June of 1993. One copy of this manuscript includes the following comment: "In addition, the standard immunotoxicologic assessment defined by the National Toxicology Program needs to be conducted for PFOA," and a hand-written comment says, "bring to attention of L.Zobel, R.Perkins, S. Gordon."[uuu] As with 3M's monkey study from 1978 that revealed immunotoxic effects [140] (see below), the leukocyte count results were never published, and the recommended immunotoxicology assessment was apparently not conducted.

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[ooo] AR226-0473. Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. thesis, University of Minnesota), with Summary. Page 003247.

[ppp] 3MA10017137, # Transmittal Of Revised Versions Of Three Manuscripts Concerning PFOA Exposed Chemolite Employees. page 3MA10017137.

[qqq] Gilliland, Frank D., and Jack S. Mandel. "Mortality among employees of a perfluorooctanoic acid production plant." *Journal of Occupational and Environmental Medicine* 35.9 (1993): 950-954.

[rrr] Gilliland, Frank D., and Jack S. Mandel. "Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins, and cholesterol: a study of occupationally exposed men." *American journal of industrial medicine* 29.5 (1996): 560-568. doi:10.1002/(SICI)1097-0274(199605)29:5<560::AID-AJIM17>3.0.CO;2-Z.

[sss] Olsen, Geary W., et al. "An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid." *Journal of occupational and environmental medicine* 40.7 (1998): 614-622.

[ttt] 3MA00323876. Frank D. Gilliland and Jack S. Mandel. Peripheral Blood Lymphocyte Count in Men Occupationally Exposed to Perfluorooctanoic Acid. Pages 3MA00323876 to 3MA00323890.

[uuu] 3MA10016749. Frank D. Gilliland and Jack S. Mandel. Peripheral Blood Lymphocyte Count In Men Occupationally Exposed To Perfluorinated Acid. Page 3MA10016756.



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### 2. Toxicological evidence

Epidemiological evidence showing an association between PFC exposure and adverse effects on human immune system functions finds additional support in various toxicological studies of immune system functions. Experimental studies have provided substantial documentation of immunotoxic effects [5, 17, 141]. Immunotoxicity of PFCs has been demonstrated in a wide variety of species and models, as well as *in vitro* in relation to human white blood cells.

a. Already by 1980, there was an interest in the immunotoxicity associated with perfluorinated organic compounds, where effects observed included decreased antibody formation against sheep red blood cells and spleen enlargement [142]. There seems to have been little or no follow-up in the published literature on these early findings, as also noted by Dr-Gilliland.

b. An early 3M-commissioned 90-day study carried out in monkeys in 1978 demonstrated toxicity effects on the gastrointestinal tract and the reticuloendothelial system (i.e. immune system).[vvv] In this 90-day study labeled 226-0447,[www] the doses of FC-143 (PFOA) given were 0, 3, 10, 30 and 100 mg/kg/day. All monkeys at the 100 dosage and three out of four at 30 mg/kg/day died; compound-related microscopic lesions were seen in adrenals, bone marrow (hypocellularity), spleen and lymph nodes (atrophy of lymphoid follicles in both), as also highlighted by Dr. Gilliland in his thesis from 1993, where he added: "No follow-up studies of these observations have been reported."[xxx]

c. This monkey study and other toxicology studies carried out in or about 1978 were reviewed the following year with colleagues from DuPont, who agreed that there were compound-related effects indicated in both monkey and rat studies, and that additional adverse effects were revealed in the data (although these additional adverse effects were not reported by 3M in the text of the studies) (226-1456, page 000140).[yyy] Certain of the findings were summarized in a published review article [44] from 1980.

d. Recent interest in experimental immunotoxicity of the PFCs began after year 2000, at first focusing on reductions in lymphoid organ weights, lymphoid cell numbers, and de novo antibody synthesis [141]. These studies clearly document adverse immune system effects and support the notion of PFC immunotoxicity [5]. Using a standard immunological challenge of injecting sheep erythrocytes into PFOS-exposed mice, adverse effects were seen at serum concentrations similar to levels observed in occupational exposure, and a calculation of safe exposures was similar to the highest serum concentrations in people with background PFOS exposure [143], while PFOA immunotoxicity occurred at higher serum concentrations [144].

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[vvv] 3MA02512309. F.D. Griffith and J.E. Long. Animal Toxicity Studies with Ammonium Perfluorooctanoate.

[www] AR226-0447. Final Report, Ninety Day Subacute Rhesus Monkey Toxicity Study, International Research and Development Corporation, Study No. 137-090, November 10, 1978.

[xxx] AR226-0473. Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. thesis, University of Minnesota), with Summary. Page 003214.

[yyy] AR226-1456. March 5, 1979 - DuPont reviewed 3M's new C-8 rat and monkey studies and agreed that there are compound-related effects indicated in both studies, and that additional adverse effects apparently were revealed in the data but not reported by 3M in the text of the studies. (Exhibit P (EID 123133).



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Other studies have shown PFC effects on immune measures, such as cytokine expression and signaling related to inflammation and T helper cell responses [141].

e. In regard to response to infections, a study in mice demonstrated that PFOS exposure at levels associated with deficient immune functions showed elevated PFOS concentrations in blood, but also in thymus, spleen, and lungs as well as reduced survival after influenza A infection [145].

f. Further, studies of mice injected with sheep erythrocytes, as a standard test of immune system function, demonstrate deficient immune system responses from PFCs, in parallel to the human studies of vaccine responses. Several rodent studies have applied this experimental model to assess any effects on the antibody response. In a study of PFOS, the lowest observed effect level (LOEL) for males was 0.05 mg/kg total dose and 10-fold higher in females (which excrete PFOS more rapidly). Measured serum-PFOS concentrations at these dose levels were 91.5 ± 22.2 ng/g and 666 ± 108 ng/g (mean ± SD), respectively [143]. The concentrations would be almost the same if measure in ng/mL, the unit used for human blood sdamples. Thus, the serum levels measured in the male mice at the lowest dose applied were similar to the highest conccentrations measured in residents in the exposed area. Yet, these levels were associated with significant adverse effects. As no lower doses were applied, the data do not allow consideration to which extent lower concentrations may also be associated with adverse effects in this animal model.

g. Available information on immune system effects from developmental exposure also supports a link between PFC exposure and adverse immune system effects. In one study of gestational exposure, male pups were again more sensitive than females to the effects of PFOS and confirmed that the developing immune system is vulnerable to PFC exposures and that functional deficits in innate and humoral immunity are detectable at adult age [146].

h. Human white blood cells provide a meaningful *in vitro* model to assess immune system effects, and studies have been carried out to determine the *in vitro* effects of PFC exposure, generally with a focus on cytokine secretion [141]. PFOS was found to be the most toxic of several PFCs studied while PFBS was more potent than PFOA [147]. Thus, white blood cells from human volunteers showed effects at PFOS concentrations of 0.1 µg/mL (or 100 ng/mL) [147], i.e., similar not only to concentrations seen both in affected male mice in toxicology studies, [143] but also to levels in residents exposed to contaminated drinking water [63].

**3. Perspective**

a. In connection with the need to identify safe limits for contamination of drinking water with PFOS and PFOA, the EPA surveyed the PFC literature and summarized its results in PFOA and PFOS risk assessment reports [148, 149]. The EPA draft risk assessment documents finds that PFCs exhibit immunotoxicity in experimental models and that the epidemiological evidence is additive, although mixed exposures complicate the attribution of effects to specific PFCs.



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b. A similar conclusion was reached in the more recent ATSDR ToxProfile on the perfluoroalkyls [4]. As I wrote in my written comments to the Agency, the coverage of human immunotoxicity is unusually very brief in the ToxProfile, and no mention of this potential is made in the chapters on public health. In addition, PFAS-associated immunotoxicity in children was not even included as a potential critical effect of these substances. More specifically, ATSDR stated (p. 176) that the benchmark calculations that we generated [150] could not be used because of the absence of a "control group." The human evidence was therefore not considered in the calculation of a Minimal Risk Level. I note that the requirement of an unexposed control group is unrealistic and also unnecessary, as described, e.g., by EFSA [2].

c. More recently, the National Toxicology Program (NTP) in 2016 reviewed the immunotoxicity information on PFOS and PFOA and concluded that both are "presumed" to constitute immune hazards to humans [5]. Both PFCs suppress the antibody response in animal studies, with a "moderate" level of evidence from studies in humans. The evidence indicating that PFOA and PFOS affects multiple aspects of the immune system supports the overall conclusion that both can be presumed to alter immune function in humans, even though the mechanisms are not clearly understood. The reason for considering the human evidence "moderate" is that all studies are observational (not experimental) and refer to mixed exposures, where the individual and joint roles of PFOS and PFOA are difficult to extract. The term "presumed" is the strongest below "known" in the NTP vernacular.

d. The European Food Safety Authority likewise in their initial opinion in 2008 [1], to which I contributed, relied on experimental toxicity studies at a time where little information on immunotoxicity and few human studies was available. An updated version is expected in the fall of 2017.

e. According to the recent evaluations, the epidemiological evidence demonstrating an association between (mixed) PFC exposure and adverse effects on the human immune system is strong and is supported by ample toxicological evidence on effects of PFOS and PFOA, while other PFCs have been addressed only in few studies. Nonetheless, a recent 3M-financed review [151] has argued against the associations being causal by highlighting uncertainties and minor discrepancies between studies.

f. In a letter to JAMA, three 3M scientists criticized our article that was published in JAMA in 2012 [reviewed at A.1.a. above] [83]. They suggested that antibodies toward diphtheria and tetanus were of no public health interest, as the diseases are rare and not likely to occur in the community under study. According to their view, our findings would reflect the immune system response only to the specific vaccine antigens, which in my mind is an inappropriately narrow interpretation. The evidence reviewed above show similar tendencies for different antibodies under different circumstances, and our understanding of immune system does not suggest that each specific vaccination activates functions that are different from those triggered by other vaccines. In arguing against a link between PFCs and clinically important immunotoxicity, the 3M authiors referred to the Danish National Birth Cohort study that relied on hospitalizations only and imprecise PFC analyses [129]. In addition, numerous diseases of different origins were merged, and the likely impact of multiple social, demographic and other



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factors at different childhood ages were ignored. Thus, this study should be regarded non-informative and not as a proof that PFCs are not immunotoxic.

The 3M authors also refer to a 3M-supported mouse toxicological study that reported no immunological effects at a high dietary PFOS exposure [152]. This reported conclusion, however, is at odds with the conclusions of other studies of the same strain of mice showing PFOS immunotoxicity [98, 141], as well as with the evidence reviewed above. To support their view that interactions with cellular receptors vary substantially between animal species and affect PFC toxicity, the authors cite a publication [99] that acknowledges two of the 3M authors for "critical review and helpful suggestions."

Still, species differences are of importance. This is certainly true in regard to the capacity to eliminate PFC from the blood, and recent rodent studies have therefore expressed exposures in terms on serum-PFC concentration levels for more appropriate comparison between species [141]. Further, some modes of immunotoxic action likely differ between rodents and humans due to differences in the expression of certain nuclear receptors. However, experimental evidence suggests that at least some immunotoxicity effects are independent of PPARα, as demonstrated, e.g., by studies with PPARα knockout models exposed to PFOA [153]. In addition, PPARα is also expressed in humans, although to a lesser degree than in rodents, and potential PPARα dependence or independence may therefore affect species dependence of PFC immunotoxicity [153]. Thus, mechanistic investigations of PFC-induced suppression of cytokine secretion from human immune cells have demonstrated that PPARα activation was involved in the PFOA-induced immunotoxicity, while other pathways appeared responsible in regard to PFOS immunotoxicity [154]. In agreement with the very detailed NTP review [5], we find that the species differences do not invalidate our conclusions that PFC exposure likely presents a human immunotoxicity risk [123, 155].

The caveats mentioned above regarding interspecies comparisons indicate that dose-dependence may differ between humans and rodents, but also that such differences do not argue against the immune system being a major target organ for PFC toxicity in both humans and laboratory animals. 3M's arguments are not weighty enough, and some are clearly flawed, such that they do not change my opinion that, based on the weight of the epidemiological evidence, and supporting toxicity evidence, PFCs pose a substantial present and potential hazard to the human immune system functions with likely severe consequences. Thus, in agreement with the NTP review [5], I conclude that the human evidence strongly supports the existence of PFC-dependent immunotoxicity at background exposure levels, although the relative role of individual PFCs is somewhat unclear. However, detailed statistical calculation show that PFOA-related effects on specific antibody concentrations appear to be independent of other PFC exposures (which are more closely correlated) [120]. Experimental studies document that all PFCs tested have immunotoxic effects. Regarding PFBS, *in vitro* studies so far show that it is less potent than PFOS, but more than PFOA [147].

### B. Reproductive toxicity

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to human reproductive system functions, with risks of adverse effects to the next generation.



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The focus in this section is primarily on obstetrical appearances of PFC toxicity, including pregnancy hypertension and preeclampsia, which conditions were determined by the C8 Panel to have a probable link to C8 exposure [156]. I also address pregnancy outcomes, including miscarriage, birth weight, decreased sperm quality and fecundity. These outcomes may or may not be mediated by endocrine disruption mechanisms, but are dealt with in this section, as they refer to pregnancy and pregnancy outcomes. Taken as a whole, PFC exposure at levels similar to or below those reported from the East Metro area are associated with a range of reproductive toxicity effects.

Other outcomes considered more clearly to reflect endocrine disruption are considered in the following section and include changes in serum concentrations of sex hormones, delayed development including delayed puberty, inhibited lactation and shorter breastfeeding durations, early menopause, and changes in reproductive hormone concentrations in serum.

Regarding developmental toxicity affecting the next generation functionally and in regard to subsequent disease risks, i.e., so-called Developmental Origins of Health and Disease (DOHaD), these aspects are properly discussed in regard to the relevant organ systems (such as the immune system).

### 1. Epidemiological evidence

Data from my review of available epidemiological studies demonstrate a strong link between PFC exposure and adverse effects on human reproductive system functions. One early and important aspect of reproduction is fecundity, i.e., the capability of achieving pregnancy, and other endpoints are then discussed in proper sequence.

#### *Fecundity*

As a parameter commonly used in epidemiological studies, time-to-pregnancy (TTP) is a measure of couple fecundity. However, both female and male risk factors must be taken into regard, and studies in this vary in regard to the validity of data collected [157].

a. TTP was obtained in a Danish study of 1240 women, who had achieved pregnancy, thus excluding infertility. The subjects with serum-PFOS in the highest quartile had a 26% reduced chance of becoming pregnant within the same cycle month as compared to women in the lowest quartile [158].

b. A recent Canadian study of over 1,700 women demonstrated that increasing concentrations of PFCs in serum were associated with both reduced fecundability, as measured by increased time to pregnancy, and infertility [159]. Specifically, an increase in one standard deviation in the serum-PFOA concentration was associated with a 31% increase in the odds of infertility and an 11% reduction in fecundability. Adverse effects from PFHxS were similar, with a 27% increase in the odds of infertility and a 9% reduction in fecundability.

c. When my colleagues and I examined PFC exposures in a prospective study of 222 Danish first-time pregnancy-planners without previous reproductive experience (129 attained pregnancy within 6 months), we calculated the fecundability ratio (FR) using



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discrete-time survival models [160]. The results showed little, if any, difference associated with serum-PFC concentrations, although the study may have been too small to reveal an effect.

d. None of these studies involved cohorts with significantly elevated exposures, such as workers in PFC manufacturing plants or residents of contaminated areas. Still, the available evidence suggests that background exposures to PFCs affect TTP to a limited extent, as suggested by a Norwegian study [161].

e. None of the recent epidemiological studies used sophisticated technologies that have become available in more recent years. In fact, the waiting-time-to-pregnancy (or time required to conceive) measure relies on a simple questionnaire that has been in use since the 1980s [162]. It is therefore unfortunate that no studies have been located from major PFC producers regarding fecundity of exposed employees.

***Puberty development, irregular cycles, and menopause***

f. A cross-sectional study of PFOA and PFOS regarding indicators of sexual maturation was carried out in the Mid-Ohio River Valley. Participants were 3076 boys and 2931 girls aged up to 18 years. They were classified as having reached puberty based on either hormone levels (total >50 ng/dL and free >5 pg/mL testosterone in boys, and estradiol >20 pg/mL in girls) or onset of menarche. For boys, there was a relationship of reduced odds of reaching puberty with increasing PFOS (delay of 190 days between the highest and lowest quartile). For girls, higher concentrations of PFOA or PFOS were associated with reduced odds of postmenarche (130 and 138 days of delay, respectively) [163]. This study may well have underestimated the effects, as it was based on current serum-PFC values only

g. A more recent study focused on 2,292 children aged 6-9 years who had been examined in 2005-2006 in regard to their exposure to PFOA in the Upper Ohio River Valley [164]. In boys, a higher serum-PFOA concentration was linked to lower testosterone, and PFOS with lower estradiol, testosterone and insulin-like growth factor (IFG-1); in girls, a higher PFOS was associated with decreases in both testosterone and IGF-1.

h. In regard to puberty development, a British birth cohort at background levels found that PFOA concentrations in stored maternal pregnancy serum were slightly higher for 218 daughters who had reached menarche before age 11.5 years compared to a similar number of controls with later onset [165]. The results in this study, however, were not statistically significant.

i. In a Danish study of prenatal exposures judged from maternal serum analysis, 367 daughters' menarche was significantly delayed at higher prenatal PFOA exposures [166]. An important strength is that this study focused on prenatal exposure, although with no adjustment for postnatal exposure from breastfeeding and other sources.

j. In 950 pre-pregnant women, higher serum concentrations of PFOA, PFOS, PFNA, and PFHxS showed increased odds of self-reported history of irregular menstrual cycle and long menstrual cycle [167], i.e., disruptions that may be related to an increased risk of subfecundity [168].



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k. The C8 Health Project examined 25,957 women aged 18–65 years regarding serum estradiol concentrations and onset of menopause [169]. The odds of having experienced menopause increased significantly at higher exposures to PFOA and PFOS within the subgroup of middle-aged women.

***Semen quality***

l. A joint analysis of data from three countries suggested a substantially lower proportion of morphologically normal sperm cells at increased serum concentrations of PFOS and PFHxS, while a small increase (opposite direction) appeared to be related to PFOA exposure [170]. Effects on reproductive hormones were also measured and will be dealt with separately below.

m. In a study of 256 men examined at a fertility clinic, no association between the current serum concentrations of PFOA and PFOS and semen parameters was found [171]. However, the concomitant concentrations may not reflect the exposures at the most vulnerable developmental stage or stages where negative effects on semen formation may have happened.

n. In 105 young Danish men from the general population, those with elevated combined serum concentrations of PFOS and PFOA had a median sperm count that was 2.5-fold lower than the median for men with low PFOS–PFOA exposures [172]. Other associations were not statistically significant, but suggested altered pituitary–gonadal hormones at higher PFOS–PFOA exposures.

o. From a pregnancy cohort established in Denmark in 1988-1989, about one-third of the men (169) was recruited at age 20 years to obtain a semen sample and a blood sample [173]. PFOA and PFOS were measured in banked maternal pregnancy serum samples. In utero PFOA exposure was associated with lower sperm concentrations and sperm counts, while PFOS did not appear to be associated with any of these outcomes.

p. According to a recent review, a total of sixteen studies have explored the association between PFC exposure in men and semen parameters, reproductive hormone levels, or TTP. Despite somewhat inconsistent results, subtle associations between higher PFOS and lower testosterone or abnormal semen morphology have been found in some of the studies and cannot be ignored. Also, eleven studies assessed the association between PFAS exposure in women and Time To Pregnancy (TTP), as a measure of fecundity, or reproductive hormones levels. Four of eight studies found prolonged TTP with higher PFOS or PFOA, while one of the four found an association when restricting to nulliparous women [174]. Again, a concern is the time of blood collection for exposure assessment, as adverse effects could be due to, say, pre-puberty exposures.

***Miscarriage***

q. Available evidence suggests that miscarriage and stillbirth are associated with PFC exposure, although the evidence is not yet strong. This is perhaps not surprising as miscarriage and stillbirth, like mortality, are extreme outcomes. A recent study that included more than 300 miscarriages found a tendency towards a positive association with PFOS exposure



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in the Mid-Ohio River Valley, but no association between PFOA exposure and miscarriage [175].

r. A subsequent Danish case-control study of 51 miscarriages utilized serum collected in first trimester and found a significantly increased risk associated with C9 and C10, and a tendency in the same direction for PFHxS, but no clear association for PFOA and PFOS [176]. This study likely had too low a statistical power to reveal minor adverse impacts.

***Pre-eclampsia and higher blood pressure during pregnancy***

s. The C8 Science Panel concluded that PFOA exposure is associated with reproductive toxicity, i.e., an increased risk of pre-eclampsia and higher blood pressure during pregnancy [156].

t. This conclusion rests on extensive studies in the contaminated Upper Ohio River Valley. Data were obtained on 1,845 pregnancies within the 5 years preceding the serum-PFOA analysis and on 5,262 pregnancies analyzed for PFOS. Preeclampsia was weakly associated with PFOA and PFOS [177].

u. However, a more recent study is less convincing. Relying on the serum-PFC analyses from the health examinations in 2005 and 2006, birth records from singleton pregnancies were obtained to identify the 106 cases of pregnancy-induced hypertension. Serum PFOA and PFOS were both positively associated with the diagnosis [178].

v. Using data from the Norwegian Mother and Child Cohort Study, a study was conducted of 976 nulliparous pregnant women, of whom 466 had a validated diagnosis of preeclampsia. No strongly positive associations between PFAS levels and preeclampsia in this population with low background exposures [179]. Thus, the conclusion today is less clear than it was when the C8 Panel based its conclusions solely on the findings in the highly contaminated communities.

***Preterm birth and low birth weight***

w. The C8 Science Panel also evaluated the evidence on preterm birth, birth weight and fetal growth. Some studies available by then suggested small negative shifts at high PFOA exposures [180, 181], but the Panel considered them uncertain and therefore insufficient to conclude the presence of a probable link. EPA in its most recent evaluation considered decreased birth weight in rats one of the critical outcomes for PFOS [149].

x. Others have reached the same conclusion that these reproductive outcomes are too uncertain [182, 183]. However, this conclusion may be arguable, given that decreased fetal growth and lowered birth weight are crude measures that may only weakly reflect more important effects on growth and functional development. On the other hand, the association can be affected by distribution factors, rather than toxicity, and dietary intakes of, e.g., n-3 fatty acids play an important role and is difficult to control for [184] in observational population studies.

y. Relating to the C8 studies, women who reported reproductive histories and who provided serum for the C8 study at the examinations were linked to data on preterm birth



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and birth weight. Elevated serum concentrations of PFOA and PFOS at the health examination in 2005-2006 were associated with a greater frequency of lower birth weight at term [178].

z. A study in Denmark demonstrated increased birth weight in girls at higher exposures to PFOS, PFOA, and PFHxS and reduced birth weight in boys, thereby suggesting sex-dimorphic effects [185]. In support of this notion, the same study also measured the anogenital distance in 511 children and observed decreases in girls, though not in boys, at elevated maternal PFC exposures.

aa. As mentioned above, the C8 Science Panel evaluated the evidence available at that time on preterm birth, birth weight and fetal growth. Some studies suggested small negative shifts at high PFC exposures [180, 181], but the Panel considered them too uncertain and therefore insufficient to support a probable link.

bb. Others have reached the same conclusion that these outcomes are uncertain [182, 183]. However, this conclusion may be arguable, given that decreased fetal growth and lowered birth weight are measures that, although crude, may reflect more important effects on functional development. On the other hand, the association may be affected by a variety of other factors, in addition to fetal toxicity.

cc. In a recent study, birth weight in Norway was apparently not affected by background levels of PFC exposures [186].

dd. On the other hand, the most recent report from the Japanese Hokkaido cohort shows that low background exposures to PFOS and PFOA are associated with decreases in birth weight, and the study also highlights that hormones such as leptin and adiponectin may play a role [187].

ee. A British study of the ALSPAC birth cohort collected serial data on weight and height up to age 20 months and showed that elevated maternal serum concentrations of PFOS, PFOA and PFHxS were associated with decreased birth weights in girls but that higher PFOS exposures were then associated with increased body weight at 20 months [188].

ff. A similar study from the Faroes revealed that a higher maternal pregnancy serum-PFOS concentration was associated with increased weight (and overweight) in the child at age 18 months, while PFOA rather showed a similar association with weight at 5 years of age [189]. These findings suggest that birth weight as an outcome at a particular point in time may need to be seen as part of an intrauterine-postnatal growth profile.

gg. None of the recent studies of birth weight and postnatal growth involved cohorts with significantly high parental PFC exposures, such as workers in PFC manufacturing plants or residents of contaminated areas, even though studies might have been easy to carry out. Overall, the available evidence suggests that fertility and pregnancy outcomes may not be highly sensitive targets of PFC toxicity, at least not easily detectable in the presence of many other determinants, but the evidence suggests minor adverse effects at elevated levels of background exposure.



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hh. I am aware of Professor David Sunding's statistical analysis in connection with this case showing a pattern of increased incidences of premature births, low birth weights, and decreased general fertility rates in Minnesota communities that I understand are, and have been, most affected by PFC-contaminated ground water. His findings are consistent with the evidence summarized above showing associations between PFC exposure and adverse effects on human reproductive functions, in particular risks of adverse effects on fetal growth.

***Developmental defects and delays***

Early indications of potential reproductive harm from PFCs comes from 3M's and DuPont's own experience. Some incidents were rather anecdotal and could have been random observations, but the evidence is still noteworthy and troubling. It is supported by toxicological evidence from animal studies, as discussed below.

ii. One of the first indications of developmental toxicity from PFCs was the observation that two of seven children born between 1979 and 1981 to female workers at a Dupont PFC plant had birth defects. One of the DuPont employees with heavy exposure to PFOA had a miscarriage followed by a normal pregnancy. Given the sample size, this may have been a chance event, but such occurrences should clearly trigger intensive surveillance and toxicology follow-up. 3M revealed that they planned to review in detail an experimental teratogenesis study and if a positive finding was made, women of childbearing potential would be removed from jobs with exposure.[zzz]

jj. A September 15, 1981 letter from DuPont's Washington Works to the Shimizu Corporation in Japan proposed an employee blood sampling program. The letter had an attachment on pregnancy outcomes among female production workers, according to which one child had unconfirmed eye and tear duct defect. A younger child had one nostril and an eye defect,[aaaa] both exceedingly rare and very unlikely to occur among as few as seven births.

kk. In December of that year, two DuPont female employees raised questions on the status of the C8 teratogenesis study; one of the women had a child with congenital eye defects and wanted to know if the 3M studies found any malformations affecting the eye.[bbbb] As noted below, the studies did in fact reveal developmental effects from PFCs on the eyes of rodents.

Apart from malformations, developmental toxicity in a more general sense may affect several organ systems and is sometimes reported in connection with reproductive toxicity. My review of available epidemiological data on developmental toxicity covers these aspects relating to the individual organ systems. The overall impression from these data is that only

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[zzz] AR226-1375. March 25, 1981 - DuPont's Medical Director, Dr. Bruce Karrh, summarized the birth defect data received from 3M and DuPont's knowledge of the pregnancy outcome status of Washington Works employees exposed to C-8. page 000098.

[aaaa] AR226-1390. September 16, 1981 - A DuPont employee updated by hand DuPont's May 14, 1981 chart summarizing birth and pregnancies among female Washington Works employees to incorporate the C-8 blood results received in July of 1981. (Exhibit R (EID079371-5)). page 000175.

[bbbb] AR226-1393. December 18, 1981 - Questions on C-8 stats report (Ref: C-8 (FC-143) status report, December 15, 1981 (Exhibit U (EID07954)). page 000180.



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suggestive evidence surfaced during the early years, i.e., by about 1980, and it took 20-25 years before more detailed evidence was published from studies of developmental toxicity in the general population with PFC exposure.

### 2. Toxicological evidence

A significant part of the early toxicological evidence concerning reproductive harm from PFCs comes from 3M's and DuPont's own studies. More extensive information on reproductive toxicity in animal models are available in recent reviews [4, 6].

a. An experimental study conducted by 3M in 1981 showed birth defects in eye lens of rats exposed to PFOA (the report was filed as a TSCA 8e document with the U.S. EPA) [90]. In fact, a total of three teratology studies were carried out, all of them finding lens abnormalities in exposed animals. In March 1981, 3M informed DuPont of the rat study, and DuPont then removed all female employees from C8 exposed jobs, although without telling them why.[cccc]

b. Later, Dr. E. G. Lamprecht, a 3M consultant, argued that the fetal rat lens abnormality was incorrectly interpreted as a teratogenic change and that later studies could not repeat the finding of a teratogenic effect.[dddd] The following year, 3M's E. Marshall Johnson, in a letter to William C. McCormick, III agreed with the position that the teratogenic finding in the teratology studies on PFOS, ethyl FOSE, and PFOA was an artifact.[eeee] A 3M Employee Communication therefore reported that no teratogenic effect was found.[ffff] Much later, in 1998, Dr. Marvin Case, a 3M corporate scientist, reviewed the teratology studies and also agreed that "neither FC 95 nor FC 143 causes teratogenic effects in animals when dosed at levels which are maternally toxic. … The lens change observed in rat pups in Riker Laboratories studies was allegedly a sectioning artifact and was not found upon repeat studies at independent laboratories."[gggg] Still, in my opinion, the very rare eye and facial malformations in children born to highly-exposed female PFC production workers are unusual and highly worrisome, even though experts hired by 3M called the eye malformation in the dosed animals an artifact – an unusual critique of a highly-experienced test laboratory. I find this explanation unusual and rather far-fetched. In addition, congenital eye defect concerns also arose in later rodent studies commissioned by 3M, and it seems from my reading of the files that they have not been explained away. However, as my focus is on the epidemiological studies, I have not attempted to locate all documents on this issue.

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[cccc] AR226-1378. March 31, 1981 - DuPont notified its employees that all female workers would be removed from jobs "Where there is potential for exposure to C-8" at DuPont's Washington Works. In standby questions and answers for those employees. page 000116.

[dddd] AR226-0287. Memorandum to Riker Study Files: Fetal Rat Lens Artifact -- Summary of Developments to Data. page 004333.

[eeee] AR226-0530. Letter from E. Marshall Johnson to William C. McCormick, III re Riker teratology studies on PFOS and ethyl FOSE, dated November 12, 1982. page 004139.

[ffff] AR226-1395. March 1, 1982 - C-8 (FC-143) Employee Communication (Exhibit W (EID089464)). page 000183.

[gggg] AR226-0468. 3M Memo re FC 95 and 143 Teratology, from Marv Case to Georjean Adams, dated May 26, 1998, enclosing an analysis of the eye lens defect. page 003116.



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c. In regard to PFBA, a recent study on reproductive effects in mice reported full-litter loss only at the very highest exposure and a significant delay in eye-opening in the offspring in all three PFBA groups [190]. In the same study, the age at which the mouse offspring reached puberty was determined by monitoring vaginal opening in females, and significant, dose-dependent delays were observed. The MDH relied on these effects when determining a limit for PFBA concentrations in ground water [63].

Subsequent sections will focus on endocrine disruption, including serum-hormone concentrations and breast development that appear to be critical adverse effects in humans, while also documented in laboratory animals.

### 3. Perspective

The C8 Science Panel did not conclude that there is a probable link between exposure to PFOA and birth defects [191], and more recent evidence has not added further support for such linkage. A link only to pre-eclampsia was considered sufficiently justified by the Panel [156]. At the time, a link to decreased birth weight was not found, but more recent evidence suggests that the evidence on decreased fetal growth should consider time-dependent growth patterns.

The C8 Panel did not look as broadly at reproductive and related developmental issues, given that consideration needed to be given to the findings that could be made based on the use of methodologies and population groups available at the time. Recent evidence is highly suggestive of adverse effects on female reproduction, as indicated by increased occurrence of puberty development, irregular menstrual cycles and decreased fecundity. Male toxicity is also much better documented now, although exposure misclassification needs to be carefully considered.

Therefore, based on the weight of all the evidence, that PFCs pose a substantial present and potential hazard to human reproductive system functions.

## C. Endocrine disruption

Outcomes usually considered to reflect endocrine disruption will be dealt with in the present section, including changes in reproductive hormone concentrations in serum and inhibited lactation as indicated by shorter breastfeeding durations in exposed women.

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFC exposure at levels similar to or below those reported from the East Metro area pose a substantial present and potential hazard to human endocrine functions.

Endocrine disruption effects are usually defined as adverse effects in an intact organism or its progeny that have an endocrine mode of action, i.e., that it alters the function(s) of the endocrine system. Due to the serious human health consequences, endocrine disruption has become a top priority in chemicals control efforts in the EU and elsewhere [192].



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Based on the available evidence, PFCs are convincingly associated with endocrine disrupting effects that may have substantial impacts on vulnerable population groups. While endocrine disruption is often thought to be related to reproductive toxicity, a wide variety of hormones play a role for various physiological functions, and their disruption can cause a variety of dysfunctions and diseases. Hormones addressed by PFC research include sex hormones, thyroxin, and insulin. The serum concentrations of some hormones vary during the day or with food intake, and variability of sampling times and lack of statistical control for such factors may hide or attenuate PFC-associated changes in hormone concentrations.

**1. Epidemiological evidence**

***Serum-hormone concentrations***

a. Early evidence on endocrine disruption associated with PFC exposure originates from a doctoral thesis project, where Frank Gilliland, MD, studied clinical pathology parameters in 111 male workers in 3M's Chemolite plant in Cottage Grove, MN. There was a positive correlation between PFOA exposure measured as serum total organic fluorine and estradiol (an adverse effect), and a negative correlation with free testosterone (also an adverse effect) with this association being stronger in older men. Dr. Gilliland therefore concluded that PFOA may affect male reproductive hormones.[hhhh] This study was not reported on its own in a scientific journal, but was referenced in a subsequent article led by 3M authors [88].

b. This subsequent follow-up study further explored serum hormone abnormalities in exposed workers and likewise showed a positive correlation between PFOA exposure and serum-estradiol (an adverse effect) [88] in 111 and 80 production workers studied in 1993 and 1995. The 10% increase in mean estradiol levels observed among those employees with the highest serum-PFOA concentration was argued to be potentially confounded by body mass index (although the risk of obesity may be increased at higher PFC exposures, see section VII.E). Despite the fact that two sets of data were available, and 68 participated in both (and some likely were also examined by Dr. Gilliland), the authors chose not to conduct comparisons over time, allegedly due to variability of the hormone analyses. The 3M authors concluded that the results provided reasonable assurance that, in this production setting, and contrary to the directionality of Dr. Gilliland's findings, there were no significant hormonal changes associated with PFOA at the serum levels measured. A memo from Dr. G. Olsen in 1998 proposes that the hormone concentrations were affected by misclassified body mass index as a confounder.[iiii] Interestingly, an anonymous reviewer who assessed the manuscript for a major occupational health journal questioned why the authors would present scatterplots for PFOA and some endpoints that were all non-significant, but not for the estradiol/testosterone results, which were statistically significant.[iiii]

c. The C8 Health Project examined 25,957 women aged 18–65 years regarding serum estradiol concentrations [169]. There was a significant inverse association between PFOS and estradiol, though not between PFOA and estradiol, thereby suggesting that

[hhhh] AR226-0473. Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. thesis, University of Minnesota), with Summary. Page 003246.
[iiii] 3MA00652081.Memo to file. Geary Olsen. 1/15/98.
[iiii] 3MA00630994. Reviewer 1, Occupational And Environmental Medicine 1997/187, page 3MA00630995.



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endocrine effects from PFC exposure may differ between men and women. As mentioned in section B, there was also an increased odds of having experienced menopause at elevated exposures to PFOA and PFOS among study participants.

d. In a study of nearly 2,300 children living near a PFOA production facility in the Mid-Ohio River Valley, increased PFC exposure was found to be correlated with lower levels of sex hormones. Especially in boys, increased PFOS concentrations were associated with lower testosterone, estradiol, and IGF-1 levels, and increased PFOA concentrations were correlated with lower testosterone levels. In girls, increased PFOS concentrations were associated with lower testosterone and IFG-1 levels [164]. Again, this study supports the notion that the PFCs are endocrine disruptors and that effects may differ also by age.

e. A study of postpubertal women at age 15 years whose mothers were exposed to PFCs at background levels in the UK found that higher levels of maternal exposure to PFOS, PFOA, and PFHxS were correlated with higher testosterone concentrations. Findings from this study suggest that prenatal exposure to PFCs leads to adverse effects that may be lasting and may be expressed during or after puberty [193]. Again, differential effects may be observed in regard to different developmental stages.

f. A study of 540-person cohort in Taiwan found that increased serum concentrations of PFOA and PFOS were correlated with decreased levels of sex hormones in adolescents and young adults at ages 12-30 years [194]. In particular, PFOS was associated with a significant decrease in follicle-stimulating hormone (FSH) levels in young men aged 12-17, and in serum testosterone levels in young women of the same age. PFOA was associated with a significant decrease in serum levels of sex-hormone binding globulin (SHBG) in the young women aged 12-17 years, and negative associations between PFC exposures and the hormones measured were particularly strong in the young women

g. From the Danish pregnancy cohort established in 1988-1989, the 169 men at age 20 showed higher adjusted levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) associated with higher prenatal PFOA exposures [173]. PFOS did not appear to be associated with hormone concentrations.

h. In 105 young Danish men at background exposures, hormone profiles suggested poorer function of Leydig cells (which produce testosterone) at higher PFC exposures. However, the associations in this small study were not statistically significant [172].

***Duration of breastfeeding***

i. A study of 1,400 Danish women reported that the duration of breastfeeding, as recorded by two telephone interviews, decreased at increasing serum-concentrations of PFOA and PFOS, although only in multiparous women [195]. In multiparous women, previous breastfeeding might confound the association, and this finding therefore did not provide strong support for a causal association.

j. A recent study in the U.S. [196], however, found that increased maternal serum-PFOA concentrations were correlated with a decreased duration of breastfeeding, and that



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this association was not confined to multiparous women and is independent of potential confounders, thereby supporting a hypothesis of endocrine disrupting effects. Although the recording of duration of exclusive breastfeeding may have been somewhat imprecise, the fact that the women were not aware of their own exposure levels excludes any important bias.

k. These findings are supported by a subsequent study of 1,130 new mothers in the Faroe Islands [197]. A doubling of maternal serum PFAS concentrations was associated with a reduction in duration of both total and exclusive breastfeeding, most pronounced for PFOS, where a doubling was associated with a reduction in total breastfeeding of about six weeks. Similar effects were seen for PFOA, though not for PFHxS. These associations were evident among both primiparous and multiparous women, and thus cannot be explained by confounding from previous breastfeeding.

**2. Toxicological evidence**

Endocrine disruption effects in humans are supported by a substantial number of experimental animal studies [4, 7, 9, 148, 149]. A few key studies are highlighted below.

a. An early study of the effects of APFO (the ammonium salt of PFOA) exposure in rats showed a substantial increase in hepatic aromatase activity [198]. An increase in aromatase activity is likely to increase the formation of estradiol from testosterone, thus a decrease in serum-testosterone and increased estradiol.

b. Accordingly, changes in serum concentrations of testosterone and estradiol are considered likely to be due to PFC-mediated changes in the hepatic aromatase activity [199], but interference with sex hormone receptors has also been reported [200]. Such modes of action could well mediate the PFC-associated endocrine disruption findings in epidemiology studies.

c. A recent study examined the effect of PFOA and PFOS exposure on proteins and cells related to the male reproductive system and demonstrated that both PFOA and PFOS inhibit important drug transporting proteins present in the blood-testis barrier, thereby potentially contributing to male infertility [201].

d. Endocrine disruption effects appear to be independent of PPAR activation and therefore are likely relevant to human PFOA toxicity [7]. Among reported mechanisms, PFOA can activate nuclear receptors other than PPAR, i.e., the constitutive androstane receptor (CAS) and the pregnane X receptor (PXR), and activation of the estrogen receptor (ER) may also be involved [202, 203]. Local testicular effects are indicated by induction of Leydig cell hyperplasia and adenoma in experimental studies, apparently independent of PPAR activation [17].

e. A toxicological study designed to evaluate the impact of PFC exposure on androgen secretion in the testis examined the effects of PFC exposure on inhibition of human and rat microsomal enzymes. The study demonstrated that PFOS is a potent inhibitor of human 17β-hydroxysteroid dehydrogenase 3 enzyme in testicular cells. The results support the conclusion that PFOS exposure adversely affects reproductive hormones, as the enzyme



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inhibition demonstrated in this study may well contribute to decreased androgen secretion in the testicles [204].

f. Experimental studies show that mammary gland development in mice is inhibited by PFOA exposure during early development at serum concentrations similar to those occurring in the East Metro residents [7, 9, 205]. The State of New Jersey regards this as one of the most sensitive non-carcinogenic endpoints [206] (see section VIII).

**3. Perspective**

a. Regarding endocrine disruption, substantial research activity has emerged during the last 20 years or so, and much improved toxicologic understanding of the mechanisms involved has resulted. In addition, a wealth of epidemiological studies has documented the adverse human health consequences [192]. Although the studies of serum-hormone concentrations at 3M coincided with early discoveries on endocrine disruption, this issue was apparently not treated as a priority for further studies at the time.

b. As mentioned under C.1.b, the paper co-authored by 3M scientists and Dr. Gilliland in 1998 reported on clinical pathology results from serum analyses, including reproductive hormones and concluded that there were no significant hormonal changes associated with PFOA at the serum levels measured [207].[kkkk] While this conclusion was counter to Dr. Gilliland's findings in his thesis project, the data analysis in the published paper seems inadequate. One difference between the 1998 and Dr. Gilliland's thesis is that Dr. Gilliland relied on total organofluorine concentrations, and the subsequent study referred to PFOA, but this issue was not explored in the published paper. However, in September of 1998, Dr. Olsen wrote a proposal for a study titled "fluorochemicals exposure assessment of Decatur Chemical and Film plant employees." According to this document, "approximately 1/3 of these film plant employees had past work history experience in the chemical plant." [llll] Thus, truly low-level exposures were difficult to locate. The article lists the lowest serum-PFOA level as "0.00 ppm," i.e., below 10 ng/mL, thus reflecting a high detection limit that would not allow analysis of current-day exposures of the general population.

c. It is worth noting that all or most of the studies above used only concurrent blood samples for PFC analysis, and less or no information therefore is available on the impact of prenatal exposures. In one of our recent prospective studies focused on PCBs, another pollutant also suspected of causing endocrine disruption including Leydig cell dysfunction, the results showed that changes in hormone concentrations were correlated with PCB concentrations in cord blood. However, only scattered relationships were observed in relation to PCB concentrations in concurrent blood samples [208]. There is reason to believe, therefore, that PFC levels in cord blood could show even stronger correlations than those shown

[kkkk] AR226-0474. Geary W. Olsen, et al., An Epidemiological Investigation of Reproductive Hormones in Men with Occupational Exposure to Perfluorooctanoic Acid, 40 JOEM 614-619 (July 1, 1998), with Summary of study. page 003468.

[llll] AR226-0950. Fluorochemical Exposure Assessment of Decatur Chemical and Film Plant Employees (Data Summary, Protocol and Final Report). page 001249.



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in the studies above using concurrent blood samples, showing increased adverse effects from PFCs on human health during vulnerable developmental time windows.

d. Serum-hormone changes observed in relation to semen quality suggest that they are both related to endocrine disruption mechanisms, as also indicated by experimental studies in laboratory animals. A concern is again that most studies have relied upon PFC concentrations measured in serum obtained at the wrong time, i.e., not regarding the most vulnerable developmental stage. Such exposure misclassification will likely result in an underestimation of the true PFC effects [101]. Thus, in my opinion, results showing adverse effects could be even stronger during vulnerable developmental time windows is also supported by our studies on prenatal exposure to pesticides [208-210]. Further, the findings may be of greater public health relevance, given the known excess mortality associated with decreased serum-testosterone concentrations in men [211].

## D. Thyroid hormones and related diseases

Although thyroid function is usually dealt with as part of the endocrine spectrum of functions, PFC effects on the thyroid gland appear to be independent of other forms of endocrine disruption and are therefore dealt with separately. The same is the case regarding insulin and metabolic abnormalities (see section VII.E). For the sake of clarity, these specific gland-related effects are dealt with in separate sections.

It is my opinion, based on the weight of the epidemiological evidence and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to human thyroid functions, with related adverse effects.

Based on the available evidence, the thyroid gland appears to be a target organ for PFC toxicity, as supported by laboratory experimental data [212] and recognized by the C8 Panel [213]. The Panel report is quite comprehensive, and the coverage of thyroid dysfunction will therefore emphasize major and recent studies. Taken as a whole, PFC exposure at levels similar to or below those reported from the East Metro area are associated with thyroid disruption effects.

Even subclinical hypothyroidism is a health concern, especially during pregnancy, as fetal brain development is highly vulnerable to deficiency in maternal thyroid hormone supplies [214, 215]. Moreover, as the thyroid gland is the target for a substantial number of environmental chemicals, PFCs are likely to contribute to joint effects in combination with exposures to other thyroid toxicants [216].

### 1. Epidemiological evidence

a. Dr. Gilliland analyzed in his doctoral thesis data from his cross-sectional study of 3M production plant workers regarding thyroid effects associated with organofluorine concentrations in serum. A positive correlation was seen between organic fluorine and the thyroid stimulating hormone (TSH) in serum.[mmmm] Elevated TSH is often seen when thyroid

[mmmm] AR226-0473. Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. theses, University of Minnesota), with Summary. Page 003247.



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functions are deficient. In a later paper on thyroid function measurements in about 500 workers from 3M production plants in Alabama and Belgium, 3M scientists argued that variable associations with thyroid hormones (and all other clinical pathology parameters measured in this study) were of limited, if any, clinical relevance [217]. Attention is drawn to lifestyle factors, while sex-dependent associations, more sophisticated exposure classification, duration of exposure, and additional data available from Minnesota were clear weaknesses.

b. A cross-sectional data set from the C8 Health Project on 52,296 adults with a year or more of exposure to contaminated drinking water showed that both PFOA and PFOS in serum were associated with significant elevations in serum thyroxine (T4) and a significant reduction in T3 uptake in all participants, thus showing disruption of thyroid functions [218].

c. A later study of 33,254 exposed community members and production workers applied calculated temporal trends in serum-PFOA concentrations [219]. The occurrence of 2,109 cases of functional thyroid disease, i.e., hyperthyroidism and hypothyroidism, was associated with PFOA exposure in women, while exposed men showed a tendency of hypothyroidism at elevated exposures.

d. In 10,725 children and adolescents aged 1-17 years examined within the C8 community study, a tendency was seen toward an increased risk of an increased serum concentration of total T4 concentrations was found for PFOS, but was not significant for PFOA. Further, an increased odds ratio for hypothyroidism (observed in 39 cases) was found at the highest quartile of PFOA exposure [220].

e. In a study based on NHANES data on 3,974 adults, serum concentrations of PFOA and PFOS were compared between subjects with and without self-reported thyroid disease [221]. Women with a serum-PFOA concentration in the highest quartile were more than twice as likely to report current treated thyroid disease compared to women with low PFOA levels. The same tendency was seen in men, although it was of borderline significance. For PFOS, the trend was significant in men, but not in women.

f. In a similar NHANES-base study of 1,181 adults, higher serum concentrations of PFOA were associated with increased serum concentrations of T3, while PFHxS was linked to increases in both T3 and T4, but to lower T4 in men [222]. These findings suggest sex-dimorphic effects of PFCs on thyroid functions.

**2. Toxicological evidence**

a. Thyroid dysfunction in humans exposed to PFCs is supported by a wide range of studies in laboratory animals [4], and the sensitivity of thyroid functions to environmental chemicals is well documented [223]. Most of the evidence regards PFOS and PFOS, with some studies also covering PFHxS and longer-chain PFCs.

b. Regarding PFBA, an experimental study reported morphological changes in the thyroid gland and decreased serum concentrations of total T4 [224]. The MDH relied on



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this study and additional information from first author Dr. J.L.Butenhoff from 3M (see section VIII) [63].

### 3. Perspective

a. Although the very detailed report from the independent C8 Panel found a probable link between PFCs and adverse thyroid function effects [213], even the fairly recent reports from 3M purported to show no such link [217, 225-227].

b. Dr. Gilliland reported a positive correlation between PFOA (measured as serum total organic fluorine) and the thyroid stimulating hormone (TSH) in serum.[nnnn] As mentioned above (section D.1.a), 3M scientists argued in a later paper that variable associations caused any thyroid effects to be of limited, if any, clinical relevance [217]. However, when more recent findings pointed again to adverse effects on the thyroid gland, the summary from an internal 3M workshop on research prioritization said: "Unanswered questions, how to explain away the findings: measurement issue, thyroid economy – long term effects/ consequence?"[oooo] Unfortunately, the document does not describe how findings could be or were explained away, although the intention is obvious.

c. Recent evidence suggests that thyroid toxicity is of particular relevance in pregnant women with a pre-existing thyroid dysfunction [228]. This issue has not yet been explored regarding PFC effects, and the evidence so far does not allow any conclusion on impact of PFC exposure in the presence of borderline iodine deficiency. In addition, sex-dimorphic differences in thyroid vulnerability to PFC exposures need to be characterized. In general, the lack of assessment of PFC exposures at the most vulnerable time, lack of assessment of contributing factors, and other determinants will tend to weaken any true association between PFC exposure and adverse effects on the thyroid gland.

## E. Insulin and diabetes

Based on the weight of the epidemiological evidence and supporting toxicity evidence, I conclude that PFCs pose a substantial present and potential hazard to human health regarding increased risks of developing diabetes and metabolic disease or dysfunction. These outcomes include an increased risk of developing overweight or obesity. As these conditions are common and increasing in prevalence, even a small increase in diabetes risk and obesity would be of major public health impact [229, 230].

Although the C8 Science Panel concluded that the evidence available to them at the time was insufficient to conclude that PFOA is linked to the development of type 2 diabetes (T2D) [231], recent evidence suggests that PFC exposure has a potential of causing adverse metabolic effects, including the development of type 2 diabetes (T2D) and obesity, as part of

[nnnn] 226-0473.pdf, Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. theses, University of Minnesota), with Summary. Page 003173.
[oooo] 3MA00432615. Results of Research Prioritization Workshop / PFOS Research Prioritization Workshop Outcomes June 2-3 2005. Page 3MA00432616.



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current exposures to so-called obesogenic chemicals [232], especially in regard to developmental exposures [233].

### 1. Epidemiological evidence

I have not been able to identify early studies on metabolic changes associated with PFC exposures. The global distribution of PFCs and the emerging obesity epidemic and increasing T2D occurrence might have inspired more studies in this field.

Glucose metabolism parameters are likely more sensitive and precise than diagnostic records and death certificates. But many of the existing studies rely on the latter. Thus, PFC-induced insulin insensitivity needs attention, in particular in prospective studies.

a. In regard to diabetes, an increased mortality due to this diagnosis has been reported in PFC-exposed workers [73, 76], and the increase was significant in comparison with unexposed company controls. This increased risk is noteworthy, as diabetes itself is usually not a primary cause of death. However, functional studies of exposed workers, e.g., utilizing oral glucose tolerance testing, have not been identified.

b. In a community study, PFOA exposure in 54,000 adults was not found to associated with development of T2D, and neither was the fasting serum glucose concentration associated with the exposure [234].

c. In an extension of this study, the C8 Science Panel did not find any indication that PFOA exposure was related to diabetes [219] [231]. However, as diabetes as a cause of death on death certificates is not a reliable way of obtaining information on the occurrence of this disease, the absence of clear associations should not be regarded as proof that diabetes is not associated with PFC exposure. In addition, data from the study suggest that fasting serum insulin decreases at higher PFOA exposures [235], and these results would need to be explored further in regard to the possible effects of cofactors, such as age and age-dependent exposure profiles.

d. Additional support for background PFAS exposure being a risk factor for T2D comes from certain cross-sectional studies such as the NHANES data [236, 237]. Given that the data are cross-sectional, the validity of these results is somewhat uncertain, and they may likely underestimate the true diabetogenic impact of PFC exposure.

e. In a study in Taiwan, PFOA in adults was positively correlated (adverse effect) with their beta cell function (possibly as a sign of compensation for insulin resistance), and PFOS was positively correlated (adverse effect) with blood insulin, insulin resistance (homeostasis model assessment), and beta cell function [236].

f. Data on 499 prepubertal children [238] showed that current exposures to PFCs are linked to increased risk of overweight and deficient glucose homeostasis. In 811 children from the Danish national birth cohort, prenatal exposure to PFOA and PFOS did not seem to be associated with height and weight at age 7 [239], but the validity of the PFC measurements has later been called into doubt [100].



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g. Additional evidence exists that PFC exposure may be related to overweight, which is also a risk factor for T2D diabetes. Thus, PFOA in stored pregnancy serum from a birth cohort of 422 subjects examined again at age 20 years was positively correlated (adverse effect) with body mass index (BMI) and other indicators of obesity [240].

h. Similar findings were reported from a birth cohort of 1,006 children in Boston [241], where higher prenatal exposure to PFOA, PFOS and PFHxS was associated with higher BMI, skinfold thicknesses and DXA assessment of total body fat, although only in girls at 7-8 years of age. Additional support derives from a birth cohort study that relied on joint data from Greenland and the Ukraine [242].

i. In Faroese children, born in 2007-2009, maternal pregnancy serum concentrations of PFOS and PFOA were associated with increased BMI and/or overweight risk at age 5 years [189].

j. In a recent review of the epidemiological evidence, the joint impact of PFCs and other endocrine disruptors on overweight and obesity is highlighted, with the recommendation that future studies should examine multiple exposures, rather than one at the time [243]. This is indeed a concern, as exposures usually include more than one PFC, and often many other toxicants.

**2. Toxicological evidence**

a. Given the epidemiological and experimental evidence (described below), we have used computer modeling to ascertain links between T2D and environmental chemicals, as recently described [244]. We first identified genes and proteins known to be involved in the pathogenesis of T2D and obesity development and then analyzed interactions with proteins and protein-protein interactions to establish links between environmental chemicals and T2D. Both PFOS and PFOA appeared to trigger mechanisms associated with T2D risk (unpublished results), but whether the modeled interactions with the diabetes-related genes and proteins result in disease requires confirmation. Nonetheless, this finding supports the notion that PFCs should be considered as likely diabetogens.

b. Reviews of experimental evidence on obesogenic and diabetogenic chemicals cover the evidence in greater depth [232, 245], also regarding developmental exposures [233].

c. Rodent studies have demonstrated that glucose homeostasis is adversely affected by PFC exposure [246].

d. While PPAR activation may play a role, the adverse outcome pathway for development of T2D may also involve PPAR-independent pathways, such as activation and disruption of the hepatocyte nuclear factor 4α [247].

e. That the pancreas may be a target organ for PFC toxicity is also suggested by an increased occurrence of pancreatic cancer in PFC-exposed rodents [17].



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f. In mice, prenatal exposure to PFOA induced elevated serum concentrations of leptin and insulin, and overweight in mid-life [78].

g. A separate study demonstrated that prenatal exposure to PFOA affected expression of genes involved in the control of lipid and glucose metabolism [235].

### 3. Perspective

As diabetes develops over many years and may even be programmed prenatally [248], the evidence available needs to be considered in regard to the validity of exposure parameters that may not reflect the PFC exposure at the relevant age or developmental stage, where disease initiation may have begun. Likewise in regard to obesity, approximately one-third of adults and 17% of youth in the United States are obese [249]. Recent prospective studies of birth cohorts suggest that early-life exposures impact anthropometric measures in childhood and adolescence.

Much attention is currently being paid to these issues regarding PFC exposures, but in birth cohorts and in prospective studies of adult populations. I am aware of a study carried out in American nurses, currently under publication, that serum-PFC concentrations measured in serum samples collected in the 1990s were associated with an increased risk of subsequently developing T2D (Qi Sun et al.). Another study based on the POUNDS Lost intervention study, showed that participants with higher serum-PFC concentrations had greater difficulty maintaining the weight loss induced by calorie restriction than those with lower exposures (Liu et al.). Studies like that are likely to substantially extend the data base to evaluate the adverse impacts of PFC exposures.

Recent information suggests that obese persons are healthier and live longer now than in previous decades, likely because of better care and risk-factor management [250]. However, the joint public health effect of increased prevalence and decreased mortality leads to more years spent with obesity and more time for the damaging coexisting illnesses, such as type 2 diabetes and chronic kidney disease, to develop.

## F. Neurobehavioral functions

My above conclusions in regard to adverse PFC effects on thyroid functions is relevant also in regard to possible developmental neurotoxicity, as hormones are crucial to brain development [251], in particular the thyroid hormone [215]. A recent neurotoxicology review suggested that developmental effects due to PFASs may be mediated by thyroid toxicity, influence on calcium homeostasis, protein kinase C, synaptic plasticity and cellular differentiation, perhaps as part of a cocktail of substances that in combination reach harmful concentrations [252]. Given the PFC-associated hormonal disruptions that may occur during fetal development, neurodevelopmental toxicity is likely. Taken as a whole, PFC exposure at levels similar to or below those reported from the East Metro area are associated with a range of adverse neurobehavioral effects.

Concerns regarding adverse effects on brain development were apparently not explored during the early years, but evidence is now emerging. The developing brain is a highly sensitive target for environmental chemicals [253], and the available evidence shows that the



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human brain is also likely to be vulnerable to PFC toxicity, although assessment of the magnitude of PFC-associated neurotoxic risks is not yet possible.

**1. Epidemiological evidence**

a. Neurobehavioral outcomes were assessed regarding maternal pregnancy serum concentrations of PFOA and PFOS in 1400 members of the Danish National Birth Cohort. Maternal serum-PFOS was found to be associated with delayed gross motor development in the first two years of life [254], but no other significant associations were found with crude developmental milestones during the first two years of life or children's subsequent behavioral or coordination problems at age 7 (mailed questionnaire) [96]. All results were adjusted for duration of breast-feeding, although lactational PFC exposure was not modeled. Despite the size of the study that should provide some statistical power, the outcome measures used may not be sufficiently sensitive and also too non-specific.

b. Two studies have considered children's serum PFC concentrations in relation to parental reports of ADHD. First, cross-sectional NHANES data from 1999-2000 and 2003-2004 for adolescents aged 12-15 years (N = 571) found significantly increased adjusted odds ratios (ORs) for ADHD [255]. However, cross-sectional data on subjects aged 5-18 years (N = 10,546) from the C8 Health Project showed an OR that was significantly low for PFOA, significantly high for PFHxS, and not significant for PFOS [177]. These cross-sectional data are difficult to evaluate, as a causative exposure would have to precede the diagnosis, and because ADHD behaviors could conceivably affect PFC exposure levels in children. In addition, a more recent follow-up of 321 of these children showed disagreements between maternal and teacher reports on children's behavior, thus making it difficult to draw a conclusion from these data [256].

c. In a small cross-sectional study of 63 children aged 9-11 years in Oswego, New York, serum-PFC concentrations were measured and compared to a neuropsychological measure of differential reinforcement of low rates of responding. Higher concentrations of PFOS and other PFCs were associated with significantly shorter inter-stimulus response times as a measure of response inhibition or impulsivity [257], i.e., functions that are impaired in ADHD. This study had the advantage of using a standardized and specific neurobehavioral task, but was limited by the cross-sectional design and the small size of the population examined.

d. More recently, increased maternal serum-PFOS concentrations in a U.S. birth cohort were associated with poorer behavior regulation, metacognition, and executive function [258]. While PFOA did not show any adverse associations in the 256 mother-child pairs, increases in maternal serum-PFOS were associated with poorer behavior regulation, metacognition, and global executive functioning in the child.

e. Our own birth cohort study in the Faroes assessed behavioral difficulties by the parent-reported Strengths and Difficulties Questionnaire (SDQ) at age 7 years [259]. While no associations were observed with prenatal exposures in the 539 children, overall SDQ scores were associated with postnatal PFOA exposure, and significant adverse associations were found regarding hyperactivity, peer relationship, and conduct problems, as well as internalizing and externalizing problems and autism screening scores.



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f. Neurological abnormalities have also been linked to PFC exposures, such as cerebral palsy [260]. Although the mechanism is unknown, it is possible that PFCs contribute to a multicausal etiology so that elevated exposure is associated with an increased risk of this outcome. The blood samples in this study were analyzed by a Danish laboratory, not by 3M as in previous reports on this cohort.

**2. Toxicological evidence**

a. Developmental neurotoxicity has been demonstrated in various experimental models, mainly in rodents and *in vitro* [4]. A few studies will be highlighted due to their potential significance for effects in humans.

b. Neonatal exposure to PFOS and PFOA seems to affect the cholinergic system, as indicated by a hypoactive response to nicotine, diminished habituation to a novel environment and lack of activity [261]. Similar experimental outcomes have been described for well-established human neurotoxicants, such as PCBs.

c. A recent neurotoxicology review suggested that developmental effects due to PFCs may be mediated by thyroid toxicity, influence on calcium homeostasis, protein kinase C, synaptic plasticity and cellular differentiation, perhaps as part of a cocktail of substances that in combination reach harmful concentrations [252]. In particular, the PFC-associated effects on thyroid function (see section D) would appear to be highly relevant.

**3. Perspective**

Only recently has scientific attention focused on developmental neurotoxicity as a highly sensitive outcome that can have serious consequences, also in regard to economic costs to society [253]. While it could have been relevant and appropriate to examine neurotoxicity from prenatal exposures, and while evidence of such effects due to lead contamination were well known already in the 1980s [262], this issue was not explored at the time, and the C8 Panel did not make this a priority, presumably because little evidence at the time suggested that the developing brain could be an important target organ in regard to PFC exposures. My judgment therefore relies on the coverage and directionality of very recent research and the likelihood that established neurotoxic mechanisms are triggered by PFC exposure.

**G. Liver toxicity**

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to human liver functions, with related adverse health effects.

The liver is an important target organ for PFC toxicity in humans as in animals, and such effects have been referred to by regulatory agencies in regard to determining safe exposure limits [1, 4, 148, 149]. Taken as a whole, PFC exposure at levels similar to or below those reported from the East Metro area are associated with a range of liver toxicity effects.

PFC's adverse effects on liver functions are reflected by elevations of serum-cholesterol concentrations and other important serum lipid parameters. Even small increases are



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likely to have negative implications regarding cardiovascular disease and mortality. In this regard, the C8 Panel concluded that PFOA is linked to an increased risk of elevated serum-cholesterol, and but not (yet) hypertension and coronary artery disease [263]. As hypercholesterolemia and cardiovascular disease are of major public health concern, these issues are discussed under a separate heading (Section VII.G).

### 1. Epidemiological evidence

a. Increased serum-cholesterol concentrations at elevated PFC exposures likely relate to toxic effects on liver functions, and increased concentrations of liver enzymes in serum at higher PFOA exposures support this notion in about a dozen epidemiological studies. An early mention of adverse liver effects from PFCs in workers is from 1978, when DuPont medical officers found elevation in liver function tests among a group of workers leading to the conclusion that "it is possible that C-8 may be causing very minimal, and certainly not clinically apparent, toxic effects to the liver. Because the total number of records reviewed is small (31), I do not believe any findings of this study are statistically valid."[pppp] It appears that these results were discussed with the 3M medical colleagues. External consultant, Professor Harold Hodge in 1978 reported to 3M's medical director, Dr. F.A.Ubel: "There appears to be indications of liver change from the physical examination results. In terms of indicators of liver disorder, there are [sic] a higher percentage at Chemolite than at Decatur and the organically bound fluorine level at Chemolite is correspondingly higher."[qqqq]

b. In early 1980, DuPont shared the results of a pilot study called "liver enzyme study of workers exposed to C-8 at Parkersburg," where they found elevated mean serum concentrations of aspartate aminotransferase (AST, previously referred to as SGOT) and alkaline phosphatase (AP) among workers operating the TFE process. [rrrr] DuPont provided memoranda summarizing their findings. On June 9, 1980, the assistant medical director Vann A. Brewster wrote to L. F. Percival that "I am concerned that the 'Draft' implies that the Medical Division will not continue the study of liver tests on those employees potentially exposed to C-8. Even though we have found no 'conclusive evidence of an occupationally related health problem,' we still cannot explain why the mean SGOT [same as AST] was significantly higher among TFE process workers and that the mean AP was significantly higher among FEP process and service workers."[ssss] I have been unable to identify evidence that liver tests were of continued.

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[pppp] AR226226-1453.pdf, September 20, 1978 - DuPont Washington Work's Medical Director, Dr. Younger pared a memo summarizing his review of the medical records of eleven operators and eighteen laboratorians [at the Washington Works Plant] who have had long-term exposure to C-8. (Exhibit L (EID080236-40)). Page 000135.

[qqqq] 3MA00967742. (1978.08.23). Minutes of Meeting with H.C. Hodge, p. 3MA00967744.

[rrrr] AR226226-1465.pdf, January 28 1980, Liver Enzyme Study of Workers exposed to C-8 at Parkersburg, Exhibit CC (EID099433-34). Page 000186.

[ssss] AR226-1469. June 9, 1980 - DuPont prepared a memo expressing his concern that a draft communication to DuPont's Washington Works employees regarding the outcome of DuPont's liver study of employees "implies that the Medical Division will not continue the study of liver tests on those employees potentially exposed to C-8." (Exhibit GG (EID102477)). Page 000192.



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c. In his thesis, Dr. Gilliland found increases in serum concentrations of SGOT and SGPT (now referred to as AST and ALT), as well as a tendency toward lower HDL cholesterol, as markers of adverse effects on liver function.[tttt] Other cross-sectional studies [191, 248] were not informative in this regard, perhaps because a variety of other factors can impact on liver functions. The studies were reviewed in greater detail in regard to immune function parameters in Section VII.A.

d. The fact that the liver was an important target organ recognized by 3M's Dr. Richard Purdy, and in 1999 he wrote to 3M colleagues, Drs. John Butenhoff and Andrew Seacat that his calculations showed that a "general population member with 70 ppb (in one's blood) could have 36 times more in his liver"[uuuu] due to life-time accumulation. However, I have been unable to determine how this conclusion was dealt with at 3M.

e. Further analyses of medical surveillance data on PFOA-exposed workers in Minnesota led to a 3M paper that relied on cross-sectional analyses of PFOA and liver function data collected in 1993, 1995 and 1997 [66]. While the wording differs from a previous report [207], the authors concluded that employees' serum PFOA levels were not positively associated with either clinical hepatic toxicity nor hepatic responses to obesity and alcohol.[vvvv]

f. Drs. Olsen and Mandel reported in 1998 results on PFOS-exposed Antwerp and Decatur male fluorochemicals production workers, in which they concluded that hematological, clinical chemistry and hormonal abnormalities were not associated with serum PFOS levels up to 6 ppm (6,000 ng/mL).[wwww] Although deviations occurred at higher exposures, the authors disregarded these findings, basing this decision on a determination there were too few subjects to allow a firm conclusion [264]. A later analysis of medical surveillance data from a fairly small number of employees again howed a positive association between the serum-PFOA concentration and both cholesterol and triglycerides. These findings were considered implausible, as they are not in accordance with animal data at much higher exposures.[xxxx] Another limitation that the 3M authors emphasized was the possible non-adherence by some workers to the fasting requirement, although blood-glucose was not affected.[yyyy]

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[tttt] AR226-0473. Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. thesis, University of Minnesota), with Summary. Page 003247.

[uuuu] 3MA01403075. Thoughts on human safety factors. Page 3MA01403075.

[vvvv] AR226-0477. Geary W. Olsen, et al., An Epidemiologic Investigation of Plasma Cholecystokinin and Hepatic Function in Perfluorooctanoic Acid Production Workers, 3M Final Report EPI-0003 (1997), with Summary of study, Protocol, and Manuscript accepted for publication in 2000, Drug & Chemical Toxicology. Page 003511.

[wwww] AR226-0030. An Epidemiologic Investigation of Clinical Chemistries, Hematology and Hormones in Relation to Serum Levels of Perfluorooctane Sulfonate in Male Fluorochemical Production Employees (List of Section Attachments is first page of this File). Page 001074.

[xxxx] 3M_MN02334964. Final report, A Longitudinal Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) Levels in Relation to Lipid and Hepatic Clinical Chemistry Test Results from Male Employee Participants of the 1994/95, 1997 and 2000 Fluorochemical Medical Surveillance Program. Page 3M_MN02334966.

[yyyy] 3MA01784788. An AnalYsis of the 2000 Pluorochernical (Perfluorooctanoate, PFOA) Medical Surveillance Program at 3M Company's Antwerp (Belgium), Cottage Grove (Minnesota), and Decatur (Alabama) Facilities. Page 3MA01784817.



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g. Although these findings would justify, at a minimum, further follow-up, it is not clear if that happened and if the findings were ever analyzed and published.

h. The C8 Health Project examined 47,092 adults for effects of PFOA and PFOS on alanine transaminase (ALT), gamma-glutamyltransferase, and bilirubin as markers of liver function. These results showed a positive association between serum PFOA and PFOS concentrations and the serum ALT concentration [265], usually interpreted as a sign of hepatocellular damage.

i. When serum-PFOA concentrations were modeled as cumulated concentrations, the adverse effect on serum ALT concentrations was replicated in a mixed Ohio River Valley population [266].

j. Likewise, in a general population sample from the NHANES study, liver enzymes showed significant, though small, increases at higher serum-PFOA concentrations [267].

k. Several occupational studies, both cross-sectional and prospective, have assessed liver function parameters in serum, the most recent ones [66, 268, 269] showing that, in general, liver enzymes tend to increase, while bilirubin decreases at higher PFC exposure levels.

**2. Toxicological evidence**

a. Although liver dysfunction in exposed workers was discovered fairly early, it was not taken seriously for many years. A study conducted in 1976 by Dr. Taves from the University of Rochester reported PFOA stimulated lipid peroxidation (LP) in an *in vitro* experiment. The author noted that, at the time, *in vivo* effects of PFOA were unknown.[zzzz]

b. The liver was early identified as a main target organ in rodents [44]. Although toxic mechanisms may differ between rodents and humans [7, 17], as I discussed above, the PPAR-related mechanism is no longer believed to be the differentiator 3M once made it out to be [10].

c. Detailed discussion of liver toxicity in experimental models is included in recent evaluations by regulatory agencies [4, 148, 149], to which little recent evidence adds only little.

d. One aspect deserves consideration, i.e., the intrahepatic lipid metabolism. Some PFASs have the potential to induce hepatic lipid accumulation in cynomolgus monkey [270] and induce lipid synthesis gene expression in human hepatocytes [271].

e. In mice, PFOS administration induced hepatic steatosis in time-and dose-dependent manner along with corresponding CD36 and Lpl expression induction and decreased mitochondrial β-oxidation in mice [272]. Also, in exposed animals, accumulation of lipid

[zzzz] 3MA02512169. Comparison of Lipid Peroxidation by Perfluoro-Octanoic Acid or CCL4. Page 3MA02512169.



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droplets in hepatocytes was observed. These findings suggest that steatosis and fatty liver degeneration may be relevant outcomes of elevated PFC exposure.

f. In regard to PFBA, the MDH [63] noted liver weight changes and morphological changes in liver in experimental studies carried out by a private laboratory in Japan [273]. The article provides no information on funding.

### 3. Perspective

Even though the liver and lipid metabolism were identified early on as likely targets of PFC exposure, it appears that the understanding of the impact on workers' health and on exposed communities in general developed very slowly and that great hesitation was repeatedly voiced in regard to accepting a hypothesis of PFC hepatotoxicity.

a. During a meeting on March 16, 1983, a handout prepared by 3M's Don Roach mentioned preliminary data from a study of "abnormal" liver enzymes from film vs. chemical plant workers. No details were given in the document.[aaaaa] However, a report previously prepared by D.E. Roach reported results from certain health evaluations beginning in late 1976. In this paper, he refers to serum gamma-glutamyl-transferase (S-GGT) being elevated, but he considered it, without a fully supported explanation, as "traceable to alcohol consumption." During the three-year monitoring program, there was a decline in the number of individuals with "abnormal" laboratory findings, but Dr. Roach attributed that, again without clearly supported explanation, to health care counseling and improved lifestyles.[bbbbb]

b. The first systematic studies were carried out by Dr. Frank Gilliland in connection with his thesis project. [ccccc]

c. Additional health studies appear to have been carried out at 3M subsidiaries. In 1995, 3M issued an internal report based on a 3M Belgium blood testing program in Antwerp. The report stated, "There was weak relationships found between PFOA and triglycerides (corr.coef=.48, p=0.0005)." The authors claimed, "the relationship has never appeared in the medical or toxicology literature and is likely to be a chance finding."[ddddd] Considering the high correlation coefficient and the extremely low p value, that conclusion seems inappropriate and defensive.

d. Dr. Mandel later asked Dr. Schmickler from 3M Belgium about the reporting requirements for fluorocarbons, i.e., whether they need to report findings from toxicology studies. The reply was that it was required to report to the safety committee of the

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[aaaaa] 3MA00047974. Handouts and Transparencies for your Files from March 16, 1983 Fluorochemical Study Committee Meeting. Page 3MA00047975.

[bbbbb] 3MA00047519. Health Status of Plant Workers Exposed to Fluorochemicals - a Preliminary Report. Page 3MA00047524.

[ccccc] AR226-0473. Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. thesis, University of Minnesota), with Summary.

[ddddd] AR226-0175. Antwerp Blood Testing Results from June 1995. Page 004265.



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company but not governmental institutions.[eeeee] I did not find any such reports, and perhaps this judgment explains the apparent secrecy about any findings of adverse effects.

e. As late as 2003, 3M authors argued that a positive association between PFOA exposure and cholesterol in 3M workers "is contrary to the substantial body of toxicological literature that suggests a negative association in laboratory animals" [217]. However, in a more recent article [274], the 3M authors relied on a species difference in liver metabolism (associated with the PPAR receptor) and for this reason concluded that hepatocellular tumors in rats are "not likely to be relevant to humans." However, these positions are inconsistent. It is not appropriate in one connection to require similar hepatotoxic effects in different species and in another to raise doubt about such similarity.

f. In regard to liver steatosis, up to 10% of adolescents have non-alcoholic fatty liver disease (NAFLD) [275, 276]. As a considerable and apparently growing public health problem of partially unknown origin, this outcome requires attention in future studies of PFC-associated adverse human health effects.

## H. Risk factors for cardiovascular disease

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to human health due to elevated cholesterol and increased risk of cardiovascular disease.

Based on the available evidence, the kidney may also be a likely target organ for PFC toxicity in humans as in animals. However, this evidence is yet uncertain, as decreased kidney function of other causation may impair the elimination of PFCs and thereby indirectly cause elevated serum-PFC concentrations. The evidence is nevertheless strong that PFCs cause adverse cardiovascular effects, in part associated with elevated cholesterol and whether or not kidney disease is a contributing factor.

An autopsy study showed that PFBA in particular lodges in the human kidney [52], but virtually no information is available on nephrotoxicity and cardiovascular toxicity related to this PFC.

As discussed above, serum concentrations of total cholesterol and other important serum lipid parameters increase at higher PFC exposures. Even a small increase would likely have negative implications regarding cardiovascular disease and possibly mortality. The C8 Panel concluded that PFOA is linked to an increased risk of hypertension in pregnancy, elevated serum-cholesterol, and potentially also coronary artery disease, although the latter was not considered sufficiently supported by the evidence available at the time.

[eeeee] 3MA00000688. Email between Jeffrey H. Mandel and Dokter Schmickler with the subject "reporting." Page 3MA00000688.



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Due to the high incidence of cardiovascular disease, even a small increase in life-time risk is of serious public health importance. An article recommends immediate action to prevent even 'background' exposures to PFOA [277].

**1. Epidemiological evidence**

a. The early 3M occupational study by Dr. Gilliland addressed serum chemistry abnormalities in exposed workers [207] and showed an inverse correlation (adverse effect) between organic fluorine compounds (assumed to be mainly PFOA) and HDL cholesterol.

b. In other 3M production plant workers, serum PFOA and total organic fluorine (TOF) were positively and significantly associated with cholesterol and triglycerides in a longitudinal study.[fffff] A positive correlation (adverse effect) with total cholesterol (PFOS and PFOA) and triglycerides (PFOA) was later found in regard to PFC concentrations in serum in one study, though not in another [217, 278].

c. A later study of current and former Cottage Grove employees showed both PFOA and PFOS were positively and significantly associated with total cholesterol, LDL, and triglyceride levels above healthy reference ranges.[ggggg] PFOS was significantly associated with metabolic syndrome, as well. Oddly, 3M discontinued this study showing significant adverse effects in its workers.[hhhhh]

d. Similar evidence from cross-sectional and, in particular, prospective studies of workers at other plants also suggested that increased PFOA exposure is associated with higher serum-cholesterol concentrations [268, 269, 279].

e. Cross-sectional data on 1216 subjects from the 1999-2003 NHANES showed that increasing serum-PFOA concentrations were positively associated with self-reported cardiovascular disease, including coronary heart disease and stroke, and objectively measured peripheral arterial disease (an ankle-brachial blood pressure index of less than 0.9). The highest PFOA quartile showed a doubling of cardiovascular disease after confounder adjustment [280].

f. Community and general population groups with lower levels of PFOA exposure have also revealed positive correlations (adverse effects) between PFOA and cholesterol concentrations in serum [65, 281-283].

g. In some populations, other PFCs were also measured, and positive associations were found in regard to PFOS exposure [281-283], a finding that we have replicated

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[fffff] 3M_MN02334964. Final report, A Longitudinal Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) Levels in Relation to Lipid and Hepatic Clinical Chemistry Test Results from Male Employee Participants of the 1994/95, 1997 and 2000 Fluorochemical Medical Surveillance Program, page 3M_MN02334966.

[ggggg] 3MA02543911. Untitled draft. *See also* Deposition Testimony of Dr. Geary W. Olsen (Sept. 8, 2017), 142:13-150:21.

[hhhhh] Deposition Testimony of Dr. Geary W. Olsen (Sept. 8, 2017), 158:24-160:06.



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in elderly subjects from the Faroe Islands, where exposure levels are similar to background levels in the US (unpublished results).

h. Data from the C8 project showed that total cholesterol and LDL-cholesterol increased at higher PFOA exposures (and HDL increases in women) [235]. The variability in PFC-associated cholesterol changes is quite large [8], although a variety of factors, such as age, sex, and body mass index could affect the degrees of the relationship [284].

i. Indirect evidence suggests that PFC metabolism is not linked to changes in lipid metabolism (which would suggest a reverse causation), thereby rejecting a hypothesis that both PFCs and cholesterol could be affected by a common cause that would produce apparent positive associations between PFCs and cholesterols in serum. Thus, subjects who are taking statins to decrease their serum-cholesterol do not show any lower serum-PFC concentrations [282]. This report agrees with our findings in the Faroes (unpublished).

j. While early data from Cottage Grove suggested no risk, an increased risk of cerebrovascular disease was indicated by a mortality study that relied on comparisons with the general population [285]. The subsequent 3M-supported follow-up [76] again showed strongly elevated risk of cerebrovascular death in workers with high exposure, especially when compared to an internal control group. The draft report by Drs Lundin and Alexander from the University of Minnesota[iiiii] provides a balanced presentation, but the published article that was co-authored by 3M's Dr. Olsen calls the association "inconsistent" because the mortality was not clearly elevated when compared to the general Minnesota population.

k. Cross-sectional NHANES data suggest that serum-PFOA concentration is associated with systolic blood pressure and the risk of hypertension [286]. Hypertension may relate to an increased risk of cerebrovascular mortality.

l. NHANES data suggest that increased serum concentrations of PFOA and PFOS are associated with an increased risk of chronic kidney disease, as defined by a low glomerular filtration rate [287].[iiiii] Here, reverse causation cannot be ruled out, i.e., that kidney disease prevents PFC excretion via the urine[59]. A major caveat, however, is that PFBA was not considered, as it may not have been detectable in the serum, while the major accumulation in the body is in the kidneys [52].

m. Regarding uric acid, the C8 Project examined its association with serum PFOA levels after adjustment for potential confounders. An increased risk of elevated uric acid was found in adults, including clinically defined hyperuricemia [288]. Again, this evidence is yet somewhat uncertain, as reverse causation may be present.

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[iiiii] 3MA02557439.pdf. Final report, Mortality of Employees of an Ammonium Perfluorooctanoate Production Facility, August 22, 2007.

[iiiii] I note that the first author of this article, and co-author of five other publications on cardiovascular outcomes in PFOS-exposed populations, has provided erroneous information to the West Virginia University regarding his educational background. The articles in question were co-authored be established colleagues, and none of them has been retracted.



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### 2. Toxicological evidence

a. Detailed discussion of elevated cholesterol and other risk factors in experimental models is included in recent evaluations by regulatory agencies [4, 148, 149].

b. In regard to PFBA, experimental findings in laboratory models included exposure-related decreased in red blood cell counts, hematocrit and hemoglobin, effects that were highlighted by the MDH in regard to setting a safe limit for PFBA concentrations in water [63]. Further information is given in Section VIII.

### 3. Perspective

a. Due to the impact of covariates and the fact that cholesterol concentrations in the C8 study were lower than elsewhere in the U.S., selection bias in this study has been suggested [284]. However, although some selection forces likely played a role, there is little evidence to suggest that it caused bias away from the null hypothesis regarding PFOA exposure and cholesterol. Even though PFC-associated increases in cholesterol in most studies seem to be fairly small, the overall impact at population level could be substantial. The strongest associations in general refer to total cholesterol, but some studies have also examined lipoprotein fractions and found that especially low-density (LDL-cholesterol) increases at higher serum-PFC concentrations.

b. Even if PFC exposure explains only a small part of the variation in serum-cholesterol concentrations, still small increases in total and LDL cholesterol are associated with increased risks of cardiovascular disease. Some have noted that an increased mortality attributed to this cause has not been documented so far [8]. Thus, previous studies have suggested that cardiovascular mortality in PFC workers is below expectation. However, this could arise from a healthy worker effect. Some evidence of increased risk 10 years after first employment was noted [74], as would be expected when the healthy-worker effects wears out.

c. Other serum parameters that may reflect kidney dysfunction, such as creatinine and blood urea nitrogen (BUN), were assessed in occupational studies. However, no clear associations with PFC exposure biomarkers were found [279].

## I. Carcinogenicity

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFCs pose a substantial present and potential hazard to human health as carcinogens.

As detailed evaluations have been recently published[6], I shall briefly summarize the early reports along with the most recent evaluations.

Early studies in PFC-exposed workers suggested a risk of prostate cancer, and support for this association comes from more recent studies that also include populations exposed at background levels. While early studies usually referred to cancer mortality, which is appropriate for sites like liver and pancreas due to the high fatality of these diseases, other sites



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are better explored using incidence data, while considering the impact of screening efforts, e.g., for prostate cancer.

A variety of subsequent studies demonstrate that PFC exposure is associated with development of cancer at several sites. PFOA has been found to satisfy the EPA's criteria to be classified as "likely to be carcinogenic to humans" [289]. The IARC concluded last year that PFOS is a possible (Group 2B) human carcinogen [6]. The C8 Science Panel concluded that there is a probable link from PFOA exposure to testicular cancer and kidney cancer. All of these effects have been reported at background levels or at elevated exposures overlapping with those documented in East Metro residents. The main organs affected are the kidneys, testicles, prostate, and perhaps bladder and breast.

Based on the available evidence, exposure to PFCs has a substantial potential to cause cancer, most clearly in regard to cancers of the kidneys and the testicles, and highly likely also in regard to prostate cancer and bladder cancer. A possible risk of breast cancer is also of concern.

**1. Epidemiological evidence**

***Cancer risk assessments***

a. In the most recent evaluation of cancer risk association with PFOA exposure, the IARC classified this substance as a possible human carcinogen (Group 2B) and concluded that there was relevant, though limited, evidence in humans that PFOA causes testicular and kidney cancer, while evidence for human carcinogenicity at other sites, such as bladder, prostate, thyroid, liver and pancreas was inadequate at the time of the evaluation; relevant evidence in experimental animals was also considered limited [6].

b. The EPA's Science Advisory Board in 2006 reviewed the information available on PFOA at the time and suggested that the cancer data were consistent with the EPA Guidelines for Carcinogen Risk Assessment descriptor "likely to be carcinogenic to humans" [289]. The evidence available for PFOS and/or other PFCs may also be sufficient for this classification, but no conclusion was reached.

c. As I describe in more detail below, the C8 Science concluded that there is a probable link from PFOA to testicular cancer and kidney cancer. The C8 Science Panel conducted further studies, including an update of a previous occupational study [73]. Data on prostate cancer did not provide further support for the associations already referred to, although caveats described below must be kept in mind.

d. I am aware of Professor David Sunding's statistical analyses in connection with this case showing a pattern of increased occurrences of total cancer as well as cancer at specific sites in areas in Minnesota that I understand have been most affected by PFC-contaminated ground water. His findings are consistent with the evidence summarized below showing correlations between PFC exposure and cancer rates at individual sites.

***Occupational studies***



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e. As described below, a dose-associated increased risk of kidney cancer was observed in workers in a fluoropolymer production plant in West Virginia, USA, and in the local community exposed to releases from the plant. Likewise, an increased risk of testicular cancer occurred in highly exposed local residents. Relevant evidence in humans also referred to other cancers [6].

f. Occupational mortality studies have been carried out in PFOS-exposed worker populations from the 3M production plant in Alabama [285, 290] and PFOA-exposed workers from West Virginia [291] and Minnesota [93]. In evaluating this evidence, account must be taken of duration of exposure, exposure assessment methods, age at entry, and duration of follow-up, as discussed by IARC [6]. In addition, follow-up and case-control studies have focused on exposed communities. Some reports are not considered here, as small numbers of cases or other weaknesses make them less relevant to the evaluation. While the recent evaluation report relied on published evidence, some internal studies have been conducted in the past and provide some supplementary evidence. A key concern in these studies is the choice of comparison population, cf. the comments made above in regard to the "healthy worker effect" (see section V.A.1).

g. In April 1989, DuPont issued an Internal Report, "An investigation into the occurrence of leukemia at Washington Works." The standardized mortality ratio was 2.1, but was determined by DuPont not to be statistically significant.[kkkkk] Leukemia has not been considered in recent reports that mainly relied on mortality data, that are not a reliable source for hematopoietic cancer incidence.

h. In a subsequent report from 1992, DuPont examined the cancer surveillance data for 1956-1989 and mortality data for 1957-1991. For cancer, DuPont found a null result overall, but significant findings existed for specific sites, such as buccal cavity, pharynx, kidney and leukemia, among male employees (too few female employees). For mortality, mostly seen were deficit deaths (healthy worker effect) among males; among females, there was a significant excess of residual causes of deaths.[lllll] Insufficient information is available to judge this report, but it illustrates that attention was paid to cancer risks early on.

i. In response to the concerns about PFC-associated cancer risks, the Minnesota Cancer Surveillance System on cancer incidence includes Dakota and Washington counties and related zip codes, and data from the period 1988-2004 have been published [292]. A recent update does not appear to be available. The results relate to the patient residence at the time of diagnosis, and this report therefore has limited power to detect excess cancer rates associated with past PFC exposure from contaminated drinking water in parts of these counties. Unsurprisingly, none was found. In interpreting such studies, one must also note that the period

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[kkkkk] AR226226-1308-1.pdf, DuPont Internal Report, "An Investigation Into The Occurrence of Leukemia At Washington Works" (April 1989) (EID584220-30) DuPont Internal Final Report, "A Case-Control Study of Leukemia At the Washington Works Site" (12/3/91) (EID151953-65). Page EID584221.

[lllll] AR226-1546. Washington Works Cancer Surveillance Data Mortality and Cancer Incidence. Pages EID521396 and EID521399.



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from first exposure to the development of clinical cancer may be longer than 20 years, while the residence is likely to change at least once during this period.

***Kidney cancer***

j. Regarding kidney cancer, the C8 Panel concluded: "For kidney cancer, the worker mortality study conducted by the Science Panel showed a higher risk in the most highly exposed group compared to lower exposure groups among the workforce, but the risks were not elevated compared to the US population. In the cohort study, there was a gradient of increasing risk with increasing exposure but most strongly in the analyses that included exposure up to the time of diagnosis. When the 10 years of exposure prior to diagnosis was excluded, the association was less evident. No association was seen in the prospective analysis of cohort data, although the latter is limited by small numbers. In the geographic study, some results suggested an increasing risk of kidney cancer with increasing exposure and others did not. The science panel considers that the excesses observed indicate a probable link between PFOA and kidney cancer."

k. The C8 Panel reviewed and relied on several studies, as did the IARC working group. Increased risk of kidney cancer with a statistically significant exposure-response trend was reported in workers in a fluoropolymer production plant in West Virginia and in an exposed community near the plant [291, 293].

l. In further detail, elevated mortality from malignant kidney disease was documented among 5,791 workers exposed to PFOA in West Virginia [291]. No clear risk was seen in the PFOS-exposed workers from Minnesota [93]. However, community-based evidence [293, 294] showed an elevated incidence of kidney cancer associated with PFOA exposure.

***Testicular cancer***

m. The C8 report concludes: "For testicular cancer, there is evidence of a positive trend in risk across exposure groups, in some analyses, with the highest exposure group in both the internal analyses of the cohort study and the geographical cancer study showing estimated relative risks ranging from 3 to over 6 comparing the highest to lowest exposure groups. [...] The high exposure group, where the higher risk was observed, comprises only six cases therefore there remains some uncertainty. The Science Panel notes that there is experimental evidence of testis cancer being increased in exposed animals. The Science Panel considers observed excesses to indicate a probable link between PFOA and testicular cancer."[mmmmm] The conclusions from IARC [6] are similar in regard to testicular cancer.

n. Mortality studies are unlikely to identify all cases of testicular cancer, and better evidence must rely on incidence data. The C8 Panel and IARC emphasized the results from the community study that documented an elevated incidence of testicular cancer at higher PFOA exposures in the Mid-Ohio River Valley near the production plant [293, 294].

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[mmmmm] 3M's Dr. Butenhoff agrees and takes no issue with the C8 Science Panel's conclusion of a statistical link between PFCs and testicular cancer in humans. Butenhoff Dep. Tr. at 139.



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***Prostate cancer***

Both prostate cancer and bladder cancer are diagnoses that may not necessarily appear on a death certificate, as the patient may die from some other disease, rather than the cancer, because the cancer is often curable or may not be fatal for several years. In addition, cancer risks in these types of studies often are calculated on the basis of small numbers of cases and may therefore not deviate with statistical significance from expectation. Thus, although the risk may not be significantly elevated, the upper confidence limit could be 5 or higher, suggesting that, at the same time, a 5-fold increased risk or greater cannot be ruled out. However, based on published evidence, neither the C8 Panel nor the IARC considered prostate cancer a probable risk in regard to PFC exposure.

o. In a follow-up to 3M's 1989 mortality study carried out by Dr. Mandel, involving almost 3,000 male 3M workers at Cottage Grove from 1947 to 1983, ten years of employment in exposed jobs was associated with a statistically significant increase in prostate cancer mortality (more than three-fold). Still, this calculation was based on four cases among the exposed workers [72]. Unfortunately, comparisons with the general population of Minnesota probably biased the results of this study toward underestimated risks.

p. In 1993, Dr. Gilliland and Dr. Mandel of 3M published a paper based on the new mortality study included in Gilliland's thesis.[nnnnn] There were mostly null findings, except, as before, for prostate cancer (a 3.3-fold increase in mortality). Again, the number of cases was small (n = 6). The paper sought to explain the observed prostate cancer deaths as due to a purported higher prevalence of prostate cancer in Minnesota than the U.S. (control group) and/or as a chance finding.[ooooo] However, subsequent analyses provided to 3M by the author indicated that prostate cancer was actually *less* prevalent in Minnesota than in the U.S., suggesting an even greater excess among 3M workers.[ppppp]

q. In a mortality study of almost 4,000 employees exposed to PFOA, no clear tendencies were found for liver, pancreatic or testicular cancer. An increased standardized mortality ratio, however, was found for prostate cancer, and a 6.6-fold increased risk was found in workers with definite exposure. I note that the statistical significance relied upon two cases among the workers with known high exposure [76].

r. The most recent update is from a thesis completed in 2013.[qqqqq] Using air monitoring results (and ignoring non-respiratory intakes), this study of 9,000 workers hired after 1947 compared deaths at Cottage Grove with those at the unexposed St. Paul plant through to 2002. When dividing the workers into six different exposure groups, a dose-dependent risk appeared for prostate cancer, although not statistically significant. The author concluded that the results supported previous findings of a prostate cancer risk. However, in the published report

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[nnnnn] AR226226-0472.pdf, Frank S. Gilliland & Jack S. Mandel, Mortality Among Employees of a Perfluorooctanoic Acid Production plant, 35 JOM 950-954 (September 1993), with Summary of study. Page 003166.

[ooooo] AR226-0471. Jack S. Mandel & Leonard M. Schuman, "Mortality Study at the 3M Chemolite Plant" (January 1989), with Summary of study. Pages 003148-003149.

[ppppp] 3MA00632313. Letter from Jack S. Mandel to Larry Zobel (Apr. 6, 1989); 3MA00632314. Table 5 (attachment to Mandel letter to Zobel) (Apr. 6, 1989).

[qqqqq] 3M MN03059185. Cancer mortality in 3M chemical workers (PhD thesis by Katherine Koehler Raleigh).



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[93] that was co-authored by 3M's Dr. Olsen, emphasis was on comparisons with the general population, no clear trend was found in quartile exposure groups, and the lack of association of prostate cancer with the exposure estimate was said to be in agreement with the findings in other studies. In discussing the possible risk factors, the Discussion section of the published article notes that family history of prostate cancer may play a role (see section t. below). The difference from the thesis becomes clear when considering the preference expressed by Drs. Olsen and Zobel in a 14-page letter to Dr. Alexander, who was supervisor of Dr. Raleigh's thesis project. In the letter,[rrrrr] which related to an earlier Cottage Grove mortality study, the 3M doctors advocated using a control group from the general population rather than conducting the within-cohort analysis which revealed a statistically significant excess risk of prostate cancer mortality among highly exposed employees.

s. In support of prostate cancer as a potential outcome of PFC exposures, a nested case-control study of cancer incidence (based on diagnosis reporting, rather than mortality) in a Danish general population group focused on 713, 332, 128, and 67 cases of prostate, bladder, pancreatic, and liver cancers found during a follow-up of approximately 10 years after a baseline examination with blood sampling. At the background exposure with a small variance, modest positive associations were found between serum concentrations of both PFOA and PFOS in regard only to prostate cancer morbidity [97].

t. A recent case-control study from Sweden showed similar serum-PFC concentrations in 201 cases and 186 population-based controls. Heredity, i.e., a first-degree relative with the disease, was a risk factor, as has been documented before, and among those with a positive family history, elevated serum concentrations of both PFOA and PFOS were associated with a significantly increased risk of prostate cancer [94]. Accordingly, PFC exposure may contribute to the etiology of this cancer type, although this may not be evident, unless family history is taken into account.

***Bladder cancer***

The current evidence is less strong as to bladder cancer, in part because mortality studies are unlikely to reflect this diagnosis, in part because incidence studies carried out relied on self-reports of past diagnoses. In addition, some studies included too few cases to support statistical analyses, and the two evaluations by the C8 Panel and IARC did not consider the evidence sufficient to draw a conclusion.

u. A study of PFOS-exposed workers showed that bladder cancer mortality was elevated among individuals with at least one year of exposure. I note that this finding was based on three deaths only, all of which occurred in workers deemed to have been highly exposed [285]. In addition, the results were obtained in comparison with the Alabama general population, and the low mortality ratio for lung cancer did not suggest that smoking was an important confounder.

v. In a subsequent reevaluation of the same cohort, mail questionnaires were used to include incident cases of bladder cancer. The incidence was not found to differ much

[rrrrr] 3MA02557490.pdf. Letter of July 14, 2006 from Drs. Olsen and Zobel to Dr. Alexander.



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from expectation, although an increased risk among the most highly exposed workers could not be ruled out [290]. In an unpublished version of this study, Dr. Alexander, the principal investigator, remarked that the study's statistical power to detect excess risks was "inherently low and prohibited a convincing exposure response analysis."[ssssss] The most recent follow-up by these authors used a job-exposure matrix to complement exposure estimates for comparison with cancer registry data; the findings do not support elevated bladder cancer risks otherwise observed in comparison with state averages, although the study cannot rule out the possibility of a risk [93]. Although serum-PFAS measurements were available for many employees, these data were not included. In addition, as smoking is a risk factor for bladder cancer, a comparison between rates for lung cancer and bladder cancer would have elucidated whether smoking-related cancer risks were similar in the occupational groups and in the comparison population. For example, the plausibility of a bladder cancer risk in fluoride-exposed workers [295]is supported by the observation of a greater increase in bladder cancer risk than in lung cancer risk among the workers, although the latter risk is much greater in smokers. The pattern was the same in the PFOA-exposed workers, with a greater excess in bladder cancer than in lung cancer.

Considering uncertainties in mortality data for bladder cancer and the wide confidence intervals asssociated with small numbers of cases, these studies showed non-significant associations, but could not rule out effects of a magnitude that would be of substantial public health concern.

***Other sites***

w. Thyroid cancer seemed elevated in one analysis, and the same was true for pancreatic cancer [296].[ttttt] Risk of liver cancer was apparently not elevated in any study [6]. In rodents, PFOA acts as a PPARα agonist, which is linked to the development of liver tumors, pancreas acinar cell adenomas, and Leydig cell tumors. Thus, in regard to tumor site, animal studies are not predictive of the most relevant sites in humans.

x. Apart from the focused studies referred to above, a recent review by the Institute of Medicine suggested that PFOA exposure may lead to breast cancer [297]. Likewise, the EPA's Science Advisory Board called attention to this potential, given the elevated occurrence of fibroadenomas and adenocarcinomas of the breast in two feeding studies in rats [298]. Although breast cancer may also be plausible from the evidence of endocrine disruption, only limited epidemiological support is at hand.

y. For example, a study of 31 breast cancer cases in Greenland found elevated current serum PFC concentrations as compared to controls [299]. An extended study of 77 cases and 84 controls [300] again showed higher serum-PFC concentrations in cases

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[ssssss] 3MA00755705. Bruce Alexander, *Bladder Cancer in Perfluorooctanesulfonyl Fluoride Manufacturing Workers* (Nov. 21, 2004). Page 3MA00755720.

[ttttt] 3M's Dr. Butenhoff agrees, and recognized as early as 2001, that a study of the effects of PFOS on rats showed "significant increases in liver, pancreatic, and thyroid tumors," noting that "[h]epatocellular combined adenoma and carcinoma is clearly significant in the femals at the high dose," and that the "responses in the males [are] just over the border on the positive side" (3MA02608788).



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compared to controls, but similar differences also occurred in lipophilic contaminants (such as PCBs), and it is impossible to determine the possible contribution by PFCs alone.

**2. Toxicological evidence**

a. Cancer effects in humans from PFCs are supported by experimental animal studies. The IARC evaluation considered the published evidence regarding mechanisms of PFOA-associated carcinogenesis to be moderate, which did not lead to a change in the overall classification of PFOA as a Group 2B carcinogen [6]. I understand that PFOA is currently being tested in two-year bioassays by the National Toxicology Program.

b. PFOA was examined for carcinogenicity by the oral route of exposure in two studies in rats, with some initiation-promotion studies, as reviewed by the IARC in the evaluation discussed above [6].

c. The results from a rat bioassay sponsored by 3M were submitted to the EPA in 1983 and almost 30 years later released in a journal publication in 2012 [225]. The results of this 2-year study documented dose-related PFOA-induced liver tumors and Leydig cell tumors of the testicles [224], and subsequent review suggested effects on pancreatic acinar cell adenoma and carcinoma, while mammary gland lesions were found not to reflect possible breast cancer development [6].

d. Results from a second rat study showed elevated incidence of hepatocellular adenoma, testicular Leydig cell adenomas, and pancreatic acinar cell adenoma and carcinoma [301]. So far, no bioassay has been conducted in another mammal species.

e. In mice, PFOA exposure induced stromal hyperplasia in mammary glands at 18 months, an effect that is hypothesized to increase susceptibility for tumor growth in rodents and humans [9].

f. Certain scientists, particularly those at 3M, argue that a PPAR-related mechanism may explain liver carcinogenicity in some animal models. However, as discussed above, and as concluded in a recent risk assessment, both human and mouse PPAR-alpha are activated by PFOA *in vitro* [10]. When 3M discussed Dupont's results on cancer in male rats with colleagues from the UK company ICI in 1995, the latter strongly espoused that APFO should be considered an animal carcinogen, as the benign tomours observed are simply early lesions that ultimately lead to malignant tumors (a view that is in agreement with interpretations adopted by the IARC, PG), but the 3M representatives diagreed.[uuuuu]

g. Also, certain studies have used specially-bred rodents to control for any such possible affect of the PPAR. In any event, EPA guidelines suggest that the non-PPAR dependent tumors, where available data do not justify establishing a rodent-specific mode of action, should be presumed to be relevant to humans [7, 17]. Still, the liver does not appear to be a primary target for cancer in humans.

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[uuuuu] 3MA10024469.pdf.



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### 3. Perspective

Evidence of carcinogenicity in humans can be somewhat equivocal, mainly when occupational populations are small and relatively young, follow-up durations are short, historical exposure levels are uncertain, individuals have had simultaneous exposures to other compounds, when cancer cases may be incompletely ascertained, and when preexisting conditions may complicate the evaluation. The imprecise or incomplete data often limit the information that can be extracted from these studies [8]. Still, the weight of the evidence shows a likely PFC carcinogenicity, as the C8 Panel for example found for testicular cancer and kidney cancer [296].

When the numbers suggest a lack of statistical significance, that is only one side of the coin. The other side regards the magnitude of a possible adverse effect that could have been overlooked, given the available data. Some researchers might conclude that the absence of a statistically significant excess risk suggests that the risk is absent, while others, including myself, representing what is becoming the leading view, believe that such results must be interpreted in light of the total information at hand [79]. How large an effect could be overlooked or ignored as 'non-significant'? Often, available studies of young working populations with limited follow-up, possible incomplete ascertainment of cases, with healthy worker bias, and other limitations, cannot provide confidence that a risk is absent (see Table 1).

a. Regarding occupational mortality studies, a retrospective cohort study was completed in 1980 by Dr. Mandel in 1980 at the 3M Chemolite plant (Cottage Grove, Minnesota) site, as summarized in Dr. Gilliland's thesis.[vvvvv] No significant findings were observed, but the standardized mortality ratio for some cancers exceeded one (e.g., for cancer of the prostate and testis), a finding that would seem worrisome, given the anticipated healthy-worker effect and short follow-up time. Continued surveillance for mortality was said to be warranted.[wwwww]

b. In the mortality study of PFOA production workers carried out as part of Dr. Gilliland's thesis project, a 3.3-fold increase in prostate cancer mortality compared to no employment in PFOA production, although based on only six prostate cancer deaths [72]. When 3M sent their customers (Eastech Chemical Inc., Timberland Company, and W.L. Gore & Assoc.) a list of published articles regarding worker safety and fluorochemicals, they inexplicably did not include Dr. Gilliland's mortality paper.[xxxxx]

c. In a retrospective cohort mortality study from 1995 on 3M employees in Decatur Alabama, data were collected through 1991. No significant excess in mortality was seen. It was recommended to follow up in 1998 when the 1992-1996 data would be available.[yyyyy] Presumably, this may have been the origin of the observations on bladder cancer in workers employed through the end of 1997, published in 2003 [285], while a later follow-up report in

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[vvvvv] AR226-0473.pdf, Frank Davis Gilliland, Fluorocarbons and Human health: Studies in an Occupational Cohort (October 1992) (unpublished Ph.D. theses, University of Minnesota), with Summary. Pages 003173, 003217.

[wwwww] AR226-0470.pdf, Leonard M. Schuman & Jack S. Mandel, an Epidemiologic Mortality Study of Employees at the Chemolite Plant (February 1980), with Summary of Study. Page 003126.

[xxxxx] 3M_MN01238940. Published Articles Re Worker Safety And Fluorochemicals. Page 3M_MN01238940..

[yyyyy] AR226-0032. Mortality Study of Employees at 3M Plant in Decatur, Alabama. Page 001643.



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2007, also by 3M scientists, challenged those findings of excess bladder cancer, as ascertained by postal questionnaire only [290].

d. At the request of the C8 Panel, a similar retrospective follow-up study in West Virginia included over 6,000 men and women employed during 1948-2002 and followed up through 2002. The results found little deviation that would suggest an excess cancer risk [73], although the findings as well could also not exclude the presence of an importantly elevated risk.

e. In regard to experimental toxicology studies, early *in vitro* mutagenicity assays commissioned by 3M concluded that PFOA was not mutagenic under the test conditions,[zzzzz] and this finding has been replicated in several studies since then, thus suggesting that PFOA genotoxicity is not a relevant mechanism [6].

f. Among other potential mechanisms, immunotoxicity may be involved (see Section A). The genotoxicity question gave rise to some controversy at 3M. In connection with a 1999 13-week dietary toxicity study on N-MeFOSE exposed rats, Dr. Andrew Seacat from 3M asked Dr. Peter J. Thomford from the contractor, Covance Laboratories Inc., to increase the calculated NOAEL, and 3M refused to accept the study report.[aaaaaa] A mutagenicity study was not approved, the main concern being that a compound with lower PFOS concentrations (T-6316) had been used instead of in terms of T-6906, and the reported data were insufficient to reach a valid conclusion regarding the mutagenic activity of the substance in this assay.[bbbbbb] Although differences in opinion may well occur, a variety of validated genotoxicity tests are available, including some that rely on human white blood cells. Still, although insufficient testing was carried out at the time, negative results have been obtained in the vast majority of genotoxicity tests carried out since then [6].

g. Animal toxicity studies carried out by 3M in 1978 caused some discussions with DuPont on what to conclude. On March 5, 1979, Nancy Chrewry from DuPont reviewed 3M's new C-8 rat and monkey studies and wrote in a letter to Bill Krauss at 3M that there were compound-related effects indicated in the animal studies, and that additional adverse effects apparently were revealed in the data though not reported by 3M in the description of the studies. [cccccc] At a meeting of 3M scientists in 1979, recent results from the Fluorochemicals in Blood Program and the data from the 90-day subacute toxicity studies on PFOS and PFOA, J.R. Mitchell commented "Some of the symptoms in animals from these 90 day studies are similar to

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[zzzzz] 3MA02512309. F.D. Griffith and J.E. Long. Animal Toxicity Studies with Ammonium Perfluorooctanoate.

[aaaaaa] AR226-0301. Letter from 3M to Covence regarding errors in Audited Final Draft Report [226-0300]. Page 005100.

[bbbbbb] AR226-0254. Letter to 3M from Covence Laboratories reviewing the Study (226-0253) and concluding that it was technically inadequate. Page 001393.

[cccccc] AR226-1456. March 5, 1979 - DuPont reviewed 3M's new C-8 rat and monkey studies and agreed that there are compound-related effects indicated in both studies, and that additional adverse effects apparently were revealed in the data but not reported by 3M in the text of the studies. (Exhibit P (EID 123133)). Page 000140.



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those observed with carcinogens."[dddddd] However, such concerns about carcinogenicity apparently did not lead to any further 3M studies in the short term.

h. Regarding a study conducted at Riker Laboratories, Inc. in 1983, 3M and an independent research institute again had different interpretation on the tumorigenesis data obtained from a study to determine the chronic toxicity and carcinogenic potential of the FM-3924 (N-EtFOSE) in rats. 3M reported "the overall incidence of hepatocellular adenomas and carcinomas was low in both control and FM-3924-treated groups with only the high-dose female rats possibly having a tumor incidence outside historical control limits . . . . Based on tumor incidence, types of tumors, onset time of tumor appearance, malignancy patterns of tumors and the final mortality values at two years, FM-3924 was not considered to be carcinogenic in the rat."[eeeeee] Later in 1988, 3M amended the report to emphasize that the results were not statistically significant. The text revision was "the overall incidence of hepatocellular adenomas and carcinomas was low in both control and FM-3924-treated groups with only the high-dose female rats possibly having a tumor incidence that, while not statistically significant, was outside historical control limits." [ffffff]

In 1998, however, the tumorigenesis data were sent to Pathology Associates International (PAI, West Chester, OH) for review. 3M regarded the original pathology interpretations as adequate, and examination of microscopic tissue sections was not included in the review process. On November 25, 1998, PAI concluded that liver cancer in fact was correlated with the PFC exposures, stating "It is my opinion that dietary FM-3924 for 2 years resulted in chronic liver changes (megalocytosis) in males at all dose levels (10, 30, 100 ppm) and for females at the high dose concentration (100 ppm). . . Incidence values for liver proliferative lesions indicated that FM-3924 should be regarded as a liver carcinogen for SD rats." [gggggg]

## VIII. PFHXS, PFBA, AND OTHER SHORT-CHAIN PFCs

To date, PFHxS, PFBA and other short-chain PFCs have been less studied than longer-chain PFCs such as PFOA and PFOS and their precursors that were commercially dominant for many years, and as a result they understandably garnered most of the attention from the scientific community. The scientific community lags, and often cannot keep up with, changing industry strategies and technologies, particularly as to PFCs as to which companies like 3M can develop and synthesize a large number of PFC variants, including precursors. Short-chain PFCs have been less studied despite the fact that human exposures to short-chain PFCs, including PFBA, are apparently increasing [302]. For example, when 3M analyzed serum samples from the Danish national birth cohort, only PFOA and PFOS were quantified [254]. The

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[dddddd] 3MA10034826. Meeting Minutes Meeting With Jr Mitchell # Re Review Of Recent Results Relevant To The Fluorochemicals In Blood Program (1979.04.26). Page 3MA10034828.

[eeeeee] 226-0257. Two Year Oral (Diet) Toxicity/Carcinogenicity Study of Fluorochemical FM-3924 in Rats, Volume 1, age 001488.

[ffffff] AR226-0262.pdf, Report Amendment No. 1: Two Year Oral (Diet) Toxicity/Carcinogenicity Study of Fluorochemical FM-3924 in Rats. Page 003085.

[gggggg] AR226-0264. Pathology Review of Reported Tumorigenesis in a Two Year Study of FM-3924 in Rats. Page 003104.



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MDH has determined that insufficient evidence is available for a proper risk assessment of both PFHxS and PFBA.

Certain scientists, particularly industry-affiliated scientists, have assumed that short-chain PFCs such as PFBA have lower or no toxicity based on PFBA's short apparent elimination half-life (T½) in blood serum. However, a recent study shows that PFBA is retained significantly in human kidneys and lungs, rather than blood. In this autopsy study, PFCs were measured in different organs. Short-chain PFCs are barely detectable by standard LC-MS techniques in blood serum, but in human body organs PFBA showed the highest concentrations in human lung tissue, and PFBA also was the predominant PFC in human kidneys [52]. Thus, the fact that PFBA appears in lower concentrations in blood than the longer-chain PFCs is probably misleading as to its toxicity. Rather, given that PFBA is known to accumulate in the kidney and the lung, it is reasonable to assume that PFBA exposures likely contribute to target organ effects, especially in kidneys. PFHxS is retained in several organs, including the brain [52].Animal studies already have begun to bear this out, as I discuss below.

The short-chain PFCs, moreover, are equally as bio-persistent as the long-chain PFCs, in that they are synthetically made, are not found in nature, and do not degrade. The molecular structure of PFBA and other short-chain PFCs also are highly similar to the structure of long-chain PFCs, particularly at the end group of the chain.

Given the similar structure of PFBA and other short-chain PFCs to more-studied PFCs, particularly at the end group of the chain, and their equal bio-persistence, and given the adverse human health effects that have been shown as to PFOA and PFOS, many in the scientific community have called for short-chain PFCs to be assumed to be, and treated as, equally risky. In their Madrid Statement, this large group of scientists in the field concluded: "While some shorter-chain fluorinated alternatives seem to be less bioaccumulative, they are still as environmentally persistent as long-chain substances or have persistent degradation products. Thus, a switch to short-chain and other fluorinated alternatives may not reduce the amounts of PFCs in the environment. In addition, because some of the shorter-chain PFCs are less effective, larger quantities may be needed to provide the same performance." These colleagues also noted that, "While many fluorinated alternatives are being marketed, little information is publicly available on their chemical structures, properties, uses, and toxicological profiles" [81].

In an accompanying editorial to the Madrid Statement which I co-authored with Dr. Linda Birnbaum, Director of the National Institute of Environmental Health Sciences, we emphasize concern about the "potential risks of the short-chain" PFCs, and call for studies especially regarding low-dose endocrine disruption and immunotoxicity [303].

In response to these statements by academic researchers, the industry FluoroCouncil agreed to much of the content, but stated that "the short-chain PFAS substances studied to date are not expected to harm human health or the environment," as they "are eliminated more rapidly from the body and are less toxic than long-chain substances" [304]. While that may be true for blood serum, short-chain substances like PFBA clearly linger in certain organs [52], as already mentioned, and the potential risks of these compounds are in no way clear. They therefore clearly cannot be considered "safe" at this point [303].



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Even with few studies concerning PFBA, and the somewhat greater number addressing PFHxS, many of those have shown adverse effects. Indeed, even early 3M-sponsored studies showed adverse effects from PFBA in laboratory animals in the liver, thyroid system, cholesterol levels, and negative developmental effects on the next generation. I will briefly describe these studies, which are supportive of my opinion. For PFHxS, several epidemiology studies have already been mentioned, and a brief summary is given here.

a. The autopsy study already mentioned analyzed a total of 21 PFCs in 99 sets of tissue samples from autopsies in Spain (brain, liver, lung, bone, and kidney) [52]. In kidney and lung, PFBA was the most frequently determined PFC, and at the highest concentrations (with medians of 68 and 141 ng/g, respectively, i.e., greatly in excess of concentrations measured on blood, including those of major PFCs like PFOS and PFOA). Lung tissues accumulated the highest total PFC concentrations. PFHxS is retained particularly in liver, kidney, lungs and brain. The authors suggest that the accumulation of different PFCs in human tissues should be of high importance for the validation of toxicokinetic models and should lead to further studies on the distribution of PFCs in the human body to help interpreting non-detectable concentrations in serum.

b. Experimental animal studies on PFBS likewise show a distribution in the body that differs from PFOS [305], supporting the view that one should not assume that serum concentrations necessarily reflect organ retention levels.

c. In its review of PFBA, the MDH referred to the following adverse effects seen in experimental studies: delayed eye opening and delayed vaginal opening, as mention in section A, changes in cholesterol, thyroid function, and liver function [63], as referred to above in the relevant sections. For PFHxS, the MDH noted adverse effects on thyroid function in a toxicity test study and certain epidemiology findings [306], but considered the evidence too incomplete to derive an exposure limit.

d. PFBA has been shown to modulate gene expression and cause enlarged liver size and toxicity through a PPAR-related mechanism that reflects similarities with PFOA toxicity [307]. Most of the effects also occurred in PPAR-alpha humanized mice, thus suggesting that species differences were of limited consequence.

e. Among known effects of the related C4, PFBS, is inhibition of the enzyme aromatase, an effect that would suggest potential endocrine disruption, and changes in lipid metabolism, in placental cells [199].

f. Epidemiological evidence cited above shows that elevated serum-PFHxS concentrations are associated with lowered antibody responses to vaccinations [35, 126, 128], lowered fecundity [159], abnormalities of menstrual cycles [167], lowered sperm count [170], greater risk of miscarriage [176], changes in birth weight [188], hormonal changes [193], including thyroid hormone changes [222], and metabolic changes [242]. However, the toxicology evidence is far from sufficient, and proper animal bioassays are missing. A 3M-commissioned rat study of developmental PFHxS exposure noted that the pups were "potentially" exposed via milk [308], although an article published about the same time [309]



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showed detectable concentrations of PFHxS in human milk collected in Massachusetts [309]. Both articles were authored by 3M's Dr. Butenhoff.

As major adverse effects have only recently been addressed in scientific publications, new evidence in this area will likely emerge in the future. Thus, the true risk of PFC-associated adverse health effects is probably even greater than it appears so far, especially for PFBA, known to accumulate in human tissues, though not in blood.

That said, even based on the evidence to date, given the similar structure of PFBA and PFHxS to other more-studied PFCs particularly at the end group of the chain, given the adverse human health effects that have been shown as to PFOA and PFOS, and given the adverse effects already shown as to PFBA and PFHxS, it is my opinion that both PFBA and PFHxS pose a substantial present and potential hazard to human health.

## IX. RISK ASSESSMENTS AND CURRENT LIMITS FOR PFC EXPOSURE

When translating scientific insight and documentation into public rule making, the evidence is scrutinized in a process usually referred to as risk assessment. If the evidence is substantial, it is often easier to reach a conclusion, but oftentimes, there are major reservations or limitations that make it difficult to conduct a formal evaluation. In Section V, I described some of the major caveats in regard to drawing conclusions on incomplete evidence.

The weaknesses of risk assessment as currently practiced were highlighted by a committee of the U.S. National Research Council (NRC) [111]. A particular concern was the default assumptions (or lack of same), in particular the so-called "untested chemical assumption," i.e., that a chemical is innocuous, unless testing shows otherwise. As noted by prominent scientists from the U.S EPA earlier this year, risk assessment has failed when adverse health effects are demonstrated at exposure levels predicted from animal studies to be safe for humans [310]. That seems to be the case regarding the PFCs. To further illustrate this issue, I recall how I participated in the drafting of EFSA's opinion on PFOS and PFOA in 2007-2008 [1]. To begin with, we received a tentative list of topics to cover in a logical sequence, i.e., a draft table of contents. On the list, there were a variety of issues for consideration. If there was no evidence, we should just leave out the topic. At the time, there was little evidence on immunotoxicity, so it was not discussed. The deletions did not have any impact on the conclusions, which were based solely on the evidence available. As noted by the NRC, such default decisions are inappropriate and could be invalidated by subsequent discoveries, i.e., in regard to immunotoxicity of PFCs in the present case.

In the present context, two main concerns will be highlighted, i.e., the identity of the population(s) at greatest risk, and the likely target organs that may suffer adverse effects at the lowest doses. This section will also include a brief review of exposure limits.

Pregnant women and young children must be considered populations at increased risk due to the vulnerability during early development. Other population groups at increased risk include adults with pre-existing diseases of the kidneys, the liver, or the cardiovascular system, in particular those with a high intake of water.



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Regarding target organs, most risk assessments have focused on the liver, as rodent studies have clearly documented increased liver size and some functional changes as being strongly related to elevated PFC exposures. However, species differences, particularly in regard to PPAR expression may complicate the translation of rodent data to the human situation. Other potential target organs, such as the immune system and the endocrine system, have been considered in animal studies, but only in part covering the subtler effects that are of concern in regard to human health. Thus, reliance on animal studies of liver toxicity now appears not to protect adequately against adverse effects on the latter organ systems.

Adverse effects on immune functions and on breast development have been recently documented at background exposure levels. Consequently, many U.S. regulatory agencies have set current limits for PFCs in drinking water that appear insufficient, to protect against adverse health risks, especially in vulnerable subgroups. Benchmark calculations based on decreased response to vaccine suggest that existing limits may be 100- to 1000-fold too high [150].

At this time, the UN Stockholm Convention included in 2009 PFOS and its precursors on the list of substances to be phased out, and it seems that PFOA will likewise be included in the very near future. The European Chemicals Agency (EChA) has already listed PFOA and recently added PFHxS to the Candidate List of substances of very high concern (SVHCs) for mandatory authorization procedures. As these two groupings require substantial evidence to justify the listing, the fact that other PFCs are not included only means that sufficient evidence is not yet available, not that they are not persistent, bioaccumulative, highly toxic, and therefore undesirable.

As noted by the NRC [111], risk assessments can take a very long time and can be difficult to revise, once a consensus has been obtained. Nonetheless, as scientific evidence accumulates, revision of the health limits would appear necessary. In the case of PFCs, the substances accumulate in the body, and present-day exposures will contribute to the body burden for many years in the future. Proposed calculations from 2013 [150], which relied on epidemiology findings, have not yet been applied in formal risk assessments.

## A. Drinking water limits

The limits set by the EPA, the states, and various foreign governments vary from each other (see Table 3), based on values and assumptions used, and based on how recently the limits have been set or revised [311]. Differences between the acceptable limits are often due to differences in default values, e.g., for uncertainty factors used in the calculations, although estimates of water intakes and lifetime accumulation also differ. In addition, there is a clear tendency that limits decrease over time, as more evidence becomes available.

Table 3. Examples of current limits for PFC concentrations (ng/L) in drinking water in different jurisdictions.

| PFC | PFOS | PFOA | PFHxS | PFBA | Total PFCs |
|---|---|---|---|---|---|
| U.S.EPA | 70 | 70 | - | - | - |
| MDH | 27 | 35 | 300 | 7,000 | - |



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| | | | | | |
|---|---|---|---|---|---|
| Canada | 600 | 200 | - | - | - |
| Sweden | - | - | - | - | 90 |

Most limits address individual PFCs, but the Swedish limit, for example, accounts for the sum of major PFC contaminants. Likewise, some agencies have decided for a joint limit for PFOS and PFHxS. Recent toxicology evidence suggests that adverse effects from some PFASs may not be additive, and synergistic effects have been identified [312, 313]. The epidemiology offers little guidance, and toxicology studies suggest that at least PFOA has a mode of action that differs from the one of PFOS [147, 247].

The present subsection will first summarize the most relevant limits, mainly for concentrations in drinking water. The great variability in the numbers illustrated by the above table must be considered in light of changing needs for exposure limits in different settings, emerging scientific insight, and the latency within regulatory agencies in regard to developing new guidelines. Also, the limits have been developed based on different definitions and assumptions. In the subsequent subsection, I shall discuss the major approaches to setting exposure limits.

### 1. Federal and state drinking water limits

#### *EPA*

In 2009, the EPA issued provisional health advisories of 0.4 µg/L (400 ng/L) for PFOA, and 0.2 µg/L (200 ng/L) for PFOS [314]. At the time, EPA concluded that "[e]pidemiological studies of exposure to PFOA and adverse health outcomes in humans are inconclusive at present." Also, the evidence for the carcinogenicity of PFOS is considered "suggestive of carcinogenicity." Similar conclusions were drawn in 2015, when EPA updated their previously proposed limits for PFOA and PFOS in water to 0.07 µg/L (70 ng/L) for both, as based on calculations relying on the most recent toxicological and supporting data [148, 149]. The U.S. EPA has selected 0.00002 mg/kg/day (or 0.02 µg/kg·d) as the Reference Dose (RfD) for PFOA and 0.00003 mg/kg/day (or 0.03 µg/kg·d) as the RfD for PFOS. Incidentally, the RfD for PFOS is 6-fold higher than the safe reference level calculated by 3M's Dr. Butenhoff.[hhhhhh]

#### *Agency for Toxic Substances and Disease Registry*

The Agency for Toxic Substances and Disease Registry (ATSDR) first issued a draft toxicological profile in 2009, but concluded that there was insufficient evidence at the time to develop a minimal risk level [17]. An updated version from 2015 [4] again focused on the experimental animal studies to develop a Minimal Risk Level of 0.02 µg/kg·day for PFOA and 0.03 µg/kg·day for PFOS, as the only PFCs that had sufficient evidence to allow this calculation. The MRLs are the same as the EPA's RfDs. ATSDR stated that changes in birth weight and serum liver enzymes in humans are small and not likely biologically relevant; the same applied to immune function changes, and the findings in children were not even mentioned in the section discussing exposure limits. In fact, ATSDR rejected a calculated benchmark dose for immunotoxicity as the study did not include an unexposed group of children (which is clearly

[hhhhhh] 3MA01366219.pdf.



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wrong). Still, if calculated for a woman weighing 50 kg (110 pounds), the MRL would result in intakes of 1 and 1.5 µg per day, and allowing water consumption of at least one liter per day to contribute up to 10% of the daily PFC intake, these MRLs are in agreement with the EPA water limits.

***Minnesota Department of Health***

The MHD in 2008 issued Health Risk Limits (HRLs) for PFOS and PFOA, i.e., upper limits in concentrations in water that are believed at the time to pose little or no appreciable risk to a person drinking the water [315]. The HRLs are proposed and adopted as rules by the State following a public rule-making process. These two HRL values of 0.3 µg/L (300 ng/L) were based on PFOS effects on the liver and thyroid, and PFOA effects on the liver, fetal development, reduction in red blood cell numbers, and immune system changes in experimental studies [292].

These limits have recently been revised. In May of 2017, MDH released its updated limits of 0.027 µg/L and 0.035 µg/L for PFOS and PFOA, respectively. The lowered limits were considered to better protect the fetus and the breastfed infant. The MDH relied on the toxicology evaluation carried out by the EPA [148, 149], but then applied toxicokinetic calculations to take into account increased serum-PFC concentrations during infancy in connection with breastfeeding [37], while still emphasizing life-time exposures. This resulted in a decreased of 50% or more, as compared to the EPA limits, and close to a 10-fold decrease compared to the 2008 values.

Notably, in regard to the RfD for PFOS of 0.0051 µg/kg/day and the corresponding serum concentration of 63 ng/ml, the MDH provides the following caveat: "Note: this serum concentration is inappropriate to use for individual assessment. Serum concentration is useful for informing public health policy and interpreting population-based exposures. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals." This statement would generally apply to such calculations, although in this case, where a much lower limit is suggested by epidemiological evidence, it makes less sense. Also, 3M's Dr. Butenhoff calculated that a reference level in plasma for chronic PFOS exposure from all sources would be 1.5 ppb, or 1.5 ng/mL.[iiiiii]

Previously, MDH had established HRLs for PFBA and PFBS, with chronic exposure limits of 7 µg/L. These two HRLs were based on PFBA effects on liver, thyroid, blood, cholesterol, and developmental changes, and PFBS effects on blood, kidney and liver changes in experimental studies. The RfDs established based on animal studies are 0.0042 mg/kg·day (or 4.2 µg/kg·day) for PFBS and 0.0038 mg/kg·day (or 3.8 µg/kg·day) for PFBA [316]. The corresponding water limits are 9 and 7 µg/L. Neither of these two C4 compounds have been examined with a view to immunotoxicity, and likewise, no carcinogenicity data exist.

MDH also released guidance regarding PFHxS that identified effects of PFHxS on body weight, blood, and cholesterol in experimental studies that occurred at a similar human

[iiiiii] Op.cit.



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equivalent dose as was determined for the PFOS HRL. MDH has indicated that while it awaits further information, the HBV for PFOS of 0.027 µg/L will apply to PFHxS [306].

***Other U.S. states***

Using slightly different assumptions, the state of New Jersey at first decided on a limit of 0.04 µg/L (40 ng/L) (and recently lowered that, see below) for PFOA. New Jersey relies on an adult drinking water intake rate of 2 liters per day (for a BW of 70 kilograms), which is about half of the water intake rate (at the 95$^{th}$ percentile) used for calculations in Minnesota.

New Jersey's revised limits are among the most recent revisions [10], and it took into account a cancer risk assessment. Based on evidence on testicular cancer in rats, a cancer slope factor was calculated, and a lifetime risk of 1 x $10^{-6}$ was found to correspond to a water concentration of 14 µg/L. Almost the same level was found when using liver weight as a sensitive non-cancer outcome and taking into regard uncertainty factors. Previously, scientists from New Jersey used data on breast development in a rodent study to calculate BMDL for an endocrine disruption outcome [7]. In this case, the BMDL was translated to a safe serum-PFOA concentration in humans of 0.8 ng/mL, thus suggesting that endocrine disruption may occur at low exposure levels where immunotoxicity is otherwise the only adverse effect deocumented so far. However, delayed mammary gland development was not recommended as a critical effect because of lack of precedent for use of this endpoint as the primary basis for risk assessment [10]. Three independent epidemiological studies have now shown decreased duration of breastfeeding in lactating women at elevated PFC exposures (see section VII.C.1).

Several other states have decided on PFC limits for drinking water. Limits published several years ago tend to be higher. For example, the State of North Carolina used assumptions similar to those previously used by New Jersey, but North Carolina had åreviously decided on a limit of 0.63 µg/L (630 ng/L) for PFOA. Although my review of existing limits for PFAS in drinking water may not be up to date, I have noted a range of PFOA limits from 0.014 µg/L (New Jersey) to 24 µg/L (Oregon). Likewise, PFOS limits for drinking water developed by state authorities vary from 0.011 µg/L (Michigan) to 1.3 µg/L (Alaska). Although some of the very high limits may have been rescinded, the range illustrates the impact of emerging evidence over time and of state-level default practices. I have not found limits for PFBS and PFBA, while Australia has a PFHxS limit of 0.5 µg/L. As far as I am informed, calculation of water limits are generally based on adverse outcome measures in animal studies (e.g., liver weight), and not driven by epidemiological evidence. In addition, cancer and delayed breast development in animals have been considered as critical effects by the state of New Jersey only, at least so far.

**2. Foreign exposure limits**

***European Food Safety Authority***

The European Food Safety Authority (EFSA) in 2008 released its recommended Tolerable Daily Intake (TDI) at 1.5 µg/kg·day for PFOA and 150 ng/kg (0.15 µg/kg·day) for PFOS [1]. These limits rely on the same animal toxicology data as the assessments published by the EPA and the ATSDR about the same time, and the TDI values correspond to the initial RfD and MRL values arrived at. Some EU member states have later published national limits for PFC



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concentrations in drinking water, and some of the member states (such as Sweden, see above table) have decided for total-PFC concentration limits, i.e., including all of the (C8, C6 and C4 compounds considered here. These limits are therefore stricter than most current limits. EFSA is expected to release an updated opinion with revised TDI levels in the fall of 2017.

### 3. Fish consumption advice

In the aquatic environment, some PFCs accumulate in fish. In Mississippi River Pool 2, for example, PFOS was generally detectable in surface water samples up to a level of 136 ng/L [23]. As reviewed above under exposure sources, PFC contamination of waterways results in biomagnification in aqueous food chains, with PFOS causing much higher accumulation than PFOA or PFHxS [20-23]. Average PFOS concentrations have been reported to be up to 275 ng/g.

Using similar risk assessment methodologies and calculations as described in regard to the water limit, below, with a meal size of 227 g fish for a 70-kg adult, the MDH has issued a health-based fish consumption advice of > 40 ng/g PFOS (1 meal/week) and > 200 ng/g PFOS (1 meal/month) for the several lakes in the Twin Cities area and portions of the Mississippi River with elevated concentrations of PFOS in fish tissue. In total, specific consumption advice has been issued for 34 lakes and the Mississippi River Pool 2 [24].

## B. Setting drinking water health limits

Generally speaking, a health limit is calculated from a "point of departure," which in turn is based on a calculation starting from a benchmark dose, or from a LOAEL or NOAEL. The point of departure is usually derived from animal toxicity studies reflecting a point of critical effect. As cancer risk has not been formally applied so far, the discussion here focuses on non-cancer risks, and a brief section below will summarize the approach to cancer risks.

The point of departure is then adjusted using knowledge of the half-life of the relevant PFC in humans, and of the differences between humans and animals in the toxicity study in terms of water intake and retention, to arrive at a "human equivalent dose."

Then, because PFCs might not affect humans in exactly the same way that they affect, say, cynomolgus monkeys or laboratory rats tested in toxicity studies, we adjust the human equivalent dose by applying "uncertainty factors." There are multiple types of uncertainty factors that may be appropriate, depending on the nature of the animal study, what is known about the differences between the animal in the study and humans, and the strength of the "database" of knowledge about the health effects of PFOA. One uncertainty factor that might be applied concerns potential differences in toxicodynamics (differences in the flow of PFCs within the bodies of animals versus humans). Another concerns intraspecies variability (recognizing that PFCs might affect human subpopulations differently, including more vulnerable populations such as children). Other uncertainty factors that may be appropriate include a "subchronic to chronic extrapolation" (for when we have a subchronic exposure value, but there is a risk that a chronic exposure could lead to harm at lower levels), a "LOAEL-to-NOAEL" extrapolation (for when we have evidence from studies of a low level at which adverse effects occur, but no good data on an exposure level at which no effects occur), and a "database uncertainty" factor (for



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when there have not been enough animal studies of certain types to have some degree of confidence that the results are a reasonable measure of risk and harm). The various uncertainty factors are then multiplied to arrive at a total uncertainty factor.

The human equivalent dose is divided by the total uncertainty factor leading to a "reference dose." The reference dose is then plugged into a formula to arrive at a health limit, for example a formula like this:

$$\frac{\text{(Rfd) x (RSC) x (Conversion factor)}}{\text{(Chronic intake rate, L/Kg/d)}}$$

Where RfD is the reference dose, RSC is the "relative source contribution," the conversion factor changes milligrams into micrograms, and the "chronic intake rate" is the rate chosen to represent the time-weighted average intake rate over the number of years estimated to achieve a steady-state serum concentration based on the half-life of the PFC.

The RSC is often a default based on EPA guidance such as 0.2 (or 20%), representing an assumption that 80% of a person's exposure to the PFC comes from non-drinking water sources. Appropriate values for an RSC typically range from 0.2 (common) to 0.8 (more appropriate for a pharmaceutical drug where exposure from other sources is less likely). If there is additional information about exposure sources for a chemical, there may also be justification for departing from the 0.2 default.

The chronic intake rate depends on the half-life of the chemical and reasonable estimations of how much water people drink. There is a different rate for calculating an acute dose level, or a sub-chronic level.

As cancer is a likely outcome of PFC exposure, I shall briefly refer to a recent calculation of cancer risk, although this has not been formally applied so far. I shall then review the methods for non-cancer risks used in risk assessments.

### 1. Cancer slope factor

The basic assumption generally applied is that the cancer risk increases with the dose. Although this may not be correct for non-genotoxic substances, such as the PFASs, the calculation will most likely err to the conservative side and provide improved protection. The goal is then to calculate the exposure level that will cause a life-time cancer risk of one in a million. New Jersey arrived at a cancer slope factor of 0.021 $(mg/kg \cdot day)^{-1}$ for PFOA, as based on increased incidence of testicular tumors in a chronic rat study. New Jersey used this slope factor to develop a health-based limit protective for cancer effects at the $1 \cdot 10^{-6}$ (one in one million) lifetime cancer risk level, arriving at a water concentration limit of 0.014 µg/L (14 ng/L) [10].

This limit is identical to New Jersey's health-based limit based on non-cancer endpoints, and is one-fifth of the most recent water limit value proposed by the EPA [148].

My conclusion is that, on the basis of current evidence, cancer risk alone is unlikely to drive the risk assessment for PFASs, because specific target organ effects are likely to



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be at least as important. This conclusion is supported by the observation that the PFASs appear not to be genotoxic. Any carcinogenicity is likely due to other mechanisms, such as immunotoxicity and endocrine disruption, i.e., non-cancer endpoints that are already considered highly vulnerable to PFAS exposures.

### 2. Benchmark dose

The various regulatory agencies appear to be in overall agreement in using a benchmark dose model to calculate non-cancer health limits for drinking water [2].

In this method, a dose-response function is fitted to the data or adopted from a default assumption. The benchmark dose (BMD) is defined as the dose which leads to a specific loss (or degree of abnormality) known as the benchmark response (BMR) in the outcome variable. The BMR must be specified before the analysis.

In epidemiological studies, a 5% change is often used for the BMR. A larger BMR will lead to a higher BMD. The statistical uncertainty in the BMD estimation is taken into account by calculating its lower one-sided 95% confidence limit, the benchmark dose level (BMDL). The BMDL is then used as the point of departure for calculation of the exposure limit.

An advantage of this approach is that reliance on smaller and less certain studies, everything else being equal, can result in more protective standards, which would be in accordance with the precautionary principle [317].

## C. Applications of benchmark dose calculations

A common endpoint that has been used to set a benchmark dose is an increase in liver weight observed in rodent studies. Similar numbers have been used by the EPA, EFSA and MDH for their standards setting efforts. For PFOA, the MDH relied on a BMDL of 23 μg/mL serum, which was estimated to correspond to a human equivalent dose of 0.0023 mg/kg· d based on the uptake, distribution within the body, and elimination of PFOA by humans (first order kinetics) [292].

Similar calculations showed a BMDL at 35μg/mL for PFOS in serum, with a human equivalent dose of 0.0025 mg/kg· d. Uncertainty factors were included, while also taking into regard that the data base regards subchronic exposure effects only.

The MDH averaged drinking water exposure over each period (starting from birth) using data from national studies of large numbers of people. Intake (using the 95th percentile of intake) over the first 19 years of life is 0.053 L/kg· d and intake over the first 27 years of life is 0.049 L/kg· d. Drinking water standards generally are calculated to allow for other exposure sources, so that the dose from drinking water contributes a portion (usually 20 percent) of the reference dose.

Benchmark dose calculations for PFCs have been carried out using data from other toxicological studies, including a study in pregnant mice [318] and a study on breast development in pups [7]. The New Jersey committee [10] showed that these findings would result an RfD as low as 0.11 ng/kg· day – much below the concentration levels relied on by the



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MDH – after consideration of the uncertainty factors. When modeling the results in terms of serum-PFOA concentrations, they showed that the Target Human Serum Level (analogous to the RfD expressed on a serum level basis) would be 0.8 ng/mL, i.e., below the median serum PFOA level in the U.S. general population. Again, the New Jersey committee refrained from using this information for calculating a safe drinking water limit.

### D. Comparison of existing limits with recent research information

Recent evidence have identified adverse effects of PFCs on sensitive outcomes in laboratory animals following developmental exposure [9] and on immune system functions in children [35]. It is then appropriate to take into account the existence of likely effects that target the programming of organ system function and future disease risks [248]. When developmental toxicity is likely, a National Research Council committee 20 years ago proposed to include an extra 10-fold uncertainty factor to protect children against food contaminants [319]. Using existing data and benchmark dose calculations, more precise results can be obtained that reflect the importance of developmental vulnerability, rather than average sensitivity during decades of exposure.

More specifically, as noted by the New Jersey committee [10], data now available on mammary gland development in mice suggest that clear delays result from much lower developmental exposures at serum-PFOA concentrations of about 25 ng/mL [9]. Immunotoxicity has been demonstrated in mice at concentrations of the same order of magnitude [141]. Using these data, and making benchmark dose calculations using a 10% BMR and an interspecies 10-fold uncertainty factor, results in a BMDL serum-PFOA concentration of 23-25 ng/mL [7]. One could argue that this mouse experiment was not based on chronic exposures, so that additional default 3-fold uncertainty factor would be appropriate, thus reducing the BMDL to 8 ng/mL.

Formal limits for water or total intake will likely differ between jurisdictions, as default values used by different agencies will differ and will therefore result in slight deviations. However, my opinion is that, as science improves, PFC exposure limits in the various jurisdictions will continue to decline and we will later view many of the current exposure limits for PFOA and PFOS as too high, likely by a factor of 100 to 1,000.

Moreover, as science improves and drinking water limits are lowered to account for increased concern about the adverse effects of PFCs, the new limits typically refer to long-term exposures, perhaps for a lifetime, not to exceed the limit. They do not take into account past exposures above that level. However, as the water limits in Minnesota have been applied and subsequently lowered, many people, particularly in the East Metro area, were in the past exposed to PFCs in excess of the drinking water limits, especially the most recent visions – in some cases, for decades. The PFC body burdens of those individuals would reflect a history of higher exposure than would be contemplated under a newly-adopted limit, and, without an entirely PFC-free source of drinking water, the PFC body burdens of these individuals would exceed that contemplated by the revised drinking water limits for many years, if not decades.



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## E. Proposed limits based on recent epidemiological evidence

Benchmark doses derived from animal studies and the decisions on applicable uncertainty factors needed for extrapolation to humans always include some degree of uncertainty, and reliance on human data would be preferable. On the other hand, while benchmark dose calculations from toxicology studies are fairly straightforward, using epidemiological studies is more complicated due to the need for covariate adjustments, the absence of a non-exposed control group, and more complex decisions on the shape of the dose-response curve [317]. Solutions to the statistical problems can be obtained both by the so-called hybrid method and relative methods [2], but decisions on dose-response models may have important consequences for the BMDL results.

In our recent study of immunotoxicity [35], five PFCs were measured to assess prenatal and postnatal exposure in regard to associations with concentrations of two specific antibodies against childhood vaccines. The antibody responses could be categorized either in terms of the concentration as such or whether it was below the clinically protective concentration of 0.1 IU/mL. With a benchmark response of 5%, we calculated that the BMDL for the diphtheria antibody concentration at age 7 years is 0.7 ng/mL, 0.6 ng/mL, and 1.1 ng/mL for the child's serum concentrations of PFOS, PFOA, and PFHxS, respectively. Results for tetanus were higher. For prenatal exposure in regard to diphtheria antibody concentration at age 5, the results were 0.6 ng/mL, 1.0 ng/mL, and 3.4 ng/mL for the same PFCs. For prenatal exposure in regard to the limit of 0.1 IU/mL for the diphtheria antibody concentration at age 5 years, the results were 0.8 ng/mL, 0.4 ng/mL, and 1.0 ng/mL. Linear dose-response curves generally resulted in higher BMDL results, likewise also with a BMR value of 10% [150]. These results are fairly similar and much below the BMDL values from animal studies.

Given the correlation of the major PFCs, it is difficult to include mutual adjustment in the models. However, in agreement with the regression results, the benchmark dose levels suggested that PFHxS is less immunotoxic than PFOS and PFOA. Our recent calculations show that PFOA, after adjustment for other PFCs, shows clear negative impacts on immune system responses to vaccinations, but it is not possible to separate the effects of PFOS and PFHxS [120]. Our calculations rely on the association between early-life exposure to PFCs in regard to deficient immune system responses to vaccinations later on in childhood, as well as adverse developmental effects already considered by the MDH and the EPA. While the immune system-related associations are statistically significant, the exact curve shape for the associations id unknown, and assumptions must be made to judge the approximate magnitude of the point of deviation, from which an exposure limit can be derived.

In addition, the immune system-related calculations were based on serum concentrations measured at age 5 years, assuming that this level is representative for the exposure at the most vulnerable age. This assumption may not be true [113], and the results may therefore be biased toward higher and less protective levels. Nonetheless, we applied several different models and then applied standard default factors that correspond to routine practice within the EPA and other regulatory agencies. Thus, when calculated based on both immune-system related effects and developmental endpoints, current exposure limits in the United States remain too high.



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## F. Underestimation of hazards posed by PFCs

As discussed in section V.A, there are important tendencies that will result in underestimations of PFC toxicity. The previous section shows that reliance on animal toxicity data with a focus on enlarged livers and similar routine outcomes from rodent toxicity studies can greatly underestimate the risk to human health. More targeted studies on immunotoxicity and endocrine disruption have recently been carried out in mice and revealed adverse effects at much lower exposures than those that lead to liver damage, especially when exposures were determined on the basis of blood concentrstions and not on the amount in the feed. Subsequently, human studies demonstrated that deficient antibody responses to routine vaccinations occur at elevated background PFC exposures. Supporting studies showing more frequent infectious disease in children at higher PFC exposure emphasize that the immune system is a highly vulnerable target organ. As a result, recent scientific insight suggests that, as it relates to children's immune systems and endocrine disruption, further consideration of protective levels may be necessary.

As an indication how new data can reveal adverse effects at exposure levels previously thought to be safe, the ATSDR Toxicology Profile in 2009 concluded that no data were available on immunotoxicity in humans [17], but the authors did not know that our study in the Faroes was under way and was to be published a couple of years later [35]. The recent report from the NTP considers PFOS and PFOA "presumed" immunotoxicants (the level just below "known") [5], but this conclusion has not yet impacted risk assessments carried out by regulatory agencies at state level or otherwise.

Given the fact that much of the leading scientific literature is fairly recent, the conclusions that can be drawn at this point must be regarded tentative to some extent, and they may even represent underestimations. Current understanding of the PFCs is very different from 3M's assertion in 2000, that "the presence of these materials at these very low levels do not pose a human health or environmental risk" (see Section IV.D). Current understanding is also very different from 2008 when the first formal risk assessments were published [1, 315]. At the present time, the main uncertainty regards effects on the most vulnerable target organs and critical exposure conditions, such as prenatal exposures, that have yet to be studied in greater depth. The most appropriate conclusion that can be drawn is that adverse effects on breast development and on adaptive immune system development likely represent critical effects and that BMDLs should focus on these outcomes. In drawing conclusions, we must still consider what we could possibly know today from the types of evidence available to us, and what we do not yet know. In this light, my above conclusions may well be underestimated.



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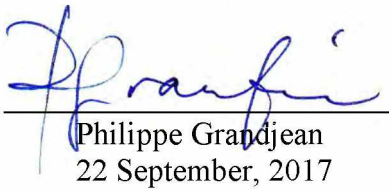
## X. AFFIRMATION

I affirm under penalty of perjury that the foregoing is a true and correct statement of my opinions in this matter and the grounds for those opinions.



Philippe Grandjean
22 September, 2017



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# EXHIBIT A

## ABBREVIATIONS

| | |
|---|---|
| ADHD | attention deficit hyperactivity disorder |
| ALT | alanine transaminase |
| APFO | ammonium perfluorooctanoate; |
| AP | alkaline phosphatase, liver enzyme |
| AST | aspartate aminotransferase, liver enzyme |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMD | benchmark dose |
| BMDL | lower limit benchmark dose |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| BW | body weight |
| C8 or C-8 | perfluorinated octanol compounds |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| EPA | Environmental Protection Agency |
| EtFOSE | see N-EtFOSE |
| Et-PFOSA-AcOH | 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid |
| FC-143 | PFOA (with up to 3.5% C6, C7, and C9 compounds) |
| FC-807 | N-ethyl perfluorooctane sulfonamido ethanol-based phosphate esters (metabolized into PFOS) |
| FC-95 | see PFOS |
| FDA | Food and Drug Administration |
| FEP | fluorinated ethylene propylene |
| FM-3924 | see N-EtFOSE |
| GGT | gamma-glutamyl-transferase, liver enzyme |
| GOT | glutamic-oxaloacetic transaminase, same as AST |
| HDL | high density lipoprotein |
| HRL | Health Risk Limit |
| IARC | International Agency for Research on Cancer |
| LC/MS/MS | liquid chromatography/tandem mass spectrometry |
| LD50 | lethal dose, 50% kill |
| LDL | low density lipoprotein |
| LOAEL | lowest-observed-adverse-effect level |
| MDH | Minnesota Department of Health |
| MeFOSE | see N-MeFOSE |
| NHANES | National Health and Nutrition Examination Survey |
| N-EtFOSE | 2-(N-ethylperfluoro-1-octanesulfonamido)-ethanol |
| N-MeFOSE | 2-(N-methylperfluoro-1-octanesulfonamido)-ethanol |
| NOAEL | no observed adverse effect level |
| NRC | National Research Council |
| NTP | National Toxicology Program |



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| | |
|---|---|
| OR | odds ratio |
| PFAS | see PFC |
| PFBA | perfluorobutyric acid |
| PFBS | perfluorobutane sulfonic acid |
| PFC | perfluorinated compound |
| PFDA | perfluorodecanoic acid |
| PFHxA | perfluorohexanoic acid |
| PFHxS | perfluorohexane sulfonic acid |
| PFNA | perfluorononanoic acid |
| PFOA | perfluorooctanoic acid; |
| PFOS | perfluorooctane sulfonic acid |
| PFOSA | perfluorooctane sulfonamide |
| POSF | perfluorooctanesulfonyl fluoride |
| PPAR | peroxisome proliferator activated receptor |
| T½ | biological half-life |
| T2D | type 2 diabetes |
| T3 | triiodothyronine |
| T4 | thyroxine |
| T-6316 | N-EtFOSE-containing product |
| TFE | tetrafluoroethylene |
| TOF | total organic fluorine |
| TSCA | Toxic Substances Control Act |
| TSH | thyroid-stimulating hormone |



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# EXHIBIT B

## PHILIPPE GRANDJEAN, M.D. (CV)

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P.O. Box 390589
Cambridge, MA 02139
Tel: 617-331-3317

Academic degrees
1974, M.D., University of Copenhagen
1975, Diploma in basic medical research, University of Copenhagen
1979, D.M.Sc. (dr.med.), University of Copenhagen

Chronology of employment

| | |
|---|---|
| 1974-1975 | Postgraduate training fellowship, University of Copenhagen |
| 1975-1978 | Research fellow, Institute of Hygiene, Univ. Copenhagen |
| 1978-1980 | Senior research fellow, University of Copenhagen<br>Visiting fellow, Department of Community Medicine,<br>Mount Sinai School of Medicine, New York |
| 1980-1982 | Director, Department of Occupational Medicine,<br>Danish National Institute of Occupational Health |
| 1982- | Professor of Environmental Medicine, Odense University |
| 1983-2017 | Consultant in Toxicology, Danish Health Authority |
| 1994-2002 | Adjunct Professor of Public Health (Environmental Health)<br>and Neurology, Boston University School of Medicine |
| 2003- | Adjunct Professor of Environmental Health, Harvard School of Public Health |

Awards and honors



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Prize essay in medicine, University of Copenhagen (1972)
Fulbright senior research scholarship (1978)
Keynote speaker, Odense University anniversary (1983)
Gitlitz Memorial Lecture, Association of Clinical Scientists, USA (1985)
Knight of the Dannebrog, awarded by the Queen of Denmark (1990)
The Dannin prize for medical research (1991)
Fellow, American Association for the Advancement of Science (1994)
Irish Congress Lecturer, Royal College of Physicians of Ireland (1996)
Knight of the Dannebrog, First Degree, awarded by the Queen of Denmark (2003)
'Mercury madness award' for excellence in science in the public interest from eight US environmental organizations (2004)
Emeritus Fellow, International Union of Pure and Applied Chemistry, IUPAC (2009)
Honorary Research Award, International Order of Odd Fellows (2010)
Science Communication Award, University of Southern Denmark (2012)
Bernardino Ramazzini Award (2015)
Basic & Clinical Pharmacology & Toxicology Nordic Award (2015)
Margrethegaarden honorary prize (2016)
John R. Goldsmith Award, International Society for Environmental Epidemiology (2016)

Editorial boards
American Journal of Industrial Medicine (1987-2017)
Applied Organometal Chemistry (1985-1991)
Arbejdsmiljø (Occupational Environment, in Danish, 1983-1990)
Archives of Environmental Health (European Editor, 1986-1992)
Archives of Toxicology (1987-)
Biomarkers (1996-2001)
Central European Journal of Occupational and Environmental Medicine (2015-)
Critical Reviews in Toxicology (1985-2012)
Danish Medical Bulletin (1994-2003)
Environmental Health (Editor-in-Chief, 2002-)
Environmental Health Perspectives (2003-)
Environmental Research (1981-1994 and 2014-, Associate Editor, 1995-2014)
Industrial Health (2000-2005)
International Journal of Hygiene and Environmental Health (2001-)
International Journal of Occupational and Environmental Health (1994-2011)
International Journal of Occupational Medicine & Environ Health (1991-
Journal of Clean Technology, Environmental Toxicology, and Occupational Medicine (1992-1998)
Journal of Environmental Medicine (1998-1999)
Naturens Verden (Natural Science, in Danish) (1987-1991)
Ugeskrift for Læger (Danish Medical Journal, in Danish) (1991-2007)

Scientific societies
American Association for the Advancement of Science (Fellow, 1994)
American Public Health Association
Collegium Ramazzini (Fellow, 1987; Member of the Council, 2005-2013)



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Danish Medical Association
Danish Societies of Clinical Chemistry, Epidemiology, Occupational and Environmental Medicine, and Public Health
Faroese Society of Science and Letters
International Commission on Occupational Health
International Society for Environmental Epidemiology

Research support as Principal Investigator since 2000
2000-2006 NIEHS
Mercury associated neurobehavioral deficit in children
2001-2003 Nordic Arctic Research Programme (NARP)
Changing patterns of biomagnified pollutants in the northern marine environment
2001-2004 Danish Medical Research Council
Exposure assessment for endocrine disruptors
2002-2004 Danish Medical Research Council
Environmental epidemiology research
2003-2004 European Commission
Assessment of Neurobehavioral Endpoints and Markers of Neurotoxicant Exposures (ANEMONE)
2003-2005 Danish Medical Research Council
Research in hormone related substances
2003-2006 NIEHS ES11687
Effects of perinatal disruptors in children
2003-2007 EPA STAR RD-83075801-0
Children's vulnerability to environmental immunotoxicant
2004-2011 NIEHS ES12199
Epidemiology of immunotoxicant exposure in children
2006-2011 NIEHS ES13692
Health effects of lifetime exposure to food contaminants
2006-2012 NIEHS ES14460
Three-generation human study of reproductive effects of marine food contaminants
2008-2012 Danish Council for Strategic Research
Environmental pollutant impact on antibody production against current and new childhood vaccines
2007-2013 NIEHS ES009797
Mercury associated neurobehavioral deficit in children

Major Current Funding as Principal Investigator
2011-2017 NIEHS ES012199
Epidemiology of immunotoxicant exposure in children
2012-2018 NIEHS ES021993 and NSF OCE-1321612
Immunotoxicity in Humans with Lifetime Exposure to Ocean Pollutants
2013-2018 NIEHS ES021477
Glucose Metabolism in Adults Prenatally Exposed to Diabetogenic Pollutants
2013-2018 NIEHS ES021372
Pollutant-related diabetes in the Nurses' Health Study II



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2014-2017 NIEHS ES023376
Gut Microbiome in Adults with Early Life Exposures to Environmental Chemicals
2017-2022 NIEHS P42ES027706
Sources, Transport, Exposure and Effects of PFASs (STEEP)

Major committees, boards and elective offices

*Danish:*

Danish Medical Association: Member, Prevention Council (2011-2014)
Danish Medical Research Council: Consultant on environmental medicine (1985-1990); Member, Joint Research Council Committee on Environmental Research (1986-1991); Member of DMRC (1992-1998)
Danish Society of Community Medicine: Secretary (1977-1978)
Danish Society of Industrial Medicine: Board Member (1974-1983)
Ministry of Education: Member, Committee on Toxicology (1984-1986); Member, Committee on Environmental Education (1986-1987)
Ministry of the Environment: Member, Council on Environmental Chemicals (1983-1989); Member, Environmental Appeal Board (1986-2010); Member, Environmental Research Council (1990-1992); Member, Advisory Committee on Pesticide Research (1995-2004); Member, Advisory Committee on Arctic Research (1996-2004)
Ministry of Health: numerous committee appointments; Chair, Committee on Risk Perception (2000-2001)
Ministry of Labour: Consultant on Occupational Health, Council on Occupational Safety and Health (1983-1993); Member, Occupational Health Council Research Committee (on behalf of the Danish Medical Research Council) (1984-1990 and 1999-2003)
Ministry of Research: Chair, Committee on Research at the Faroe Islands (1995-1996); Member, Committee on Scientific Dishonesty (2004-2006); Chair, Committee on Non-Ionizing Radiation (2004-2009)
Odense University (from 2000 University of Southern Denmark), elected offices: Chairman, Institute of Community Health (1982-1985; 1996-1999); Member of Executive Committee, Institute of Community Health (from 2000 Institute of Public Health) (1986-1995; 2000-2005); Member, Faculty Research Committee (1983-1985); Member, Curriculum Committee (1984-1986); Member, Faculty Council (1985-1993); Vice-Dean (1991-1993); Member, Scientific Integrity Committee (2003-)

*United States and international:*

Academy of Finland: member of panel evaluating the National Institute of Public Health (1995), site visit of center of excellence (2001)
Agency for Toxic Substances and Disease Registry: Workshop Rapporteur, Neurobehavioral Test Batteries for Use in Environmental Health Field Studies (1992); Member, Expert Panel of Mercury (1998)
Association of Schools of Public Health in the European Region: Treasurer (1975-1977)
BioMedCentral: Member, Editors Advisory Group (2011-2013)
Boston Environmental Hazards Center: Consultant (1994-1999)
Collegium Ramazzini: President, International Conference, The precautionary principle: Implications for research and prevention in environmental and occupational health (2002); Member, Executive Council (2005-2013)



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Commission of the European Communities: National Expert, Working Party on Environmental and Lifestyle-Related Diseases (1988-1990); ad hoc Consultant for evaluation of research applications; ad hoc Scientific Advisor on Risk Assessment (2009-); Member, SCHER Working group on Dental Amalgam (Human Health) (2012-2013)

European Environment Agency: Member, Scientific Committee (2012-2018)

European Food Safety Authority: Member, Panel on Contaminants in the Food Chain responsible for 85 opinions (2003-2009); Member of Working Groups on mercury, polychlorinated biphenyls, cadmium, lead, and benchmark dose

Food Advisory Committee, U.S.FDA, Methylmercury: invited expert (2002)

INMA (Infancia y Medio Ambiente), Spain: Member, Project Steering Committee (2010-)

Institut de Recherche Santé, Environnement et Travail, France: Member, Board of Advisers (2015-)

International Agency for Research on Cancer: Member of Task Group, Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47 (1988), Vol. 49 (1989), as chairman, Vol. 58 (1993), and as Subgroup chair, Vol. 100C (2009)

International Commission on Occupational Health: Danish Delegation Secretary (1982-90); Member, Scientific Committee on the Toxicology of Metals (1987-); Member of the Board (1990-1996)

International Programme on Chemical Safety: Member of Task Group, Environmental Health Criteria, Vol. 36 (1984) and 72 (1986)

International Society for Environmental Epidemiology: Councillor (1991-1994)

International Union of Pure and Applied Chemistry: Member, Subcommittee on the Toxicology of Nickel (1979-1989); Titular Member (1985-1991) and Chairman (1987-1991), Commission on Toxicology; Chairman, Subcommittee on Risk Assessment (1985-1989)

Karolinska Institute (Stockholm, Sweden): Member of international evaluation panel on environmental medicine (1993)

Ministry for Scientific Policy (Belgium): Consultant on national research program on health hazards (1990 and 1994)

National Institutes of Health (USA): Member of Special emphasis panels (2009-)

NATO Priority Area Panel on Environmental Security: Member (1996-1997)

Norwegian Research Council: ad hoc reviewer (2001-2008); Chairman of Environment and Health Review Group (2009-2010); member of steering committee (2011-2015)

Prenatal programming and Toxicity (PPTOX) conferences: Organizer/Chair/ Co-chair, Torshavn (2007), Miami (2009), Paris (2012), Boston (2014), Kita-Kyushu (2016)

Society of Occupational and Environmental Health: Member, Governing Council (1990-1993)

Swedish Council for Work Life Research: Member, Priority Committee on Chemical Health Risks (1997-1998)

U.N. Environment Programme: Member, Global Mercury Assessment Working Group (2002)

U.S. Environmental Protection Agency: Member, SAB/SAP Endocrine Disruptor Screening Program Subcommittee (1998-1999); Member, Food Quality Protection Act (FQPA) Science Review Board (SRB)(1999-2003)

White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)

World Health Organization: Temporary Adviser or Consultant on several occasions, five times elected Rapporteur; Member, European Advisory Committee on Health Research (2011-)



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# EXHIBIT C

## LIST OF GRANDJEAN PUBLICATIONS FROM RECENT 10 YEARS

Publications in international peer-reviewed journals

167. Grandjean P, Budtz-Jørgensen E. Total imprecision of exposure biomarkers: Implications for calculating exposure limits. Am J Industr Med 2007; 50: 712-9.
168. Grandjean P. Methylmercury toxicity and functional programming. Reproduct Toxicol 2007; 23: 414-20.
169. Grandjean P, Murata K. Developmental arsenic neurotoxicity in retrospect (editorial). Epidemiology 2007; 18: 25-6.
170. Wermuth L, Bech S, Petersen MS, Joensen P, Weihe P, Grandjean P. High prevalence and incidence of Parkinson's disease in the Faroe Islands. Acta Neurol Scand 2008; 118: 126-31.
171. Murata K, Grandjean P, Dakeishi M. Neurophysiological evidence of methylmercury neurotoxicity. Am J Industr Med 2007; 50: 765-71.
172. Budtz-Jørgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. Environ Health Perspect 2007; 115: 323-7.
173. Andersen HR, Nielsen F, Nielsen JB, Kjaerstad MB, Baelum J, Grandjean P. Xeno-oestrogenic activity in serum as marker of occupational pesticide exposure. Occup Environ Med 2007; 64: 708-714.
174. Andersen HR, Schmidt IM, Grandjean P, Jensen TK, Budtz-Jørgensen E, Kjaerstad MB, Baelum J, Nielsen JB, Skakkebaek NE, Main KM. Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy. Environ Health Perspect 2008; 116: 566-72.
175. Petersen MS, Halling J, Damkier P, Nielsen F, Grandjean P, Weihe P, Brøsen K. Polychlorinated biphenyl (PCB) induction of the CYP3A4 enzyme activity in Healthy Faroese adults. Toxicol Appl Pharmacol 2007; 224: 202-6.176. Choi AL, Budtz-Jørgensen E, Jørgensen PJ, Steuerwald U, Debes F, Weihe P, Grandjean P. Selenium as a potential protective factor against mercury developmental neurotoxicity. Environ Res 2008; 107: 45-52.
177. Grandjean P. Seven deadly sins of environmental epidemiology and the virtues of precaution. Epidemiology 2008; 19: 158-62.
178. Grandjean P. Late insights into early origins of disease. Basic Clin Pharmacol Toxicol 2008; 102: 94-9.
179. Petersen MS, Weihe P, Choi A, Grandjean P. Increased prenatal exposure to methylmercury does not affect the risk of Parkinson's disease. Neurotoxicology 2008; 29: 591–5.
180. Petersen MS, Halling J, Bech S, Wermuth L, Weihe P, Nielsen F Jørgensen PJ, Budtz-Jørgensen E, Grandjean P. Impact of dietary exposure to food contaminants on the risk of Parkinson's disease. Neurotoxicology 2008; 29: 584–90.
181. Halling J, Petersen MS, Brosen K, Weihe P, Grandjean P. Genetic predisposition to Parkinson's disease: CYP2D6 and HFE in the Faroe Islands. Pharmacogenet Genomics 2008; 18: 209-12.
182. Choi A, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: The case of methylmercury in fish and seafood. Crit Rev Toxicol 2008; 38: 877-93.
183. Grandjean P, Ozonoff D. Environmental Health: the first five years. Environ Health 2007; 6: 27.



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184. Grandjean P, Choi A. The delayed appearance of a mercurial warning. Epidemiology 2008; 19: 10-1.
185. Pouzaud F, Ibbou A, Blanchemanche S, Grandjean P, Krempf M, Philippe H-J, Verger P. Use of advanced cluster analysis to characterize seafood consumption patterns and methylmercury exposures among pregnant women. J Exp Anal Environ Epidemiol 2010; 20: 54-68.
186. Grandjean P, Perez M. Developmental neurotoxicity: Implications of methylmercury research. International Journal of Environment and Health 2008; 2: 417-28.
187. Choi AL, Grandjean P. Methylmercury exposure and health effects in humans. Environ Chem 2008; 5: 112-20.
188. Weihe P, Kato K, Calafat AM, Nielsen F, Wanigatunga AA, Needham LL, Grandjean P. Serum concentrations of polyfluoroalkyl compounds in Faroese whale meat consumers. Environ Sci Technol 2008; 42: 6291-5.
189. Grandjean P, Budtz-Jørgensen E, Barr DB, Needham LL, Weihe P, Heinzow B. Elimination half-lives of polychlorinated biphenyl congeners in children. Environ Sci Technol 2008; 42: 6991–6.
190. Coccini T, Manzo L, Debes F, Weihe P, Grandjean P. Application of lymphocyte muscarinic receptors and platelet monoamine oxidase-B as biomarkers of CNS function in a Faroese children cohort prenatally exposed to methylmercury and PCBs. Biomarkers 2009; 14: 67-76.
191. Budtz-Jørgensen E, Debes F, Weihe P, Grandjean P. Structural equation models for meta-analysis in environmental risk assessment. Environmetrics 2010; 21: 510-27.
192. Choi AL, Weihe P, Budtz-Jørgensen E, Jørgensen PJ, Salonen JT, Tuomainen T-P, Murata K, Nielsen HP, Petersen MS, Askham J, Grandjean P. Methylmercury exposure and adverse cardiovascular effects in Faroese whalingmen. Environ Health Perspect 2009; 117: 369-72.
193. Bjørling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. Environ Health 2008; 7: 50.
194. Julvez J, Grandjean P. Neurodevelopmental toxicity risks due to occupational exposure to industrial chemicals during pregnancy. Industr Health 2009; 47: 459-68.
195. Grandjean P, Budtz-Jørgensen E. An ignored risk factor in toxicology: The total imprecision of exposure assessment. Pure Appl Chem 2010; 82: 383-91.
196. Kirkegaard M, Sonne C, Dietz R, Letcher RJ, Jensen AL, Hansen SS, Jenssen BM, Grandjean P. Alterations in thyroid hormone status in Greenland sledge dogs exposed to whale blubber contaminated with organohalogen compounds. Environ Qual Saf 2011; 74: 157-63.
197. Blair A, Saracci R, Vineis P, Cocco P, Forastiere F, Grandjean P, Kogevinas M, Kriebel D, McMichael A, Pearce N, Porta M, Samet J, Sandler DP, Costantini RS, Vainio H. Epidemiology, public health and the rhetoric of false positives. Environ Health Perspect 2009; 117: 1809-13.
198. Schlezinger JJ, Bernard PL, Haas A, Grandjean P, Weihe P, Sherr DH. Direct assessment of cumulative aryl hydrocarbon receptor agonist activity in sera from experimentally exposed mice and environmentally exposed humans. Environ Health Perspect 2010; 118: 693-8.
199. White RF, Palumbo CL, Yugelun-Todd DA, Heaton KJ, Weihe P, Debes F, Grandjean P. Functional MRI approach to developmental methylmercury and polychlorinated biphenyl neurotoxicity. Neurotoxicology 2011; 32: 975-80.
200. Lincoln RA, Vorhees DJ, Chesney EJ, Shine JP, Grandjean P, Senn DB. Fish consumption and mercury exposure among Louisiana recreational anglers. Environ Health Perspect 2011; 119: 245-51.



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201. Yorifuji T, Tsuda T, Grandjean P. Unusual cancer excess after neonatal arsenic exposure from contaminated milk powder. J Natl Cancer Inst 2010; 102: 360-1.
202. Harari R, Julvez J, Murata K, Barr D, Bellinger DC, Debes F, Grandjean P. Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides. Environ Health Perspect 2010; 118: 890-6.
203. Grandjean P, Satoh H, Murata K, Eto K. Adverse effects of methylmercury: Environmental health research implications. Environ Health Perspect 2010; 118: 1137-45.
204. Mahaffey KR, Sunderland EM, Chan HM, Choi AL, Grandjean P, Mariën K, Oken E, Sakamoto M, Schoeny R, Weihe P, Yan C-H, Yasutake A. Balancing the benefits of n-3 polyunsaturated fatty acids and the risks of methylmercury exposure from fish consumption. Nutrit Rev 2011; 69: 493-508.
205. Julvez J, Debes F, Weihe P, Choi A, Grandjean P. Sensitivity of continuous performance test (CPT) to mercury exposure at age 14 years. Neurotoxicol Teratol 2010; 32: 627–32.
206. Dalgård C, Petersen MS, Schmedes AV, Brandslund I, Weihe P, Grandjean P. High latitude and marine diet: Vitamin D status in elderly Faroese. Br J Nutr 2010; 104: 914-8.
207. Heilmann C, Budtz-Jørgensen E, Nielsen F, Heinzow B, Weihe P, Grandjean P. Serum concentrations of antibodies against vaccine toxoids in children exposed perinatally to immunotoxicants. Environ Health Perspect 2010; 118: 1434-8.
208. Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants. Environ Health Perspect 2010; 118: 1429-33.
209. Grandjean P, Henriksen JE, Choi AL, Petersen MS, Dalgård C, Nielsen F, Weihe P. Marine food pollutants as a risk factor for hypoinsulinemia and type 2 diabetes. Epidemiology 2011; 22: 410-7.
210. Yorifuji T, Debes F, Weihe P, Grandjean P. Prenatal exposure to lead and cognitive deficit in 7- and 14-year-old children in the presence of concomitant exposure to similar molar concentration of methylmercury. Neurotoxicol Teratol 2011; 33: 205-11.
211. Grandjean P. Even low-dose lead exposure is hazardous. The Lancet 2010; 375: 855-6.
212. Spulber S, Rantamäki T, Nikkilä O, Castrén E, Weihe P, Grandjean P, Ceccatelli S. Effects of maternal smoking and exposure to methylmercury on Brain-Derived Neurotrophic Factor (BDNF) concentrations in cord serum. Toxicol Sci 2010; 117: 263–9.
213. Mozaffarian D, Shi P, Morris JS, Spiegelman D, Grandjean P, Siscovick, Willett WC, Rimm EB. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. N Engl J Med 2011; 364: 1116-25.
214. Ozonoff DM, Grandjean P. Milestones and impact factors (editorial). Environ Health 2010; 9: 35.
215. Needham LL, Grandjean P, Heinzow B, Jørgensen PJ, Nielsen F, Patterson DG Jr, Sjödin A, Turner WE, Weihe P. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ Sci Technol 2011; 45: 1121-6.
216. Yorifuji T, Grandjean P, Tsuda T, Kashima S, Doi H. Cancer excess after arsenic exposure from contaminated milk powder. Environ Health Prev Med 2011; 16: 164-70.
217. Grandjean P, Herz K. Methylmercury and brain development: Imprecision and underestimation of developmental neurotoxicity in humans. Mt Sinai J Med 2011: 78: 107-18.
218. Pichery C, Bellanger M, Zmirou-Navier D, Glorennec P, Hartemann P, Grandjean P. Childhood lead exposure in France: benefit estimation and partial cost-benefit analysis of lead hazard control. Environ Health 2011; 10: 44.



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219. Wohlfahrt-Veje C, Main KM, Schmidt IM, Boas M, Jensen TK, Grandjean P, Skakkebæk NE, Andersen HR. Lower birth weight and increased body fat at school age in children prenatally exposed to modern pesticides: A prospective study. Environ Health 2011; 10: 79.
220. Wohlfahrt-Veje C, Andersen HR, Schmidt IM, Aksglaede L, Sørensen K, Juul A, Jensen TK, Grandjean P, Skakkebæk NE, Main KM. Early Breast Development in Girls after Prenatal Exposure to Non-Persistent Pesticides. Int J Androl 2012; 35: 273-82.
221. Dalgård C, Petersen MS, Weihe P, Grandjean P. Vitamin D status in relation to type 2 diabetes development. Diabetes Care 2011; 34: 1284-8.
222. Julvez J, Debes F, Weihe P, Choi AL, Grandjean P. Thyroid dysfunction as a mediator of organochlorine neurotoxicity in preschool children. Environ Health Perspect 2011; 119:1429-35.
223. Audouze K, Grandjean P. Application of computational systems biology to explore environmental toxicity hazards. Environ Health Perspect 2011; 119: 1754-9.
224. Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C. Decreased serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 2012; 307: 391-7.
225. Grandjean P, Eriksen ML, Ellegaard O, Wallin JA. The Matthew effect in environmental science publication: A bibliometric analysis of chemical substances in journal articles. Environ Health 2011; 10: 96.
226. Vestergaard S, Nielsen F, Andersson AM, Hjøllund NH, Grandjean P, Andersen HR, Jensen TK. Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive. Human Reproduct 2012; 27: 873-80.
227. Wohlfahrt-Veje C, Andersen HR, Jensen TK, Grandjean P, Skakkebaek NE, Main KM. Smaller genitals at school age in boys whose mothers were exposed to non-persistent pesticides in early pregnancy. Int J Androl 2012; 35: 265-72.
228. Grandjean P, Weihe P, Nielsen F, Heinzow B, Debes F, Budtz-Jørgensen E. Neurobehavioral deficits at age 7 years associated with prenatal exposure to toxicants from maternal seafood diet. Neurotoxicol Teratol 2012; 34: 466-72.
229. Grandjean P, Grønlund C, Kjær IM, Jensen TK, Sørensen N, Andersson AM, Juul A, Skakkebæk NE, Budtz-Jørgensen E, Weihe P. Reproductive hormone profile and pubertal development in 14-year-old boys prenatally exposed to polychlorinated biphenyls. Reprod Toxicol 2012; 34: 498-503.
230. Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, Grandjean P, Korrick S. Evidence on the human health effects of low level methylmercury exposure. Environ Health Perspect 2012; 120: 799-806.
231. Grandjean P, Ozonoff D. Portrait of the journal as a young adult. Environ Health. 2012; 11: 30.
232. Budtz-Jørgensen E, Bellinger D, Lanphear B, Grandjean P, International Pooled Lead Study Investigators. An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children. Risk Anal 2013; 33: 450-61.
233. Færch K, Højlund K, Vind BF, Vaag A, Dalgård C, Nielsen F, Grandjean P. Increased serum concentrations of persistent organic pollutants among prediabetic individuals: potential role of altered substrate oxidation patterns. J Clin Endocrinol Metab 2012; 97: E1705-13.
234. Yorifuji T, Murata K, Bjerve K, Choi AL, Weihe P, Grandjean P. Visual evoked potentials in children prenatally exposed to methylmercury. Neurotoxicology 2013; 37: 15-8.
235. Pichery C, Bellanger M, Zmirou-Navier D, Fréry N, Cordier S, Roue-LeGall A, Hartemann



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P, Grandjean P. Economic evaluation of health consequences of prenatal methylmercury exposure in France. Environ Health 2012; 11: 53.
236. Andersen HR, Wohlfahrt-Veje C, Dalgård C, Christiansen L, Main KM, Christine Nellemann C, Murata K, Jensen TK, Skakkebæk NE, Grandjean P. Paraoxonase 1 polymorphism and prenatal pesticide exposure associated with adverse cardiovascular risk profiles at school age. PLoS ONE 2012; 7(5): e36830.
237. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: A systematic review and meta-analysis. Environ Health Perspect 2012; 120: 1362-8.
238. Mozaffarian D, Shi P, Morris JS, Grandjean P, Siscovick D, Spiegelman D, Willett W, Rimm E, Curhan G, Forman J. Mercury exposure and risk of hypertension in US men and women in two prospective cohorts. Hypertension 2012; 60: 645-52.
239. Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P, Sun Q. Plasma levels of persistent organic pollutants and risk of type 2 diabetes: a prospective analysis in the Nurses' Health Study and meta-analysis. Environ Health Perspect 2013; 121: 153-61.
240. Barouki B, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable diseases and dysfunctions: Implications for research and public health. Environmental Health 2012: 11: 42.
241. Julvez J, Davey-Smith G, Golding J, Ring S, St. Pourcain B, Gonzalez JR, Grandjean P. Prenatal methylmercury exposure and genetic predisposition to cognitive deficit at age 8 years. Epidemiology 2013; 24: 643-50.
242. Balbus JM, Barouki R, Birnbaum LS, Etzel RA, Gluckman PD, Grandjean P, Hancock C, Hanson MA, Heindel JJ, Hoffman K, Jensen GK, Keeling A, Neira M, Rabadán-Diehl C, Ralston J, Tang KC. Early-life prevention of non-communicable diseases (Comment). Lancet 2013; 381: 3-4.
243. Dietz R, Sonne C, Basu N, Braune B, O'Hara T, Letcher RJ, Scheuhammer T, Andersen M, Andreasen C, Andriashek D, Asmund G, Aubail A, Baagøe H, Born EW, Chan HM, Derocher AE, Grandjean P, Knott K, Kirkegaard M, Krey A, Lunn N, Messier F, Obbard M, Olsen MT, Ostertag S, Peacock E, Renzoni A, Rigét FF, Skaare JU, Stern G, Stirling I, Taylor M, Wiig O, Wilson S, Aars J. What are the toxicological effects of mercury in Arctic biota? Sci Total Environ 2013; 443: 775-790.
244. Bellanger M, Pichery C, Aerts D, Berglund M, Castaño A, Čejchanová M, Crettaz P, Davidson F, Esteban M, Fischer ME, Gurzau AE, Halzlova K, Katsonouri A, Knudsen LE, Kolossa-Gehring M, Koppen G, Ligocka D, Miklavčič A, Reis MF, Rudnai P, Tratnik JS, Weihe P, Budtz-Jørgensen E, Grandjean P. Economic benefits of methylmercury exposure control in Europe: Monetary value of neurotoxicity prevention. Environ Health 2013; 12: 3.
245. Halling J, Petersen MS, Jørgensen N, Jensen TK, Grandjean P, Weihe P. Semen quality and reproductive hormones in Faroese men – a cross-sectional population-based study of 481 men. BMJ Open 2013; 3: e001946.
246. Grandjean P, Budtz-Jørgensen E. Immunotoxicity of perfluorinated alkylates: Calculation of benchmark doses based on serum concentrations in children. Environ Health 2013; 12: 35.
247. Choi AL, Mogensen UB, Bjerve K, Weihe P, Grandjean P, Budtz-Jørgensen E. Negative confounding by essential fatty acids in methylmercury neurotoxicity associations. Neurotoxicol Teratol 2014; 42: 85-92.
248. Mozaffarian D, Shi P, Morris JS, Grandjean P, Siscovick DS, Spiegelman D, Hu FB. Methylmercury exposure and incident diabetes mellitus in US men and women in two prospective cohorts. Diabetes Care 2013; 36: 3578-84.



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249. Audouze K, Brunak S, Grandjean P. Computational approach to chemical etiologies of diabetes. Sci Comm 2013; 3: 2712.
250. Fonseca MF, Hacon SS, Grandjean P, Choi AL, Bastos WR. Iron status as a covariate in methylmercury-associated neurotoxicity risk. Chemosphere 2014; 100: 89-96.
251. Grandjean P, Clapp R. Changing interpretation of human health risks from perfluorinated compounds. Publ Health Rep 2014:129; 482-5.
252. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol 2014; 13: 330-8.
253. Kim BM, Choi A, Ha EH, Pedersen L, Nielsen F, Weihe P, Hong YC, Budtz-Jørgensen E, Grandjean P. Effect of hemoglobin and selenium on partition of mercury between maternal and cord blood. Environ Res 2014; 132: 407-12.
254. Grandjean P, Ozonoff D. Transparency and translation of science in a modern world. Environ Health 2013; 12: 70.
255. Tang-Peronard JL, Heitmann BL, Andersen HR, Steuerwald U, Grandjean P, Weihe P, Jensen TK. Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands. Am J Clin Nutrit 2014; 99: 5-13
256. Timmermann CAG, Rossing LI, Grøntved A, Ried-Larsen M, Dalgård C, Andersen LB, Grandjean P, Nielsen F, Svendsen KD, Scheike T, Jensen TK. Adiposity and glycemic control in children exposed to perfluorinated compounds. J Clin Endocrinol Metab 2014; 99: E608-14.
257. Julvez J, Grandjean P. Genetic susceptibility to methylmercury developmental neurotoxicity matters. Front Genet 2013; 4: 278.
258. Vesterholm Jensen D, Christensen JH, Virtanen HE, Skakkebæk NE, Main KM, Toppari J, Veje CV, Andersson AM, Nielsen F, Grandjean P, Jensen TK. No association between exposure to perfluorinated compounds and congenital cryptorchidism: a nested case-control study among 215 boys from Denmark and Finland. Reproduction 2014; 147: 411-7.
259. Li M, Sherman LS, Blum JD, Grandjean P, Mikkelsen B, Weihe P, Sunderland EM, Shine JP. Assessing sources of human methylmercury exposure using stable mercury isotopes. Environ Sci Technol 2014; 48: 8800-6.
260. Grandjean P, Herz KT. Trace elements as paradigms of developmental neurotoxicants. J Trace Elem Med Biol 2015; 31: 130-4.
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