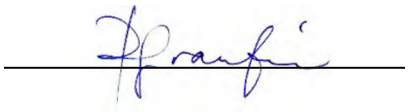
STATE OF MINNESOTA DISTRICT COURT FOR THE COUNTY OF HENNEPIN FOURTH JUDICIAL DISTRICT

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

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.

[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]

[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.

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.

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.

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.

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.

[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.