National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

PFOA exposure and health

A review of scientific literature

RIVM Report 2017-0086

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PFOA en mogelijke gezondheidseffecten

Een overzicht van wetenschappelijke literatuur

Er zijn enkele verbanden gevonden tussen concentraties PFOA in het bloed van mensen met mogelijke gezondheidseffecten en de werking van het lichaam. Dit blijkt uit een literatuuronderzoek door het RIVM van de wetenschappelijke literatuur over onderzoek in mensen. Het is niet zeker dat PFOA in het bloed daadwerkelijk de oorzaak is of dat er andere verklaringen zijn voor de gevonden verbanden.

Aanleiding voor het onderzoek zijn vragen van omwonenden van de Dupont/Chemours-fabriek in Dordrecht over mogelijke gezondheidseffecten als gevolg van de emissie van PFOA door de fabriek. Het rapport geeft meer inzicht in wat uit de literatuur bekend is over welke mogelijke effecten samenhangen met blootstelling aan PFOA bij de mens, de concentraties PFOA in het bloed waarbij deze mogelijke effecten worden gevonden en de omvang van deze effecten. Concentraties PFOA in het bloed geven aan in welke mate mensen zijn blootgesteld aan deze stof.

Het wetenschappelijke bewijs verschilt tussen de gevonden effecten. De meest duidelijke aanwijzingen zijn er voor een verband tussen de blootstelling aan PFOA met hogere zogeheten totaal-cholesterolgehalten in bloed, hogere concentraties van het leverenzym ALT in het bloed en een lager geboortegewicht. Voor alle andere mogelijke effecten zijn de aanwijzingen minder duidelijk. Er zijn aanwijzingen voor een verband met hogere concentraties in het bloed van andere leverenzymen, LDL-cholesterol en urinezuur. Ook zijn aanwijzingen gevonden voor een grotere kans op chronische darmontsteking (colitis ulcerosa), zaadbal- en nierkanker, hoge bloeddruk tijdens de zwangerschap en zwangerschapsvergiftiging. Verder zijn er aanwijzingen voor een verband tussen de blootstelling en een verminderde toename van antilichamen in het bloed na vaccinaties, hogere of lagere concentraties in het bloed van schildklierhormonen en schildklierziekten.

Kernwoorden: PFOA, C8, perfluoroctaanzuur, epidemiologie, review

Synopsis

PFOA and possible health effects
A review of scientific literature

Associations were found between blood concentrations of PFOA in humans and possible health effects and functioning of the body. This is the result of a review of previously performed reviews of the scientific literature on studies conducted among humans by the National Institute for Public Health and the Environment. It is not certain whether PFOA is the true cause or whether there are other explanations for the observed associations.

This study was performed because of questions raised by residents who live in the vicinity of the Dupont/Chemours factory in Dordrecht concerning possible health effects due to the emission of PFOA by the factory. The objective of this review was to address the question what biological and physiological parameters and diseases are associated with blood PFOA concentrations in humans, to determine in what ranges of blood concentrations the associations are observed and to provide an indication of the magnitude of the associations. Concentrations of PFOA in blood are an indication of the level of exposure to this chemical.

The strength of evidence for the existence of a possible association differs between the observed effects. The clearest evidence has been found for a relationship between exposure to PFOA and higher total cholesterol concentrations in blood, higher concentrations of the liver enzyme ALT in blood and a lower birth weight. For all other examined associations, the evidence is less clear. There are indications of an association with higher blood concentrations of other liver enzymes, LDL-cholesterol and uric acid. Indications have also been found for a higher risk of chronic inflammation of the bowel (ulcerative colitis), testis and kidney cancer, as well as pregnancy-induced hypertension and preeclampsia. Furthermore, associations have been found between exposure to PFOA and a decreased vaccination response, changes in concentrations of thyroid hormones in blood and thyroid disease.

Keywords: PFOA, C8, perfluorooctanoic acid, epidemiology, review

Contents

Summary

Perfluorooctanoic acid (PFOA or C8) is used for a wide range of consumer and industrial products, such as the production of Teflon. The exposure to PFOA of people living in the direct neighbourhood of the Dupont/Chemours factory in Dordrecht as a result of emissions from the factory from 1970 to 2012 has prompted questions to be raised about the possible health effects.

In 2016 the National Institute for Public Health and the Environment made a risk assessment based on toxicological studies. This risk assessment used a limit value for chronic exposure based on the critical effect (i.e. the most sensitive effect) in animals. However, a more in-depth evaluation of epidemiological studies was then recommended in order to indicate whether or not other health conditions or diseases require further attention.

In recent years, a number of evaluations have been performed by recognized national and international organizations in which epidemiological evidence for associations between PFOA and biological and physiological parameters and diseases has been reviewed. These evaluations were based on epidemiological and toxicological studies.

The objectives of this literature review were to address the following questions:

- What biological and physiological parameters and diseases are associated with blood PFOA concentrations in humans?
- In what concentration ranges are these associations observed?
- And to provide an indication of the magnitude of the associations.

First, conclusions from the previous evaluations were reviewed to determine what biological and physiological parameters and diseases are associated with blood PFOA concentrations. Then epidemiological studies were selected from the previous reviews and from a search done in a digital scientific database. The epidemiological studies were not evaluated individually in terms of things such as study quality. The findings from the selected epidemiological studies were used to answer the study questions regarding PFOA concentration ranges and the magnitude of the associations.

Three types of study populations can be identified in the context of exposure to PFOA, i.e. the general population, high-exposure communities (i.e. communities exposed to air and/or drinking water contaminated with PFOA, e.g. because of emissions of PFOA from a factory nearby or land contaminated by waste from water treatment) and occupational study populations (i.e. populations of workers in factories using or producing PFOA). On average, concentrations of PFOA in blood are higher in individuals that are part of a high-exposure community than they are in the general population. Concentrations of PFOA in blood are on average highest in occupational study populations.

The strength of evidence for the existence of an association and the magnitude of the associations differ between the examined biological and physiological parameters and diseases. Conclusions drawn from previous reviews are clearest with respect to evidence for associations between PFOA and total blood cholesterol concentrations, blood concentrations of the liver enzyme ALT and birth weight. For all other examined associations, the evidence is less clear. Associations were observed in individuals with blood PFOA concentrations as found in the general population and at higher concentrations. But it has yet to be established whether the associations observed in the epidemiological studies are causal. For most biological and physiological parameters and diseases there is supporting evidence from experimental animal studies, but the mode of action that explains how PFOA exerts its effects has not been fully characterized. The findings from this literature review will be used as a background document to assess the potential health consequences of PFOA exposure in residents living in the direct vicinity of the DuPont/Chemours factory in Dordrecht.

1 Introduction

1.1 Background

There is concern regarding possible health effects on people living in the direct neighbourhood of the Dupont/Chemours factory in Dordrecht as a result of emissions of perfluorooctanoic acid (PFOA) over many years. PFOA is used for a wide range of consumer and industrial products, e.g. for the production of teflon. In the Dupont/Chemours factory in Dordrecht, PFOA was used from 1970 to 2012. Since 2012, PFOA has not been used in the Dutch DuPont/Chemours factory.

The National Institute for Public Health and the Environment (RIVM) has estimated the concentrations of PFOA in the blood between 1970 and 2030 of residents living in the direct neighbourhood of the DuPont/Chemours factory in Dordrecht through model calculations (Zeilmaker et al., 2016). The exposure to PFOA through the air, drinking water and food was estimated based on emission data and calculations. It was estimated that residents living in the direct vicinity of the DuPont/Chemours factory in Dordrecht were exposed to PFOA mainly through the air and not through food (not accounting for home-grown food) or drinking water. Based on model calculations, PFOA concentrations in the drinking water in Dordrecht were not elevated compared with the rest of the Netherlands, which is to be expected as drinking water for the area surrounding the factory in Dordrecht does not originate from Dordrecht (Zeilmaker et al., 2016). It was estimated that in the 1990s the residents may have had the highest serum concentrations, with average values of up to 130 ng/mL. Current typical serum concentrations were estimated to be around 10 ng/mL (Zeilmaker et al., 2016).

RIVM also determined a serum limit value for chronic exposure (Zeilmaker et al., 2016) below which no adverse health effects are expected. This evaluation by RIVM followed previous reviews and limit value derivations conducted by EFSA (2008), ATSDR (2015), ECHA-RAC (2015a) and US-EPA (2014). The limit value (i.e. 89 ng/mL) as derived by RIVM takes into account the accumulation of PFOA in the human body during long-term exposure. In the most unfavourable case, the limit value for chronic exposure could have been exceeded for a period of 25 years for residents living in the direct vicinity of the DuPont/Chemours factory in Dordrecht (Zeilmaker et al., 2016).

The limit value for chronic exposure as derived in 2016 was based on animal data. In agreement with the evaluations conducted by other organizations (i.e. US-EPA, EFSA, ATSDR, ECHA-RAC), RIVM concluded that animal data were the preferred basis for dose response analysis. Epidemiological data were considered less informative for dose-response analysis. As is usual for these kinds of limit values, the value was based on the critical effect (i.e. the most sensitive effect; in this case, liver toxicity) in animals and therefore, in principle, it covers all potential health effects. However, a more in-depth evaluation of epidemiological

studies was recommended in order to indicate whether other health conditions or diseases require further attention.

In recent years, a number of literature reviews have been conducted in which epidemiological evidence for associations between PFOA and biological and physiological parameters and diseases has been evaluated. In the current study, these previous evaluations were reviewed.

The result of this review should allow a further evaluation of the likelihood of any health effects at the exposure level calculated and measured for the residents in the direct vicinity of the Dupont/Chemours factory in Dordrecht. Also, it should allow a further evaluation of whether or not the health of the residents needs to be examined. Although neither of these questions will be discussed in the current report, they will be discussed in a different document.

1.2 Objectives

The objective of this review was to address the question of what biological and physiological parameters and diseases are associated with PFOA concentrations in the blood of humans. This question was answered by evaluating reviews conducted by recognized (inter)national authorities. In addition, the objective was to determine the ranges of blood concentrations within which the associations are observed and to give an indication of the magnitude of the associations. These questions were answered by summarizing findings taken from the available epidemiological publications.

1.3 Organization of this report

Section 1.4 provides information on the measurement of PFOA concentrations in blood and the half-life of PFOA in humans. An overview of the levels of measured and estimated PFOA concentrations in blood that are reported in epidemiological studies is given in section 1.5. The Methods, Results and Discussion of the results are described in Chapters 2, 3 and 4, respectively.

1.4 PFOA in blood as a biomarker of exposure

In epidemiological studies, blood concentrations of PFOA are used as a biomarker of exposure to PFOA, reflecting combined exposure from all sources. PFOA can be measured in serum, plasma or whole blood. The serum or plasma to whole blood ratio for PFOA is 2:1 (Ehresman et al., 2007). In epidemiological studies, PFOA concentrations are most often examined in the serum component (e.g. Barry et al. (2013); Gallo et al. (2012)). In some studies, PFOA concentrations are measured in plasma (e.g. Fei et al. (2007); Starling et al. (2014b)). In the current review, no epidemiological study has been found in which whole blood was examined. Concentrations of PFOA in serum and plasma are comparable. The concentration level observed in serum will also be observed in plasma and vice versa, i.e. a ratio of 1:1 is suggested (Ehresman et al., 2007). So, in the current report, when blood PFOA concentrations are mentioned, they refer to concentrations of PFOA measured in serum or plasma.

Blood PFOA concentrations depend on the level and duration of exposure. Also, PFOA accumulates in the body because it is slowly eliminated from the body. Varying half-lives have been reported. In retired fluorochemical production workers, a mean elimination half-life for PFOA of 3.8 years was measured (Olsen et al., 2007). In a German population, a mean plasma concentration half-life of 3.3 years (range: 1.0-14.7 years) was measured (Brede et al., 2010). In the C8 population, a median (i.e. 50% of the examined study population had a value equal or below that value) half-life of 2.3 years was measured (Bartell et al., 2010). Findings from the C8 Health Study suggest that half-lives may be concentration-dependent or time-dependent with higher clearance at higher concentrations (Seals et al., 2011).

1.5 Blood PFOA concentrations in different populations

Three types of study populations are examined in epidemiological studies: the general population, high-exposure communities (i.e. communities exposed to air and/or drinking water contaminated with PFOA, e.g. because of emissions of PFOA from a factory nearby or land contaminated with waste from water treatment) and occupational study populations (i.e. populations of workers in factories using PFOA).

1.5.1 General population

In the *general population*, median serum PFOA concentrations are encountered between 1-5 ng/mL, i.e. 'background' exposure, with extremes of up to 100 ng/mL. Many serum PFOA concentration measurements come from the US. Mean values observed in various studies among the general population in the US are 2.1-9.6 ng/mL (ATSDR, 2015). In the general population, serum PFOA concentrations range approximately from values below the limit of detection to 100 ng/mL (US-EPA, 2016a). The National Health and Nutrition Examination Survey (NHANES) is a programme of studies designed to assess the health and nutritional status of the general population in the United States. In 1999-2000, a geometric mean serum PFOA concentration of 5.05 ng/mL was measured in men and 4.06 ng/mL was measured in women (Lin et al., 2010). In 2007-2010, a geometric mean serum PFOA concentration of 3.5 ng/mL (for both women and men) was measured using NHANES data (Gleason et al., 2015). Concentrations in North American populations appear to be higher than they are in European populations, where PFOA concentrations range from 0.5 to 40 ng/mL (Fromme et al., 2009).

The German HBM-Kommission (2009) reported on some European studies in which serum PFOA concentrations in general populations were measured. In Germany, the highest range of concentrations was measured in the general population living in the South of Germany (i.e. 1.7-39.3 ng/mL), with a median serum PFOA concentration of 6.8 ng/mL. Studies in which median serum or plasma concentrations (whole blood concentrations were converted to be comparable with serum and plasma blood concentrations) were measured in the general population of Belgium, Italy, Poland and Sweden were also reported. In Belgium, a median serum PFOA concentration of 4.3 ng/mL was measured in men and 2.4 ng/mL was measured in women (Kannan et al., 2004). In Siena, Italy, a median serum PFOA concentration of less than 3 ng/mL was

measured in both men and women. In Danzig, Poland, men had a median concentration of 18.4 ng/mL and women had a median concentration of 23.4 ng/mL. A median serum PFOA concentration of 5.0 ng/mL was measured in men and women living in Sweden.

1.5.2 *High-exposure communities*

Information on blood concentrations among *high-exposure communities* mainly comes from the C8 Health Study, a series of studies conducted among residents who live in contaminated water districts in Ohio and West Virginia near the Dupont factory in Parkersburg. The C8 Health Study is mainly work conducted by the C8 Science Panel. The C8 Health Study consists of a number of studies, in part based on the cross-sectional data collection study, the C8 Health Project, that are conducted among residents living in contaminated water districts in Ohio and West Virginia in the US that are affected by PFOA emissions from a PTFE production facility of Dupont. In the C8 Health Project, the population median serum PFOA concentration based on over 65,000 serum samples was 28.2 ng/mL and the mean was 82 ng/mL in the 2005-2006 period, with variation between the different water districts, age and sex groups (Frisbee et al., 2009). Values ranged from below the limit of detection to over 1,000 ng/mL (http://www.hsc.wvu.edu/media/5354/overall-c8-c8s-results.pdf). Median serum PFOA concentrations reported (Frisbee et al., 2009) were 32.6 ng/mL in children aged <12 years, 25.7 ng/mL in adolescents aged 12-19 years, 21,8 ng/mL in adults aged 20-39 years, 30.7 ng/mL in adults aged 40-59 years and 41.9 ng/mL in ≥60 year-olds in 2005-2006. It should be noted that peak emissions occurred during the 1980s and 1990s and PFOA emissions from the factory had declined by the 2005-2006 period (Woskie et al., 2012).

In addition to the C8 Health Project population, there is another high-exposure population in the United States that was exposed to concentrations of PFOA above background concentration, i.e. a community living in Minnesota. Similar to the community living in Ohio and West Virginia, residents there were also exposed to water contamination coming from factories. In Minnesota, the blood PFOA concentration of a selection of residents who were exposed to contaminated drinking water was measured. Like in most Western countries, exposure to PFOA has apparently decreased in Minnesota in recent years. The mean PFOA concentration was 15 ng/mL in 2008, 11 ng/mL in 2010 and 5 ng/mL in 2014 (MDH, 2015).

1.5.3 *Occupationally exposed populations*

In workers who are occupationally exposed to PFOA, mean blood PFOA concentrations are about three orders of magnitude higher than they are in the general population, and maximum concentrations can reach over 100,000 ng/mL (Fromme et al., 2009). Chang et al. (2014) reports that the highest median PFOA concentrations are found among directly exposed workers, ranging from approximately 1,000 to 2,880 ng/mL (Olsen et al., 2000; Olsen et al., 2003; Olsen and Zobel, 2007; Woskie et al., 2012).

2 Methods

Firstly, reviews previously performed by recognized national and international organizations were used to determine which biological and physiological parameters and diseases (referred to as 'endpoints' in the current report) are associated with PFOA. Secondly, epidemiological studies were selected from the previous reviews and from a search made in a digital scientific database in order to determine the exposure levels at which associations were observed.

The previously performed reviews that were used in the current review are described below. Then the selected endpoints and the process of selecting epidemiological studies and extracting data from the epidemiological studies are described. Lastly, how the data from the reviews and the epidemiological studies are integrated is described.

2.1 Previously performed reviews

A number of reviews performed by recognized national and international organizations have been published in which epidemiological and toxicological studies (animal and in vitro studies) on the association between serum or plasma PFOA concentrations and endpoints were summarized. All endpoints reported to be associated with exposure to PFOA by these organizations were included in the present review. The reviews considered here are those which were most recently published, i.e. reviews performed by the C8 Science Panel (reviews focused on various endpoints were published between 2011 and 2012) (C8 Science Panel, 2011a; C8 Science Panel, 2011b; C8 Science Panel, 2012a; C8 Science Panel, 2012b; C8 Science Panel, 2012c; C8 Science Panel, 2012d; C8 Science Panel, 2012e), Health Council of the Netherlands (2013), ATSDR (2015), ECHA-RAC (ECHA-RAC, 2015a; ECHA-RAC, 2015b), DWQI (2016), IARC (2016), NTP (2016) and US-EPA (2016a).

2.1.1 Background and objectives of previous reviews

Communities in the Mid-Ohio Valley in the United States were potentially exposed to PFOA (also called C8) from the 1950s onwards (C8 Science Panel, 2017). The C8 Science Panel carried out exposure and health studies in the Mid-Ohio Valley communities and published their evaluations and reviews online. The C8 Science Panel no longer exists. The task of the C8 Science Panel was to make a judgment regarding the evidence linking PFOA to the risk of disease. The Panel had to determine whether there is or is not a 'probable link' between a disease and exposure to PFOA. In its assessment, the C8 Science Panel implemented a definition of 'probable link' as follows: '…given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease'. Thus, the conclusions drawn by the C8 Science Panel refer to the population of 'class members' defined as 'individuals in West Virginia or Ohio whose drinking water had been contaminated by quantifiable levels of PFOA' (Frisbee et al., 2009). Therefore, the C8 Science Panel focused their conclusions exclusively on a high-exposure community in the US. In all other previous reviews considered in the current review,

the potential health effects of PFOA were evaluated for all serum or plasma PFOA concentration ranges.

The task of the Health Council of the Netherlands is to advise the Dutch government and parliament regarding public health and health (care) research. This can happen on request, but the Health Council also has an 'alerting' function: it can give unsolicited advice (Health council of the Netherlands, 2017).

ATSDR (the Agency for Toxic Substances and Disease Registry) is a federal public health agency of the United States Department of Health and Human Services (ATSDR, 2016a). They perform functions focused on the effect of hazardous substances in the environment on public health, such as public health assessments of waste sites, applied research in support of public health assessments, and education and training with respect to hazardous substances. ATSDR is involved at a number of sites related to perfluoroalkyl and polyfluoroalkyl substances (PFAS), either directly or through assisting state and federal partners (ATSDR, 2016b). ATSDR published a draft of a Toxicological Profile for Perfluoroalkyls (ATSDR, 2015). To our knowledge, this draft has not been updated since its publication.

The ECHA (the European Chemical Agency), for instance, helps companies to comply with chemicals legislation, advances the safe use of chemicals, provides information on chemicals and addresses chemicals of concern (ECHA, 2017b). RAC (the Committee for Risk Assessment) prepares the opinions of ECHA concerning the risks of substances to human health and the environment. The European Commission takes the final decision (ECHA, 2017a). ECHA-RAC summarized the studies in their 'Background document' (2015a). The Background document was used to provide background for the opinion on the restriction proposal, based on the Persistent, Bioaccumulative, Toxic (PBT) / very Persistent, very Bioaccumulative (vPvB) properties of the substance. In general, the risks of PBT/vPvB substances cannot be adequately addressed in a quantitative way due to the high uncertainties present regarding long-term exposure and effects. However, the background document explores the possibility of formulating an opinion on the specific question of whether or not a potential risk of PFOA on health can *be quantified*. The opinion was formulated in a separate document; none of the evaluated endpoints were considered 'robust enough to include in a quantitative assessment' (ECHA-RAC, 2015b).

The New Jersey DWQI (Drinking Water Quality Institute) Health Effects Subcommittee develops Maximum Contaminant Levels (MCL) or standards for hazardous contaminants in drinking water. In addition, they are responsible for 'recommending those standards and making recommendations for the implementation of the drinking water quality programme to the Commissioner of the New Jersey Department of Environmental Protection (NJDEP)' (State of New Jersey, 2017).

IARC is part of the World Health Organization (WHO) and is specialized in epidemiological and laboratory research into the causes of cancer.

A systematic review (NTP, 2016) was performed by NTP's (National Toxicology Program, US Department of Health and Human Services) Office of Health Assessment and Translation (OHAT) with the purpose of evaluating whether PFOA is associated with immune-related health. They evaluated both epidemiological and toxicological studies.

The mission of the US-EPA (i.e. the US Environmental Protection Agency) is to 'protect human health and the environment' (US-EPA, 2016b). To accomplish their mission, they develop and enforce regulations, give grants and study environmental issues, among other things. The US-EPA wrote the review into the potential health effects of PFOA in order to provide a health advisory, such as developing a regulation to control PFOA in drinking water.

2.2 Selection of endpoints

In the current review, all endpoints about which at least one (inter)national organization has concluded that an association exists with PFOA concentrations in blood were selected (for an overview, see Table 1 in the Results section). Therefore, endpoints that were evaluated in the previous reviews, but about which it was concluded that insufficient evidence exists for an association with PFOA, were not included in the current review.

2.3 Selection of epidemiological studies from previous reviews

To determine the ranges of concentrations in which the associations are observed, data were extracted from epidemiological studies included in the previous reviews. Epidemiological studies were included that present results from studies in all different populations (general population, high-exposure communities and occupational populations). No further selection was made based on study quality. In the previous reviews, findings taken from epidemiological studies were evaluated in terms of consistency, strength of associations, biological plausibility and the influence of chance or bias

2.4 Update with recent studies

The most recent comprehensive reviews were performed by DWQI (2016) and the US-EPA (2016a). The DWQI literature search included studies published up to 30 April 2015 and US-EPA studies published up to December 2015. Therefore, relevant epidemiological studies were searched in PubMed from 1-1-2016 to 26-10-2016 using US-EPA's search terms:
Search ((((((perfluorooctanoate OR "perfluorooctanoic acid" OR "perfluoroctanoic acid" OR pfoa OR "perfluorinated chemicals" OR "perfluorinated compounds" OR "perfluorinated homologue groups" OR "perfluorinated contaminants" OR "perfluorinated surfactants" OR perfluoroalkyl acids OR "perfluorinated alkylated substances" OR "perfluoroalkylated substances" OR "fluorinated surfactants")) AND human [tw] AND ("2016/01/01"[Date - Publication] : "3000"[Date - Publication])))))*

In addition, the following search terms were used to determine whether relevant epidemiological reviews had been published (after 1-1-2006) that were not included in the reviews:

Search (((((((((perfluorooctanoate OR "perfluorooctanoic acid" OR "perfluoroctanoic acid" OR pfoa OR "perfluorinated chemicals" OR "perfluorinated compounds" OR "perfluorinated homologue groups" OR "perfluorinated contaminants" OR "perfluorinated surfactants" OR perfluoroalkyl acids OR "perfluorinated alkylated substances" OR "perfluoroalkylated substances" OR "fluorinated surfactants")) AND human [tw])))))))) AND review[Publication Type]*

In total, an additional four epidemiological studies and four epidemiological reviews were found that were relevant.

2.5 Extraction of data from epidemiological studies and reviews

Conclusions from previous reviews were summarized. From each original publication, the following information was extracted and summarized in tables:

- Name(s) of authors and publication year (reference).
- Details on the study characteristics: general study characteristics were reported, i.e. study population, age range, % of men, study design, study years and the number of individuals examined ('N total').
- Blood PFOA concentration: if available, the median, mean and range of measured or estimated concentrations (ng/mL) were reported. Additional information was sometimes provided. For instance, the interquartile range was provided if quartiles were used in analyses or if the full range was not reported.
- Endpoint studied and association with PFOA: which endpoints were studied, whether an association was found with the examined endpoints and the magnitude of the association (effect size).

2.6 Integration of findings

In the present review, the consistency of the conclusions taken from the previous reviews is discussed in Chapter 4. The epidemiological data taken from original studies were used (if possible) to give an indication of the magnitude of the association and of the range of blood PFOA concentrations in which associations were observed. The original studies were not evaluated in terms of study quality, as this had already been done in the previously performed reviews.

3 Results

Chapter 3.2 briefly summarizes the general conclusions taken from previous reviews regarding the endpoints that are associated with blood PFOA concentrations. Table 1 shows the endpoints that were selected for the current review and the wording used to describe the evidence in the previous reviews. Table 2 shows the number of epidemiological studies that were included in each previous review and in the current review. In Chapters 3.3 to 3.11, the general conclusions are discussed per endpoint and the results from epidemiological studies are discussed per endpoint.

3.1 General conclusions from previous reviews

It can be seen from Table 1 that the conclusions drawn by (inter)national organizations differ, regarding which endpoints are associated with PFOA, as well as the rating of the strength of the evidence.

The C8 Science Panel concluded that there is a probable link with testicular and kidney cancer (C8 Science Panel, 2012b), pregnancy-induced hypertension (including preeclampsia) (C8 Science Panel, 2011a), ulcerative colitis (C8 Science Panel, 2012a), thyroid disease (C8 Science Panel, 2012e), and high cholesterol (C8 Science Panel, 2012d).

Both the Health Council of the Netherlands (2013) and IARC (2016) evaluated cancer only. A wide range of cancers, including testicular cancer and kidney cancer, were evaluated by both. The Health Council considered the available data to be insufficient to evaluate the carcinogenic properties of PFOA. IARC (2016) considered PFOA as possibly carcinogenic to humans.

ATSDR (2015) concluded that associations were consistently found between serum PFOA and increases in liver enzymes, decreases in birth weight, increases in uric acid levels, and serum lipid levels. They note that other effects have been reported, but those associations were not consistently found in similar types of studies or were only found in a single study.

ECHA-RAC (2015b) seems to emphasize (i.e. they give more attention to those two endpoints in their report) in their opinion document that associations with birth weight and cholesterol were observed. They also conclude that none of the endpoints were suitable for examining health-based cut-off values for blood concentrations of PFOA.

The DWQI (2016) concluded that, of the endpoints they evaluated comprehensively, the evidence for associations with PFOA was strongest for the liver enzyme ALT, uric acid and serum levels of cholesterol. They added that, for these endpoints, the dose-response was steepest in serum PFOA concentrations found in the general population and communities with drinking water exposures, with a much flatter curve at higher serum concentrations. Associations with fetal growth and cancer were evaluated by DWQI by evaluating comprehensive reviews

performed by other scientific groups, which found those endpoints potentially associated with PFOA.

The NTP (2016) presumes that PFOA is ‘an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans.’ They further note that, from the human studies, there is only a low level of confidence that an association exists with the autoimmune disease ulcerative colitis and hypersensitivity responses in childhood, but a moderate level of confidence that an association exists with the suppression of the antibody response.

The US-EPA (2016a) concluded that human epidemiology data report associations between PFOA exposure and increased concentrations of liver enzymes, testicular and kidney cancer, pregnancy-induced hypertension and preeclampsia, decreased vaccination response, thyroid disorders and high blood cholesterol concentrations.

Table 1. Endpoints reported to be associated[1] with PFOA in at least one of the previous reviews

Selected endpoints in the current review	Reviews							
	C8 Science Panel (2011, 2012)	Health Council NL (2013)	ATSDR (2015)	ECHA-RAC (2015a; 2015b)	DWQI (2016)	IARC (2016)	NTP (2016)	(US-EPA, 2016a)
Liver enzymes	No probable link	NE	Consistent evidence (ALT and bilirubin)	NE	Consistent evidence (ALT)	NE	NE	Consistent evidence (ALT and GGT)
Liver disease	No probable link	NE	No association	NE	Limited evidence	NE	NE	Few studies and no association
Testicular cancer	Probable link	Insufficient data for evaluation	Evidence was equivocal	No firm conclusions were made by ECHA-RAC (refer to C8 and IARC)	Association was observed	Evidence credible and unlikely to be explained by bias and confounding.	NE	Associations were reported
Kidney cancer	Probable link	Insufficient data for evaluation	Evidence was equivocal	No firm conclusions were made by ECHA-RAC (refer to C8 and IARC)	Association was observed	Evidence credible, but chance, bias and confounding cannot be excluded.	NE	Associations were reported
Pregnancy-induced hypertension and preeclampsia	Probable link	NE	No firm conclusions	Relationship is not clearly established	NE	NE	NE	Some evidence
Birth weight	Evidence insufficient to evaluate (low birth weight, i.e. <2,5kg)	NE	Consistent findings with small decrease in birth weight	Studies suggest the existence of a relationship	Sufficient evidence	NE	NE	No evidence for a relationship

Selected endpoints in the current review	Reviews							
	C8 Science Panel (2011, 2012)	Health Council NL (2013)	ATSDR (2015)	ECHA-RAC (2015a; 2015b)	DWQI (2016)	IARC (2016)	NTP (2016)	(US-EPA, 2016a)
Uric acid concentration	NE	NE	Consistent evidence	NE	Evidence was found	NE	NE	An association was observed, but potentially confounded
Vaccination response	NE	NE	Evidence is not consistent	NE	Limited evidence	NE	Moderate confidence that an association exists	Association was observed
Ulcerative colitis	Probable link	NE	No firm conclusions	No firm conclusions	No firm conclusions	NE	Low confi-dence in the evidence	No firm conclusions
Thyroid effects	Probable link (thyroid disease)	NE	No association	No firm conclusions	Limited evidence (thyroid disease) Limited or no evidence (TSH and thyroid hormones)	NE	NE	Association was observed (in women)
Blood lipid concentration	Evidence of a shift (average cholesterol) Probable link (hypercholest erolemia)	NE	Associations were found (total cholesterol)	Associations were suggested by studies (total cholesterol & LDL)	Evidence was found of an association (total cholesterol)	NE	NE	Associations were found (total cholesterol and LDL)

[1]Blue shading: reported to be associated with PFOA

NE=Not Evaluated

Table 2. Number of epidemiological studies per endpoint included in previous reviews and the present review.

Selected endpoints in the current review	C8 Science Panel (2011, 2012)[1]	Health Council NL (2013)	ATSDR (2015)	ECHA-RAC (2015a)	DWQI (2016)	IARC (2016)	NTP (2016)	(US-EPA, 2016a)[2]	This review (2017)
Liver enzymes and liver disease	7	NE	10	NE	15	NE	NE	10	15
Testicular and kidney cancer	3	4	4	4	3[3]	4	NE	3	4
Pregnancy-induced hypertension and preeclampsia	3	NE	4	2	NE	NE	NE	4	6
Birth weight	8	NE	12	1[4]	1[4]	NE	NE	12	15
Uric acid concentration	NE	NE	5	NE	7	NE	NE	4	8
Vaccination response	NE	NE	3	NE	5	NE	4	3	6
Ulcerative colitis	Unpublished at the time only	NE	C8[5]	C8[5]	C8[5]	NE	2	C8[5]	2
Thyroid effects	10	NE	9	7	19	NE	NE	14	25
Blood lipid concentration	9	NE	15	7	23	NE	NE	16	24

[1]Unpublished studies are described by C8 Science Panel in their evaluation, but not included in the number of studies in this table (as no references are available).

[2](US-EPA, 2016a) only considered the most recently updated studies.

[3]Described reviews performed by IARC (2015), USEPA (2006) and C8 Science Panel.

[4]Described only the meta-analysis performed by Johnson et al 2014.

[5]Described only the conclusions drawn by the C8 Science Panel and/or the epidemiological studies from the C8 Science Study

NE=Not Evaluated

3.2 Liver enzymes and liver disease

As an indication of liver health, blood concentrations of liver enzymes can be measured. The examined liver enzymes are alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP); direct ('conjugated') bilirubin and total bilirubin are examined as well. In general, an increase in these enzymes may be indicative of liver problems, although normally they vary so it is difficult to determine when health is affected.

3.2.1 Conclusions from previous reviews

The C8 Science Panel (2012c) concluded that there is *no* probable link between exposure to PFOA and liver disease. They did not attempt to evaluate the link with liver enzymes. They argued that, although associations with the blood levels of liver enzymes were observed, the magnitude of effects on liver lay within a normal physiologic range and there is no evidence that it results in liver disease.

ATSDR (2015) concluded in their draft review that consistent findings were found for the association between serum PFOA and the blood levels of liver enzymes. They refer to one study of residents who were highly exposed to PFOA and they found significant associations between serum PFOA and ALT and bilirubin levels. They note that, although associations were found, the magnitude of increased blood levels of liver enzymes were not great. In addition, in studies examining workers, no associations were consistently found between serum liver enzymes (primarily ALT, AST and GGT) and serum PFOA concentrations. Regarding liver disease, ATSDR (2015) reports that studies have not found increases in deaths from liver cirrhosis or increases in the incidence of liver disorders or cirrhosis (only occupational populations were examined).

DWQI (2016) concluded that limited evidence of an association between blood levels of liver enzymes GGT and AST, bilirubin and liver disease has been found and that no evidence was found of an association with the liver enzyme ALP. In contrast, they concluded that consistent evidence has been found for an association between PFOA and increases in the blood levels of the liver enzyme ALT in large studies conducted among the general population and high-exposure communities. They consider the evidence with ALT to be one of the strongest.

The US-EPA (2016a) concluded that epidemiological studies report an association between exposure to PFOA and increased blood levels of liver enzymes. They reported that studies have consistently shown an association between serum PFOA concentrations and elevations in the serum levels of ALT and GGT. These associations were observed in all types of study populations, i.e. workers, high-exposure communities and the general population in the US. (US-EPA, 2016a) discussed the possibility that the association found between PFOA and the levels of liver enzymes in the blood of workers might depend on co-variates (e.g. BMI and the use of lipid lowering medicine). They also concluded that the associations were not large in magnitude. However, the fact that associations were found indicates the potential of PFOA to affect liver function. Regarding liver disease, the US-EPA concluded that few studies

have examined the relationship between PFOA and liver disease, and they reported that most studies found no association.

3.2.2 Summary of studies

Table 3 summarizes the results of epidemiological studies. In total, 15 epidemiological studies were included.

Three cross-sectional studies were performed in a *general population* (Gleason et al., 2015; Jiang et al., 2014; Lin et al., 2010). A higher ALT concentration was observed in those with higher serum PFOA concentrations in a study population (i.e. the NHANES study, with an interquartile range of 2.9-5.95 ng/mL) (Lin et al., 2010). They observed a stronger association in particularly obese individuals. Gleason et al. (2015) observed an association between serum PFOA and higher AST, ALT, GGT and total bilirubin (also in the NHANES study; interquartile range: 2.5-5.2 ng/mL). Jiang et al. (2014) found no association between serum PFOA and blood levels of liver enzymes (i.e. AST, ALT and total bilirubin) in a general population in China (range: 1.82-33.2 ng/mL).

Three studies were performed in *high-exposure communities* (all part of the C8 Health Study population) in which the relationship between serum PFOA concentration and blood levels of liver enzymes was examined. Two studies were cross-sectional (Emmett et al 2006; Gallo et al 2012). One of those cross-sectional studies had PFOA concentrations of 0-3,000 ng/mL and reported no significant association with blood levels of liver enzymes (Emmett et al., 2006). This is, however, a study that carried less weight because it is a relatively small study (n=371). In the other study (Gallo et al., 2012), a median PFOA concentration of 28.0 ng/mL (interquartile range: 13.5-70.8 ng/mL) was observed among 47,092 individuals. They found an association between PFOA and ALT. In addition, Gallo et al. (2012) discuss that a study previously performed by Steenland et al (2009) observed an association between individual serum levels of PFOA and the water district of residence. Factors related to the water district of residence may therefore have affected the examined association between PFOA and ALT. For this reason, Gallo et al. (2012) examined the association within and between water districts, thereby adjusting for those factors related to the water district. Associations were found both within and between water districts, which strengthens the notion that a relationship between PFOA exposure and the blood levels of liver enzymes exists. Darrow et al (2016) performed a longitudinal study and observed an association between modelled PFOA concentrations and higher ALT and lower direct bilirubin (a median serum PFOA concentration of 16.5 ng/mL was observed and a full range of 2.6-3,559 ng/mL). No association was found between serum PFOA and liver disease (diagnosis of liver disease was validated by healthcare providers).

Multiple studies were performed in which *occupational study populations* were examined. Similar to the results taken from studies conducted among the general population and a high-exposure community, associations were found, although not consistently. Cross-sectional occupational studies observed some associations with the blood levels of liver enzymes (although inconsistent, i.e. sometimes only in a certain factory or certain year of examination) (Olsen et al., 2000; Olsen and

Zobel, 2007). Those studies examined individuals with serum PFOA concentrations ranging between 0.1-81,300 ng/mL (Olsen et al., 2000), 7-92,030 ng/mL (Olsen and Zobel, 2007), 5-9,550 ng/mL (Sakr et al., 2007a) and 200-47,040 ng/mL (Costa et al., 2009). One occupational study conducted among workers with 40-12,700 ng/mL of serum PFOA concentration found no association between PFOA and the blood levels of liver enzymes (Olsen et al., 2003). Gilliland and Mandel (1996) observed no association between serum fluorine (examined as a proxy for PFOA) and changes in GGT. Three longitudinal studies were performed. One longitudinal study found some association (serum concentration range: 0-2,266 ng/mL) (Sakr et al., 2007b). Another longitudinal study conducted among an occupational population with serum PFOA concentrations ranging from 0.1-10,000 ng/mL found no association with blood levels of liver enzymes (Olsen et al., 2012). No association of estimated cumulative PFOA concentrations with non-hepatitis liver disease was found in a longitudinal study among an occupational population with a median PFOA concentration of 113 ng/mL (full range not reported) (Steenland et al., 2015).

3.3 Testicular and kidney cancer

3.3.1 Conclusions from previous reviews

The (C8 Science Panel, 2012b) concluded that there is a probable link between PFOA and both testicular and kidney cancer. The Panel gave the most weight to studies conducted among the high-exposure community of the C8 Health Study, as they regarded other studies to be of limited value for assessing risk in the C8 study area because exposures were much lower and/or were very small with little data of value for specific cancers.

The Health Council of the Netherlands (2013) concluded that the available data on PFOA and its salts are insufficient to evaluate its possible carcinogenicity. Studies performed in workers cohorts, high-exposure communities and among the general population were reviewed by the Health Council of the Netherlands (2013). They conclude that a relatively high number of longitudinal studies were conducted into the relationship with cancer in general, but the results are of such a high degree of inconsistency that they consider the human data as being insufficient for drawing firm conclusions.

ATSDR (2015) reported that some increases in kidney and testicular cancer have been found in high-exposure communities near a production plant or in workers (i.e. the C8 Health Panel).
Yet ATSDR noted that these results should be interpreted cautiously because the results were inconsistent, the number of cancer cases was low and a causal relationship between PFOA and cancer cannot be established from these studies.

It was not the objective of the background document (ECHA-RAC 2015a) to draw any firm conclusions regarding the association between PFOA and health. So no firm conclusions were drawn regarding cancer, but they do describe the epidemiological studies performed on the relationship with kidney and testicular cancer in their background document. In addition, they refer to the conclusions drawn by IARC and

C8 regarding a potential association with cancer. As described before, none of the endpoints evaluated by ECHA-RAC were considered 'robust enough to include in a quantitative assessment' (ECHA-RAC 2015b).

DWQI (2016) used recently published comprehensive reviews performed by other recognized scientific groups (C8 Science Panel, 2012b; IARC, 2016; US-EPA, 2005; US-EPA, 2006; US-EPA, 2016a) for their evaluation with respect to testicular and kidney cancer. DWQI concluded that PFOA was associated with an increased incidence of testicular and kidney cancer in high-exposure communities. They reported that those studies have accounted for smoking history and other relevant factors.

IARC (2016) has classified PFOA as 'possibly carcinogenic to humans' based on studies conducted in humans and animals. IARC (2016) considered the evidence for specifically testicular cancer to be 'credible and unlikely to be explained by bias and confounding'. However, they also noted that the estimates were based on small numbers. IARC (2016) also considered the evidence for kidney cancer to be credible. But they concluded that, for kidney cancer, the influence of 'chance, bias, and confounding could not be ruled out with reasonable confidence'.

US-EPA concluded that PFOA is 'likely to be carcinogenic to humans' based on animal studies. But in a peer review of the draft report it was stated that PFOA is carcinogenic to humans (US-EPA, 2006). In a more recent report (US-EPA, 2016a) in which the EPA reviewed epidemiological studies, they concluded that associations between PFOA exposure and testicular and kidney cancer have been reported in human epidemiological studies. Two studies involving people in the C8 Health Study area showed a positive association between PFOA concentrations and kidney and testicular cancers (Barry et al., 2013; Vieira et al., 2013). They also reported that two occupational cohorts do not support an increased risk of testicular and kidney cancers, but both studies were limited by small numbers.

Update with recent studies: reviews

One review was published after 2006 that examined the association between exposure to PFOA and cancer (Chang et al., 2014). The project was funded by the 3M Company, but the company was not involved in the preparation or approval of the report. Chang et al (2014) concluded that the existing epidemiological evidence does not provide evidence for a relationship between exposure to PFOA and cancer. They note, for instance, that in some epidemiological studies statistically significant associations were observed (with cancers of the kidney and testis, as well as prostate and thyroid), but those results were counterbalanced by negative associations and no evidence has been observed in animals.

3.3.2 Summary of studies

Table 4 summarizes the results of epidemiological studies. In total, four epidemiological studies were included that examined an association between serum PFOA concentrations and kidney cancer and testicular cancer. Two studies were conducted in the C8 study area. Of those two studies, one study examined both *workers and a high-exposure community* (i.e. the C8 Health Study) (Barry et al., 2013) and one study

examined a *high-exposure community* only (also the C8 Health Study) (Vieira et al., 2013). Two studies examined mortality in *occupational study populations* (Lundin et al., 2009; Steenland and Woskie, 2012).

Barry et al. (2013) observed that individuals were significantly more likely to have testicular cancer if they had higher estimated cumulative ln-transformed serum PFOA concentrations (i.e. the sum of estimated serum concentrations over the examined years; i.e. ng/mL-years; annual serum PFOA concentrations were estimated at 2.8-9217 ng/mL, with a median value of 19.4 ng/mL; median or range of estimated cumulative concentrations were not reported). However, they only found a modest, non-significant association with kidney cancer (p=0.1). In contrast, Vieira et al. (2013) observed that individuals examined in the high-exposure community (full range of annual estimated serum PFOA concentration were 3.7-655 ng/mL) were more likely to have kidney cancer when their estimated annual serum PFOA concentrations were 30.8-109 ng/mL (OR=2.0) and 110-655 ng/mL (OR=2.0), compared with unexposed individuals (<3.7 ng/mL), assuming 10 years of residency in a contaminated water district. Residence in the most exposed water district was associated with a higher likelihood of testicular cancer (OR=5.1), but the analysis of an individually modelled serum level showed a lower and non-significant risk. In both studies performed in occupational study populations (Lundin et al., 2009; Steenland and Woskie, 2012) there were insufficient cases or no cases to examine testicular cancer. Lundin et al. (2009) found no association with kidney cancer. Steenland and Woskie (2012) observed that kidney cancer was more likely to occur in DuPont workers in Parkersburg, who had estimated cumulative blood concentrations of 1,819 ppm-years (ppm=parts per million; 1 ppm=1000 ng/mL). To illustrate what ppm-years entail, Steenland and Woskie (2012) reported that, for example, 100 ppm over five years would be equal to 500 ppm-years.

3.4 Pregnancy-induced hypertension and preeclampsia

Pregnancy-induced hypertension refers to elevated blood pressure with or without protein in the urine. Preeclampsia specifically refers to elevated blood pressure with protein in the urine.

3.4.1 Conclusions from previous reviews

The C8 Science Panel notes that pregnancy-induced hypertension and preeclampsia cannot be distinguished clearly in the epidemiological studies they considered (because of reporting bias). Therefore, pregnancy-induced hypertension refers to both pregnancy-induced hypertension and preeclampsia in their evaluation. The C8 Science Panel (2011a) considered the existing evidence to be sufficient. It concluded that there is a probable link for an association between PFOA exposure and pregnancy-induced hypertension. The Panel added that the associations are not strong and there is no evidence of a dose-response relationship (i.e. higher risk when exposed to higher levels of PFOA). Nevertheless, they concluded that there is a probable link because associations were observed in multiple, differently performed analyses, which limits the possibility of bias influencing the results. Also, the associations were stronger for pregnancies that were closest in time to

the measurement of serum PFOA values, when exposure assignment is likely to be most accurate.

ATSDR (2015) does not report a firm conclusion on whether an association exists. They reported that Savitz et al. (2012b) found no consistent association between PFOA (predicted serum PFOA concentrations) and pregnancy-induced hypertension. In contrast, Darrow et al. (2013) observed a higher risk of pregnancy-induced hypertension in women with higher PFOA (≥6.9 ng/mL) among highly exposed residents. Two studies (of highly exposed residents) found a (weak) association between PFOA and preeclampsia (Savitz et al., 2012a; Stein et al., 2009), however no dose-response relationship was found (Stein et al., 2009).

In their background document, ECHA-RAC (2015a) stated that "pregnant women may be particularly vulnerable to PFOA-induced increase in total cholesterol, but the relationship between elevated PFOA serum levels and preeclampsia has not been clearly established." None of the evaluated endpoints by ECHA-RAC were considered to be 'robust enough to include in a quantitative assessment' (ECHA-RAC 2015b).

The US-EPA (2016a) concluded that each of the studies they considered in their evaluation (Darrow et al., 2013; Savitz et al., 2012a; Savitz et al., 2012b; Stein et al., 2009) have provided some evidence of an association with pregnancy-induced hypertension or preeclampsia. The most robust findings were found in the study they considered to be the strongest study methodologically (Darrow et al., 2013).

3.4.2 Summary of studies

Table 5 summarizes the results of six epidemiological studies that examine the relationship between plasma, serum or full blood PFOA concentrations and pregnancy-induced hypertension or preeclampsia in a general population and a high-exposure community.

Two studies were performed among the *general population* (i.e. both in the Norwegian Mother and Child Cohort Study), in which plasma PFOA concentrations were measured up to 5.15 ng/mL (i.e. 95th percentile). Both found no association with validated preeclampsia (Starling et al., 2014a) or the biomarkers of preeclampsia (Starling et al., 2014b).

Four studies were performed in a *high-exposure community*, i.e. the C8 Health Study. The studies produced some inconsistent results. Two studies examined the relationship with pregnancy-induced hypertension (Darrow et al., 2013; Savitz et al., 2012b). Darrow et al. (2013) found a higher risk of pregnancy-induced hypertension in those with higher serum PFOA concentrations (i.e. with an increase in 1 lnPFOA; OR=1.27, CI=1.05-1.55; full serum PFOA concentration range: 0.6-459.5 ng/mL). They also observed that pregnancy-induced hypertension was more likely in individuals with serum PFOA concentrations in the second through fifth quintiles, compared with the lowest quintile (i.e. <6.9 ng/mL) (Darrow et al., 2013). Savitz et al. (2012b) observed an association (i.e. OR=1.5, CI=1.1-2.1) only in those women who had estimated PFOA concentrations between the 60 and 80th percentiles (i.e. 19.6 to 53.1 ng/mL), compared with <40th percentile (3.9 to <8.9 ng/mL), but not in the other percentiles (full estimated range: 3.9 - 934.3 ng/mL).

Regarding preeclampsia in a *high-exposure community*, one study modelled a higher risk of preeclampsia for an increase of 100 ng/mL (i.e. OR=1.08, CI=1.01-1.15) and a relative risk of 1.1–1.2 was observed across the upper three quintiles of estimated serum PFOA concentrations (i.e. 6.1-717.6 ng/mL) (Savitz et al., 2012a). The other study found no significantly increased risk for preeclampsia (Stein et al., 2009) (range of measured serum PFOA concentration: 0.25-894.4 ng/mL). The study performed by Stein et al. (2009) is possibly less accurate because they did not model blood PFOA concentration at the time of the pregnancy, but rather measured blood PFOA concentrations after pregnancies occurred (i.e. pregnancies occurred within the 5 years preceding exposure measurement), in contrast with (Savitz et al., 2012a).

Pregnancy-induced hypertension and preeclampsia can be measured by self-reports or by birth certificate codes. It has been discussed that pregnancy-induced hypertension and preeclampsia are often reported incorrectly, either through self-reports or retrieved from birth certificates (Savitz et al., 2012b). For example, Darrow et al. (2013) discussed the fact that pregnancy-induced hypertension recorded on the birth record generally does not specify whether it concerns pregnancy-induced hypertension or preeclampsia.

3.5 Birth weight

Insufficient growth during pregnancy potentially affects the health of the newly born child. Epidemiological studies have examined both absolute birth weight and the occurrence of low birth weight (<2.5 kg). Absolute birth weight does not necessarily provide information on whether or not the baby's health is affected. Low birth weight (<2.5 kg; notably different from 'small for gestational age', which can be defined as an infant with birth weight below the 10th percentile at a specific gestational age in weeks), is a clinical outcome with potential health consequences. On the other hand, a decrease of absolute birth weight in a large group of people may have a relevant impact, i.e. for babies with already low birth weight. Therefore, absolute birth weight may also be relevant from the standpoint of public health.

3.5.1 Conclusions from previous reviews

The C8 Science Panel (2011b) reports that the evidence of an association between PFOA exposure and *low birth weight* (i.e. <2.5 kg) is insufficient to evaluate whether a probable link exists. They note that there is some evidence, although inconsistent, suggesting small changes in average birth weight at the highest PFOA exposure concentrations. However, those changes are not necessarily medically relevant. The C8 Science Panel, therefore, only considered studies that examined low birth weight to be relevant for their evaluation.

The ATSDR (2015) concluded that there were consistent findings for an association between serum PFOA and decreases in birth weight. They added that, although studies found significant associations, the decreases were small and so they considered them potentially not to be biologically relevant.

In their background document, ECHA-RAC (2015a) stated that the evaluated studies suggest the existence of a relationship between higher

blood PFOA concentrations and lower birth weight. They discussed a recently published, systematic review by Johnson et al. (2014) may have drawn different conclusions from those of the C8 Science Panel because the C8 Science Panel: 1) mostly considered studies that examined low birth weight as opposed to a continuous measure of birth weight, 2) considered studies in which PFOA exposure was determined less accurately and 3) because Johnson et al. (2014) were able to consider more recent studies in which some suggestions of an association were found (although they were not necessarily significant) (Chen et al., 2012; Maisonet et al., 2012; Whitworth et al., 2012). In addition, ECHA-RAC (2015a) noted that, in the literature, an alternative explanation for the association between maternal PFOA concentration and reduced birth weight has been discussed, i.e. women who give birth to babies with a low birth weight have a lower glomerular filtration rate (GFR). A lower GFR, in turn, decreases the removal of PFOA from the blood. It is therefore possible that women who give birth to babies with a lower birth weight have higher serum PFOA concentrations because of a lower GFR. Yet in another study conducted by the researchers of the meta-analyses, it was reviewed whether an association exists between GFR and foetal growth (Lam et al., 2014). The existing studies for such a relationship are of insufficient quality and therefore, although they did not find an association, they cannot be sure there is no association (Lam et al., 2014). In their opinion document, ECHA-RAC (2015b) concluded that the association was relatively small and that there are uncertainties with respect to dose-response. On these grounds, they concluded that the epidemiological data cannot be used for quantification.

The DWQI (2016) did not make their own evaluation of foetal growth, but reported on the systematic review performed by Johnson et al. (2014). The authors of the review concluded that ‘sufficient’ human evidence has been published to establish an association between exposure to PFOA in the general population during development and a reduction in foetal growth (e.g. birth weight) in humans. Johnson et al. (2014) reported that an increase of 1 ng/mL in blood PFOA concentrations is associated with a decrease of 18.9 grams (95% confidence interval [CI] = -29.8, -7.9) in birth weight. They assumed a linear relationship (examining untransformed PFOA) and pooled data from various general population studies. They discussed the fact that many studies found an association in the same direction, i.e. a higher blood PFOA concentration was associated with lower birth weight. However, those individual studies did not often find statistically significant associations. By combining single studies in the meta-analysis, the statistical power was increased, which explains why Johnson et al. (2014) found a significant association and concluded that there is sufficient evidence of an association between PFOA exposure and reduced foetal growth. It should be noted that Johnson et al. (2014) only included studies performed among the general population.

The US-EPA (2016a) evaluated individual studies, as well as the review performed by Johnson et al. (2014). The US-EPA (2016a) reported that higher blood PFOA concentrations were associated with lower birth weight in several studies. Yet they also noted that the association may have another explanation, i.e. a lower GFR, as described above. Whether or not this is the case is uncertain. Johnson et al. (2014) also examined whether a low GFR could explain the relationship between

PFOA and birth weight. They concluded that the available studies on foetal growth and GFR were inadequate to draw conclusions on the association between both measures. So they concluded that they could not exclude a decreased GFR as an alternative explanation for the association between higher PFOA and lower birth weight.

Update with recent studies: reviews

Two reviews were published after 2006 that explored a relationship between exposure to PFOA and birth weight (Bach et al 2015; Lam et al 2014). Lam et al. (2014) used similar data as Johnson et al. (2014), but Lam et al. (2014) additionally review nonhuman evidence. Lam et al. (2014) concluded that sufficient evidence exists for an association between developmental exposure to PFOA and decreased foetal growth, but, as described above, it is not yet clear whether this relationship can be explained by the influence of GFR. Bach et al. (2015) concluded that most studies show an association between higher PFOA concentrations and lower birth weight, but it is often not statistically significant. For this reason, they considered the existing epidemiological studies insufficient to confirm or reject an association with lower birth weight.

3.5.2 Summary of studies

Table 6 summarizes the results of the epidemiological studies. In total, 15 studies were included that examined a relationship between serum PFOA concentration (of the mother during pregnancy or the umbilical cord) and birth weight.

Ten studies examined the *general population*, with measured serum or plasma PFOA concentrations ranging up to 41.5 ng/mL. Seven studies conducted among the general population in different countries observed no association with birth weight (Apelberg et al., 2007; Chen et al., 2012; Hamm et al., 2010; Lee et al., 2013; Monroy et al., 2008; Washino et al., 2009; Whitworth et al., 2012). Maisonet et al. (2012) observed lower birth weights in babies of mothers with serum PFOA concentrations of >4.4 ng/mL, compared with 1-3.1 ng/mL (range: 1-16.4 ng/mL). Birth weights did not differ in the babies of mothers with serum PFOA concentrations of 3.1-4.4 ng/mL, compared with 1-3.1 ng/mL. Fei et al. (2007) observed an association between higher maternal plasma PFOA (concentrations of up to 41.5 ng/mL were measured) and babies with lower birth weight. In contrast, Ashley-Martin et al. (2016) found that babies' with a higher gestational weight gain were more likely to have above-median cord serum PFOA concentration (i.e. >0.39 ng/mL), compared with below-median cord blood PFOA concentrations.

Four studies were performed in *high-exposure communities* (C8 Health Project community) (Darrow et al., 2013; Savitz et al., 2012a; Savitz et al., 2012b; Stein et al., 2009) with PFOA concentrations of up to 934.3 ng/mL (Savitz et al., 2012a). Darrow et al. (2013) and Savitz et al. (2012a) did not find any association. Savitz et al. (2012b) found some inconsistent findings with birth weight and no dose-response relationship. Stein et al. (2009) found a higher risk of lower birth weight in mothers with serum PFOA concentrations of 50-120.6 ng/mL (measured after birth and not measured or estimated at the time of the birth), compared with 0.25-<21.3 ng/mL. However, no association was

found in mothers with blood PFOA concentrations of 21.3-50 ng/mL or 120.6-894.4 ng/mL, compared with mothers with serum PFOA concentrations of 0.25-<21.3 ng/mL. Stein et al. (2009) therefore concluded that no linear dose-response relationship could be found.

One study examined an occupational study population (serum PFOA concentrations range: 5.5-58.5 ng/mL) and found an association between higher serum PFOA concentrations in pregnant women (selected from workers at an electronic waste recycling area and from the general population; serum PFOA concentrations ranged from 4.4 to 58.5 ng/mL) and lower birth weight (Wu et al., 2012).

3.6 Uric acid concentration

Uric acid occurs in blood when certain foods (specifically containing purines) and human cells are broken down in the body. Uric acid is broken down and partly removed by the kidneys. A higher uric acid concentration in the blood may indicate the presence of clinical conditions. Hyperuricemia is having uric acid concentrations in the blood above a certain cut-off value.

3.6.1 Conclusions from previous reviews

The C8 Science Panel has not evaluated a relationship between serum PFOA and uric acid concentrations.

ATSDR (2015) concluded that consistent associations were found between higher serum PFOA and higher uric acid concentrations. They noted that, while the relationship with uric acid concentration was not examined to be as good as, say, serum lipids, the five studies that were reviewed by ATSDR (2015) all found significant associations. Those studies were performed in disparate study populations, i.e. in occupational populations, high-exposure communities and among the general population. In the latter two groups, associations were also found between higher serum PFOA concentrations and hyperuricemia.

DWQI (2016) concluded that evidence has been found for an association between PFOA and increases in serum concentrations of uric acid. Six out of seven studies reviewed by DWQI observed a significant association. Those six studies examined the general population, high-exposure communities and occupational studies, thus examining a wide range of exposures. A dose-response relationship was found between PFOA and uric acid in general population studies and a high-exposure community study. Usually, a steep dose-response curve was found in the general population, with a flattened slope at higher PFOA concentrations. However, the DWQI also discussed the fact that the epidemiological evidence still has some limitations, e.g. the primary one being that cross-sectional studies are examined, which limits the possibility of examining the influence of confounding. There remain questions regarding the biological plausibility of the relationship. Still, they concluded that uric acid is one of the endpoints for which they considered the evidence to be the strongest.

US-EPA (2016a) also concluded that an association has been observed between higher serum PFOA concentrations and uric acid concentrations

measured in blood. Yet they noted that the concentration of PFOA in serum depends on exposure and the rate at which PFOA is excreted from the body by intestines and the kidneys. Both PFOA and uric acid concentrations may be higher because of reduced kidney function, not because PFOA affects uric acid concentrations. Kidney disease may therefore confound the relationship.

3.6.2 Summary of studies

In Table 7, the total of eight epidemiological studies are summarized. They all found an association between higher serum or plasma PFOA concentration and higher uric acid concentration (Costa et al., 2009; Geiger et al., 2013; Gleason et al., 2015; Qin et al., 2016; Sakr et al., 2007a; Shankar et al., 2011; Steenland et al., 2010b) – except for one (Lin et al., 2013a). The studies that examined a relationship with hyperuricemia also found an association between higher serum or plasma PFOA concentration and a higher prevalence of hyperuricemia (Geiger et al., 2013; Shankar et al., 2011; Steenland et al., 2010b).

Five studies examined the *general population* in the United States (Geiger et al., 2013; Gleason et al., 2015; Lin et al., 2013a; Qin et al., 2016; Shankar et al., 2011). The NHANES study was the primary study used (Geiger et al., 2014; Gleason et al., 2015; Shankar et al., 2011). Shankar et al. (2011) observed a higher mean change in uric acid (mg/dL), with higher plasma PFOA concentrations in blood, starting from quartile 2 (2.4-3.4 ng/mL) up to quartile 4 (>5.1 ng/mL), compared with quartile 1 (<2.4 ng/mL), and a higher risk of hyperuricemia in quartiles 3 and 4. Similar results were found for hyperuricemia (Shankar et al., 2011). Geiger et al. (2013) examined children only (12-18 years). The children had similar serum PFOA concentrations in their blood (75^{th} ercentile: >5.4 ng/mL). However, in contrast to the results found by Shankar et al. (2011), an association was found only in those with PFOA concentrations in the highest quartile, i.e. >5.4 ng/mL, compared with the lowest quartile (<2.9 ng/mL). Also, a higher risk (OR=1.62) of hyperuricemia was found in children that had serum PFOA concentrations >5.4 ng/mL, compared with those with <2.9 ng/mL (Geiger et al., 2013). An association was observed between serum PFOA and uric acid (75^{th} percentile: >5.2 ng/mL) (Gleason et al., 2015). Lin et al. (2013a) examined the association between serum PFOA and uric acid in Taiwanese children aged 12-30 years and found no significant association (serum PFOA concentration range: 0.75-52.2 ng/mL). Qin et al. (2016) examined Taiwanese children aged 12-15 years and observed an association between higher serum PFOA concentration and higher uric acid concentrations in boys only (median serum PFOA concentration: 0.5 ng/mL; 75^{th} percentile: >1.3 ng/mL).

One study examined a *high-exposure community* (C8 Health Study) with serum PFOA concentrations ranging up to ≥188.7 ng/mL (Steenland et al., 2010b). Uric acid concentration in serum increased by approximately 0.2-0.3 mg/dL from the lowest (0-7.8 ng/mL) to the highest (>=188.7 ng/mL) decile of PFOA (Steenland et al., 2010b). Also, a higher risk of hyperuricemia was found with higher PFOA quintiles, starting at PFOA concentrations in the second quintile (i.e. 11.4-20.6 ng/mL). For instance, individuals with serum PFOA concentrations of 11.4-20.6 ng/mL

had a higher risk of hyperuricemia than individuals with serum PFOA concentrations of <11.4 ng/mL.

Costa et al. (2009) examined an *occupational population* in Italy with measured blood PFOA concentrations of 200 ng/mL or higher. They observed higher uric acid concentrations (mg/mL) with higher PFOA concentrations (µg/mL) (β=0.026, CI=0.001-0.053). In another occupational study (Sakr et al., 2007a), blood PFOA concentrations of 5 through 9,550 ng/mL were observed. The authors reported that they found an association with uric acid, but did not quantify their results.

Steenland et al. (2010a) reviewed various studies in which a relationship between PFOA and various health endpoints were examined. Regarding the relationship with uric acid, they pointed out that causality cannot be inferred from cross-sectional data and the relationship between uric acid and PFOA may be a result of reverse causality due to competition between PFOA and uric acid for renal excretion. It is, however, a matter of speculation as to whether this hypothesis applies to humans. All studies summarized in the current review on the relationship between uric acid and PFOA were cross-sectional.

3.7 Vaccination response

The purpose of vaccination is to help develop immunity against an infectious disease. Epidemiological studies have examined the concentration of antibodies following vaccination in relation to blood concentrations of PFOA.

3.7.1 Conclusions from previous reviews

The C8 Science Panel did not evaluate a link with vaccination response.

The ATSDR (2015) reported that limited information is available regarding immunotoxicity (which includes vaccination response), but no firm conclusions were drawn.

The DWQI (2016) concludes that, although an association between PFOA and decreased antibody concentrations following vaccination has consistently been found in longitudinal studies, most of the vaccine types were evaluated in only one or two studies and there is limited evidence for exposure-response relationships.

The NTP (2016) concluded that there they are moderately confident that an association exists between PFOA exposure and suppression of the antibody response. They observed heterogeneity in the findings, but explain that the heterogeneity is possibly the result of differences in the methodologies used between studies.

The US-EPA (2016a) concluded that epidemiological studies showed an association between serum PFOA concentrations and decreased vaccination response. They report that two studies in children (Grandjean et al., 2012; Granum et al., 2013) and one study in adults (Looker et al., 2014) observed a decrease in response to one or more vaccines.

Update with recent studies: reviews
One review was published after 2006 (Chang et al., 2016). The 3M Company was not involved in the preparation or approval of the report, but the project was funded by 3M. The authors concluded that associations were observed, but most studies had methodological limitations and were unable to exclude confounding, bias or chance.

3.7.2 Summary of studies

Six epidemiological studies were summarized (Table 8); one study examined a *high-exposure community* population (Looker et al., 2014) and five studies examined a study population from the *general population* (Grandjean et al., 2012; Granum et al., 2013; Kielsen et al., 2016; Mogensen et al., 2015; Stein et al., 2016).

In a high-exposure community (full measured serum PFOA concentration range: 0.25-2,140 ng/mL; 75% of the study population had PFOA concentrations below 90.3 ng/mL; aged 18+ years), an association was observed between higher serum PFOA concentration quartiles and reduction in seroprotection (Looker et al., 2014). Higher serum PFOA concentration quartiles were therefore associated with a reduced antibody response to the A/H2N2 Influenza vaccine and consequently a higher risk of not attaining the antibody threshold necessary to offer long-term protection against this virus (Looker et al., 2014).

In four general population studies, childhood vaccinations were examined. Childhood vaccination responses are a useful way of examining the relationship between PFOA exposure and vaccination response because children receive the vaccinations at approximately the same age, thereby limiting bias from differences in vaccination and age. Grandjean et al. (2012) found that 75% of all examined mothers had serum PFOA concentrations below 4.01 ng/mL and 75% of all children at the age of five had serum PFOA concentrations below 4.96 ng/mL. An association was observed between higher serum PFOA concentrations in children and lower serum antibody concentrations against tetanus and diphtheria (Grandjean et al., 2012). Higher PFOA concentrations were therefore related to reduced immune response to childhood immunizations. Mogensen et al. (2015) extended their analyses with additional serum PFOA concentrations in children at age seven. As a result, they were able to examine whether the children were exposed between the ages of five and seven. Median serum PFOA concentrations were 4.1 ng/mL at five years old and 4.4 ng/mL at seven years old. The researchers found a significant association between serum PFOA concentrations at five and seven years old with reduced immune response to antibody concentrations (diphtheria: β=-34.7, CI=-52.5, -10.2; tetanus: β=-38.2, CI=-56.1, -13.0). Granum et al. (2013) found that 75% of the study population of young children had plasma PFOA concentrations below 1.4 ng/mL. They observed an association between plasma PFOA concentrations and reduced antibody levels of the rubella vaccine (Granum et al., 2013). The authors discussed the possibility that prenatal exposure to PFOA may lead to immunosuppression in early childhood. The individuals examined by Stein et al. (2016) had a geometric mean of 4.13 ng/mL. Stein et al. (2016) found an association between higher serum PFOA concentrations and lower levels of mumps and rubella antibody concentrations, especially in seropositive

individuals (i.e. it is assumed that seropositive children are children that have been exposed to the vaccine strain of these viruses). No association was observed with measles antibody concentration.
No significant association was observed in one study that examined adults in the general population in Denmark (Kielsen et al., 2016) (75% had a serum PFOA concentration below 2.79 ng/mL). Only 12 individuals were examined and the analyses had a low statistical power, which may explain why no association was observed.

3.8 Ulcerative colitis

Ulcerative colitis is a condition that results in inflammation and ulcers of the colon and rectum. It is the result of an abnormal response by the immune system. The cause of ulcerative colitis is unclear.

3.8.1 Conclusions from previous reviews

The C8 Science Panel (2012a) concluded that there is a probable link between PFOA exposure and ulcerative colitis. They reported that, because of a lack in other relevant epidemiological research and virtually no toxicology (i.e. cell and animal studies) on this topic, they base their conclusion solely on research done in the C8 cohort study. They concluded that a very clear and positive dose-response relationship was found, with a large elevation in the risk of ulcerative colitis developing in the highest exposure group.

The NTP (2016) concluded that, based on two epidemiological studies, there is a low level of confidence that exposure to PFOA is associated with ulcerative colitis because the evidence is restricted to one study population (C8 Health Project). There is no information available for other study populations. This lowers their confidence in the evidence.

The ATSDR (2015), ECHA-RAC (2015a), DWQI (2016) and US-EPA (2016a) all described the conclusions drawn by the C8 Science Panel and/or the epidemiological studies from the C8 Science Study and did not provide firm conclusions on whether or not an association with ulcerative colitis exists. None of the endpoints evaluated by ECHA-RAC were considered ‘robust enough to include in a quantitative assessment’ (ECHA-RAC 2015b).

3.8.2 Summary of studies

Table 9 summarizes the results of studies that examine an association between serum PFOA concentrations and ulcerative colitis.

A total of two studies were found. One study was conducted in a combination of a *high-exposure community* and an *occupational study population* (Steenland et al., 2013). The other study was conducted in an *occupational study population* (Steenland et al., 2015) (both from the C8 Health Study). Higher quartiles of cumulative, estimated PFOA concentrations were related to a higher incidence of ulcerative colitis in both studies. Compared with estimated, cumulative serum PFOA concentrations of <158 ng/mL-years, ulcerative colitis was more likely to occur in those with serum PFOA concentrations of 158-586, 586-3,500 and >3,500 ng/mL-years (i.e. OR=1.76, OR=2.63, and OR=2.86, respectively) (Steenland et al., 2013). In the second study, it was found

that, compared with estimated, cumulative serum PFOA concentrations of <800 ng/mL-years, ulcerative colitis was more likely to occur in those with estimated cumulative serum PFOA concentrations of 800-3,440, 3,440-7,040 and >7,040 ng/mL-years (i.e. OR=3.0, OR=3.26 and OR=6.57, respectively) (Steenland et al., 2015).

3.9 Thyroid effects

Epidemiologic studies have examined associations between PFOA and TSH (thyroid stimulating hormone), thyroglobin (TGN), thyroid stimulating immunoglobulins (TSI) and thyroid hormones, i.e. triiodothyronine (T3) and thyroxine (T4). Most of the T4 and T3 circulate in the blood bound to protein. However, a small percentage is free. Either free or total T4 and T3 are measured in studies. Total T4 and total T3 are the sum of free and bound T4 and T3. TSH, T3, T4, TGN and TSI are all related to the functioning of the thyroid and the production of thyroid hormones. Thyroid hormones (T3 and T4) control numerous physiological processes, including breathing, heart rate, digestion and body temperature. In the case of thyroid disease, the thyroid releases not enough (hypothyroidism) or too many (hyperthyroidism) thyroid hormones. Hypothyroidism is more common than hyperthyroidism. The prevalence of thyroid disease is highest among women and people over the age of 60. During pregnancy, temporally adaptations in maternal thyroid hormone production occur. Before approximately 20 weeks of gestation, maternal thyroid hormones are the only source of thyroid hormones for the developing baby. Altered thyroid metabolism of the mother during early pregnancy may therefore influence the baby's development.

3.9.1 Conclusions from previous reviews

The C8 Science Panel (2012e) concluded that, despite inconsistencies in the evidence, there is a probable link between PFOA and thyroid disease. The Panel considered the strongest positive evidence to be an increased occurrence among the C8 community of medically validated thyroid disease (hyperthyroidism in women, hypothyroidism in men), with increasing blood PFOA concentrations in prospective analyses.

The ATSDR (2015) concluded that, based on the results in adolescents, adults and pregnant women, PFOA in blood does not appear to result in thyroid toxicity.

In their background document, the ECHA-RAC (2015a) describes the studies and conclusions reported by the C8 Science Panel and added some studies performed in occupational studies. As previously noted, none of the endpoints were considered by the ECHA-RAC to be 'robust enough to include in a quantitative assessment' (ECHA-RAC 2015b). The evaluation of the DWQI (2016) is that, overall, studies in which thyroid hormones, TSH and thyroid disease are examined provide inconsistent evidence of any associations with PFOA. The DWQI concluded that there is limited evidence of an association with thyroid disease and limited or no evidence of an association between PFOA and TSH and thyroid hormones.

The US-EPA (2016a) concluded that human epidemiology studies report an association between PFOA and thyroid disorders. Blood PFOA

concentrations are associated with diagnosed thyroid disease in females and female children, most often hypothyroidism. This was the case in the highly exposed C8 community and in the general population with background exposure. PFOA was not consistently associated with thyroid hormone concentrations. However, PFOA was associated with TSH concentrations in pregnant women with anti-TPO antibodies. In contrast, no association between PFOA and TSH was observed in women who had not been diagnosed with thyroid disease.

Update with recent studies: reviews

In a systematic review (Ballesteros et al., 2017), studies were reviewed that examined an association between prenatal or childhood (<19 years) exposure to PFOA (as well as other perfluoroalkyl substances) and TSH, T3, T4 or thyroid dysfunctions. They conclude that the heterogeneity (i.e. study design, study setting, timing of exposure assessment, timing and type of thyroid-related outcome assessment, adjustment for potential confounders and statistical approach) was too great to compare results within each of the included study populations, except for specifically mothers (n=4 studies) and 11 to 19 year-old children (n=3 studies). They observed no consistent evidence for an association between PFOA concentrations and TSH, T3, T4 or thyroid dysfunctions.

3.9.2 Summary of studies

Table 10 summarizes the 25 studies that were included in one or more of the previous reviews.

Sixteen studies examined *the general population*, among newborns, children, pregnant women or adults with plasma and serum PFOA concentrations ranging from 0.05 to 123 ng/mL (Berg et al., 2015; Bloom et al., 2010; Chan et al., 2011; de Cock et al., 2014; Jain, 2013; Ji et al., 2012; Kim et al., 2016; Lin et al., 2013b; Melzer et al., 2010; Shah-Kulkarni et al., 2016; Shrestha et al., 2015; Wang Y. et al., 2014; Wang Y. et al., 2013; Webster et al., 2014; Wen et al., 2013; Yang et al., 2016). In eight studies (i.e. among newborns, children, pregnant women or adults), no association was observed with any of the thyroid effects they examined, which were TSH (Bloom et al., 2010; Ji et al., 2012; Lin et al., 2013b; Shah-Kulkarni et al., 2016; Shrestha et al., 2015; Wang Y. et al., 2014; Wang Y. et al., 2013), (total) T3 (Shah-Kulkarni et al., 2016; Shrestha et al., 2015; Wang Y. et al., 2014), (free or total) T4 (Bloom et al., 2010; Ji et al., 2012; Lin et al., 2013b; Shah-Kulkarni et al., 2016; Shrestha et al., 2015; Wang Y. et al., 2014) and hypothyroidism (Chan et al., 2011; Lin et al., 2013b). In two studies that examined pregnant women, higher blood concentrations of PFOA were associated with higher TSH blood concentrations (median serum concentrations were 1.7 ng/mL (Webster et al., 2014) and 1.53 ng/mL (Berg et al., 2015)). The authors noted that, although the associations were modest, the observed small changes may have implications for foetal health and development (Berg et al., 2015; Webster et al., 2014). In three studies that examined adults, associations were found with greater occurrence of thyroid disease in women only (Melzer et al., 2010), changes in T3 in women only (Wen et al., 2013) and free T3 (Wen et al., 2013; Yang et al., 2016). Three studies examined newborns or children and observed an association of blood PFOA concentrations

with T4 in girls (de Cock et al., 2014), total T3 (Jain, 2013) and TSI (Kim et al., 2016).

Three studies were performed in *high-exposure communities* (interquartile range of serum PFOA concentrations: 184-571 ng/mL (Emmett et al., 2006); full range of serum PFOA concentrations: 0.05-3,987 ng/mL (Lopez-Espinosa et al., 2012); full range of serum PFOA concentrations: 0.25-564.3 ng/mL (Knox et al., 2011)). Emmett et al. (2006) and Knox et al. (2011) found no association between serum PFOA and TSH. Lopez-Espinosa et al. (2012) found that, in those with higher serum PFOA concentrations, TSH decreased in girls, T4 increased in both boys and girls and thyroid disease was more likely. Knox et al. (2011) observed an association of higher serum PFOA concentrations with higher T4 in women (20-50 and >50 years) and men (aged >50 years). One study examined *both workers and a high-exposure community* and observed an association between higher PFOA concentrations and more functional thyroid disease (i.e. excluding neoplasms), hypothyroidism and hyperthyroidism in women only (Winquist and Steenland, 2014b).

In populations that were *occupationally* exposed to PFOA, serum PFOA concentrations ranged between 7-92,030 ng/mL (Olsen and Zobel, 2007), 5-9,550 ng/mL (Sakr et al., 2007a), 10-12,700 ng/mL (Olsen et al., 2003) and 0.00-114,100 ng/mL (Olsen et al., 1998). Steenland et al. (2015) did not report a range, but did report a median-measured serum PFOA concentration of 113 ng/mL. Higher serum PFOA concentrations were associated with higher T3 (Olsen et al., 2003; Olsen and Zobel, 2007) and lower free T4 (Olsen and Zobel, 2007). Higher TSH was observed in those with serum PFOA concentrations of 10 to <30 ng/mL, compared with lower (Olsen et al., 1998). In contrast, no association was observed with T4 (Olsen et al., 2003; Olsen and Zobel, 2007), with TSH (Olsen et al., 2003; Sakr et al., 2007a) and with thyroid disease (Steenland et al., 2015).

3.10 Blood lipid concentrations

The following blood lipids have been examined in epidemiological studies: total cholesterol, high-density lipid (HDL), non-HDL (i.e. LDL+VLDL), low-density lipid cholesterol (LDL), triglycerides, very low-density lipid cholesterol (VLDL), the ratio of total cholesterol to HDL and the ratio of HDL to LDL.
LDL is a protein that transports cholesterol throughout the body. LDL easily attaches to arteries and, if concentrations are too high, LDL may cause atherosclerosis. HDL helps prevent the build-up of cholesterol in arteries by transporting cholesterol to the liver. Insufficiently low blood concentrations of HDL are associated with an increased risk of cardiovascular disease. Together with cholesterol, triglycerides are packed with LDL and VLDL for transportation in the body and are gradually broken down in the blood stream into LDL and triglycerides. Triglycerides are lipids that, like cholesterol, occur in blood. Enhanced concentrations of triglycerides in combination with unfavourable cholesterol concentrations increase the risk of cardiovascular disease.

3.10.1 *Conclusions from previous reviews*

The C8 Science Panel (2012d) concluded that there is evidence of both a shift in average cholesterol and an increased risk of high cholesterol in relation to PFOA. The panel added that longitudinal analyses and analyses by water district performed by the C8 Science Panel in the Mid-Ohio Valley suggest that the association is less likely to be explained by confounding factors. A probable link was only evaluated for high cholesterol, which entailed cholesterol concentrations high enough for a doctor to prescribe medication. The C8 Science Panel concluded that a probable link exists between PFOA and high cholesterol (hypercholesterolemia).

According to the ATSDR (2015), most but not all studies found significant associations between PFOA and serum lipid concentrations, most consistently for increased total cholesterol concentration and not as strong for other serum lipids.

ECHA-RAC (2015a) described that, in addition to the conclusions drawn by the C8 Science Panel, cross-sectional and longitudinal epidemiological studies also support an association between higher PFOA concentrations and total cholesterol and LDL. They noted that the studies suggest a low dose effect, i.e. larger changes in cholesterol were observed in general than were observed in occupational study populations. Yet they suggest that differences in age and sex distributions between general and occupational study populations may also explain the difference in the observed magnitude of changes.

The DWQI (2016) concluded that limited evidence of an association with LDL has been found and no evidence has been found for an association with HDL. In contrast, they also concluded that evidence has been found for an association between PFOA and increases in serum concentrations of cholesterol. They found that studies of the general population and large high-exposure community studies and occupational studies with longitudinal designs found consistent evidence for an association. They concluded that, of all health endpoints they reviewed, the evidence for an association with PFOA is strongest for serum cholesterol (in addition to liver enzyme ALT and uric acid). The results for that association showed ‘consistency, strength, dose-response and some evidence of temporality’.

The US-EPA (2016a) has concluded that, for total cholesterol and LDL cholesterol, generally positive associations have been observed with serum PFOA in studies examining workers and in studies conducted in high-exposure communities among adults and children (aged 1–18 y). Despite some exceptions, the results are relatively consistent and robust. Associations were not seen with HDL cholesterol. In the general population, associations of PFOA with total cholesterol are seen, but because of similar results for PFOS and moderately strong correlations between blood PFOA and PFOS concentrations, the interpretation of findings taken from studies conducted in the general population is limited (US-EPA 2016a).

3.10.2 *Summary of studies*

Table 11 summarizes the results of the epidemiological studies. A total of nine studies were conducted among members of the general

population, six in high-exposure communities (including two studies in which workers were also examined, i.e. Wang J. et al. (2012) and Winquist and Steenland (2014a)) and nine in occupational settings.

All seven studies that measured total blood cholesterol concentration in the *general population* found a positive association between serum or plasma PFOA and total cholesterol (Eriksen et al., 2013; Fisher et al., 2013; Fu et al., 2014; Geiger et al., 2014; Nelson et al., 2010; Starling et al., 2014b; Zeng et al., 2015). In five (Eriksen et al., 2013; Fu et al., 2014; Geiger et al., 2014; Nelson et al., 2010; Zeng et al., 2015) of the seven studies, the association was statistically significant. LDL was also measured in seven studies. Three studies (Fu et al., 2014; Geiger et al., 2014; Zeng et al., 2015) observed a positive statistically significant association, two studies (Fisher et al., 2013; Starling et al., 2014b) a non-significant positive association and two studies (Lin et al., 2013a; Nelson et al., 2010) non-significant negative associations. Nelson et al. (2010), however, although they did not find an association with LDL-cholesterol, did find a positive statistically significant association between PFOA and non-HDL (i.e. LDL + VLDL) cholesterol. HDL-cholesterol was measured in seven studies. In one study positive and negative, statistically significant associations were found in adolescent girls and elderly men, respectively. The other six studies found statistically non-significant positive and negative associations.

Six studies were conducted in high-exposure communities, four of which were from the C8 Health Project (Fitz-Simon et al., 2013; Frisbee et al., 2010; Steenland et al., 2009; Winquist and Steenland, 2014a), one was conducted in the C8 Health Project area (Emmett et al., 2006) and one was conducted in a community in China (Wang J. et al., 2012). Three studies from the C8 Health Project found positive and statistically significant associations between serum PFOA concentrations and total and LDL-cholesterol concentrations. These studies included cross-sectional studies in 46,294 adults (Steenland et al., 2009) and 12,476 children (Frisbee et al., 2010) and one longitudinal study in 560 adults (Fitz-Simon et al., 2013). Two studies also found an association between PFOA and elevated total cholesterol concentrations (Frisbee et al., 2010; Steenland et al., 2009), and one study between PFOA and elevated LDL-cholesterol levels (Frisbee et al., 2010) (not studied in Steenland et al. (2009)). A longitudinal study from the C8 Health Project included both workers and members of the high-exposure community and used modelled serum PFOA concentrations (Winquist and Steenland, 2014a). They also found a higher incidence of medically validated diagnosis of hypercholesterolemia with medication in those with higher cumulative, modelled serum PFOA concentrations, i.e. hazard ratios were significantly higher in quintiles 2 (>142 ng/mL per year) through 5 (≥3,579 ng/mL per year) (hazard ratios in quintiles 2 through 5: 1.24, 1.17, 1.19, 1.19, see table 11) (Winquist and Steenland, 2014a). The study conducted by Emmett et al. (2006) in the C8 Project area studied total cholesterol levels and found a positive non-significant association with PFOA, but this study was based on a much smaller data set (n=371) and did not adjust for potential confounders in the statistical analysis. The study from China (Wang J. et al., 2012) included 132 residents and did not find associations with total, LDL or HDL cholesterol or triglyceride concentrations.

None of the community studies found an association with HDL-cholesterol. An association with triglycerides was found in the two large cross-sectional studies from the C8 Health Project (Frisbee et al., 2010; Steenland et al., 2009), but not in the longitudinal study (Fitz-Simon et al., 2013) or the study from China (Wang J. et al., 2012).

Nine studies included workers from PFOA production plants. As mentioned above, one study included both an occupational study population, as well as a high-exposure community. Five studies (Costa et al., 2009; Olsen et al., 2003; Olsen and Zobel, 2007; Sakr et al., 2007a; Sakr et al., 2007b) found positive and statistically significant associations between blood PFOA and total cholesterol concentrations. Positive non-significant associations were reported in three studies (Gilliland and Mandel, 1996; Olsen et al., 2000; Wang J. et al., 2012). One study reported a negative non-significant association (Olsen et al., 2012) and one study (Steenland et al., 2015) did not include total cholesterol concentrations (but self-reported elevated cholesterol with medication).

In six studies, LDL-cholesterol was also determined. Five studies (Gilliland and Mandel, 1996; Olsen and Zobel, 2007; Sakr et al., 2007a; Sakr et al., 2007b; Wang J. et al., 2012) showed positive associations with PFOA concentrations, one of which (Sakr et al., 2007a) was statistically significant. One study reported cholesterol concentrations per tertile of PFOA, with no apparent positive or negative association (Olsen et al., 2000).

HDL-cholesterol was studied in nine studies. Five studies (Gilliland and Mandel, 1996; Olsen et al., 2000; Olsen and Zobel, 2007; Sakr et al., 2007a; Wang J. et al., 2012) found negative associations with PFOA, two of which (Olsen and Zobel, 2007; Wang J. et al., 2012) were statistically significant. One study (Sakr et al., 2007b) found a non-significant positive association. Two studies (Costa et al., 2009; Olsen et al., 2012) found non-significant associations that were either positive or negative, depending on the statistical model, and in one study (Olsen et al., 2003) the association was not quantified.

4 Discussion and Conclusions

The objective of this literature review was to address the questions of what biological and physiological parameters and diseases are associated with PFOA concentrations in the blood of humans and in what concentration ranges these associations can be observed, as well as to give an indication of the magnitude of these associations. As recommended in a risk assessment of the emission of PFOA (Zeilmaker et al., 2016), an evaluation of epidemiological studies may indicate whether there are any potential effects of PFOA for which attention should be given to the people living in the vicinity of the Dupont/Chemours factory in Dordrecht. In recent years, a number of reviews have been performed by recognized (inter)national organizations (ATSDR, 2015; C8 Science Panel, 2011a; C8 Science Panel, 2011b; C8 Science Panel, 2012a; C8 Science Panel, 2012b; C8 Science Panel, 2012c; C8 Science Panel, 2012d; C8 Science Panel, 2012e; C8 Science Panel, 2017; DWQI, 2016; ECHA-RAC, 2015a; ECHA-RAC, 2015b; IARC, 2016; NTP, 2016; US-EPA, 2016a). In these reviews, both human (epidemiological) and toxicological (animal and in vitro) studies were reviewed in order to assess what biological and physiological parameters and diseases can result from exposure to PFOA.

Nine biological and physiological parameters and diseases were evaluated as being associated with higher PFOA concentrations in the blood by at least one (inter)national organization: increased concentrations of levels of liver enzymes in blood, concentrations of (total and LDL-) cholesterol in blood, thyroid effects, kidney and testicular cancer, pregnancy-induced hypertension and preeclampsia, reduced birth weight, increased uric acid concentrations in the blood, decreased vaccination response, and ulcerative colitis. The level of evidence for an association with PFOA concentrations in the blood differs between the various endpoints. Also, the evidence for a particular endpoint was evaluated differently in the different reviews. For example, The ATSDR (2015) described the evidence for an association between PFOA and uric acid concentrations in the blood as ‘consistent evidence’ (ATSDR, 2015), while the US-EPA (2016a) mentions that ‘an association was observed, but potentially confounded’. In the present review, the evaluations of the epidemiological evidence for these endpoints from the previous reviews have been summarized. The results of the epidemiological studies were summarized in tables, but the studies were not reviewed individually; they were used to gain an impression of the range of PFOA concentrations in human blood in which associations with endpoints have been observed and an impression of the magnitude of the associations.

4.1 Discussion per endpoint

Below, for each endpoint, there will be a discussion of how strong the evidence from epidemiological studies is, according to (inter)national organizations, for an association with PFOA and about the study population (i.e. general population, high-exposure community, occupational study population) in which associations with these

endpoints have been observed, as well as what the magnitude of these associations is.
It was beyond the scope of the present review to provide a quantification of the associations based on the findings of all available studies. To provide an impression of the magnitude of these associations, examples are given below from studies in the general population and/or high-exposure communities in which associations were found. As these are examples based on one or two studies, a formal meta-analysis may result in smaller or larger estimates of effect sizes.

4.1.1 Liver enzymes and liver disease

The ATSDR (2015), DWQI (2016) and US-EPA (2016a) have concluded that consistent evidence has been observed for the existence of an association between serum PFOA concentrations and certain liver enzymes (all agree on the liver enzyme ALT). The epidemiological studies in which associations were observed were performed in study populations from the general population, high-exposure communities and workers. Three organizations (ECHA-RAC, 2015a; ECHA-RAC, 2015b; Health Council of the Netherlands, 2013; NTP, 2016) did not evaluate blood levels of liver enzymes or liver disease. The C8 Science Panel (2012c) concluded that there is no probable link with liver disease, although they did report on associations with shifts in liver function, mainly within the normal physiologic range. The ATSDR (2015), DWQI (2016) and US-EPA (2016a) also concluded that there is no or limited evidence of a relationship between serum PFOA concentration and the occurrence of liver disease. The changes in the blood levels of liver enzymes were reported to be small. In summary, all previous reviews that evaluated liver effects concluded that PFOA is associated with small changes in blood concentrations of liver enzymes, but not with liver disease.

4.1.2 Testicular and kidney cancer

Of the four epidemiological studies that investigated an association with kidney and/or testicular cancer, one was performed in a high-exposure community, two were conducted in an occupational study population and one in a combination of both study populations, which were all part of the C8 Health Study. The incidence of testicular cancer and kidney cancer (WHO, 2017) in the general population is low and large study populations are required to obtain sufficient statistical power. This might explain why no studies were performed in the general population. The Health Council of the Netherlands (2013) concluded that the available data examining PFOA and cancer was insufficient to determine a potential association with cancer. Several international organizations, on the other hand, have concluded that PFOA may be associated with testicular and kidney cancer (C8 Science Panel, 2012b; DWQI, 2016; IARC, 2016; US-EPA, 2016a). It has also been noted, however, that the results need to be interpreted with caution because the results are inconsistent, the number of cancer cases was low, a causal relationship between PFOA and cancer cannot be established from these studies (ATSDR 2015) and it cannot be ruled out that the evidence, specifically for kidney cancer, has been influenced by chance, bias and confounding (IARC 2016). Regarding the magnitude of an effect, a doubling in the risk of kidney cancer was observed among residents in the community of the C8 Health Study, with estimated blood PFOA concentrations above

30.8 ng/mL, compared with those with concentrations <3.7 ng/mL (Vieira et al., 2013).
In summary, four out of seven international organizations have concluded that an association potentially exists between PFOA exposure and testicular and kidney cancer, but the epidemiological studies still have some limitations. It should also be noted that the number of epidemiological studies that have investigated testicular and/or kidney cancer is limited and were performed only in study populations that are part of the C8 Health Study.

4.1.3 Pregnancy-induced hypertension and preeclampsia

Pregnancy-induced hypertension and preeclampsia have been studied in the general population and the high-exposure community of the C8 Health Project. The C8 Science Panel (2011a) has concluded that the associations were not strong and no dose-response relationship was apparent. Still, they concluded that a probable link between exposure to PFOA and pregnancy-induced hypertension and preeclampsia may exist in the C8 Health Study because associations were observed in multiple, differently performed analyses, which limits the possibility of bias influencing the results. Also, the associations were stronger for pregnancies that were closest in time to the measurement of serum PFOA values, when exposure assignment is likely to be most accurate. After publication of the probable link report, a study was published (Darrow et al., 2013) which showed a non-monotonically increased risk of pregnancy-induced hypertension in the 2nd (6.9-11.1 ng/mL) to 5th quintiles (37.2-459.5 ng/mL) of PFOA, with odds ratio's ranging from 2.4 to 3.4. The US-EPA (2016a) also concluded that a relationship exists between exposure to PFOA and pregnancy-induced hypertension and preeclampsia. The ATSDR did not report a firm conclusion. ECHA-RAC (2015a) stated that the relationship has not yet been clearly established.

4.1.4 Birth weight

The C8 Science Panel (2011b) and US-EPA (2016a) have concluded that there is not enough evidence for an association between PFOA exposure and low birth weight (<2.5 kg) and average birth weight, respectively. The C8 Science Panel (2011b) noted that, although a relationship with small changes in birth weight was found in epidemiological studies, it was not consistently observed. The ATSDR (2015) has concluded that associations between PFOA exposure and small changes in birth weight have been found. Both ECHA-RAC (2015a) and DWQI (2016) refer to the meta-analysis performed by Johnson et al. (2014), in which several studies performed in the general population were pooled and the authors of the meta-analysis concluded that 'sufficient' human evidence exists for a relationship between developmental PFOA exposure and decreases in birth weight. In the meta-analysis performed by Johnson et al. (2014), the decrease in birth weight was 19 g per increase of 1 ng/mL of serum PFOA. In the opinion document of ECHA-RAC (2015b), it was noted that observed decreases were relatively small and that there were uncertainties in dose-response. The US-EPA (2016a) evaluated individual studies and the meta-analysis performed by Johnson et al. (2014). The US-EPA (2016a) concluded that the association observed between PFOA exposure and birth weight could possibly be explained by the influence of the glomerular filtration rate (GFR). In analyses performed by Verner et al. (2015) in which GFR was

taken into account, the association between PFOA and a decrease in birth weight was smaller. The DWQI (2016) concluded, on the basis of the results of Verner et al. (2015), that GFR does not account for the major portion of the decrease in birth weight associated with PFOA. Johnson et al. (2014) concluded that chance, bias and confounding could be ruled out with reasonable confidence. Nevertheless, it is not yet clear to what extent a low GFR could contribute to the relationship between serum PFOA concentrations and lower birth weight.

Therefore, most organizations agree that associations with birth weight have been found in the general population, but there is some debate as to whether or not these associations can be explained by other factors. In addition, inconsistent results were produced in studies examining an association between serum PFOA concentrations and birth weight in high-exposure communities (that reflected much larger exposure contrasts of PFOA and had more statistical power than the general population studies). As a consequence, the association with birth weight observed in the general population cannot be extrapolated to higher blood concentrations of PFOA.

4.1.5 Uric acid concentrations

The ATSDR (2015) concluded that evidence was found for an association between higher PFOA concentrations in the blood and higher uric acid concentrations in the blood. Both the DWQI (2016) and US-EPA (2016a) concluded that consistent evidence has been observed, but the relationship is potentially confounded. The C8 Science Panel did not evaluate a relationship between PFOA and uric acid concentrations because they only evaluated diseases. Discussed in the reports is the fact that an association with uric acid has been less frequently examined than was done for, say, blood lipids (ATSDR 2015), that the relationship may be confounded by the presence of kidney disease (US-EPA 2016a; DWQI 2016) and that a steep dose-response curve has been observed in the general population, with a flattened slope at higher PFOA concentrations (DWQI 2016). The epidemiological studies in which associations were observed were conducted in the general population, high-exposure communities and occupational populations. Differences in uric acid concentrations in blood between the first category (the reference category) and higher categories of PFOA concentrations in blood were in the order of 0.1-0.3 mg/dL. The evidence that PFOA is associated with hyperuricemia is limited. An association with hyperuricemia has been observed in two studies conducted among the general population (relative risks (RR) were 1.62 in the 4th quartile of PFOA concentrations in the blood of adolescents (Geiger et al., 2013) and 1.90 and 1.97 in the 3rd and 4th quartiles in adults (Shankar et al., 2011)) and one in the high-exposed community from the C8 health Project (RR were 1.33 to 1.47 in quintiles 2-5) (Steenland et al., 2010b). Although associations were observed, they may be confounded by individual differences in kidney clearance.

4.1.6 Decreased vaccination response

The ATSDR (2015) concluded that the evidence for an association between blood levels of PFOA and decreased vaccination response is not consistent. The DWQI (2016) reported consistent findings with evidence of temporality, but also limited evidence of an exposure-response

relationship between the blood levels of PFOA and decreased vaccination response. The US-EPA (2016a) concluded that an association had been observed and the NTP (2016) concluded that they have a moderate level of confidence that an association exists. However, as discussed by the DWQI (2016), most of the specific vaccine types were evaluated in only one or two studies. More research is therefore needed to confirm these findings. For this reason, most organizations have concluded that there is not enough evidence available yet to determine whether an association between blood levels of PFOA and decreased vaccination response exists.

Associations were observed in the general population and the C8 Health Project. The NTP mentions decreases in circulating antibody levels of 15-35% for a doubling in blood PFOA concentrations (NTP, 2016). Associations with inadequate seroprotection have also been reported. For example, in a study conducted by Grandjean et al. (2012), the odds ratios of antibody concentrations falling below the protective level for diphtheria and tetanus in children at age seven, associated with a doubling of PFOA concentrations at age five, were 3.27 (95% CI, 1.43 to 7.51) and 4.20 (95% CI, 1.54 to 11.44), respectively.

4.1.7 Ulcerative colitis

Two studies have been published that examined an association with ulcerative colitis, both from the C8 Health Project. The (C8 Science Panel, 2012a) has concluded that a probable link exists. The NTP (2016) noted that it is not possible to evaluate consistency across populations and this fact lowers their confidence in the evidence. The other organizations did not evaluate ulcerative colitis themselves, but reported the conclusions made by the C8 Science Panel.

Both published studies found an association and a dose-response relationship. One was performed in the combined high-exposed community and occupational study population, and one in the occupational population of the C8 Health Project. Although no studies were conducted in the general population, individuals with low serum PFOA concentrations were also examined in those studies. In the combined study population, in the 2^{nd} – 4^{th} quartiles of PFOA concentrations (>158 ng/mL), an increased risk of ulcerative colitis (RR were 1.76-2.86) was observed (Steenland et al., 2013). In workers, the RR ranged from 3.0 to 6.57 in the 2^{nd} to 4^{th} quartiles (covering PFOA concentrations of 800 to over 7,000 ng/mL) (Steenland et al., 2015). The evidence base is limited and should be extended to other study populations.

4.1.8 Thyroid effects

The C8 Science Panel (2012e) concluded that a probable link exists with thyroid disease. The US-EPA (2016a) concluded that an association was observed between serum PFOA concentrations and thyroid hormones. The ATSDR (2015) concluded that no association was observed with thyroid effects. DWQI (2016) reported that inconsistent findings were provided. They concluded that limited or no evidence was found for a relationship with blood concentrations of TSH and thyroid hormones, and limited evidence for an association with thyroid disease. Which means the organizations drew contradictory conclusions. PFOA in relation to thyroid effects has been the topic of 25 studies in either the

general population, high-exposure communities or occupational populations. These studies provide inconsistent evidence, i.e. positive associations, negative associations and no associations were observed with various thyroid effects. An association with thyroid disease has been studied less. Of the four studies in which thyroid disease has been examined, two observed an association with PFOA concentrations in the blood in relatively large study populations (RR=1.44 per IQR of 13.1-67.7 ng/mL in children from a high-exposure community population, i.e. the C8 population (Lopez-Espinosa et al., 2012); RR=1.24, 1.27, 1.36 and 1.37 in quintiles 2 (114.7-202.2 ng/mL) through 5 (2,670-97,396 ng/mL) in women in a high-exposure community and an occupational study population (Winquist and Steenland, 2014b).

4.1.9 Blood lipid concentrations

Associations of PFOA concentrations in the blood have quite consistently been observed with total cholesterol concentrations (ATSDR, 2015; ECHA-RAC, 2015a; US-EPA, 2016a; DWQI, 2016) and, although less convincing, LDL concentrations in the blood (ECHA-RAC, 2015a; US-EPA, 2016a; DWQI, 2016), but not with concentrations of HDL-cholesterol. The C8 Science Panel (2012d) concluded that the relationship between PFOA exposure and cholesterol may be causal in the high-exposure community of the C8 Health Project and that a probable link with hypercholesterolemia exists. The DWQI (2016) specified that an association with cholesterol was consistently found in all three types of study populations and, of all other examined endpoints, they considered the evidence for blood cholesterol concentrations to be one of the strongest). The US-EPA (2016a) notes that it is not yet clear whether the association between PFOA and increased cholesterol in the general population may be explained by the simultaneous presence of PFOS in the general population. In summary, all international organizations that have evaluated blood lipid concentrations have concluded that an association exists with total cholesterol concentrations. Of all endpoints, the association with blood lipid concentrations has been one of the endpoints most often studied (see Table 2).

In the C8 Heath Study, nearly monotonic increases in total or LDL-cholesterol were found with increasing PFOA concentrations in the blood. Increases in total and LDL-cholesterol concentrations were the highest in the range of approximately 5-40 ng/mL PFOA, after which an attenuation of the slope of the dose-response curve was observed (Steenland et al., 2009). A similar dose-response curve was observed in children and adolescents (Frisbee et al., 2010). In the steep part of the dose-response curve, increases in total and LDL cholesterol concentrations in the blood were somewhere between 4-10 mg/dL. As reported by Winquist and Steenland (2014a), hypercholesterolemia with medication was significantly more likely in quintiles 2 (>142 ng/mL per year) through 5 (≥3,579 ng/mL per year) (RR in quintiles 2 through 5: 1.24, 1.17, 1.19, 1.19).

4.2 Other endpoints

A number of other endpoints have been studied in relation to serum levels of PFOA. For these endpoints, it was generally concluded in the reviews included in the present report that evidence for an association is limited

or the available evidence was not evaluated in the reviews. In 2016, the German Umwelt Bundesamt (UBA, 2016) issued a statement of the German Human Biomonitoring Commission in which HBM I values for PFOA and PFOS were set. The HBM I value represents the concentration of a substance in a body matrix below which, according to the Commission's current assessment, adverse health effects are not expected and therefore no exposure reduction measures are necessary. These values are based on associations of PFOA and PFOS with fertility and pregnancy; birth weight; lipid metabolism; immunity after vaccination, immunological development; hormonal development, age at puberty / menarche; thyroid metabolism; and onset of menopause. This list thus includes a number of endpoints that were not evaluated in the present review. For these endpoints, effects were rated as 'well proven, relevant and significantly associated with exposure to PFOA and/or PFOS'. Because no background document was available at the time of publication of the present report, it is unclear how the available epidemiological evidence was evaluated by the German Human Biomonitoring Commission and what effects were attributed by this Commission to PFOA, PFOS or both.

4.3 Experimental data

Epidemiological studies, especially cross-sectional studies, have limitations (e.g. the potential for bias and confounding) that make it difficult to definitively draw conclusions on the causality of an association. Evidence that PFOA is causally associated with an endpoint is stronger if findings from epidemiological studies are supported by results from experimental animal and in vitro studies and by knowledge about the mode of action via which PFOA affects the endpoint in question. An in-dept discussion of toxicological (animal) studies and the mode of action of PFOA is provided in the reviews by ATSDR (2015), US-EPA (2016a) and DWQI (2016). In summary, there is evidence from experimental studies in animals that PFOA causes weight loss, hepatic toxicity, effects on lipid metabolism, changes in hormone levels, immune system effects, tumours in testis, liver and pancreas in rats (the only species tested), and several types of developmental effects (Post et al., 2012). It should be noted that these effects occurred at relatively high dose levels, with serum PFOA concentrations in the mg/L range. Nevertheless, the findings in experimental animals show that for most of the endpoints considered in the present review, there is supporting evidence from animal studies. A notable exception is blood cholesterol, for which studies in rodents show a decrease rather than an increase in total and LDL-cholesterol levels in the blood (Steenland et al., 2010a).

The biological mechanism(s) that explain(s) the effects of PFOA have not been fully characterized. PFOA is chemically non-reactive and therefore is not a substrate for biochemical reactions. However, PFOA may act through the inactivation of nuclear receptors, binding to transporter and carrier proteins and interacting with membranes (Post et al., 2012). PFOA may also act through other mechanisms; and PFOA has estrogenic activity (DWQI, 2016). PFOA causes peroxisome proliferation in the liver, which may explain effects on liver size, liver enzymes and blood lipids. Peroxisome proliferation activates the nuclear receptor PPAR-alpha, which has been proposed to induce tumours and cause immune

and hormonal changes in rodents (Steenland et al., 2010a). But the relevance of this mechanism for humans is unclear, because humans are less sensitive to PPAR-alpha-mediated effects. This is an important point when assessing the relevance of animal (mainly rodent) data for humans.

4.4 Conclusions

The objective of this review was to address the questions of what biological and physiological parameters and diseases are associated with PFOA concentrations in the blood of humans and in what concentration ranges these associations have been observed, as well as to give an indication of the magnitude of these associations. Findings from epidemiological studies provide indications that associations exist between serum PFOA concentrations and several biological and physiological parameters and diseases in study populations with different levels of exposure to PFOA, i.e. the general population, high-exposure communities and occupational study populations. The body of evidence for the existence of a potential association and the magnitude of the associations differ between endpoints, as is described in section 4.1. Conclusions from previous reviews are most consistent regarding evidence for associations of PFOA with total blood cholesterol concentrations, blood concentrations of the liver enzyme ALT and birth weight. Associations were observed in individuals with PFOA concentrations in their blood as found in the general population and at higher concentrations. Yet it remains to be established whether the associations observed in the epidemiological studies are causal. For most endpoints, there is supporting evidence from experimental animal studies, but the mode of action that explains how PFOA exerts its effects has not been fully characterized. The findings from this literature review will be used as a background document to assess the potential health consequences of PFOA exposure in residents living in the direct vicinity of the DuPont/Chemours factory in Dordrecht.

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Appendix Tables 3-11: data extracted from epidemiological studies

Table 3. Summary of associations in studies on liver enzymes

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
General population				
Lin et al. (2010)	Study population: general population, NHANES US Age range: 18+ yrs % men: 49% Study design: Cross-sectional Study year(s): 1999-00 & 2003-04 N total=2,216	Serum PFOA: IQR (men and women): 2.9-5.95 ng/mL Geometric mean: 5.05 (men) and 4.06 (women) ng/mL	ALT + GGT + Total bilirubin 0	Association between serum log PFOA (per 1 ng/mL) and liver enzymes (units per litre), β (p-value): **ALT: 1.86 (0.005)** **Log GGT: 0.08 (0.019)** Total bilirubin: -0.09 (0.645)
Jiang et al. (2014)	Study population: general population (pregnant women), China Age range: not reported (ca. 18-40 yrs) % men: 0% Study design: cross-sectional Study year(s): 2012 N total: 141	Serum n-PFOA Range: 1.8-32.9 ng/mL Median: 3.95 ng/mL Serum iso-PFOA Range: 0.003-0.46 ng/mL Median: 0.04 ng/mL Serum 5m-PFOA Range: 0.001-0.05 ng/mL Median: 0.001 ng/mL Serum ∑PFOA: Range: 1.82-33.3 ng/mL Median: 3.97 ng/mL	AST 0 ALT 0 Total Bilirubin 0	Pearson correlation (r) & significance level between concentrations of PFOA (per 1 ng/mL) isomers and biomarkers: AST - n-PFOA: r=-0.037 (ns) AST - iso-PFOA: r=0.008 (ns) AST - 5m-PFOA: r=0.149 (ns) AST - %n-PFOA: r=0.026 (ns) AST - ∑PFOA: r=0.041 (ns) ALT - n-PFOA: r=-0.071 (ns) ALT - iso-PFOA: r=0.003 (ns) ALT - 5m-PFOA: r=0.139 (ns) ALT - %n-PFOA: r=-0.119 (ns) ALT - ∑PFOA: r=-0.071 (ns)
Gleason et al,	Study population: general	Serum PFOA:	AST +	Association between ln-PFOA (per 1

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
2015	population, NHANES, US population Age range: ≥12 yrs % men: not reported Study design: cross-sectional Study year(s): 2007-2010 N total: 4,333	IQR: 2.5-5.2 ng/mL Median: 3.7 ng/mL Geometric Mean (CI): 3.5 (3.4-3.7) ng/mL	ALT + GGT + ALP 0 Total Bilirubin +	ng/mL) and clinical biomarkers of liver function, β (CI): **ALT: 0.038 (0.014, 0.062)** **GGT: 0.058 (0.021, 0.096)** **AST: 0.025 (0.007, 0.043)** ALP; -0.003 (-0.023,0.016) **Total Bilirubin: 0.048 (0.016, 0.081)** Results were reported in graphs. From the graphs, only approximate ORs can be read and it can be read whether or not the association was significant. Association between quartiles of serum PFOA concentration (compared to lowest quartile; Q1) and liver enzymes: AST: Q2 & Q3: NS **Q4: p<0.05 (OR's of +/- 1.0 and 1.5 can be read from the graph)** ALT: **Q2, Q3 & Q4: p<0.05 (OR's of around 1.5 can be read from the graph)** GGT: Q2 t/m Q4: ns ALP: Q2 t/m Q4: ns Total bilirubin: Q2: ns

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
				Q3 & Q4: p<0.05 (OR's of +/- 1.5 and 2.0 can be read from the graph)
High-exposure community				
Emmett et al. (2006)	Study population: high-exposure community population, resided ≥2 years in Ohio (Little Hocking) (independent of C8 Health Study) Age range: 2-89 yrs % men: 47% Study design: Cross-sectional Study year(s): not reported N total=371	Serum PFOA: Range: 0-3000 ng/mL Median: 354 ng/mL	AST 0 ALT 0 GGT 0 ALP 0 Total bilirubin 0	Association between PFOA (per 1 ng/mL) and liver enzymes, β (p-value): AST: -0.00076 (p=0.76) ALT: -0.00183 (p=0.65) ALP: -0.00416 (p=0.65) GGT: 0.00058 (p=0.89) Total bilirubin: -0.00000467 (p=0.92)
Gallo et al. (2012)	Study population: high-exposure community population, C8 Health project, West Virginia, US Age range: >=18 yrs % men: 48% Study design: Cross-sectional Study year(s): 2005-06 N total= 46,452	Serum PFOA: Median: 28.0 ng/mL IQR: 13.5-70.8 ng/mL	ALT + GGT + Total bilirubin 0	Association between lnPFOA (ng/mL) and (transformed) liver enzymes, β (CI): **Ln ALT: 0.022 (0.018 – 0.025)** **In GGT: 0.015 (0.01 – 0.019)** In direct bilirubin: 0.001 (-0.002 – 0.004) Association between lnPFOA and having abnormal values of liver enzymes (vs. not), OR (CI): **ALT: 1.10 (1.07, 1.13)** GGT: 1.01 (0.99, 1.04) Direct bilirubin 0.97 (0.90, 1.05) Analysis of lnALT or lnGGT showed increase from 0.005 to 0.030 µg/mL,

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
				then levelling. However, no association of PFOA with abnormal values of GGT.
Darrow et al. (2016)	Study population: high-exposure community, C8 Health Panel and additional Mid-Ohio Residents Age range: 20-70+ yrs % men: 17.1% Study design: Cohort: longitudinal Study year(s): 2005-06 (blood), 2008-11 (survey) N total: liver biomarkers: 30,723 incl. 1,892 workers; liver disease: 32,254 incl. 3,713 workers	Serum PFOA concentration, measured in 2005-06: Range: 2.6-3,559 ng/mL Median: 16.5 ng/mL Cumulative exposure: For each follow-up year for each subject, we calculated a measure of cumulative serum PFOA exposure by summing all previous yearly estimates of PFOA serum concentrations (referred to as "cumulative PFOA") in units of year × ng/mL.	ALT + GGT 0 Direct bilirubin - Liver disease 0	Association between cumulative lnPFOA (y-ng/mL) and liver enzymes, β (p-value): ALT: **0.012 (0.008, 0.016)** GGT: 0.003 (-0.003, 0.008) Direct bilirubin: **-0.005 (-0.008, -0.002)** Association between measured 2005-06 PFOA (ln, ng/mL) and liver enzymes, β (p-value): ALT: **0.012 (0.009, 0.016)** GGT: 0.003 (-0.002, 0.008) Direct bilirubin: **-0.006 (-0.009, -0.003)** Association between cumulative lnPFOA (y-ng/mL) and any liver disease, HR (CI), 10y lag: 0.98 (0.93, 1.04).
Occupational study population				
Olsen et al. (2000)	Study population: occupational population, 3M Cottage Grove, US Age range: 24-61 yrs % men: 100% Study design: cross-sectional	Serum PFOA, all years: Range: 0-114,100 ng/mL Median: 1,190 ng/mL Mean: 59,930 ng/mL Serum PFOA, mean (range) per year, ng/mL: 1993: 5,000 (0-80,000)	AST 0 ALT + GGT 0 ALP 0 Total bilirubin 0 Direct bilirubin 0	Association between serum PFOA (per ppm , i.e. 1,000 ng/mL) and ALT, β (p-value) per year: 1993: 0.89 (p = 0.76) 1995: 0.81 (p = 0.75) **1997: 2.77 (p = 0.03**)

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
	Study year(s): 1993, 1995, 1997 N total: 111 (1993), 80 (1995), 74 (1997)	1995: 6,800 (0-114,100) 1997: 6,400 (0.1-81,300)		
Olsen and Zobel (2007)	Study population: occupational population, 3M Cottage Grove US, Decatur US & Antwerp. Age range: 21-67 yrs % men: 100% Study design: Cross-sectional Study year: 2000 N total: 506 (all locations), 196 (Antwerp), 122 (Cottage Grove US), 188 (Decatur US)	Serum PFOA, all locations: Range: 7-92,030 ng/mL Median: 1,100 ng/mL Mean: 2,210 ng/mL	Total: AST 0 ALT 0 GGT + ALP + Total bilirubin - Decatur: AST 0 ALT + GGT + ALP + Total bilirubin -	Results of Antwerp and Cottage Grove were not reported here because no significant association was found and limited room is available in this table. Association between serum lnPFOA (ng/mL) change in liver enzymes, β (p-value): All locations: ln AST: -0.005 (p=0.55) ln ALT: 0.025 (p=0.06) ln GGT: 0.033 (p=0.05) ln ALP: 0.009 (p=0.25) **ln total bilirubin: All -0.033 (p=0.001)** Decatur: ln AST: 0.011 (p=0.57) **ln ALT: 0.08 (p=0.02)** **ln GGT: 0.08 (p=0.02)** **ln ALP: 0.08 (p = 0.02)** **ln total bilirubin: -0.054 (p=0.01)**
Sakr et al. (2007a)	Study population: occupational population, Washington Works US (in C8 Health Project area). Age range: not reported.	Serum PFOA: Range: 5-9,550 ng/mL Median: 189 ng/mL Mean: 428 ng/mL	AST 0 ALT 0 GGT + Total bilirubin 0	Association between PFOA (1 ppm=1000 ng/mL) and transformed liver enzymes, β (p-value), excluding n=178 on lipid-lowering medications:

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
	Mean age men/women: 46.5 / 44.4 yrs % men: 76% Study design: Cross-sectional Study year: 2004 N total=1,025			ln AST: 0.023 **IU/L** (p=0.0.079) ln ALT: 0.031 **IU/L** (p=0.071) **ln GGT: 0.05 IU/L (p=0.03)** ln total bilirubin: 0.008 **IU/L** (p=0.637) (Results including those on lipid-lowering medications are similar).
Costa et al. (2009)	Study population: Occupational population, Italy Age, range: 20-63 yrs % men: 100% Study design: Cross-sectional Study year: 2000-2007 N total=56	Serum PFOA, currently exposed: Range: 200-47,040 ng/mL Median: 5,710 ng/mL Mean: 12,930 ng/mL Serum PFOA, formerly exposed: Range: 530-18,660 ng/mL Median: 4,430 ng/mL Mean: 6,810 ng/mL	AST 0 ALT + GGT + ALP + Total bilirubin – Direct Bilirubin 0	Association between PFOA (1 µg/mL = 1000 ng/mL) and liver enzymes, β (CI): AST: 0.038 (-0.003, 0.080) **ALT: 0.116 (0.054, 0.177)** **GGT: 0.177 (0.076, 0.278)** **ALP: 0.057 (0.007, 0.107)** **Total bilirubin: -0.080 (-0.137, -0.024)** Direct bilirubin: -0.034 (-0.09, 0.031) In 34 currently still exposed individuals compared with 34 matched controls or with n=107 controls: no significant associations.
Olsen et al. (2003)	Study population: Occupational population, 3M Antwerp and Decatur Age range: mean 37 (male Antwerp) and 43 (male Decatur) yrs % men: 81% Study design: Cross-sectional and longitudinal	Serum PFOA: Range: 40-12,700 ng/mL Mean: 1,780 ng/mL (n=263 Decatur) Mean: approximately 50% lower among 3M Antwerp (n=255) than Decatur plant workers.	AST 0 ALT 0 GGT 0 ALP 0 Total bilirubin 0	No associations found and quantified results were not reported.

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
	Study year(s): 1994, 1995, 2000 N total cross-sectional = 518 N total longitudinal =174			
Sakr et al. (2007b)	Study population: Occupational population, Washington works DuPont, US Age range: 22-63 yrs % men: 74% Study design: Longitudinal Study year(s): 1979-2004 (blood measures every 1 to 2 yrs) N total = 454 (≥2 measurements)	Serum PFOA, overall: Range: 0-2,266 ng/mL Mean: 1,130 ng/mL	AST + ALT 0 GGT 0 ALP 0 Total bilirubin +	Association between PFOA (per 1,000ng/mL) and liver enzymes, β (CI): **AST: (n=1326) 0.35 units (0.10, 0.60)** ALT: (n=231) 0.54 (-0.46, 1.54) GGT: (n=233) 1.24 (-1.09, 3.57) ALP: (n=1327) -0.21 (-0.60,0.18) **Total bilirubin: (n=1327) -0.008 mg/dL (-0.0139, -0.0021)**
Olsen et al. (2012)	Study population: occupational population, 3M employees and contract workers involved with demolition of PFA, US Age range: mean 40 yrs % men: 95% Study design: Longitudinal Study year(s): 2008-2010 N total=179 workers (165 contract workers, 14 3M employees)	Serum PFOA, overall: Range: 0.1-10,000 ng/mL Serum PFOA, contract workers: Median: 5.2 ng/mL Mean: 28.9 ng/mL Serum PFOA, 3M employees at baseline: Median: 595 ng/mL Mean: 881 ng/mL	AST 0 ALT 0 ALP 0 Total bilirubin 0	Association between serum PFOA (ng/ml) and liver enzymes, β (p-value): AST: 0.00515 (p=0.46) ALT: -0.00568 (p=0.60) ALP: -0.00985 (p=0.29) Total bilirubin: - 0.00011 (p=0.58)
Steenland et al. (2015)	Study population: occupational population,	Serum PFOA, measured in 2005-06 (n=1,881):	Non-hepatitis liver disease (n=35	Association between estimated cumulative PFOA exposure and non-

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
	DuPont West Virginia (Washington works) Age range: mean year of birth 1951 % men: 80% Study design: Longitudinal Study year(s): 2005-06 (PFOA measures), 2008 & 2011 (interviews) N total = 3,713 (cohort of workers)	Range: not reported Median: 113 ng/mL Mean: 325 ng/mL Historical serum levels modelled using JEM, residential exposure model and PK model. Mean cumulative occupational exposure 8.6 ppm-years	cases) 0	hepatitis liver disease, HR (CI) (no lag), Q1=ref: Q2 (3,030-6,160 ng/mL-yrs): 0.55 (0.17 to 1.77) Q3 (6,160-11,420 ng/mL-yrs): 1.27 (0.44 to 3.65) Q4 (>11,420 ng/mL-yrs): 0.88 (0.27 to 2.85) No significant trend. Also no association when 10-year lag was examined.
Gilliand et al, 1996	Study population: occupational study population, employees of PFOA production plant USA Age range: 18-60 yrs % men: 100% Study design: cross-sectional Study year(s): 1985-1989 N total: 115	Total serum fluorine was used as **proxy** of serum PFOA. ('Because the vast majority of total serum fluorine in plant employees is in the form of PFOA, total serum fluorine closely reflects serum PFOA in production workers, and its use is unlikely to introduce substantial error into the study.') Range: 0-26 ppm Mean serum fluoride: 3.3 ppm	Multivariate: GGT 0 GOT - GPT -	After adjusting for age, cigarette use, alcohol use and BMI, total serum fluorine is associated with changes in GOT, GPT & GGT by interactions with determinants of hepatitic enzymes. Association between serum fluorine (proxy for PFOA) and liver enzymes: (β), p-value: *GGT* -Total Fluorine (-1.93), p=0.36 *GOT* -**Total Fluorine (-3.23), p=.02** *GPT* **-Total Fluorine (-15.80), p=.0008**

[a] 0, no association; +, positive association; -, negative association

β=regression coefficient, OR=Odds Ratio, HR= Hazard Ratio, CI= 95% Confidence Interval, lnPFOA = natural log transformed PFOA, Q=quartile, IQR=Interquartile range, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transpeptidase, ALP= alkaline phosphatase.

Table 4. Summary of associations in studies on kidney and testicular cancer

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
High-exposure community				
Vieira et al. (2013)	Study population: high-exposure community population, C8 community (residents living near Washington Works plant), US Age range: Median age cases 67 yrs % men: 51% (among cases) Study design: longitudinal, cohort incidence study Study year(s): 1951-2008 N total: 6 public water districts, 13 counties surrounding DuPont	Serum PFOA, estimated annual concentration: Very high: 110-655 ng/mL High: 30.8-109 ng/mL Medium: 12.9-30.7 ng/mL Low: 3.7-12.8 ng/mL Reference: unexposed Serum PFOA, estimated cumulative range: Very high = 600–4,679 ng/mL-years High = 198–599 ng/mL-years Medium = 89–197 ng/mL-years Low = 3.9–88 ng/mL-years	Kidney cancer + (n=59) Testicular cancer 0 (n=11)	Association between annual serum PFOA and kidney cancer, reference=unexposed, assuming 10-year residency, OR (CI): **Very high: 2.0 (1.0-3.9) (n=9 cases)** **High: 2.0 (1.3-3.2) (n=22)** Medium: 1.2 (0.7-2.0) (n=17) Low: 0.8 (0.4-1.5) (n=11) Association between annual serum PFOA and testicular cancer, reference=unexposed, assuming 10-year residency, OR (CI): **Very high: 2.8 (0.8-9.2) (n=6 cases)** **High: 0.3 (0.0-2.7)(n=1)** Medium: 0.6 (0.2-2.2) (n=3) Low: 0.2 (0.0-1.6) (n=1) Results for cumulative PFOA serum concentrations were reported to be similar.
High-exposure community & occupational study population				
Barry et al. (2013)	Study population: high-exposure community and occupational population, C8 Health Project (DuPont) & Washington Works plant (DuPont), US Age range: >=20 yrs % men: 46% Study design: longitudinal, cohort incidence study Study year(s): 1952-2011 N: 32,254	Serum PFOA, estimated annual concentration, community: Range: 2.8-9,217 ng/mL Median: 19.4 ng/mL Serum PFOA, estimated annual concentration, workers: Range: 5.2-3,683 ng/mL Median: 174.4 ng/mL	Kidney cancer 0 (n=105) Testicular cancer + (n=17)	Association between log estimated life-time cumulative PFOA serum concentration and kidney cancer, OR (CI): No lag: 1.10 (0.98-1.24) 10-y lag: 1.09 (0.97-1.21) Association between log estimated life-time cumulative PFOA serum concentration and testicular cancer, OR (CI): **No lag: 1.34 (1,00-1,79)** 10-y lag: 1.28 (0.95-1.73) (PFOA quartiles did not show significant results)

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
Occupational study population				
Steenland and Woskie (2012)	Study population: Occupational population, Washington Works plant (DuPont), US Age range: mean year of birth 1984 % men: 81% Study design: Cohort mortality study Study year(s): 1984-2008 N exposed: 5,791 (reference: DuPont workers unexposed to PFOA & US population)	Serum PFOA, annual estimations: Mean: 350 ng/mL Median: 230 ng/mL Serum PFOA, estimated and cumulative[b]: Mean: 7.8 ppm-years Median 4.3 ppm-years	Kidney cancer + (total n=12) Testicular cancer (insufficient cases)	Association between estimated cumulative PFOA (quartiles of ppm-years) and kidney cancer, 20-year lag, Other DuPont workers = referent group: Q1 (0-515 ppm-years), (n=3 cases), SMR (CI): 1.34 (0.28-3.91) Q2 (515-1057 ppm-years), (n=1 case), SMR (CI): 0.46 (0.01-2.55) Q3 (1057-1819 ppm-years), (n=0 cases), SMR (CI): 0.00 (0.00-2.03) **Q4 (≥1819 ppm-years), (n=7 cases), SMR (CI): 3.67 (1.48-7.57)** Similar results were reported for analyses including no lag and analyses including a 10-year lag.
Lundin et al. (2009)	Study population: occupational population, Minnesota PFOA production plant, US Age range: mean age '02: 59.6 yrs % men: 80% Study design: longitudinal cohort mortality study Study year(s): 1947-2002 N total= 3,993 (n=1,792 non-exposed)	Serum PFOA (based on JEM), definite exposure: Median levels ranged from 2,600-5,200 ng/mL Probable exposure: Median levels ranged from 300-1,500 ng/mL. Nonexposed areas: no data available Full range is not reported.	Cancer in bladder and other urinary organs combined 0 Testicular cancer: no cases	Association between PFOA concentrations, general population = referent, SMR (CI): Ever definite: 0 (n=0 cases) Ever probable/never definite: 1.2 (0.3-3.5) (n=3 cases) Never: 1.4 (0.4-3.7) (n=4 cases)

[a] 0, no association; +, positive association; -, negative association

[b] ppm-years: e.g. 100 ppm (i.e. 100,000 ng/mL) over 5 years would be 500 ppm-years (Steenland and Woskie, 2012)

OR=Odds Ratio, SMR=Standardized Mortality Ratio, CI= 95% Confidence Interval, Q=quartile, ppm=parts per million (1ppm=1,000 ng/mL).

Table 5. Summary of associations in studies on pregnancy-induced hypertension and preeclampsia

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
General population				
Starling et al. (2014b)	Study population: general population (pregnant women), Norway Age range: 19-41 yrs % men: 0% Study design: cross-sectional Study year(s): 2003-04 N total: 891 women	Plasma PFOA: IQR: 1.66-3.03 ng/mL Median: 2.25 ng/mL 5th percentile: 1.05 ng/mL 95th percentile: 4.43 ng/mL	Biomarkers of preeclampsia 0	They observed no association between plasma PFOA and elevated triglycerides, total cholesterol, LDL or lower HDL cholesterol. Because those outcomes increase the risk of preeclampsia, they discussed that also no evidence of an association with preeclampsia was observed.
Starling et al. (2014a)	Study population: general population (pregnant women), Norway Age range: 16-44 yrs (at delivery) %men: 0% Study design: Study year(s): 2003-07 N total: 976 (n=466 cases)	Plasma PFOA: IQR: 2.14-3.57 ng/mL Median: 2.78 ng/mL 5th percentile: 1.43 ng/mL 95th percentile: 5.15 ng/mL	Preeclampsia 0	Association between quartiles of PFOA and preeclampsia, HR (CI), Q1=ref: Q2: 1.03 (0.70-1.50) Q3: 0.92 (0.63-1.35) Q4: 1.01 (0.69-1.48) Association between ln PFOA and preeclampsia, HR (CI): 0.89 (0.65-1.22)
High-exposure community				
Darrow et al. (2013)	Study population: High exposure C8 Health project community, US Age range: 19+ yrs at pregnancy (68% was 19-29 yrs) % men: 0% Study design: Longitudinal Study year(s): 2005-10 N total=1,600 (106 cases)	Serum PFOA: Range: 0.6-459.5 ng/mL Median: 12.9 ng/mL Mean: 31.1 ng/mL 95th percentile: 114.1 ng/mL	Pregnancy-induced hypertension +	Association between lnPFOA and pregnancy-induced hypertension, OR (CI): **1.27 (1.05, 1.55)** Association between IQR PFOA increase and pregnancy-induced hypertension, OR (CI): 1.06 (0.99-1.14) Association between blood PFOA by quintile (ref=0-6.9 ng/mL) and pregnancy-induced hypertension, OR (CI):

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
				6.9-11.1: 2.39 (1.05-5.46) **11.1-18.9: 3.43 (1.50-7.82)** **18.9-37.2: 3.12 (1.35-7.18)** **≥37.2 : 3.16 (1.35-7.38)**
Stein et al. (2009)	Study population: High-exposure C8 Health project community, US Age: 82% pregnant at 20-34 yrs % men: 0% Study design: Longitudinal Study year(s): births in 2000-05 and blood measures in 2005-06 N total=1,845 births in 2000-05	Serum PFOA, 2005-06 (pregnancies within the 5 years preceding exposure measurement): Range:0.25-894.4 ng/mL Median (IQR): 21.2 (10.3-49.8) ng/mL Mean: 48.8 ng/mL >90th: 120.6-894.4 ng/mL	Preeclampsia 0	Association between >median compared with ≤ median serum PFOA concentration and preeclampsia, OR (CI): 1.3 (0.9-1.9) No dose-response relationship: Association between serum PFOA percentiles and preeclampsia, OR (CI) (<50th = referent): 50-75th: 1.5 (1.0-2.3) 75-90th: 1.2 (0.7-2.1) > 90th: 0.9 (0.5-1.8)
Savitz et al. (2012a)	Study population: High-exposure C8 Health project community, US Age range: pregnant at 14-45 yrs % men: 0% Study design: cross-sectional Study year(s): 1990-2006 N total = 11,737 pregnancies occurring between 1990-2006 (n=730 preeclampsia)	Serum PFOA, estimated (based on serum collected in 2005, residential history, and other data) at the time of pregnancy for pregnancies occurring between: Range: 3.9 - 934.3 ng/mL Median (IQR), ng/mL: 1990–94: 6.0 (4.5, 27.6) 1995–99: 10.7 (5.1, 50.4) 2000–2005: 15.9 (5.9, 56.2)	Preeclampsia +	Association between increase in lnPFOA per IQR (2.19 ng/mL) and preeclampsia, OR (CI) = 1.13 (1.00–1.28) Association between increase in 100 ng/mL PFOA and preeclampsia, OR (CI): **1.08 (1.01–1.15)** Association between percentiles and preeclampsia, < 40th (ref): **40-60th (6.1 – 10.2 ng/mL): 1.2 (1.0, 1.5)** 60-80th (10.2 – 21.0): 1.1 (0.9, 1.4) **≥ 80th (21.0 – 717.6): 1.2 (1.0, 1.6)**

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
Savitz et al. (2012b)	Study population: High-exposure community Mid-Ohio birth records (study 1) & C8 Health project community (study 2), US. Age range: not reported % men: 0% Study design: Longitudinal Study year(s): Pregnancies in 1990-2004. Serum PFOA measured in 2005 N: 8,253 (Study 1), 4,547 (Study 2)	Serum PFOA, estimated for the early pregnancy period, study 1: IQR: 4.9-17.2 ng/mL Median: 7.7 ng/mL Serum PFOA, estimated for the early pregnancy period, study 2: IQR: 5.6-61.2 ng/mL Median: 13.4 ng/mL	Pregnancy-induced hypertension +	**Study 1:** Association between IQR lnPFOA (1.50 ng/ml) increase and pregnancy-induced hypertension, OR (CI): 1.02 (0.86-1.12) Association between 100 ng/mL PFOA increase and pregnancy-induced hypertension, OR (CI): 1.06 (0.86-1.31) Association between percentiles and pregnancy-induced hypertension, OR (CI) (ref <40th): 40-60th 1.0 (0.7-1.6) 60-80th 1.0 (0.6-1.5) ≥ 80th 1.0 (0.7-1.5) **Study 2** (Bayesian calibration of exposure): Association between increase per IQR lnPFOA (2.39 ng/mL) and pregnancy-induced hypertension, OR (CI): 1.13 (0.92-1.37) Association between increase in 100 ng/mL PFOA and preeclampsia, OR (CI): 0.97 (0.85-1.11) Association between percentiles and pregnancy-induced hypertension, OR (CI) (ref <40th=3.9 to <8.9 ng/mL): 40-60th=1.0 (0.7-1.4) **60-80th(19.6-53.1 ng/mL)=1.5 (1.1, 2.1)** ≥ 80th=1.2 (0.8, 1.7)

[a] 0, no association; +, positive association; -, negative association.

OR=Odds Ratio, HR=Hazard Ratio, CI= 95% Confidence Interval, IQR=Interquartile range, lnPFOA = natural log transformed PFOA.

Table 6. Summary of associations in studies on birth weight

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
General population				
Fei et al. (2007)	Study population: general population Danish National Birth cohort, Denmark Age range: 39% had maternal age at delivery of 25-29 yrs % men: 0% Study design: Longitudinal Study year(s): 1996-2002 N total=1,399	Plasma PFOA concentrations, maternal: Range: less than lower limit of quantitation (LLOQ, i.e. 1ng/mL) - 41.5 ng/mL Mean: 5.6 ng/mL	Change in birth weight - Low birth weight 0 Small for gestational weight 0	**Association between maternal plasma PFOA and change in birth weight (g), β (CI): -10.63 (-20.79, -0.47).** Association of blood PFOA with low birth weight (< 2500 g) and with small for gestational weight was also examined, but no association was found.
Monroy et al. (2008)	Study population: general population, Family study, Canada Age, mean at pregnancy: 32.7 (5.2) yrs % men: 0 Study design: Longitudinal Study year(s): 2004-05 N total=101	Serum PFOA, pregnant women: Range: 1.46-3.14 ng/mL Median: 2.13 ng/mL Serum PFOA, maternal serum at delivery: Range: 1.33-2.64 ng/mL Median: 1.81 ng/mL Serum PFOA, umbilical cord: Range: 1.09-2.37 ng/mL Median: 1.58 ng/mL	Change in birth weight 0	Association of blood PFOA with change in birth weight (g), β (p-value): 0.000171 (p = 0.65)
Hamm et al. (2010)	Study population: general population, Canada Age, range: 18+ yrs % men: 0 Study design: Longitudinal	Serum PFOA, pregnant women: Range: LOD-18 ng/mL Median: 1.5 ng/mL Mean: 2.1 ng/mL	Change in birth weight 0 Small for gestational age 0	Association between blood lnPFOA and change in birth weight (g), β (CI): -37.4 (-86.0, 11.2) g Association between blood PFOA (ref:

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
	Study year(s): 2005-07 N total = 252			<1.1 ng/mL) and being small for gestational age, RR (CI): 1.1-2.1 ng/mL: 0.55 (0.16-1.83) >2.1-18 ng/mL: 0.99 (0.25-3.92)
Whitworth et al. (2012)	Study population: general population, Norwegian Mother and Child Cohort Study, Norway Age, mean at enrolment: 31 yrs % men: 0 Study design: Longitudinal Study year(s): 2003-04 N total = 849	Serum PFOA, pregnant women: IQR: 1.7-3.0 ng/mL Median: 2.2 ng/mL	Change in birth weight 0	Association between blood PFOA (ref: <1.65) and change in birth weight z scores, β (CI): Q 2 (1.65-2.24): -0.06 (-0.28, 0.16) Q 3 (2.25-3.03): -0.08 (-0.32, 0.16) Q 4 (>=3.04): -0.21 (-0.45, 0.04) Association between blood PFOA and change in birth weight z scores, β (CI): -0.03 (-0.10, 0.04)
Maisonet et al. (2012)	Study population: general population, Avon Longitudinal Study of Parents and Children (ALSPAC), United Kingdom Age: 80% was 25+ yrs at delivery % men: 0 Study design: longitudinal Study year(s): 1991-92 N total=395	Serum PFOA, pregnant women: Range: 1-16.4 ng/mL Median: 3.7 ng/mL	Change in birth weight -	Association between blood PFOA (ref<3.1 ng/mL) and change in birth weight (g), β (CI): 3.1-4.4 ng/mL: -56.81 (-153.05, 39.43) **>4.4 ng/mL: -133.45 (-237.37, -29.54)**
Washino et al. (2009)	Study population: general population, Japan Age, mean (SD): 30.5 (4.8) yrs % men: 0 Study design: Longitudinal Study year(s): 2002-05	Serum PFOA, pregnant women: Range: non detectable - 5.3 ng/mL Median: 1.3 ng/mL Mean: 1.4 ng/mL	Change in birth weight 0	Association between log10 blood PFOA and change in birth weight (g), β (CI): -75 (-191, 42)

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
	N total=428			
Apelberg et al. (2007)	Study population: general population, US (Baltimore) Age: 84% were 18-35 yrs during pregnancy % men: 0 Study design: Longitudinal Study year(s): 2004-05 N total=293	Serum PFOA cord blood: Median: 1.6 ng/mL Range: 0.3-7.1 ng/mL	Change in birth weight 0	Association between lnPFOA and change in birth weight (g), β (CI): -104 (-213, 5)
Chen et al. (2012)	Study population: general population, Taiwan Birth Panel Study, Taiwan Age: 77% <35 yrs (no range) % men: 0 Study design: Longitudinal Study year(s): 2004-05 N total=429	Plasma PFOA, cord blood: Range: not reported Geometric mean (SD): 1.84 (2.23) ng/mL	Change in birth weight 0	Association between cord plasma lnPFOA and change in birth weight (g), β (CI): -19 (-63, 25)
Lee et al. (2013)	Study population: general population, South Korea Age, median: 30 yrs % men: 0 Study design: Longitudinal Study year(s): 2011 N total= 59	Serum PFOA, maternal blood at delivery: Range: 1.2-5.72 ng/mL Median: 2.62 ng/mL Mean: 2.73 ng/mL Serum PFOA, umbilical cord serum blood at delivery: Range: 0.75-5.44 ng/mL Median: 2.08 ng/mL Mean: 2.09 ng/mL	Change in birth weight 0	Association between >=median maternal serum PFOA (ref: <median) and birth weight, OR (CI): >= median birth weight (ref=< median): 0.54 (0.17-3.03) Association between >=median umbilical cord serum PFOA (ref: <median) and birth weight, OR (CI): >= median birth weight (ref=< median): 0.51 (0.17-1.59)
Ashley-Martin et al. (2016)	Study population: general population (pregnant woman, Maternal-Infant Research on	Serum PFOA, first trimester maternal blood: Range: LOD-16 ng/mL	Gestational weight gain + (more PFOA is associated with	Association between first trimester transformed PFOA (ng/mL) and total GWG, stratified by pre-pregnancy BMI, β

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
	Environmental Chemicals), Canada % men: 0% (their infants: 52% boys) Age range: maternal 18-49 yrs Study design: cross-sectional Study year(s): 2008-11 N total: 1,723 participants with first trimester maternal exposure data and 1,301 participants with cord blood exposure data.	Median: 1.70 ng/mL Serum PFOA, cord blood: Range: LOD-5.6 ng/mL Median: 0.39 ng/mL IQR: 0.22-0.61 ng/mL	higher gestational weight gain)	(CI): Underweight / normal: 0.38 (-0.03, 0.79) Overweight: 0.58 (-0.26, 1.42) Obese: 0.38 (-0.81, 1.56) **Association between GWG (per 1kg increase) and >median PFOA (i.e. >0.39 ng/mL) cord blood, OR (CI): 1.04 (1.02-1.06)** **Association between GWG (per IQR, i.e. 25th to 75th) and >median PFOA (i.e. >0.39 ng/mL) cord blood, OR (CI): 1.33 (1.13, 1.56)**
High-exposure community				
(Stein et al., 2009)	Study population: High-exposure C8 Health project community, US Age range: 82% pregnant at 20-34 yrs % men: 0% Study design: Longitudinal Study year(s): births in 2000-05 and blood measures in 2005-06 N total=1,845 births in 2000-05	Serum PFOA, 2005-06 (not estimated at the time of pregnancy): Range:0.25-894.4 ng/mL Median (IQR): 21.2 (10.3-49.8) ng/mL Mean (SD): 48.8 (77.8) ng/mL >90th PFOA: 120.6-894.4 ng/mL	Low birth weight (i.e. <2.5 kg) –	Association between ≥21.3 ng/mL PFOA (vs. 0.25-21.3 ng/mL) and low birth weight, OR (CI) = 0.7 (0.5-1.2) Association between serum PFOA and low birth weight, OR (CI) (<50th = referent): 50-75th: 1.0 (0.6-1.7) **75-90th (50-120.6 ng/mL) : 0.3 (0.1-0.9)** > 90th: 0.8 (0.3-1.9) No dose-response gradient.
Savitz et al. (2012a)	Study population: High-exposure C8 Health project	Serum PFOA, estimated (based on serum	Term low birth weight (i.e. <2.5	Association between increase in lnPFOA per IQR (2.19 ng/mL) and term low birth

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
	community, US Age range: 14-45 yrs (at time of pregnancy) % men: 0% Study design: Study year(s): 1990-2006 N total = 11,737 pregnancies occurring between 1990-2006 (n=730 preeclampsia)	collected in 2005, residential history, and other data) at the time of pregnancy for pregnancies occurring between: Range: 3.9 - 934.3 ng/mL Median (IQR), ng/mL: 1990–94: 6.0 (4.5, 27.6) 1995–99: 10.7 (5.1, 50.4) 2000–2005: 15.9 (5.9, 56.2)	kg) 0	weight, OR (CI) = 0.89 (0.66-1.20) Association between increase in 100 ng/mL PFOA and term low birth weight, OR (CI) = 0.96 (0.79-1.16) Association between percentiles and term low birth weight, < 40th (ref): 40-60th: 1.2 (0.8-1.9) 60-80th: 1.2 (0.7-1.9) ≥ 80th: 0.8 (0.4-1.4)
Savitz et al. (2012b)	Study population: High-exposure community Mid-Ohio birth records (study 1) & C8 Health Project Community (study 2), US. Age range: not reported % men: 0% Study design: Longitudinal Study year(s): Pregnancies in 1990-2004. Serum PFOA measured in 2005 N total: 8,253 (Study1), 4,547 (Study 2)	Serum PFOA, estimated for the early pregnancy period, study 1: IQR: 4.9-17.2 ng/mL Median: 7.7 ng/mL Serum PFOA, estimated for the early pregnancy period, study 2: IQR: 5.6-61.2 ng/mL Median: 13.4 ng/mL	Term low birth weight 0 Term small-for-gestation-al-age 0 Continu-ous measure of birth weight (term birth) -	**Study 1:** Association between increase in lnPFOA per IQR (1.50ng/mL) and term low birth weight, OR (CI): 1.02 (0.92-1.13). Association between increase in lnPFOA per IQR (1.50ng/mL) and small for gestational age, OR (CI): 0.91 (0.78-1.06) Association between increase in lnPFOA per IQR (1.50ng/mL) and change in term birth weight, difference (CI): -10.72 (-32.26, 10.82). Association between increase in 100 ng/mL or percentiles and low birth weight, term small for gestational age and change in birth weight were also examined but no significant associations were observed.

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
				Study 2: With Bayesian calibration of exposure: Association between increase in lnPFOA per IQR (2.39ng/mL) and term low birth weight, OR (CI): 1.16 (0.86-1.58) Association between increase in lnPFOA per IQR (2.39ng/mL) and term small for gestational age, OR (CI): 1.19 (1.00-1.43) Association between increase in lnPFOA per IQR (2.39ng/mL) and change in term birth weight, difference (CI): -21.51 (-43.62, 0.61) **Association between increase in 100 ng/mL PFOA and change in term birth weight, difference (CI): -18.55 (-31.31, -5.8).** Association between increase in 100 ng/mL PFOA and low birth weight and term small for gestational age were also examined but no significant associations were observed. Association between percentiles PFOA concentration and low birth weight, term small for gestational age and change in term birth weight were also examined but no significant associations were observed.
Darrow et al. (2013)	Study population: High-exposure C8 Health Project Community, US Age range: 19+ yrs at	Serum PFOA: Range: 0.6-459.5 ng/mL Median 14.3 ng/mL Mean 31.0 ng/mL	Low birth weight 0 Birth weight 0	Association between increase in lnPFOA and change (g) in birth weight, β (CI): -8 (-28, 12) Association between IQR increase in

Reference	Study characteristics	Blood PFOA concentrations	Association with PFOA[a]	Effect size
	pregnancy (68% was 19-29 yrs) % men: 0% Study design: Longitudinal Study year(s): Pregnancies in 2005-10 N total=1,470	95th percentile: 114.1 ng/mL		PFOA and change (g) in birth weight, β (CI): -5 (-13, 2) Association between blood PFOA by quintile (ref=0-6.9 mg/mL) and change (g) in birth weight, β (CI): 6.9-11.1 ng/mL: 35 (-33,105) 11.1-18.9 ng/mL: -9 (-79, 61) 18.9-37.2 ng/mL: 4 (-65, 72) ≥37.2 ng/mL: 0 (-68, 69) Low birth weight (< 2500 g) was also examined and, similar to change in birth weight, no significant associations were found.
Occupational study population				
Wu et al. (2012)	Study population: occupational study population (pregnant woman, working at Guiyu (an electronic waste recycling area)). % men: 0% Age mean: 26.6 yrs (controls: 26.0 yrs) Study design: cross-sectional Study year(s): 2007 N total: 108 (workers), 59 (controls)	Serum PFOA, maternal, workers: Range: 5.5-58.5 ng/mL Median: 16.95 ng/mL Serum PFOA, maternal, controls: Range: 4.4-30.0 ng/mL Median: 8.7 ng/mL	Birth weight -	**Association between maternal serum PFOA (per lg unit) and birth weight (grams), β (including both workers and controls): -267.3g (CI=-573.27 to -37.18)**

[a] 0, no association; +, positive association; -, negative association.

β=regression coefficient, OR=Odds Ratio, CI= 95% Confidence Interval, lnPFOA = natural log transformed PFOA, Q=quartile, IQR=Interquartile range.

Table 7. Summary of associations in studies on uric acid

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
General population				
Geiger et al. (2013)	Study population: general population, NHANES, US Age range: 12-18 yrs % men: 52% Study design: cross-sectional Study year(s): 1999-00 and 2003-08 N total=1,772	Serum PFOA: Mean: 4.3 ng/mL Quartile 1 (Q1): <2.9 ng/mL Q2: 2.9-4.0 ng/mL Q3: 4.1-5.4 ng/mL Q4: >5.4 ng/mL (highest value of the range not reported)	Uric acid + Hyperuricemia + 	Association between PFOA quartiles and mean change in serum uric acid (mg/dL), (Q1=ref), β (CI): Q2: 0.02 (-0.10-0.14) Q3: 0.03 (-0.11-0.17) **Q4: 0.30 (0.17-0.43)** Association between serum lnPFOA and serum uric acid (mg/dL), β (CI): **0.20 (0.11-0.29)** Association between PFOA quartiles and hyperuricemia, OR (CI), (Q1=ref): Q2: 0.94 (0.58-1.53) Q3: 1.01 (0.62-1.63) **Q4: 1.62 (1.10–2.37)** Association between serum lnPFOA and hyperuricemia, OR (CI): **1.59 (1.19-2.13)**
Gleason et al, 2015	Study population: general population, NHANES, US population Age range: ≥12 yrs % men: not reported Study design: cross-sectional Study year(s): 2007-2010 N total: 4,333	Serum PFOA: IQR: 2.5-5.2 ng/mL Median: 3.7 ng/mL Geometric Mean: 3.5 ng/mL	Uric Acid +	Association between transformed serum PFOA and uric acid, β (CI): **0.303 (0.238-0.367)** Association between serum PFOA quartiles and high uric acid (i.e. ≥75th percentile), OR (CI), ref=Q1: **Q2: 1.46 (1.16-1.85)** **Q3: 1.74 (1.35-2.25)** **Q4: 1.88 (1.37-2.58)**
Lin et al. (2013a)	Study population: general population, Young Taiwanese Cohort Study Age range: 12-30 yrs % men: 39% Study design: cross-sectional Study year(s): 2006-08	Serum PFOA: Range: 0.75-52.2 ng/mL Median: 3.49 ng/mL Geometric mean: 2.61 ng/mL (age and sex adjusted)	Uric Acid 0	Association between serum PFOA (ng/mL) and uric acid (mg/dL), mean (SE): PFOA ≤3.49 (≤50th): 6.08 (0.10) PFOA ≤6.54 (50th-75th): 6.08 (0.11) PFOA ≤9.62 (50th-90th): 6.11 (0.14) PFOA >9.62 (>90th): 6.13 (0.17) P for trend = 0.983

	N total: 644			
Shankar et al. (2011)	Study population: general population, NHANES, US Age range: >=20 yrs % men: 48% Study design: cross-sectional Study year(s): 1999–00, 2003–04, 2005–06 N total=3,883	Plasma PFOA: IQR: 2.4-5.1 ng/mL Median: 3.4 ng/mL (highest value of the range not reported)	Uric acid + Hyperuricemia + 	Association between plasma PFOA quartiles and mean change uric acid (mg/dL), β (CI), (Q1=ref): **Q2: 0.14 (0.04–0.25)** **Q3: 0.37 (0.25–0.49)** **Q4: 0.44 (0.32–0.56)** Association between plasma lnPFOA and mean change uric acid (mg/dL), β (CI): **0.22 (0.15–0.30)** Association between plasma PFOA quartiles and hyperuricemia, OR (CI), Q1=ref: Q2: 1.14 (0.78–1.67) **Q3: 1.90 (1.35–2.69)** **Q4: 1.97 (1.44–2.70)** Association between plasma lnPFOA and hyperuricemia, OR (CI): **1.43 (1.16–1.76)**
Qin et al. (2016)	Study population: general population, Taiwan Age range: 12-15 yrs % men: 45% boys Study design: cross-sectional Study year(s): 2009-2010 N total: 225	Serum PFOA: IQR: 0.4-1.3 ng/mL Median: 0.5 ng/mL	Uric Acid +	Association between transformed serum PFOA and serum uric acid (mg/dL) (adjusted for age, BMI, parental education level, exercise, environmental tobacco smoke exposure, serum creatine), β (CI): Total: 0.15 (0.01-0.28) Boys: 0.24 (0.06-0.42) Girls: 0.02 (-0.19-0.22)
High-exposure community				
Steenland et al. (2010b)	Study population: high-exposure community, C8 Health Study, West Virginia, US Age range: 20-80 yrs % men: 48% Study design: cross-sectional Study year(s): 2005-06 N total=53,458	Serum PFOA, measured in 2005-06: Range: 0-≥188.7 ng/mL Mean: 86.4 ng/mL Median: 27.9 ng/mL	Uric acid + Hyperuricemia + 	Association between serum PFOA concentration (ng/mL) and uric acid (mg/dL), estimate (SE): 0-7.8: 0 7.9-11.4: 0.09 (0.02) 11.5-15.4: 0.16 (0.02) 15.5-20.6: 0.18 (0.02) 20.6-27.8: 0.21 (0.02) 27.9-38.9: 0.21 (0.02) 39.0-56.9: 0.22 (0.02) 57.0-88.6: 0.22 (0.02)

				88.7-188.6: 0.25 (0.02) ≥188.7: 0.28 (0.02) Association between PFOA quintiles (ref=quintile 1; 0-11.4) and hyperuricemia: **Quintile 2 (11.5-20.6) : 1.33 (1.24-1.43)** **Quintile 3 (20.7-38.9): 1.35 (1.26-1.45)** **Quintile 4 (39.1-88.6): 1.47 (1.37-1.58)** **Quintile 5 (>=88.7 ng/mL): 1.47 (1.37-1.58)**
Occupational study population				
Sakr et al. (2007a)	Study population: occupational population, Washington Works US. Age, mean: 46.5 (men), 44.4 (women) yrs % men: 76% Study design: cross-sectional Study year(s): 2004 N total=1,025	Serum PFOA: Range 5-9,550 ng/mL Median: 189 ng/mL Mean: 428 ng/mL	Uric acid +	**Quantified results not reported.**
Costa et al. (2009)	Study population: occupational population, Italy Age, range: 20-63 yrs % men: 100% Study design: cross-sectional Study year(s): 2000-2007 N total=56	Serum PFOA, currently exposed: Range: 200-47,040 ng/mL Median: 5,710 ng/mL Mean: 12,930 ng/mL Serum PFOA, formerly exposed: Range: 530-18,660 ng/mL Median: 4,430 ng/mL Mean: 6,810 ng/mL	Uric acid +	Association between change per 1 µg/mL (=1,000 ng/mL) PFOA and uric acid (mg/mL), β (CI): **0.026 (0.001-0.053)**

[a] 0, no association; +, positive association; -, negative association

β=regression coefficient, OR=Odds Ratio, CI= 95% Confidence Interval, lnPFOA = natural log transformed PFOA, Q=quartile, IQR=Interquartile range.

Table 8. Summary of associations in studies on vaccination response

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
General populations				
Grandjean et al. (2012)	Study population: general population, Farou Islands Age range: 3rd trimester (PFOA measurement), 5 years (pre-booster vaccination and 4 weeks after), 7 years. % men: 53% boys Study design: longitudinal Study year(s): 1997-2000, follow-up in 2008 N total=587	Serum PFOA, maternal: IQR: 2.56-4.01 ng/mL Geometric mean: 3.2 ng/mL Serum PFOA, at 5 yrs: IQR: 3.33-4.96 ng/mL Geometric mean: 4.06 ng/mL	Immune response to tetanus vaccine: Maternal PFOA: Pre-booster 0 Post-booster 0 Year 7 0 Child PFOA Pre-booster 0 Post-booster 0 Year 7 – Immune response to diphtheria vaccine: Maternal PFOA: Pre-booster, 0 Post-booster 0 Year 7 - Child PFOA Pre-booster 0 Post-booster 0 Year 7 –	Association between Log *maternal* PFOA and change in log antibody tetanus (%), β (CI): NS Association between Log child's PFOA at 5 yrs and change in log antibody tetanus (%), β (CI): Pre-booster: -13.3 (-31.6, 9.9) Post-booster: -9.7 (-30.7, 17.7) **Year 7: -35.8 (-51.9, -14.2)** **Year 7 (adjusted for age 5): -28.2 (-42.7 to -10.1)** Association between Log *maternal* PFOA and change in log antibody diphtheria (%), β (CI): Pre-booster: -16.2 (-34.2, 6.7) Post-booster: -6.2 (-22.4, 13.3) **Year 7: -22.8 (-39.4, -1.7)** Year7 (adjusted for age 5): -16.8 (-32.9, 3.3) Association between Log child's PFOA at 5 yrs and change in log antibody diphtheria (%), β (CI): Pre-booster: -6.8 (-28.3, 21.0) Post-booster: -6.1 (-23.6, 15.5) **Year 7: -25.2 (-42.9, -2.0)** **Year 7 (adjusted for age 5): -23.4 (-39.3, -3.4)**
Mogensen et al. (2015)	Study population: general population, Faroese birth cohort Age range: 7 years % men: 52% Study design: longitudinal Study year(s): 1997-2000	Serum PFOA, at 5 yrs: IQR:3.3-5.0 ng/mL Median:4.1 ng/mL Serum PFOA, at 7 years: IQR: 3.5-5.7 ng/mL Median:4.4 ng/mL	Immune response to vaccines: Anti-diphtheria: - Anti-tetanus: -	Association between Log child's PFOA at 5 and 7 yrs and change in log antibody diphtheria (%), β (CI): **-34.7 (-52.5, -10.2)** Association between Log child's PFOA at 5 and 7 yrs and change in log antibody diphtheria (%), β (CI): **-38.2 (-56.1, -13.0)**

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
	N total = 464			
Granum et al. (2013)	Study population: general population, Norwegian mother and child cohort study, Norway Age range: birth and 3 years % men: 55% boys Study design: longitudinal Study year(s): Pregnancies 1999-08 N total=56	Plasma PFOA, maternal at delivery: Range: 0.2-2.7 ng/mL Median: 1.1 ng/mL Mean: 1.1 ng/mL	Immune response to vaccines: Rubella - Measles 0 Tetanus 0 Hib 0	**Association between pre-natal exposure to PFOA and Rubella, β (CI): -0.40 (-0.64, -0.17)** Association between pre-natal exposure to PFOA and Measles, β (CI): -0.13 (-0.35, 0.09) Association between pre-natal exposure to PFOA and Tetanus, β (CI): 0.01 (-0.01, 0.10) Association between pre-natal exposure to PFOA and Hib, β (CI): -0.05 (-3.85, 3.74)
Kielsen et al, 2015	Study population: general population, healthy volunteers among staff Copenhagen University Hospital Age range: 23-66 years % men: 50% Study design: vaccination intervention study Study year(s): 2012 N total: 12	Serum PFOA: IQR: 1.30-2.79 ng/mL Median: 1.69 ng/mL	Antibodies Tetanus: 0 Antibodies Diphteria: 0	Association between transformed PFOA and %change in antibody concentration between day 4 and 10 post-vaccination, β (CI): Diphteria:-8.2% (6.4 to -20.9) Tetanus: 0.2% (12.1 to -10.4)
Stein et al, 2016	Study population: general population, US population in NHANES 1999-2004 Age range: 12-19 years % men: 53% Study design: cross-sectional Study year(s): 1999-2004 N total: 1,191	Serum PFOA Geometric mean: 4.13 ng/mL CI: 3.76-4.53 ng/mL Median and range not reported.	Endpoints of Antibody Study: (seropositive subset) Measles: 0 Rubella: - Mumps: -	% change (95% CI) in antibody titer associated with a doubling in blood PFOA: *TOTAL POPULATION:* Measles:-0.1% (-13.8 to 15.6) Mumps: -6.0% (-12.4 to 0.9) Rubella: -2.5% (-9.1 to 5.3) *ONLY SEROPOSITIVE (*'All models were run twice: once for the full population and once restricted to the seropositive population with the

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
				assumption that seropositive children have been exposed to the vaccine strain of these viruses' *Stein et al 2016):* Measles:-3.4% (-16.7 to 11.9) **Mumps: -6.6% (-11.7 to -1.5)** **Rubella: -8.9% (-14.6 to -2.9)**
High-exposure community				
Looker et al. (2014)	Study population: High-exposure community population, C8 Health Project, West Virginia, US Age range: 18+ % men: 51% Study design: Longitudinal Study year(s): 2005-06 and 2010 N total=411	Serum PFOA: Range: 0.25-2140 ng/mL Q1: 0.25-13.7 ng/mL Q2: 13.8-31.5 ng/mL Q3: 31.6-90.3 ng/mL Q4: 90.4-2,140 ng/mL	Immune response to influenza type B, A H1N1, A H3N2 vaccine: Antibody titer rise 0 Seroconversion 0 Seroprotection -	The most consistent finding was evidence of a reduced antibody response to A/H3N2 influenza vaccine by higher PFOA concentration, reflected in the results for titer rise, titer ratio, and seroprotection, though not seroconversion. Association (adjusted) between PFOA quartiles (ref=Q1) and seroprotection - A/H2N2 Influenza, OR (CI): **Q2 0.34 (0.14-0.83)** **Q3 0.28 (0.11-0.70)** **Q4 0.36 (0.15-0.99)** No significant associations with Influenza type B and A H1N1. Association (adjusted) between transformed PFOA and transformed antibody titer rise, β (CI): -.01 (-.17-0.14) Association (adjusted) between transformed PFOA and transformed antibody titer ratio, β (CI): -.12 (-.25-0.02)

[a] 0, no association; +, positive association; -, negative association

β=regression coefficient, OR=Odds Ratio, CI= 95% Confidence Interval, lnPFOA = natural log transformed PFOA, Q=quartile, IQR=Interquartile range.

Table 9. Summary of associations in studies on ulcerative colitis

Reference	Study characteristics	Blood PFOA concentration	Association with PFOA[a]	Effect size
High-exposure community & occupational study population				
Steenland et al. (2013)	Study population: C8 High exposure population & occupational population, West Virginia, US Age range: median year at birth 1958 (=53 years in 2011) % men: 46% Study design: Longitudinal Study year(s): 2005-06 (PFOA tests), 2008 & 2011 (interviews) N total: 3,713 workers and 28.541 population (n=151 cases with ulcerative colitis)	Serum PFOA, measured in 2005-06, total: IQR: 13-68 ng/mL Median: 26 ng/mL Serum PFOA, measured in 2005-06, workers (only n=1,881 has blood measurements): IQR: 56-256 ng/mL Median: 113 ng/mL Serum PFOA, measured in 2005-06, community: IQR: 12-59 ng/mL Median: 24 ng/mL	Ulcerative colitis +	Association between estimated cumulative serum PFOA (quartiles) and ulcerative colitis (vs not), Q1 (<13)=referent, no lag, RR (CI): **Q2 (158-586 ng/mL-years): 1.76 (1.04, 2.99)** **Q3 (586-3,500 ng/mL-years): 2.63 (1.56, 4.43)** **Q4 (>3,500 ng/mL-years): 2.86 (1.65, 4.96).**
Occupational study population				
Steenland et al. (2015)	Study population: occupational population, DuPont, West Virginia (Washington works) Age range: mean year of birth 1951 % men: 80% Study design: Longitudinal Study year(s): 2005-06 (PFOA measures), 2008 & 2011 (interviews) N total = 3,713 (cohort of workers)	Serum PFOA, measured in 2005-06 (n=1881): Range: not reported Median: 113 ng/mL Mean: 325 ng/mL Historical serum levels modelled using JEM, residential exposure model and PK model. Mean cumulative occupational exposure 8.6 ppm-years	Ulcerative colitis +	Association between estimated cumulative serum PFOA (quartiles) and ulcerative colitis (vs. not), 10-year lag, Q1 (<800ng/mL-years)= referent, RR (CI): **Q2 (800-3,440 ng/mL-years): 3.00 (0.82-11)** **Q3 (3,440-7,040 ng/mL-years): 3.26 (0.7-15.1)** **Q4 (>7,040 ng/mL-years): 6.57 (1.47-29.4)**

[a] 0, no association; +, positive association; -, negative association.

RR=relative risk, CI= 95% Confidence Interval, Q=quartile, IQR=Interquartile range.

Table 10. Summary of associations in studies on thyroid effects

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
General population				
Bloom et al. (2010)	Study population: general population, US (New York State Anglers Cohort Study) Age range: 31-45 yrs % men: 87% Study design: cross-sectional Study year(s): 2003 N total: 31	Serum PFOA: Range: 0.57-2.58 ng/mL Geometric mean (95% CI) 1.33 (1.15–1.53) ng/mL	TSH: 0 Free T4: 0	Association between log-PFOA and log-TSH, β(CI): -0.06 (-0.78, 0.67) Association between log-PFOA and log-T4, β(CI): -0.01 (-0.16, 0.14)
Melzer et al. (2010)	Study population: general population, NHANES, US Age range: 20 yrs and older % men: 48% Study design: cross-sectional Study year(s): 1999-2006 N total: 3,974	Serum PFOA, men: Q1: 0.1-3.6 ng/mL Q2: 3.7-5.2 ng/mL Q3: 5.3-7.2 ng/mL Q4: 7.3-45.9 ng/ml Geometric mean (CI): 4.91 (4.64-5.2) ng/mL Serum PFOA, women: Q1: 0.1-2.6 ng/mL Q2: 2.7-4.0 ng/mL Q3: 4.1-5.7 ng/mL Q4: 5.7-123.0 ng/mL Geometric mean (CI): 3.77 (3.52-4.04) ng/mL	Thyroid disease ever: Women: + Men: 0 Thyroid disease current & medication: Women: + Men: 0	Association between serum PFOA quartiles and: *Thyroid Disease Ever, OR (CI):* Women: Q2: 0.95 (0.62-1.47) Q3: 1.11 (0.67-1.83) **Q4: 1.64 (1.09-2.46)** **Q4 vs Q1 & Q2: 1.68 (1.14-2.49)** Men: Q2: 1.11 (0.62-1.99) Q3: 0.57 (0.19-1.66) Q4: 1.58 (0.74-3.39) Q4 vs Q1 & Q2: 1.5 (0.66-3.39) *Thyroid Disease current & medication, OR (CI) :* Women: Q2: 0.7 (0.41-1.22) Q3: 0.89 (0.49-1.59) **Q4: 1.86 (1.12-3.09)** **Q4 vs Q1 & Q2: 2.24 (1.38-3.65)** Men: Q2: 1.12 (0.52-2.39)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				Q3: 0.49 (0.18-1.38) Q4: 1.89 (0.60-5.90) Q4 vs Q1 & Q2: 2.12 (0.93-4.82)
Ji et al. (2012)	Study population: general population, Korea Age range: 12-75 yrs % men: 41% Study design: cross-sectional Study year(s): 2008 N total: 633	Serum PFOA: IQR: 2.04-3.64 ng/mL Median: 2.74 ng/mL	TSH: 0 T4: 0	Association between serum PFOA and TSH and T4, β (CI): TSH: −0.066 (−0.220, 0.089) T4: −0.020 (−0.051, 0.012)
Wen et al. (2013)	Study population: general population, US, NHANES Age range: ≥ 20 yrs % men: 57% Study design: cross-sectional Study year(s): 2007-08 and 2009-10 N total: 1,181	Serum PFOA: Geometric mean (CI): 4.15 (4.02– 4.29) ng/mL	TSH: 0 T3: 0 (men), + (women) Free T3: + T4: 0 Free T4: 0	Association between lnPFOA and ln-TSH, β (CI): Men: 0004 (-0.081, 0.090) (p = 0.92) Women: -0.030 (-0.2157, 0.154) (p =0.73) Association between lnPFOA and ln-T3, β (CI): Men: 0.775 (-3.048, 4.598) (p =0.67) **Women: 6.628 (0.545, 12.7) (p = 0.035)** Association between lnPFOA and ln-FT3, β (CI): **Men: 0.016 (0.001, 0.031) (p = 0.04)** **Women: 0.027 (0.009, 0.044) (p =0.002)** Association between lnPFOA and ln-T4, β (CI): Men: 0.000 (-0.28, 0.28) (p = 1.0) Women: 0.082 (-0.369, 0.532) (p = 0.71) Association between lnPFOA and ln-FT4, β (CI): Men: -0.010 (-0.041, 0.022) (p = 0.53) Women: -0.004 (-0.047, 0.039) (p = 0.83) Association between lnPFOA and ln-T3, β (CI): In women increased T3 in Q3 (3.6 - 5.3

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				ng/mL) and Q4 (>5.3 ng/mL) relative to Q1 (≤2.4 ng/mL)
Lin et al. (2013b)	Study population: general population, Young Taiwanese Cardiovascular Cohort Study Age range: 12-30 yrs % men: 38% Study design: cross-sectional Study year(s): 2006-08 N total: 545	Serum PFOA: Median: 3.64 ng/mL GM (GSD): 2.67 (2.96) ng/mL 75th: 6.66 ng/mL 90th: 9.71 ng/mL	TSH: 0 Free T4: 0 Hypothyroidism: 0	Association between PFOA and ln TSH, per percentile, mean (SE) in linear regression models: <50th: 0.48 (0.08) (not significant; NS) 50th-75th: 0.45 (0.09) (NS) 75th-90th: 0.36 (0.11) (NS) >90th: 0.41 (0.12) (NS) Association between PFOA and FT4, per percentile, mean (SE) in linear regression models: <50th: 1.07 (0.01) (NS) 50th-75th: 1.08 (0.02) (NS) 75th-90th: 1.10 (0.02) (NS) >90th: 1.06 (0.02) (NS)
de Cock et al. (2014)	Study population: general population, Netherlands Age range: newborns % men: 62% boys Study design: cross-sectional Study year(s): 2011-13 N total: 83 newborns	Plasma PFOA, cord blood: Range: 0.2–2.7 ng/mL Median: 0.885 ng/mL Mean: 0.943 ng/mL	T4: 0 (boys), + (girls)	Association between quartile PFOA and T4, β (CI): Boys (Q1=ref): Q2 (0.59-0.87 ng/mL): 7.9 (-18.04, 33.92) Q3 (0.87-1.2 ng/mL): -2.1 (-20.94, 16.78) Q4 (>1.2 ng/mL): 6.2 (-16.08, 28.50) Girls (Q1=ref): Q2 (0.59-0.87 ng/mL): -5.9 (-26.75, 14.94) Q3 (0.87-1.2 ng/mL): 11.8 (-19.08, 42.72) **Q4 (>1.2 ng/mL): 38.6 (13.34, 63.83)**
Shrestha et al. (2015)	Study population: general population, US (Upper Hudson River Valley) Age range: 55-74 yrs % men: 59	Serum PFOA: Range: 0.6 – 42.7 ng/mL IQR: 7.1–13.1 ng/mL Median: 9.3 ng/mL Geometric mean: 9.2	TSH: 0 T3: 0 T4: 0 Free T4: 0	Association between log-PFOA and log-TSH, β (CI): 0.102 (-0.047, 0.25) Association between log-PFOA and log-T3, β (CI):

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Study design: cross-sectional Study year(s): blood collection in 2000-02 N total: 87	ng/mL		3.03 (-1.73, 7.79) Association between log-PFOA and log-T4, β (CI): 0.38 (-0.07, 0.83) Association between log-PFOA and log-FT4, β (CI): 0.016 (-0.036, 0.069)
Chan et al. (2011)	Study population: general population, Canada, pregnant women. Age range: 20-45 yrs % men: 0 Study design: cross-sectional Study year(s): 2005-06. Blood sample in 2nd trimester. N total: n=96 hypothyroxinemia cases and n=175 matched controls	Serum PFOA, pregnant women cases and controls: Geometric mean: 1.35 ng/mL	Hypothyroidism: 0	Association between lnPFOA and hypothyroidism, OR (CI): 0.94 (0.74–1.18)
Wang Y. et al. (2013)	Study population: general population, Norway, pregnant women Age range: 18-44 yrs % men: 0 Study design: cross-sectional Study year(s): 2003-04, blood sample in 2nd trimester N total: 903	Plasma PFOA, pregnant women: IQR: 1.57- 2.95 ng/mL Median: 2.15 ng/mL GM (CI): 2.13 (2.07, 2.20) ng/mL	TSH: 0	Association between ln PFOA and TSH, β (CI): −0.0001 (−0.045, 0.044)
Webster et al. (2014)	Study population: general population, Canada, pregnant women Age range: 25-34 yrs	Serum PFOA, pregnant women: Range: <0.5 -4.6 ng/mL IQR: 1.4 ng/mL	Normal anti-thyroid oxidase (TPO) antibody TSH: 0	Association between IQR PFOA and TSH, β (CI): Normal TPO antibody: 0.07 (-0.1, 0.2) **High TPO antibody: 0.7 (0.09, 1)**

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	% men: 0 Study design: cross-sectional Study year(s): 2007-08, blood samples in 2nd trimester N total: 152	Median: 1.7 ng/mL Mean: 1.8 ng/mL	Free T4: 0 High TPO antibody TSH: + Free T4: 0	Association between IQR PFOA and FT4, β (CI): Normal TPO antibody: -0.03 (-0.3, 0.2) High TPO antibody: -0.4 (-1, 0.5)
Berg et al. (2015)	Study design: general population, Norway, pregnant women Age range: not reported Median age: 32 yrs % men: 0 Study design: longitudinal Study year(s): 2007-09 N total: 375	Serum PFOA, maternal during and after pregnancy: Median: 1.53 ng/mL	TSH: +	**Results not quantified.** Women in the extreme quartiles of PFOA had higher concentrations of TSH compared with the lowest quartiles, but not significantly so after adjustment for PFOS
Jain (2013)	Study population: general population, NHANES, US Age range: age 12 and older % men: not reported Study design: cross-sectional Study year(s): 2007-08 N total: 1,540	Serum PFOA: tertile 1: ≤3.3 ng/mL tertile 2: 3.3-5.0 ng/mL tertile 3: ≥5.1 ng/mL	TSH: 0 Free T3: 0 Free T4: 0 Total T3: + Total T4: 0 TGN: 0	Association between tertiles serum PFOA concentration and TSH concentration (ORs were not reported, only p-values): TSH was significantly (p<0.01) higher in the third tertile (>=5.1 ng/mL) compared to the first tertile (<=3.3 ng/mL). Therefore, TSH levels increased with increase in PFOA concentration. Association between transformed serum PFOA concentration and transformed thyroid function variables (in a model including all thyroid function variables), β (p-value; CI not reported): FT3 0.012 (p=0.09) FT4 0.003 (p=0.83)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				TT3 0.032 (p=0.01) TT4 0.012 (p=0.43) TGN 0.057 (p=0.17)
Wang Y. et al. (2014)	Study population: general population, pregnant women and their children (Taiwan Cohort) Age range: not reported. Mean age: 28.8 yrs (SD 4.3) % men: 0% (only pregnant women) and 49% of neonates Study design: longitudinal Study year(s): 2000-2001 N total: 285 women and 116 neonates	Serum PFOA, maternal, during pregnancy: Median: 2.39 ng/mL 25th percentile: 1.54 ng/mL 75th percentile: 3.40 ng/mL 90th percentile: 5.20 ng/mL	Thyroid effects, maternal & cord Free T4: 0 Total T4: 0 Total T3: 0 TSH: 0	Association between maternal serum PFOA concentration and thyroid effects, β (CI): Free T4: -0.003 (0.012, 0.005) ng/dl (not significant; NS) Total T4: 0.011 (-0.108, 0.130) μg/dl (NS) Total T3: -0.000 (-0.002-0.009) ng/dl (NS) TSH: 0.011 (-0.057, 0.078) μIU/ml (NS)
Kim et al. (2016)	Study population: general population (patients hospital South Korea) Age range: 1-3 months after birth % men: unknown Study design: cross-sectional Study year(s): 2009-2010 N total: 27 patients and 13 controls	Serum PFOA: Range: 0.8–15.7 ng/mL Mean: 5.4 ng/ml	TSH: 0 Free T4: 0 T3: 0 Micro/Ab: 0 TSI: -	Association between PFOA and TSI vs control group, *Spearman's correlation coefficients (R2)*: **-0.482 (p<0.05)** Non-significant results were not quantified.
Shah-Kulkarni et al.	Study population: general population Age range: adults 70% ≥30 yrs,	Serum PFOA, cord blood: Range: 0.05-2.4 ng/mL Geometric mean: 0.78	T3: 0 T4: 0 TSH: 0	Association between prenatal PFOA and thyroid effects adjusted for mother's age, education, pre-pregnancy body mass index, alcohol intake

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
(2016)	babies at birth % men: 0% male adults (their children: 47% boys) Study design: cross-sectional and longitudinal Study year(s): 2006-10 N total: 279	ng/mL		history, child's parity, gestational age and gender, β (CI): T3: -0.01 (-2.22, 2.20) T4: 0.001 (-0.26, 0.26) TSH: -0.79 (-2.13, 0.55)
Yang et al. (2016)	Study population: general population (no occupational experience with PFOA and generally did not smoke) Age range: not reported. Mean age: 30 yrs % men: 0% (their children: 55% boys) Study design: cross-sectional Study year(s): 2013 N total: 157	Serum PFOA, maternal: Range: 0.73-8.11 ng/mL Median: 1.64 ng/mL Serum PFOA, cord blood: Range: 0.4-5.06 ng/mL Median: 1.15 ng/mL	Free T3: - Free T4: 0 T3: 0 T4: 0 TSH: 0	Association between maternal PFOA and maternal thyroid effects, Spearmans correlation: Free T3: 0.024 (not significant=NS) Free T4: 0.000 (NS) T3: 0.102 (NS) T4: 0.062 (NS) TSH: -0.124 (NS) Association between cord (i.e. fetal) PFOA and maternal thyroid effects, Spearmans correlation: **Free T3: -0.169 (p<0.05)** Free T4: 0.089 (NS) T3: -0.069 (NS) T4: -0.069 (NS) TSH: -0.065 (NS)
High-exposure community				
Emmett et al. (2006)	Study population: High-exposure community population. Residents Ohio in C8 Health Project area (Little Hocking) Age range: 2-89 yrs % men: 47%	Serum PFOA: IQR: 184–571 ng/mL Median: 354 ng/mL	TSH: 0	PFOA in individuals with normal TSH compared with abnormal TSH, t-test (p-value): r=0.046 (0.38)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Study design: cross-sectional Study year(s): 2004-2005 N total=371			
Lopez-Espinosa et al. (2012)	Study population: High-exposure community population (C8 Health Project), US Age range: 1-17 yrs % men: 51.5% boys Study design: cross-sectional Study year(s): 2005-06 N total: 10,725 children	Serum PFOA, modelled in utero: Median: 12 ng/mL Q1: 0.05–5.4 ng/mL Q2: 5.5–11.6 ng/mL Q3: 11.7–38.4 ng/mL Q4: 38.5–3,987 ng/mL Serum PFOA, measured: Median : 29.3 ng/mL Q1: 0.7–13 ng/mL Q2: 13.1–29.2 ng/mL Q3: 29.3–67.6 ng/mL Q4: 67.7–2,071 ng/mL	TSH: - (in girls ≤ 5 yrs) T4: + (in children ≤ 5 yrs) Thyroid disease: +	Association between quartiles of *modelled or measured* PFOA or IQR and transformed % change in TSH compared: not significant **Change in measured serum PFOA from 16 to 83 ng/mL was associated with a 4% drop in TSH in all children ≤ 5 yrs, but only in girls.** Association between quartiles of *modelled or measured* PFOA or IQR of lnPFOA and transformed % change in T4: not significant **IQR contrast of 10 to 57 ng/mL for modelled in utero PFOA was associated with a 2% increase in T4 in children up to 5 yrs of age (95% CI 0.1, 3.9)** *Thyroid disease* Association per IQR modelled PFOA and thyroid disease, OR (CI): Any thyroid disease (n = 27) 1.47 (0.95, 2.27) Hypothyroidism (n = 20) 1.61(0.96, 2.63) Subclinical hypothyroidism (n = 155) 0.94 (0.76, 1.16) Subclinical hyperthyroidism (n = 31) 1.10 (0.69, 1.74) Measured PFOA: **Any thyroid disease (n = 61) 1.44 (1.02, 2.03)** **Hypothyroidism (n = 39) 1.54 (1.00, 2.37)** Subclinical hypothyroidism (n = 365) 0.98

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				(0.86, 1.15) Subclinical hyperthyroidism (n = 78) 0.81 (0.58, 1.15)
Knox et al. (2011)	Study population: High-exposure community population (C8 Health Study), US Age range: >20 yrs % men: 50% boys Study design: cross-sectional Study year(s): 2005-06 N total: 52,296	Serum PFOA: Range: 0.25-564.3 ng/mL Mean (SD): Women 20-50 yrs: 52.6 (192.8) ng/mL Women >50 yrs: 98.6 (230.2) ng/mL Men 20-50 yrs: 91.0 (261.5) ng/mL Men >50 yrs: 124.3 (380.8) ng/mL	TSH: 0 T4: Women 20-50 yrs, women >50 yrs, men >50 yrs: + Men 20-50 yrs: 0	Association between PFOA and TSH: results not quantified Association between PFOA and T4, β (p-value): Women 20-50 yrs: 0.05 (<0.0001) Women >50 yrs: 0.08 (<0.0001) Men 20-50 yrs: not reported (NS) Men >50 yrs: 0.06 (0.001)
High-exposure community & occupational study populations				
Winquist and Steenland (2014b)	Study population: high-exposure community and occupational study (C8 Health Study), US Age range: ≥20 yrs % men: 54% Study design: longitudinal Study year(s): 2005-06, 2008-11 N total: 32,254	Serum PFOA (measured in 2005-06): IQR: 12.8-68.1 ng/mL Median: 26.1 ng/mL Mean: 86.6 ng/mL	Functional thyroid disease: + (women) Hyperthyroidism: + (women, yearly exposure estimates) Hypothyroidism: + (women)	*Women:* Association between cumulative PFOA exposure quintiles and functional thyroid disease (i.e. excludes neoplasms), HR (CI), ref=quintile 1: **Quintile 2 (114.7-<202.2 ng/mL-yrs): 1.24 (1.02-1.51)** **Quintile 3 (202.2-<497.3 ng/mL-yrs): 1.27 (1.04-1.55)** **Quintile 4 (497.3-<2676 ng/mL-yrs): 1.36 (1.12-1.66)** **Quintile 5 (2,670-97,396 ng/mL-yrs): 1.37 (1.11-1.68)** ***Similarly, significant associations were observed between cumulative PFOA exposure quintiles and hypothyroidism and yearly exposure estimates with functional***

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				thyroid disease, hyperthyroidism and hypothyroidism. *No significant associations were observed between cumulative PFOA exposure quintiles and hyperthyroidism.* *Men:* Association between cumulative PFOA exposure quintiles and functional thyroid disease, HR (CI), ref=quintile 1: Quintile 2 (114.7-<202.2 ng/mL-yrs): 1.12 (0.69-1.79) Quintile 3 (202.2-<497.3 ng/mL-yrs): 0.83 (0.51-1.37) Quintile 4 (497.3-<2676.0 ng/mL-yrs): 1.01 (0.63-1.62) Quintile 5 (2,670.0-97,396 ng/mL-yrs): 1.05 (0.66-1.66) *Similarly, no significant associations were also observed when hyperthyroidism and hypothyroidism were examined and when yearly exposure estimates were examined in men.*
Occupational study population				
Olsen and Zobel (2007)	Study population: occupational population, 3M Cottage Grove US, Decatur US & Antwerp Age range: 21-67 yrs % men: 100% Study design: cross-sectional Study year(s): 2000 N total: 506 (all locations), 196	Serum PFOA, all locations: Range: 7-92,030 ng/mL Median: 1,100 ng/mL Mean: 2,210 ng/mL	TSH: 0 T3: + T4: 0 Free T4: -	Association between ln PFOA and ln TSH, β(SE) (p-value):0.0360 (± 0.0207) (p = 0.08) **Association between ln PFOA and ln T3, β(SE) (p-value): 0.0105 (± 0.0053) (p = 0.05)** Association between ln PFOA and ln T4, β(SE) (p-value): -0.0057 (± 0.0054) (p = 0.29) **Association between ln PFOA and ln FT4,**

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	(Antwerp), 122 (Cottage Grove US), 188 (Decatur US)			**β(SE) (p-value): -0.0117 (± 0.0043) (p = 0.01)** Not considered clinically relevant by the authors because results were within normal reference ranges.
Steenland et al. (2015)	Study population: occupational population, DuPont West Virginia (Washington works) Age range: mean year of birth 1951 % men: 80% Study design: longitudinal Study year(s): 2005-06 (PFOA measures), 2008 & 2011 (interviews) N total = 3,713 (cohort of workers)	Serum PFOA, measured in 2005-06 (n=1,881): Range: not reported Median: 113 ng/mL Mean: 325 ng/mL Historical serum levels modelled using JEM, residential exposure model and PK model. Mean cumulative occupational exposure 8.6 ppm-years	Thyroid disease (self-reported, with medical record validation): 0	Association between cumulative estimated exposure PFOA quartiles and self-reported thyroid disease, no lag, ref=Q1, HR (CI): Men (n=82 cases): Q2 (3,030-6,160 ng/mL-yrs): 1.64 (0.82, 3.29) Q3 (6,160-11,420 ng/mL-yrs): 1.13 (0.50, 2.54) Q4 (>11,420 ng/mL-yrs): 2.16 (0.98, 4.77) Women (n=77 cases): Q2 (3,030-6,160 ng/mL-yrs): 1.00 (0.54, 1.87) Q3 (6,160-11,420 ng/mL-yrs): 1.02 (0.48, 2.17) Q4 (>11,420 ng/mL-yrs): 0.33 (0.08, 1.26) Association between cumulative exposure PFOA quartiles and self-reported thyroid disease, 10-year lag, ref=Q1, HR (CI): no significant association was observed.
Sakr et al. (2007a)	Study population: occupational population, Washington Works US (in C8 Health Project area). Age range: not reported. Mean age men/women: 46.5 / 44.4 yrs % men: 76% Study design: cross-sectional	Serum PFOA: Range: 5-9,550 ng/mL Median: 189 ng/mL Mean: 428 ng/mL	TSH: association with PFOA not studied. Authors note that all mean clinical endpoints were	

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Study year: 2004 N total=1,025		within the normal range	
Olsen et al. (2003)	Study population: Occupational population, 3M Antwerp and Decatur Age range: mean 37 (male Antwerp) and 43 (male Decatur) yrs % men: 81% (Antwerp), 82 (Decatur) Study design: cross-sectional and longitudinal Study year(s): 1994, 1995, 2000 N total cross-sectional = 518 N total longitudinal =174	Serum PFOA: Decatur: Range = 40-12,700 ng/mL Mean = 1,780 ng/mL (n=263) Antwerp: Range = 10-7,040 ng/mL Mean = 840 ng/mL	TSH: 0 T3: + T4: 0 Free T4: 0	Association between serum PFOA and ln T3, β (p-value): **0.016 (0.01)**
Olsen et al. (1998)	Study population: occupational population, PFOA male production workers, US, 3M Age range: median 32.5 yrs in 1993 and in those with ≥30,000 ng/mL % men: 100 Study design: cross-sectional Study year(s): 1993 & 1995 N total: 111 in 1993, n=80 in 1995, n=68 in both years	Serum PFOA, 1995: Range: 0-114,100 ng/mL Median concentrations per PFOA group: 0-<1,000 ng/mL: 310 ng/mL 1,000-<10,000 ng/mL: 3,030 ng/mL 10,000-<30,000 ng/mL: 17,110 ng/mL ≥30,000 ng/mL: 55,960 ng/mL	TSH: 1993: 0 1995: + (in 3rd category)	Significantly different mean TSH was found between categories of serum PFOA concentrations in 1995, but only in category 10,000-<30,000 ng/mL: 0-<1,000 ng/mL: 1.7 1,000-<10,000 ng/mL: 1.7 **10,000-<30,000 ng/mL: 2.9** ≥30,000 ng/mL: 1.7 P=0.002 No significant difference was observed in 1993.

[a] 0, no association; +, positive association; -, negative association.

β=regression coefficient, OR=Odds Ratio, HR= Hazard Ratio, CI= 95% Confidence Interval, lnPFOA = natural log transformed PFOA, Q=quartile, IQR=Interquartile range, TSH=Thyroid stimulating hormone, T3=triiodothyronine, T4=thyroxine, TGN=thyroglobin, TSI=thyroid stimulating immunoglobulins

Table 11. Summary of associations in studies on blood lipid levels

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
General population				
Nelson et al. (2010)	Study population: general population, NHANES, US Age range: 20-80 yrs % men: 52% Study design: cross-sectional study Study year(s): 2003-04 N total: 860	Serum PFOA: Range: 0.1–37.3 ng/mL Median 3.8 ng/mL Mean 4.6 ng/mL Median (range): Q1: 2.1 (0.1–2.7) ng/mL Q2: 3.4 (2.8–3.9) ng/mL Q3: 4.6 (4.0–5.4) ng/mL Q4: 6.9 (5.5–37.3) ng/mL	TC + LDL 0 (based on 416 persons) HDL + (adolescent girls); - (men 60-80 y) Non-HDL +	Association between 1 ng/mL PFOA and change in cholesterol (mg/dL), β (CI): TC: 1.22 (0.04, 2.40) HDL: –0.12 (–0.41, 0.16) **Non-HDL: 1.38 (0.12, 2.65)** LDL: –0.21 (–1.91, 1.49) Indication of linear increase between quartiles with bottom/top medians of 2.1 / 6.9 ng/mL; TC 9.8-mg/dL (95% CI, –0.2 to 19.7) increase from top to bottom quartile; HDL 4.3 (95% CI 0.1 to 8.5) increase from top to bottom quartile in adolescent girls; 8.7 (95% CI 1.1 to 16.3) decrease in men 60-80 y; non-HDL similar to TC
Lin et al. (2011)	Study population: Young Hypertension Cohort in Taiwan Age range: 12-30 yrs % men: 42% Study design: cross-sectional Study year(s): 2006-2008 N total: 287	Serum PFOA: Median: 2.39 ng/ml Range: 27.38 ng/ml median (range) per category (< 50th, 50 – 74, 75 –89 and >= 90th percentiles): 0.75 (0.75-2.37) ng/ml, 3.86 (2.39-5.92) ng/ml, 7.89 (6.01-9.62) ng/ml, 11.54	HDL 0 TRIG 0	Mean (SE) concentrations per PFOA category HDL: 48.06 (1.35) 47.74 (1.39) 47.69 (1.72) 47.70 (2.05) P trend 0.937 Log(TRIG):

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
		(9.64-28.13) ng/ml, respectively		4.39 (0.07) 4.32 (0.07) 4.25 (0.09) 4.14 (0.11) P trend 0.061
Eriksen et al. (2013)	Study population: general population, Denmark Age range: 50-65 yrs % men: 88% Study design: cross-sectional Study year(s): 1993-97 N total: 753	Plasma PFOA: Range: 1-28 ng/mL Mean 7.1 ng/mL	TC +	4.4 (95% CI = 1.1–7.8) mg/dL higher TC per IQR of plasma PFOA. Stronger association among women than men
Fisher et al. (2013)	Study population: general population, Canada Age range: 18-74 yrs % men: 48% men Study design: cross-sectional Study year(s): 2007-09 N total: 2,368	Serum PFOA: Geometric mean: 2.46 ng/mL Q1: 0.15–1.85 ng/mL Q2: 1.86–2.58 ng/mL Q3: 2.59–3.55 ng/mL Q4: ≥3.56 ng/mL	TC 0 LDL 0 HDL 0 Non-HDL 0 HDL/TC ratio 0 TRIG 0 high C 0	Beta (95% CI) for log(PFOA) TC: 0.03 (-0.017, 0.07) LDL: 0.02 (-0.06, 0.091) HDL: 0.0009 (-0.04, 0.04) Non-HDL: 0.036 (-0.01, 0.08) HDL/TC ratio: 0.02 (-0.016, 0.06) TRIG: -0.003 (-0.13, 0.12) High C: 1.22 (0.89, 1.67) High C, OR (95% CI), weighted Q1 ref Q2 1.61 (1.02, 2.53) Q3 1.26 (0.76, 2.07) Q4 1.5 (0.86, 2.62) P for Trend=0.10
Lin et al. (2013a)	Study population: general population, Young Taiwanese Cohort Study	Serum PFOA: Range: 0.75-52.2 ng/mL Median: 3.49 ng/mL	LDL: 0 TRIG: -	Association between PFOA categories and LDL (mg/dL), mean (SE): 107.4 (3.07)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Age range: 12-30 yrs % men: 39% Study design: cross-sectional Study year(s): 2006-08 N total: 644	Geometric mean: 2.61 ng/mL (age and sex adjusted)		105.5 (3.42) 100.3 (3.95) 100.4 (4.66) P trend 0.117 Association between PFOA categories and triglyceride (mg/dL), mean (SE): 4.37 (0.04) 4.39 (0.05) 4.32 (0.06) 4.20 (0.07) P trend 0.015
Fu et al. (2014)	Study population: Participants of health check-up in Red Cross Hospital (China). Age range: 0.3-88 yrs % men: 60% Study design: cross-sectional Study year(s): 2011 N total: 133	Serum PFOA: Median: 1.43 ng/ml Range: 0.32-39.46 ng/ml Mean: 2.95 ng/ml SD: 4.65 ng/ml Median; mean (SD); range per quartile Q1: 0.71; 0.72 (0.17); 0.32–0.99 Q2: 1.24; 1.23 (0.12); 1.02-1.43 Q3: 1.97; 2.03 (0.47); 1.44-2.85 Q4: 4.88; 7.89 (7.40); 2.95-39.46	TC: + TG: 0 HDL: 0 LDL: +	Logistic regression analysis: risk of abnormal serum lipids based on PFOA quartiles (Crude OR, Adjusted OR (95% CI), P value for trend for differences in lipid concentrations between quartiles TC (Total Cholesterol): P trend = 0.015 Q2 1.20; 0.82 (0.14-4.81) Q3 5.95; 2.60 (0.56-12.09) Q4: 2.80; 0.55 (0.09-3.31) LDL (Low Density Lipoprotein): P trend = 0.022 Q2 0.96; 0.55 (0.11-2.82) Q3 5.04; 1.70 (0.40-7.19) Q4: 2.74; 0.71 (0.14-3.49) TG: not significant; p trend = 0.298 Q2 1.73(0.57–5.21) Q3 1.03(0.33–3.20)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				Q4 1.97(0.59–6.55) HDL: not significant: p trend = 0.268 Q2 0.35(0.57–2.16) Q3 0.89(0.19–4.19) Q4 0.67(0.13–3.51) Beta (95% CI) adjusted regression models: ln(TC): 0.054 (0.011, 0.098) ln(TRIG): 0.050 (-0.045, 0.144) HDL: 0.041 (-0.030, 0.112) ln(LDL): 0.065 (0.010, 0.121)
Geiger et al. (2014)	Study population: general population, US Age range: 12-18 yrs % men: 52 Study design: cross-sectional Study year(s): merged data from NHANES 1999–00, 2003–04, 2005–06, and 2007–08 N total: 815	Mean (SE) 4.2 (0.2) ng/mL, tertiles T1 <3.2 T2 3.2–4.7 T3 >4.7 ng/mL	TC + LDL + HDL 0 TRIG 0 High TC + High LDL + Low HDL 0	Beta (95% CI) per ln-unit increase in PFOA TC 4.55 (0.90, 8.20) LDL 5.75 (2.16, 9.33) HDL -1.52 (-3.02, -0.03) TRIG 1.74 (-2.88, 6.36) Adjusted mean change (95% CI) relative to first PFOA tertile TC T2: 4.72 (-1.23, 10.67) T3: 7.00 (1.40, 12.60) P trend=0.017 LDL T2: 3.61 (-1.13, 8.36) T3: 8.18 (3.04, 13.32) P trend=0.0027 HDL

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				T2: 0.53 (-1.23, 2.30) T3: -1.19 (-2.94, 0.56) P trend=0.1769 TRIG T2: 3.00 (95% CI -5.68, 11.68) T3: 0.09 (95% CI -6.11, 6.30) P trend=0.9943 Positive association between PFOA exposure and high TC and high LDL in categorical outcome models, but not with low HDL-C or high TRIG OR (95% CI) for dyslipidemia TC T2: 1.49 (0.97, 2.29) T3: 1.49 (1.05, 2.12) LDL T2: 1.26 (0.74, 2.15) T3: 1.56 (0.98, 2.48) HDL T2: 1.06 (0.65, 1.73) T3: 1.45 (0.87, 2.41) TRIG T2: 1.35 (0.60, 3.01) T3: 0.86 (0.46, 1.64)
Starling et al. (2014b)	Study population: general population (pregnant	Plasma PFOA, (ng/mL): Median: 2.25 ng/mL	TC 0 LDL 0	Beta (95% CI)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	women), Norway Age range: 19-41 yrs % men: 0% Study design: cross-sectional Study year(s): 2003-04 N total: 891	Range: not reported IQR: 1.66-3.03 ng/mL 5th percentile: 1.05 ng/mL 95th percentile: 4.43 ng/mL	HDL 0 TRIG 0	TC Q1 ref Q2 1.49 (-6.49, 9.48) Q3 3.54 (-4.51, 11.59) Q4 3.90 (-5.00, 12.80) Per ln-ng/mL 2.58 (-4.32, 9.47) IQR 1.55 (-2.60, 5.69) LDL Q1 ref Q2 0.94 (-6.08, 7.96) Q3 4.16 (-3.19, 11.50) Q4 3.35 (CI -4.35, 11.06) Per ln-ng/mL 2.25 (-3.97, 8.48) IQR 1.36 (-2.38. 5.10) HDL Q1 ref Q2 0.22 (-2.38, 2.83) Q3 2.31 (-0.59, 5.20) Q4 3.42 (0.56, 6.28) Per ln-ng/mL 2.13 (-0.26, 4.51) IQR 1.28 (-0.15, 2.71) Ln-TRIG Q1 ref Q2 0.03 (-0.04, 0.11) Q3 0.01 (-0.08, 0.09) Q4 -0.04 (-0.12, 0.04) Per ln-ng/mL 0.00 (-0.07, 0.06) IQR 0.00 (-0.04, 0.04)
Zeng et al.	Study population: Taiwanese	Serum PFOA boys:	TC +	Multivar linear regression: β coefficient, 95%CI, p

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
(2015)	children Age range: 12-15 yrs % men: 45% Study design: cross-sectional Study year(s): 2009-10 N total: 225	Mean: 1.1 ng/ml SD: 1.4 ng/ml Median: 0.5 ng/ml Range: LOQ-3.9 Serum PFOA girls: Mean: 0.92 ng/ml SD: 0.79 ng/ml Median: 0.5 ng/ml Range: LOQ–11.3	HDL – (ns) LDL + TG +	Change in cholesterol/blood lipids level (ng/ml) per ln(ng/ml) increase in PFOA (adjusted model). TC: 6.57 (2.72 to 10.42); p=0.001 HDL: -1.56 (-3.20 to 0.08); p=0.06 LDL: 4.66 (1.67 to 7.65); p=0.002 TG: 19.63 (14.82 to 23.34); p<0.001 Difference between first and fourth quartile PFOA: TC 12.9 mg/dL
High exposure communities				
Emmett et al. (2006)	Study population: high-exposure community (in area C8 Health Project), including 18 workers from a fluoropolymer production facility, US Age range: 2.5-89 yrs % men: 46% Study design: cross-sectional Study year(s): 2004-05 N total: 371	Median 354 ng/mL; IQR 184-571 ng/mL	TC 0	TC beta 0.00021305, p=0.38 t-test PFOA in abnormal (49% of study population) vs. normal TC: p-value 0.79
Steenland et al. (2009)	Study population: high exposure community (C8 Health Project, US Age range: ≥18 yrs % men: 46% Study design: cross-sectional Study year(s): 2005-06 N total: 46,294	mean (SD) 80.3 (236.1) ng/mL; median 26.6; range 0.25–17,556.6 Q1 0–13.1 Q2 13.2–26.5 Q3 26.6–66.9 Q4 ≥67.0 ng/mL	TC + LDL + HDL 0 Non-HDL + TC/HDL ratio + TRIG + High TC +	Largely monotonic increase in log cholesterol with each decile of PFOA. Similar trends for LDL, non-HDL, and TC/HDL ratio. Positive trend with TRIG. Explained variance 10-27%. Beta (SD) log(PFOA) and log(lipids) TC 0.01112 (0.00076) LDL 0.01499 (0.00121) HDL 0.00276 (0.00094)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				Non-HDL 0.01406 (0.00104) TC/HDL ratio 0.00831 (0.00110) TRIG 0.00169 (0.00219) P<0.05 for all except HDL OR (95% CI) high TC (240 mg/dL) Q1 ref Q2 1.21 (1.12, 1.31) Q3 1.33 (1.23, 1.43) Q4 1.38 (1.28, 1.50)
Frisbee et al. (2010)	Study population: high-exposure community, C8 Health Project, US Age range: 1-18 yrs % men: 51% boys Study design: cross-sectional Study year(s): 2005-06 N total: 12,476	Serum PFOA concentration: Mean (SD) children: 32.6/77.7 (124.9) ng/mL; adolescents 26.3/61.8 (98.8) ng/mL	TC + LDL + HDL 0 TRIG + Increased TC + Increased LDL + Increased HDL 0 Increased TRIG 0	Nonlinear dose-response relationships with larger increases in lipids at the lower range of PFOA concentration Difference in mg/dL (p trend) between 1st and 5th quintile PFOA TC: children 5.8 (<0.001), adolescents 4.2 (<0.001); LDL: children 4.9 (0.001), adolescents 3.2 (0.004); HDL: children <1.0 (0.88), adolescents <1.0 (0.20); TRIG: children 2.0 (0.10), adolescents 3.8 (0.10) OR (95% CI) abnormal lipid levels (Q1=ref) TC Q2: 1.1 (1.0-1.3)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				Q3: 1.2 (1.0-1.4) Q4: 1.2 (1.1-1.4) Q5: 1.2 (1.1-1.4) LDL Q2: 1.2 (1.0-1.5) Q3: 1.2 (1.0-1.4) Q4: 1.2 (1.0-1.4) Q5: 1.4 (1.2-1.7) HDL Q2: 1.0 (0.8-1.2) Q3: 1.0 (0.8-1.2) Q4: 1.0 (0.9-1.2) Q5: 0.9 (0.8-1.1) TRIG Q2: 1.0 (0.7-1.5) Q3: 1.3 (0.9-1.9) Q4: 1.6 (1.1-2.3) Q5: 1.0 (0.7-1.6)
Fitz-Simon et al. (2013)	Study population: high-exposure community, C8 Health Project. Age range: 20-60 yrs at baseline % men: 46% Study design: longitudinal study Study year(s): 2005-06 (baseline), 2010 (follow-up) N total: 560	baseline GM 74.8 ng/mL Min 1.0 P33 44.4 P66 118.6 Max 2,495 follow-up GM 30.8 Min 0.25 P33 16.3	TC + LDL + HDL 0 TRIG 0	Predicted % decrease (95% CI) per halving serum PFOA TC 1.65 (0.32, 2.97) LDL 3.58 (1.47, 5.66) HDL 1.33 (−0.21, 2.85) TRIG −0.78 (−5.34, 3.58)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
		P66 54.2 Max 2,140		
High-exposure community & Occupational study population				
Wang J. et al. (2012)	Study population: occupational study population and nearby community residents, China Age range: adults % men: residents 57%, workers 100% Study design: cross-sectional Study year(s): 2010-11 N total: 132 residents, 55 workers	Nearby residents: Mean 378.30 ng/ml Median 284.34 ng/ml Minimum: 10.20 ng/ml Maximum: 2,436.91 Range: 2,436.71 Occupational workers: Mean 2,157.74 ng/ml Median 1,635.96 ng/ml Minimum: 84.89 ng/ml Maximum: 7,737.13 ng/ml Range: 7,652.15 ng/ml	Total Cholesterol - residents 0 - workers 0 HDL - residents 0 - workers - LDL - residents 0 - workers 0 HDL/LDL - residents 0 - workers – TRIG - residents 0 - workers 0	Linear Multivariate Regression of Lipids on PFOA, adjusted BMI & age (stand coeff., 95% CI, p) Ln TC –residents:-0.00 (-0.04 to 0.03), p=0.85 -workers: 0.02 (-0.03 to 0.07), p=0.36 Ln HDL: -residents: 0.02 (-0.02 to 0.05). p=0.39 -workers: -0.07 (-0.12 to -0.01), p=0.01 Ln LDL: -residents: -0.00 (-0.05-0.05), p=0.97 -workers: 0.03 (-0.04 to 0.09), p=0.43 Ln HDL/LDL: -residents: 0.02 (-0.04 to 0.08), p=0.57 -workers: -0.09 (-0.16 to -0.02), p=0.01 Ln TRIG: -residents: 0.02 -0.08 to 0.11) -workers: -0.05 (-0.17 to 0.06)
Winquist and Steenland (2014a)	Study population: high-exposure community & occupational, C8 population Age range: >20 years % men: Study design: longitudinal Study years(s): worked at plant 1984-2002, diagnosis 2008-2011	Measured serum PFOA concentration (2005-06): Median: 26.1 ng/mL IQR: 12.8-68.1 ng/mL	Hypercholesterolemia with medication: +	Association between estimated serum PFOA concentration quintiles and hypercholesterolemia with medication, ref=1, HR (CI): **Q2 (0.142 to < 0.234 µg/mL per year) = 1.24 (1.15-1.33)** **Q3 (0.234 to < 0.630 µg/mL per year) = 1.17 (1.09-1.26)** **Q4 (0.630 to < 3.579 µg/mL per year) = 1.19 (1.11-1.27)** **Q5 (>=3.579 µg/mL per year) = 1.19 (1.11-1.28)**

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
				No association was observed with hypertension and coronary artery disease.
Occupational study population				
Gilliland and Mandel (1996)	Study population: Employees of PFOA production plant USA Age range: 18-60 yrs % men: 100% Study design: cross-sectional Study year(s): N total: 115	Total serum fluorine was used as proxy of serum PFOA Mean serum fluoride: 3.3 ppm Range: 0-26 ppm	Univariate: TC 0 LDL 0 HDL 0 Moderate drinkers: TC 0 LDL 0 HDL +	Pearson correlation coefficient TC: 0.07 (NS) LDL: 0.02 (NS) HDL: -0.01 (NS) Effect modification by alcohol intake. Adjusted Linear multivariate regression of factors predicting HDL (β, SE(β)), p-value -Intercept (65.00, 10.07), p=0.001)-Total Fluorine (-1.61, 0.77), p=0.04 -Alcohol Low alcohol (-9.92, 3.51), p=0.006 Low alcohol * Total Fluorine (1.62, 0.80), p=0.04
Olsen et al. (2000)	Study population: occupational population, 3M Cottage Grove US Age range: 24-61 yrs % men: 100% Study design: cross-sectional Study year(s): 1993, 1995, 1997 N total: 111 (1993), 80 (1995), 74 (1997)	Serum PFOA, all years: Range: 0-114,100 ng/mL Median: 1,190 ng/mL Mean: 59,930 ng/mL Serum PFOA, mean (range) per year, ng/mL: 1993: 5,000 (0-80,000) 1995: 6,800 (0-114,100) 1997: 6,400 (0.1-81,300)	For all three study years: TC 0 LDL 0 HDL 0 TRIG 0	Hypolipidemia not associated with serum PFOA (not quantified) HDL, Beta (SE; p-value) for PFOA: 1993: -0.14 (0.33; 0.67) 1995: -0.10 (0.08; 0.18) 1997: -0.19 (0.13; 0.16) No significant differences in any study year for TC, LDL, HDL and TRIG between the categories 0 to < 1, mean ~ .400 ng/mL (2) 1 to < 10, mean ~ 3000 ng/mL (3) ≥ 10, mean ~ 30,000 ng/mL
Olsen et al. (2003)	Study population: Occupational population, 3M	Serum PFOA: Decatur:	Cross-sectional and longitudinal	Positive association (not quantified) primarily attributed to 21 Antwerp employees whose serum

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Antwerp and Decatur Age range: mean 37 (male Antwerp) and 43 (male Decatur) yrs % men: 81% (Antwerp), 82 (Decatur) Study design: Cross-sectional and longitudinal Study year(s): 1994, 1995, 2000 N total: cross-sectional = 518, longitudinal =174	GM = 1130 ng/mL Range = 40-12700 ng/mL Mean = 1780 ng/mL (n=263) Antwerp: GM=330 ng/mL Range = 10-7040 ng/mL Mean = 840 ng/mL	analyses: TC + HDL 0 TRIG +	PFOA increased from 1,320 ng/ml in 1994/1995 to 2,060 in 2000, while TC increased from 208 to 229 and TRIG from 85 to 123 mg/dL
Olsen and Zobel (2007)	Study population: occupational population, 3M Cottage Grove US, Decatur US & Antwerp. Age range: 21-67 yrs % men: 100% Study design: cross-sectional Study year: 2000 N total: 506 (all locations), 196 (Antwerp), 122 (Cottage Grove US), 188 (Decatur US)	Serum PFOA, all locations: Range: 7-92,030 ng/mL Median: 1,100 ng/mL Mean: 2,210 ng/mL Mean (median) PFOA decile concentrations ranged from the lowest decile of 60 (60) ng/mL (range 7–130) to the highest decile of 12,150 (4,940) ng/mL (range 3,710–92,030)	TC 0 LDL 0 HDL - TRIG +	Beta (SE) for log(PFOA) TC: 0.0076 (0.0059) (p = 0.20) LDL: 0.0021 (0.0090) (p = 0.81) HDL: -0.0183 (0.0069) (p = 0.01) TRIG: 0.0711 (0.0169) (p = 0.0001) HDL lower (44 vs. 50 mg/dL) and TRIG higher (172; 165; 208 vs. 145 mg/dL) in 10th and 8-10th decile of PFOA, respectively. OR for HDL ≤ 40 mg/dl and TRIG ≥150 mg/dl elevated in 10th and 8-10th decile of PFOA, respectively, but non-significant after adjustment for location. For separate locations only association with TRIG in Antwerp (n=5 in highest decile).
Sakr et al. (2007a)	Study population: occupational population, Washington Works US (in C8	Serum PFOA: Range: 5-9550 ng/mL Median: 189 ng/mL	TC + LDL + VLDL +	Increase lipids (SE) (mg/dL) per increase of 1,000 ng/mL PFOA: TC: 4.036 (1.284) (p = 0.002)

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Health Project area). Age range: not reported. Mean age men/women: 46.5 / 44.4 yrs % men: 76% Study design: cross-sectional Study year: 2004 N total=1,025	Mean: 428 ng/mL	HDL 0 TRIG 0	Excluding workers taking lipid-lowering medications: 5.519 (1.467) p = < 0.001) LDL: 2.834 (1.062) (p = 0.008) Excluding workers taking lipid-lowering medications: 3.561 (1.213) (p = 0.003) HDL: -0.178 (0.432) (p = 0.68) Excluding workers taking lipid-lowering medications: 0.023 (0.058) (p = 0.96) TRIG (log transformed): 0.018 (0.021) (p = 0.38) Excluding workers taking lipid-lowering medications: 0.030 (0.024) (p = 0.21) VLDL (log transformed): 0.045 (0.021) (p = 0.031) Excluding workers taking lipid-lowering medications: 0.055 (0.025) (p = 0.026)
Sakr et al. (2007b)	Study population: occupational population, Washington works DuPont, US Age range: 22-63 yrs % men: 74% Study design: longitudinal Study year(s): 1979-2004 (blood measures every 1 to 2 years) N total = 454 (≥2 measurements)	Serum PFOA, overall: Range: +/-0 through 2,266 ng/mL Mean: 1,130 ng/mL	TC + LDL 0 HDL 0 TRIG 0	Beta (95% CI): increase in mg/dL lipids) per increase of 1000 ng/mL PFOA TC: 1.06 (0.24, 1.88) LDL: 0.46 (-0.87, 1.79) HDL: 0.16 (-0.39, 0.71) TRIG: (0.79 (-5.99, 7.57)
Costa et al. (2009)	Study population: occupational population, Italy Age, range: 20-63 yrs % men: 100%	Serum PFOA currently exposed: Range: 200-47040 ng/mL Mean: 12,930 ng/mL	TC + HDL 0 TRIG 0	Analysis 1: t-test, 34 currently exposed matched to 34 controls Analysis 2: Linear regression, 34 currently exposed, 107 controls

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Study design: Cross-sectional Study year(s): 2000-2007 N total=56	Geometric mean: 4,020 ng/mL Median: 5,710 ng/mL Serum PFOA, formerly exposed: Range: 530-18,660 ng/mL Mean: 6,810 ng/mL Geometric mean: 3,760 ng/mL Median: 4,430 ng/mL		Analysis 3: linear regression (GEE modelling), 56 with concurrent PFOA and lipid measure TC, Analysis 1: Currently exposed: 237.0 mg/dl, Controls: 206.4 mg/dl (p = 0.003) TC Analysis 2: Beta = 21.7 (95% CI 6.83, 36.6) (p = 0.005) TC Analysis 3: Beta = 0.028 (95% CI 0.002, 0.055) (p < 0.05) HDL, Analysis 1: Currently exposed: 56.68 mg/dl, Controls: 57.82 mg/dl (p > 0.05) HDL, Analysis 2: Beta = 2.42 (95% CI -2.30, 7.13) (p > 0.05) HDL, Analysis 3: Beta = -0.018 (95% CI -0.047, 0.012) (p > 0.05) TRIG, Analysis 1: Currently exposed: 150.03 mg/dl, Controls: 155.35 mg/dl (p > 0.05) TRIG, Analysis 2: Beta = -0. 15 (95% CI -34.6, 34.3) (p > 0.05) TRIG, Analysis 3: Beta = 0.055 (95% CI -0.036, 0.147) (p > 0.05)
Olsen et al. (2012)	Study population: occupational population, 3M employees and contract workers involved with demolition of PFA manufacturing facilities, US Age range: mean 40 yrs % men: 95% Study design: Longitudinal	Serum PFOA, contract workers: Mean: 28.9 ng/mL Median: 5.2 ng/mL Mean change end-of –project to baseline +32.1 ng/mL Serum PFOA, 3M employees at baseline:	TC 0 HDL 0 non-HDL 0 TC/HDL -	NB complete with results of analysis Range in beta (increase cholesterol in mg/dL per increase in PFOA of 1 ng/mL) in four subgroups of workers: TC -0.029 to -0.003 Non-HDL -0.033 to -0.007 HDL -0.014 to 0.009 TC/HDL -0.002 to 0.000

Reference	Study characteristics	Blood PFOA levels	Association with PFOA[a]	Effect size
	Study year(s): 2008-2010 N total=179 workers (165 contract workers, 14 3M employees)	Mean: 881 ng/mL Median: 595 ng/mL Mean change end-of – project to baseline -218.3 ng/mL Serum PFOA, range overall: 0.1-10,000 ng/mL		
Steenland et al. (2015)	Study population: occupational population, DuPont West Virginia (Washington works) Age range: mean year of birth 1951 % men: 80% Study design: longitudinal Study year(s): 2005-06 (PFOA measures), 2008 & 2011 (interviews) N total = 3,713 (cohort of workers), 1,298 cases	Serum PFOA, measured in 2005-06 (n=1,881): Range: not reported Median: 113 ng/mL Mean: 325 ng/mL Historical serum levels modelled using JEM, residential exposure model and PK model. Mean cumulative occupational exposure 8.6 ppm-years	Self-reported high cholesterol with medication 0	Association between quartiles of estimated cumulative serum PFOA and self-reported high cholesterol, with medication, no lag, ref=Q1, OR (CI): Q2 (3,030-6,160 µg/mL-yrs): 1.11 (0.94 to 1.30) Q3 (6,160-11,420 µg/mL-yrs): 1.06 (0.89 to 1.27) Q4 (>11,420 µg/mL-yrs): 1.05 (0.87 to 1.27) Association between quartiles of estimated cumulative serum PFOA and self-reported high cholesterol, with medication, 10-year lag, ref=Q1, OR (CI): Q2 (800-3,440 ng/mL-yrs): 0.93 (0.79 to 1.10) Q3 (3,440-7,040 ng/mL-yrs): 1.01 (0.84 to 1.22) Q4 (>7,040 ng/mL-yrs): 0.96 (0.78 to 1.18)

[a] 0, no association; +, positive association; -, negative association.

β=regression coefficient, OR=Odds Ratio, HR= Hazard Ratio, CI= 95% Confidence Interval, lnPFOA = natural log transformed PFOA, Q=quartile, IQR=Interquartile range, TC=total cholesterol, HDL=high-density lipid, non-HDL=LDL+VLDL, LDL=low-density lipid cholesterol, TC=triglyceride, VLDL=very low-density lipid cholesterol.

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