Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

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Location: DuPont/Chemours, Dordrecht, The Netherlands

RIVM Letter Report 2016-0049
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Colophon

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Audience Summary

Risk assessment of PFOA emissions for local residents
Location: DuPont/Chemours, Dordrecht, The Netherlands

Residents near the DuPont/Chemours chemical plant in Dordrecht have been exposed to the substance perfluorooctanoic acid (PFOA) for years through the air. It is likely that as a result they have been exposed to higher levels of PFOA for a long time than the limit value for chronic exposure set by the RIVM. Several scenarios have been calculated for this exceedance. In the worst case, the limit value has been exceeded for 25 years. With such chronic exposure to PFOA, health effects, such as to the liver, cannot be ruled out. There is no increased risk of harm to the unborn child. Animal studies show that the additional risk of cancer appears to be limited. More concrete explanations of possible health effects cannot be given on the basis of this study.

In this risk assessment, RIVM has investigated to what extent the substance PFOA was released into the environment from the factory in Dordrecht between 1970 and 2012 and what possible health effects this has had on local residents. For this purpose, the distribution in air and drinking water was examined. There is no increased exposure of local residents to PFOA via drinking water around the factory.

PFOA has been used for the production of Teflon until 2012. In 2013, the substance was placed on the list of Substances of Very High Concern in Europe because the substance is difficult to degrade (persistent), bioaccumulative, harmful to reproduction and possibly carcinogenic. The RIVM limit value takes into account the 'accumulation' of PFOA in the body and long-term exposure. This limit value can therefore be used to assess the risks of exposure since 1970.

No negative effects on health are expected with long-term exposure below the level of the RIVM limit value for chronic exposure. Above the limit there is a risk of health effects. From 2002, based on the analysis, the RIVM limit value is no longer exceeded. Based on the risk assessment, recommendations are made for additional research, which can be used to determine whether a health assessment among local residents is useful.

Potential health effects in workers are beyond the scope of this study. Based on the results of this study, further research into the risks for employees is desirable.

RIVM conducted this study at the request of the Ministry of Infrastructure and the Environment (IenM) after questions from the House of Representatives. These were prompted by attention to various American studies on health effects in relation to PFOA emissions from a DuPont factory in the United States. Exposure to PFOA via drinking water and air was higher there than in Dordrecht.

Keywords: C8, perfluorooctanoic acid, Dordrecht, Sliedrecht, emission, factory, health effects, cancer risk, liver effects, exposure, air, drinking water

Synopsis

Risk assessment of the emission of PFOA
Location: Dupont/Chemours, Dordrecht, The Netherlands

People living in the direct neighborhood of the Dupont/Chemours factory in Dordrecht have been exposed to perfluorooctanoic acid (PFOA) by air for many years. It is likely that they have been chronically exposed to higher values of PFOA than the limit value for chronic exposure derived by RIVM.

Several scenarios for emission were used to estimate the exposure period above the limit value. In the most unfavourable case, the limit value was exceeded for 25 years.
At such a level of chronic exposure to PFOA, health effects, such as on the liver, cannot be excluded. The risk assessment did not indicate risks to the unborn child. The additional cancer risk seems to be limited.

RIVM made a risk assessment of the emission of PFOA from the factory in Dordrecht between the years 1970 and 2012 and possible health effects for people living in the neighborhood of the factory. This was based on an estimation of the distribution of PFOA in air and drinking water. PFOA levels were not elevated in drinking water for the population in the neighborhood of the factory.

PFOA was used up to 2012 for the production of Teflon. In 2013, PFOA was placed on the European candidate list for Substances of Very High Concern (SVHC) because the substances is persistent, bioaccumulative, toxic for reproduction and may cause cancer. The RIVM limit value takes the accumulation of PFOA in the human body and long-term exposure into account, making it suitable for a risk assessment for exposure since the year 1970.

No negative health effects are expected for long term exposure below the level of the RIVM limit value for chronic exposure. At levels above the RIVM limit value, a risk for health effects exists. This study indicates that the RIVM limit value was not exceeded anymore after the year 2002. Based on the risk assessment, further research is recommended to decide if additional health research of the population surrounding the factory is indicated.

Possible health effects of PFOA by workers of this factory were outside the scope of the present assessment. Based on the results of this study, additional research into risks for workers is indicated.

RIVM has performed this research by request of the ministry of Infrastructure and the Environment (IenM) after questions in parliament. These were triggered by various studies on the health effects related to PFOA emission by a factory in the United States, where exposure to PFOA via drinking water and air was higher than in the case of the Dordrecht factory.

Keywords: C8, perfluorooctanoic acid, Dordrecht, Sliedrecht, emission, factory, health effects, cancer risk, liver effects, exposure

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Summary

RIVM has conducted research into possible health risks for local residents as a result of the emission of the substance perfluorooctanoic acid (PFOA, perfluorooctanoic acid) during the production of, for example, Teflon at the chemical company DuPont/Chemours in Dordrecht. The Dutch attention to this subject is prompted by various American studies on PFOA due to emissions from a DuPont factory in Parkersburg in West Virginia, United States. In response to this, questions were put by the House of Representatives to the State Secretary for Infrastructure and the Environment about the health risks for local residents in Dordrecht/Sliedrecht.

RIVM has estimated the exposure to the substance PFOA via air, drinking water and food around the factory on the basis of emission data, measurement data and calculations. The calculated exposure via the air has been used to estimate the PFOA blood serum concentrations of local residents.
The RIVM study focuses on estimating the health risks for residents living in the vicinity of the factory. The current health of local residents has not been investigated in this study. Also, this study did not look at possible health risks in employees.

This RIVM investigation shows that there may have been a long-term crossing of the limit considered safe for PFOA for local residents in the vicinity of the DuPont/Chemours factory. From about 2002 the calculated concentrations are lower than this limit. This exposure may have resulted in adverse effects on the liver. The results also show that there is a zone where no exceedance has been calculated.

PFOA is a substance associated with liver effects, effects on fetal development, and a potential cancer risk. In addition, it is known that PFOA is poorly degradable in the environment and in the human body and can accumulate in the body.
That is why this study looked at possible health risks from long-term exposure and the existing health-based limit values for PFOA have been adjusted accordingly. A health-based limit value represents a limit below which the risk of adverse effects of a chemical is considered negligible.

This limit is also protective for individuals who are highly sensitive to effects caused by PFOA.

The various elements of the risk assessment for local residents are explained in more detail below, followed by a concluding section. • Exposure • Properties of PFOA • Derivation of a health-based limit value • Risk assessment

Exposure
Humans can be exposed to PFOA through consumption of food and drinking water and by inhaling air containing PFOA.

Because PFOA can accumulate in the human body, it is important to take past exposure into account when assessing the risks and thus to consider the entire period of emission (1970-2012). For exposure via drinking water, recent measurement data of PFOA in drinking water in Dordrecht ('sampled directly at the tap') was used. This drinking water concentration has not increased compared to other areas in the Netherlands, which can be explained by the fact that the drinking water in Dordrecht and Sliedrecht comes from locations that have no influx of groundwater or surface water that may have been contaminated by emissions. This is in contrast to the American situation in West Virginia, where the concentrations in drinking water in a relatively large area were increased by about a factor of 1000 compared to the Dutch situation. Exposure via food is based on the background burden as determined in 2009 for the Netherlands.

This tax does not take into account the consumption of home-grown fruit and vegetables. For exposure via air, the emissions have been translated into air concentrations for an inhaled amount. The concentrations in the air have been corrected for the ingress of PFOA aerosol particles from the outdoor air into the indoor air. For the DuPont/Chemours site, emissions data are only available for the period 1998-2012, after 2012 there are no more emissions. The magnitude of the PFOA emissions in the period before 1998 is uncertain. Therefore, based on the limited information available, three emission scenarios for the total period (1970-

2012) for which the airborne dispersion has been calculated.
The scenario with the lowest total emissions does not include emissions for the period 1970-1992. The scenario with the highest total emission assumes that the highest estimated annual emission was emitted over the period 1970-1998. In the calculations, a distinction is made between an inhabited zone close to the company, where the air concentrations are also highest, and a zone that lies around it.

The calculated exposure via air has been converted to concentrations in human blood serum using models. The various scenarios have also been calculated here. Here, the blood serum concentration is considered the most relevant measure of exposure over long periods and different routes (air, water, food). No measurements of blood serum concentrations of PFOA from local residents are available.

For the scenario with the highest assumed exposure in the period 1970-1998, blood serum concentrations up to a maximum of 130 ng/mL and 70 ng/mL have been calculated for the inhabited zone close to the farm and the zone surrounding it. Blood serum concentrations of 10 ng/mL and 5 ng/mL, respectively, have been calculated for 2016. In the risk assessment, these concentrations were compared with the health-based limit value for PFOA.

Properties of PFOA A large
number of toxicological studies in laboratory animals have been performed with PFOA and a number of epidemiological studies in humans are also available. The data from animal studies (rat, mouse and monkey) point to the liver as the organ with the lowest

exposure effects occur (liver enlargement or liver hypertrophy). In various mouse studies, adverse effects on the development of the fetus have been found when exposed to higher concentrations. The available human data in the form of epidemiological studies provide indications for various possible health effects due to PFOA. PFOA is classified as suspected of causing cancer. This classification is based on “limited evidence in laboratory animals and limited evidence in humans”. Epidemiological studies have found a relationship between PFOA exposure and the presence of kidney and testicular cancer.

Derivation of a health-based limit value To assess the possible health risks, RIVM looked at existing assessments by authoritative bodies such as ATSDR, US-EPA, RAC and EFSA[1] . In line with these assessments, RIVM has derived a new health-based limit value, which takes into account the accumulation of the substance in the human body during long-term exposure. For both the development of liver effects and effects on the development of the fetus, blood serum concentrations considered safe for humans have been derived on the basis of toxicological data for different animal species and uncertainty factors. Hepatotoxicity is the most sensitive effect in laboratory animals. The safe serum concentration for humans derived on the basis of animal studies is therefore also considered to be protective against other adverse health effects. The blood serum concentration of 89 ng/mL blood serum thus derived has been used as a health-based limit value for long-term exposure. Due to the uncertainty factors used, this limit value is also protective for people who are above average sensitive to effects caused by PFOA.

Risk assessment

The health-based limit value was then compared with the calculated blood serum concentrations of people living in the vicinity of the factory. .

These are clearly above the background concentrations in blood serum as known from the literature. This comparison shows that in the past, long-term exceedances (up to a maximum of 25 years) of the health-based limit value for PFOA have probably occurred in the zone close to the farm. During this period there was an increased risk for liver enlargement. From about 2002, the calculated blood serum concentrations of local residents in the zone immediately around the farm have been lower than the health-based limit value for PFOA in blood serum. The calculated blood serum concentration for the moment (2016) does not entail any toxicological risk.

A first indicative calculation of cancer risk in animal studies indicates an additional risk level of 'one in a million per lifetime'. That is, an estimated one in a million people can develop cancer due to the calculated exposure to PFOA. This additional risk is a negligible risk compared to other environmental factors. In

[1] ATSDR: Agency for Toxic Substances and Disease Registry (US); US-EPA: United States Environmental Protection Agency (US); RAC: Risk Assessment Committee of the European Chemicals Agency; EFSA: European Food Safety Authority.

Epidemiological studies among American residents and workers of a factory where PFOA was used found an increased incidence of kidney and testicular cancer, but due to the large differences, including in exposure, this is not easy to translate to the Dutch situation. An assessment of the probability of an increased risk for these tumor types among residents living near DuPont/ Chemours in Dordrecht therefore requires further comparison of the Dutch and American epidemiological data.

In conclusion

As usual in a risk assessment, this assessment also contains uncertainties. For example, the exposure via the air and the associated blood serum concentrations are estimates, since no measurement data are available. However, the calculated exposure in Dordrecht and Sliedrecht is lower than the exposure around the factory in West Virginia, in the United States.

There are also uncertainties in the derivation of a health-based limit value. These uncertainties have therefore been taken into account in the derivation of a health-based limit value, for example for differences in sensitivity to the substance between humans and animals and between the average person and sensitive people. It is undesirable that the health-based limit value has probably been exceeded for a long time in the past. This means that health risks cannot be ruled out.

Because this study was limited to exposure of local residents, the Dordrecht/Sliedrecht area, there is currently no certainty about the risks of PFOA in drinking water extraction north of the Merwede. It is recommended to take measurements of PFOA in individual extraction wells in the intake area of the drinking water abstraction areas north of the Merwede. Specific measures can be taken if certain extraction wells contain higher concentrations.

The current risk assessment does not yet indicate whether health research among local residents is useful. In order to draw a conclusion on this, a further evaluation of available epidemiological information is recommended. This must show whether there are possible further complaints or disorders that require further attention for the residents of DuPont/Chemours in Dordrecht.

In addition, a targeted sample can be taken among local residents to check whether the blood serum values for 2016 are indeed below the health-based limit value.
Studying the epidemiological data and targeted blood tests can lead to a better estimate of the usefulness of health research.

In this study, the focus was on the risk assessment by PFOA for local residents. The historical exposure of workers differs from that of local residents and has not been examined in this risk assessment.
It is recommended to conduct further research into the risks that employees have run.

1 Introduction

Since the autumn of 2015, special attention has again been paid to the possible health damage to residents living in the vicinity of the chemical company DuPont/Chemours in Dordrecht as a result of the emission of the substance perfluorooctanoic acid (PFOA, *perfluorooctanoic acid)* during the production of Teflon. This has led to questions in the House of Representatives and the Ministry of Infrastructure and the Environment has instructed RIVM to investigate the concentrations of PFOA in air and water that may have led to emissions and to estimate any health risks for local residents.

The Dutch attention to this subject has been prompted by various American publications on PFOA emissions from a DuPont factory in Parkersburg in West Virginia, for which extensive scientific research has been carried out, including exposure studies (particularly for drinking water) and epidemiological health research. In the Dutch company, the use of PFOA has been stopped since 2012.

The Ministry of I and M has asked RIVM to elaborate the following:
feed:

- dispersion calculation for air based on available information on the annual emission of PFOA to air at DuPont/Chemours in Dordrecht
- estimation of the consequences of the emission for the PFOA concentration in air and drinking water
- estimation of the risk of exposure of local residents to these concentrations

Our method is described below. Chapter 2 describes the existing health-based limit values for PFOA from authoritative international bodies and assesses toxicological information. A health-based limit value represents a limit below which the risk of adverse effects of a chemical is considered negligible. Taking into account the bioaccumulative properties of PFOA in humans, RIVM derives a new chronic and semi-chronic limit value, including the corresponding concentrations of PFOA in human blood serum. The thus calculated, safe serum concentration for humans is therefore protective against other adverse health effects. Chapter 3 on exposure estimation discusses the available data on exposure through food and on PFOA concentrations in drinking water at the location around the company in Dordrecht.

Emission figures and the approach to dispersion calculation for air are then described. Due to the accumulative behavior of PFOA in the human body, the risk assessment should also take into account past exposure. In the exposure analysis, serum concentrations are calculated for the total period of exposure (1970 to 2012) and also for the period up to 2030. In chapter 4 the calculated historical serum concentrations are evaluated for health-related significance using the derived limit value. Attention is also paid to the possible cancer risk due to PFOA (based on

of extrapolation from laboratory animals). The report is concluded in chapter 5 with a discussion and conclusion of the findings.

The current health of local residents has not been investigated in this study. Also, this study did not look at possible health risks in employees.

The current risk assessment does not provide an analysis of the available epidemiological studies.

2 Hazard assessment

2.1 Toxicological information on PFOA

Numerous toxicological studies in laboratory animals have been performed with PFOA and related compounds such as polyfluorooctane sulfonic acid (PFOS) as well as a large number of epidemiological studies in humans.
Source documents for this risk assessment were EFSA (2008), ATSDR (2015), ECHA/RAC (2015a) and US-EPA (2014).

PFOA is classified within the European Regulation (EC) No. 1272/2008 on Classification, Labeling and Packaging of Substances and Mixtures (CLP Regulation) as Carcinogen Category 2, Reproduction Toxic Category 1B and Specific Target Organ Toxicity after Repeated Exposure (STOT RE 1 Liver).

PFOA and the ammonium salt of PFOA (APFO) were identified as substances of very high concern (ZZS) within the European Regulation REACH (EC) No 1907/2006 in 2013 because of the persistent, bioaccumulative and toxic (PBT) properties of these substances.

2.2 Existing health-based limit values

A health-based limit value represents a limit below which the risk of adverse effects from a chemical is considered negligible. A health-based limit value is derived on the most sensitive toxicological effect. For PFOA, this is liver toxicity.

Since PFOA is classified as toxic for reproduction, it is important to derive the cut-off value for this endpoint as well.

A summary of the existing health-based limit values is given in Table 1.

What follows is a description of how these limit values are established.

Table 1 Overview of the available and derived health-based limit values for PFOA

Instance Year		Duration	limit value		Critical effect	Kind
			In the evening (of mL-1)	External dose (in kg lg-1 day-1)		
EFSA	2008 Chronic			1500	liver effects Rat Mouse	
ECHA/ RAC	2015		800		Reproduction effects liver	Mouse
US EPA	2014 Chronic		142	20	effects Rat liver effects	
ATSDR	2015 Semi chronic		173	20	Monkey	
RIVM	said report	Semi chronic	710	100	liver effects Rat	
		Chronic	89	12,5		

In 2008, EFSA derived a Tolerable Daily Intake (TDI) of 1500 ng kg lg-1 day-1 for PFOA .

EFSA gives BMDL10 values of 0.3 - 0.7 mg kg bw-1 day-1 for liver effects (weight gain, necrosis, megaocytosis) in various studies in rat and mouse. In the TDI derivation, the lowest BMDL10 of 0.3 mg kg bw-1 day-1 was divided by assessment factors of 10 for inter-species differences, 10 for intra-species differences, and an additional factor of 2 to compensate for uncertainty about internal dose kinetics. ECHA/RAC (2015a) calculated a health-based reference value (DNEL) based on a mouse reproduction effects study conducted by Lau et al. (2006). Decreased weight in the offspring was the most sensitive effect in this study with a NOAEL of 1 mg kg bw-1 day-1. This level corresponded to a mouse serum concentration of 20 µg mL-1. Dividing this concentration by assessment factors of 2.5 for the inter-species difference in mouse-human toxicodynamics and 10 for susceptible groups in the human population, ECHA/RAC calculated a DNEL expressed as a serum concentration of 800 ng mL-1. A derivation based on another mouse reproductive toxicity study by Abbot et al. (2007), which found reduced postnatal survival of offspring, with an estimated no-effect serum level of 20.8 µg mL-1 , on a comparable DNEL (ECHA/RAC 2015a). ECHA/RAC indicates that the extreme difference in the kinetic behavior of PFOA between mouse and human introduces uncertainty in the derivation but chooses to process this uncertainty in a qualitative way in the risk characterization.

The derivations by EFSA (2008) and ECHA/RAC (2015a) only take into account the large differences in bioaccumulation of perfluorinated compounds between humans and laboratory animals in a qualitative sense. However, in the case of dioxins and furans, such differences have already been quantitatively taken into account when deriving the TDI since 1998 (Van Leeuwen and Younes, 2000; SCF, 2000, 2001; JECFA/WHO 2002; 2005; US EPA, 2012a , b). Furthermore, EFSA has also applied the same method to the “polybrominated diphenyl ethers” (PBDEs)) (EFSA, 2011) and ATSDR and US EPA also for PFOS and PFOA (US EPA, 2014; ATSDR, 2015). ATSDR derived a health-based reference value for PFOA for an intermediate exposure duration, which was determined by

ATSDR is defined as a period of 14 to 365 days. This limit value, of 20 ng PFOA kg bw-1 day-1, is much lower than the values derived by EFSA and ECHA/RAC and corresponds to a human serum concentration of 173 ng mL-1. The US EPA also calculated a health-based limit of 20 ng PFOA kg bw-1 day-1 (US EPA, 2014).

ATSDR (2015), RAC (2015a) and US-EPA (2014) do not use information from epidemiological studies for the derivation of the quantitative health limit value.

2.3 Derivation of health-based limit values by RIVM

A summary of the health-based limit values derived by RIVM is given in Table 1. Below is a description of how these limit values have been established.

Hepatotoxicity and embryotoxicity have been observed in studies in rats, mice and monkeys. Rat and mouse are extra sensitive to liver toxicity by PFOA because these animal species exhibit PFOA dependent PPAR-alpha receptor activation. Humans are less sensitive to PPAR-alpha receptor-mediated action than rodents. Despite this difference in susceptibility to liver effects, studies in rodents have been used in the derivation of a health-based cut-off value. The arguments for arriving at a health-based limit value are described below.

The action via the PPAR-alpha receptor also probably plays a role in the effects on reproduction as found in several mouse studies with PFOA. In the study by Abbot et al. (2007), mice lacking a PPAR-alpha receptor (PPAR-alpha knockout mice) were significantly less sensitive to the observed effects on the offspring (NOAEL 10 times higher than in wild-type mice).

Three further studies on the reproductive effects in mice by Macon et al. (2011), White et al. (2011) and Tucker et al., (2015) found reduced mammary gland development in offspring at low doses. This effect occurred in offspring at doses ÿ 0.01 mg PFOA kg lg-1 day-1 (serum levels from around 75 ng mL-1) (ECHA/RAC, 2015b, Tucker et al. (2015)). It is unclear whether the PPAR-alpha receptor in the mouse also plays a role in the development of this effect. The significance of the effect found on the mammary glands in the mouse is not clear. For example, the scoring method used in determining mammary gland histopathology has not been validated.

Moreover, from the evaluations at different times in the Tucker et al. (2015) study, it seems that the effect found is transient. The authors indicate that the effect may indicate a hormone-disrupting effect, but all other parameters (including serum hormone levels and hormone-dependent sex organ endpoints) showed no effect. The conclusion is that these studies provide an indication for further research into the effect of PFOA exposure on the development of mammary glands, but that insufficient information is currently available to derive a NOAEL or BMDL or. health-based limit value for the risk assessment. This one

conclusion is in line with the conclusions drawn by ATSDR (2015) and ECHA/RAC (2015a) on this effect.

The findings of key animal studies with PFOA for both liver toxicity and reproductive toxicity are described below.

2.3.1 *Hepatotoxicity*

Hepatotoxicity based on the Perkins et al. (2004) study in the rat Perkins et al. (2004) exposed (male) ChR-CD rats to 1, 10, 30 and 100 ppm PFOS via diet for 13 weeks (corresponding to 0.06, 0.64, 1.94 and 6.50 mg kg bw-1 day-1).

Effects on absolute and relative liver weight and liver cell hypertrophy were found after weeks 4, 7 and 13 at doses 10 ppm. No cell degeneration was found.
When the PFOA exposure was stopped, these effects turned out to be reversible. From this study a LOAEL of 10 ppm (0.64 mg kg bw 1 day-1) for increased liver weight and a NOAEL of 1 ppm (0.06 mg kg bw-1 day-1). The serum concentration corresponding to NOAEL was 7.1 µg PFOA mL-1. The NOAEL in the rat corresponds to 1.0 µg kg bw-1 day-1 in man. Due to the extra susceptibility of rats to humans for hepatotoxicity by PFOA, an assessment factor of 1 is used for the interspecies difference in the toxicodynamics of PFOA between rats and humans. With a further assessment factor of 10 for susceptible groups in the human population, a semi-chronic health-based cut-off value of 100 ng kg bg-1 day-1 results, corresponding to a serum concentration in humans of 710 ng mL-1.

Correction is still necessary to derive a chronic health limit value (for lifelong exposure). An additional assessment factor of 8 is applied for this (for details, see Technical Addendum TA-3). This leads to a health-based limit value calculated by the RIVM for chronic exposure to PFOA equal to 12.5 ng kg bw-1 day-1, corresponding to a serum concentration in humans of 89 ng mL-1.

Liver toxicity based on the Butenhoff et al. (2002) study in monkeys In the monkey study with PFOA by Butenhoff et al. (2002), liver toxicity was observed after semi-chronic administration.

Dose levels of 0.3, 10 and 20/30 mg PFOA kg bw-1 day-1 were administered to cynomolgus monkeys for 26 weeks. In this trial, there was dose-related liver weight gain at all dose levels. The only accompanying histological/biochemical changes were mitochondrial proliferation (all dose levels) and increased serum triglycerides (10 and 20/30 mg kg-1). At 20/30 mg kg-1 , severe liver effects were found in animals that showed strong toxic reactions (eg weight loss). The latter points to a steep dose-response relationship for hepatic effects by PFOA. A similar monkey study with the related compound polyfluorooctane sulfonic acid (PFOS) also showed hepatic effects (increased liver weight in combination with cellular hypertrophy and lipid evacuolation) (LOAEL 0.75 mg kg bw-1 day-1, NOAEL 0.15 mg kg bw-1

1 day-1) (Seacat et al. 2003). In the PFOA study by Butenhoff et al. (2002), no liver weight increase was found at 10 mg/kg in two monkeys after an exposure-free period. This indicates that the liver effect is reversible at least in its mild form.

Although serum concentrations have been reported for all exposure levels in this study, the relationship of these levels to the administered dose is unclear. Therefore, this study was only used to substantiate the development of liver toxicity as the most sensitive effect in laboratory animals.

2.3.2 *Reproductive* toxicity

Reproductive **toxicity based on the Lau et al. (2006) study in the mouse** Lau et al. (2006) administered daily po during days 1-17 of gestation 1, 3, 5, 10, 20 or 40 mg PFOA kg bw -1 to CD-1 mice. Several effects were found in offspring, including fetal loss, stunted growth and developmental effects during puberty. For growth disturbance in the offspring (the most sensitive effect), a NOAEL of 1 mg kg lg-1

day-1 found (corresponding BMDL5: 0.86 mg kg bw-1 day-1). The associated serum level was 20 µg mL-1 at the end of gestation. This level in the mouse corresponds to 1.98 µg kg bg-1 day-1 in man. It is not known whether the reduced growth in the offspring as observed in the study by Lau et al (2006) is related to the PPAR-alpha receptor in the mouse. Therefore, an assessment factor of 3 is applied for the inter-species difference in the toxicodynamics of PFOA between mice and humans. A further factor of 10 for susceptible groups in the human population results in a health-based cut-off value of 66 ng mg kg bw-1 day-1, corresponding to a human serum concentration of 666 ng mL-1.

2.3.3 In summary, the lowest calculated health limit value is 12.5 ng kg *bw* -1 day-1, based on liver hypertrophy in the rat. This value corresponds to a human serum concentration of 89 ng mL-1. This serum concentration was used as a starting point in the risk assessment.

2.4 Carcinogenicity (carcinogenicity)

As indicated above, PFOA is classified within CLP as a Carcinogen category 2, “suspected of causing cancer”.
The World Health Organization (WHO) has placed PFOA in Class 2B, “possibly carcinogenic to humans”. The WHO classification is based on “limited evidence in laboratory animals” and “limited evidence in humans” (IARC 2015). The limited evidence in animal studies comes from rat studies that found increased incidences of tumors in liver, testes and pancreas. The limited evidence in humans is derived from an epidemiological study in the residents of the DuPont plant in Parkersburg in the US (Vieiria et al. 2013) and a study in the employees of the same company (Steenland and Woskie 2012). In these studies, positive associations were found between

exposure to PFOA and the prevention of kidney and testicular cancer.

The animal data consists of two oral rat experiments. In both studies, the frequencies of liver and testes tumors were increased at the highest dose and in one study the frequency of pancreatic tumors. In order to determine how relevant these findings are for the lower dose levels (compared to the laboratory animals in these studies) to which humans can be exposed, it is important to consider the mechanism of development of the tumors found. Based on the performed genotoxicity studies, PFOA is considered a non-genotoxic substance (EFSA, 2008; US-EPA 2014). Based on further mechanistic information, US EPA (2014) concludes that the liver tumors in the rat are probably the end result of the effect on PPAR-alpha receptor in the rat and that they are therefore not relevant to humans. For the testes tumors (Leydig cell tumors), a hormonal mechanism could be the explanation, but no definitive conclusion can be drawn at this time. This also applies to the pancreatic tumors found.

Because PFOA is considered a non-genotoxic substance, the health-based limit value based on the most sensitive effect is also protective against cancer. In order to give an indication of what exceeding this limit value means for the risk of cancer, a calculation can be made on the basis of animal data and dose-related cancer risk. US-EPA calculated for the testicular tumors in the rat a unit risk[2] of 0.07 mg-1 kg bw-1 day-1. For the pancreas, the dose-response relationship is too uncertain to calculate a unit risk (US EPA 2014). Based on the 'unit risk' for test tumors, the possible additional cancer risk can be estimated for the calculated exposure of people living in the vicinity of DuPont/Chemours. The outcome can be compared with the standard risk levels defined in the Dutch environmental policy for chemical substances, ie the Maximum Permissible Risk (MPR) and Negligible Risk (VR).

This assessment against MTR and VR is only possible for the observed testes tumors in laboratory animals. The dose response of the associations found in epidemiological studies for renal and testes tumors is considered too uncertain to estimate the carcinogenic potential.

[2] A unit risk means that a lifetime exposure equal to 1 mg-1 kg bw-1 day-1 corresponds to a additional cancer risk of 0.07.

3 Exposure Estimation

3.1 PFOA in drinking water and food

Concentrations of PFOA in drinking water ("tap water") have recently been determined throughout the Netherlands (Zafeiraki et al., 2015). The measured concentrations ranged from 1.9 to 11.1 ng L-1.

Recent measurements in the Dordrecht region indicate a level in drinking water of 2.5 ng PFOA L-1 (Evides mail 29-02-2016 to RIVM). Drinking water in Dordrecht is produced from Meuse water (Biesbosch basins upstream) and deep groundwater from another location where no influence of the groundwater below the industrial estate has been demonstrated (<0.5 ng PFOA L-1). Based on the available information, this concentration of 2.5 ng L-1 has been chosen as the most representative for drinking water.

For food (also for the location around DuPont/Chemours) the background load as determined in 2009 for the Netherlands is assumed. This tax does not take into account the consumption of home-grown fruit and vegetables.

Based on a PFOA concentration in drinking water of 2.5 ng PFOA L found in 2015 in the Dordrecht region and the background exposure from food in the Netherlands in 2009, [1] these routes results between 0.18 (median) and 0.44 (99 percentile) ng kg bg-1 day-1 (Table 2).

For exposure via drinking water, this report calculates with the concentration of drinking water that comes out of the taps of residents living in the vicinity of Dupont/Chemours in Dordrecht. The study assumes that the inhabitants of the area concerned consume this water.

A limited number of measurements (in the period 2014-2015) in drinking water in supply areas north of the Merwede show (see Technical Addendum concentrations of 10-40 ng PFOA L TA-1).

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These data were not used in the study because the residents who use this drinking water were not in the area studied in Dordrecht
live.

If exposure from air such as may have occurred in the vicinity of the DuPont/Chemours site is also taken into account, it appears that in the period 1998 – 2012 inhalation exposure was by far the most important exposure route (see Tables 3 and 4, for details see Technical Addendum TA-2).

Table 2. Estimated exposure to PFOA via drinking water and food from local residents in the Dordrecht region.

Exposure to PFOA from food and drinking water (Dordrecht region, ng kg lg-1 day-1)		
Nutrition	**Drinkwater**	**Total**
0.11 (to the median)	0,07	0,18
0.37 (99 percentile)	0,07	0,44

3.2 **PFOA emissions and dispersion to air** Using the OPS-PRO version 4.4.4 calculation model, dispersion calculations were performed based on the emission figures for PFOA (characteristics and annual loads) made available by the Environment Agency and DuPont/ Chemours. The OPS-PRO calculation model is suitable for calculating the concentrations of aerosols and gases. Literature research, inquiries with DuPont/ Chemours itself and the revision permit of 1998 show that the PFOA is released as a gas during a drying process. The gas coagulates as it is released and forms aerosols, small particles. In the dispersion calculation, the diameter of the particles has been assumed as follows: 90% 0-1 µm, 10% 1-2.5 µm (in accordance with DuPont/Chemours statement by e-mail dated 13-10-2015).

The annual load from chimneys L12 (PTFE, the Teflon factory), L20 (FEP factory) and L42 (Viton) has been calculated. For the years 1998 to 2003, the annual average concentrations were calculated on the basis of the meteorology of that year. For the other years, the annual average concentrations have been scaled to annual load. The distribution is calculated in a grid of 50 by 50 km. In this grid, the concentration is calculated in cells that are each 100 by 100 meters in size. The calculation result therefore does not give the exact concentration at any point, but the average concentration in the relevant 100 x 100 m grid cell.

Based on the calculated distribution pattern, two distinctive zones were chosen in which local residents could be located, one zone at a greater distance (the outer contour in the distribution map in Technical Addendum-TA-2) and a second zone with a twice higher annual average concentration (this zone corresponds to the area within the inner contour in the distribution map in Technical Addendum-TA-2).

For the period before 1998 it is only known that the emission of PFOA to air was reduced in 1998 and that the emission in the 1990s is expected to be higher than in the period from 1998 onwards. In the years prior to 1998, it was established that: “In the 1990s, emissions were expected to be higher than in the period from 1998 onwards. In the limited study of the years before 1998, it was established that from 1992 a temporary standard of 14 tons per year applied and that the calculated emission load of less than 5 tons per year was reported” (Memo Milieusdienst Zuid-Holland Zuid, 01 October 2015, PFOA emissions from Chemours and context of the data, Case number 150531). From this it can be concluded that the PFOA concentration in the air of

residents in the period 1992 – 1998 has been higher than in the subsequent period.
To reflect the uncertainty in emissions over the total period between 1970 and now when calculating expected serum levels, the following three exposure scenarios have been used:

Scenario 1
Scenario 1 is based on the PFOA concentrations in air calculated for this period on the basis of the available emission figures for this period. Between 1992 and 1998, a proportionally scaled annual average concentration in air is assumed, based on an estimated annual load of 5000 kg year-1 for this period.

Before 1992 and after 2012, no emissions took place in this scenario.

Scenario 2
This scenario is the same as scenario 1 with the extension that the annual load of 5000 kg year-1 is not only assumed for 1992-1998 but for the total period from 1970 onwards.

Scenario 3
This scenario is similar to scenario 2 except that for the period 1970-1992 a gradual build-up of the annual load has been adopted up to the level of 5000 kg year-1 in the period 1992-1998.

The calculations of the concentration in air should be regarded as indicative. There are no measurements of PFOA available to validate the model calculations. It should be noted, however, that the greatest uncertainty in the concentration calculations is most likely to be found in the emission figures.

Table 3. Estimated exposure to PFOA from food, drinking water and air (ng kg bw-1 day-1) based on annual mean concentration in air in the inner contour in the period 1998 – 2012.

Period	Food and drinking water (99 percentile) 0.44 0.44	Sky
1998	0.44 0.44 0.44	8,9
1999	0.44 0.44 0.44	9,1
2000	0.44 0.44 0.44	14,3
2001	0.44 0.44 0, 44	6,6
2002	0.44	6,3
2003		1,4
2004		1,4
2005		1,1
2006		0,9
2007		0,6
2008		0,6
2009		0,6
2010		0,9
2011		0,6
2012		0,3

* Based on body weight of 70 kg

Table 4. Estimated exposure to PFOA from food, drinking water and air (ng kg bw-1 day-1) based on annual mean concentration in air in the inner contour in the period 1998 – 2012.

Period	Food and drinking water (99 percentile) 0.44 0.44	Sky
1998	0.44 0.44 0.44	17,7
1999	0.44 0.44 0.44	17,1
2000	0.44 0.44 0.44	28,6
2001	0.44 0.44 0, 44	12,0
2002	0.44	11,7
2003		2,6
2004		3,7
2005		2,6
2006		2,3
2007		1,4
2008		1,7
2009		1,1
2010		1,7
2011		1,1
2012		0,9

3.3 **Calculation of serum concentration with kinetic model** For a risk assessment of PFOA, the serum concentration was chosen as exposure measure. Due to the bioaccumulative properties of PFOA, an exposure measure that reflects historical exposure is needed. In addition, the use of serum concentration simplifies the comparison between PFOA exposure via different routes (oral, inhalation)

A so-called one-compartment kinetic model was used to calculate the relationship between (oral or inhalation) exposure and the PFOA level in the blood serum (for details, see Technical Addendum TA-4). This model is consistent with the model used by ATSDR and US EPA to derive a health-based reference value for PFOA and also with the model used in the US to calculate the combined PFOA exposure from different exposure sources (drinking water and air) at the case in Parkersburg (Lorber and Egeghy, 2011; Shin et al., 2011a,b; Winquist et al., 2013).

In the modeling it is assumed that 20 m3 of air is inhaled daily and that 50% of inhaled PFOA is absorbed into the body (Lober and Egeghy, 2011).

PFOA is present in the air as an aerosol, especially in the submicron fraction (ÿ 1 µm) (see above). In order to take into account the difference between indoor and outdoor air and the different indoor and outdoor residence times of local residents, a correction factor of 0.6 has been applied to the PFOA concentration in the kinetic model. This factor was chosen on the basis of a study in which the penetration of particulate matter from outdoor air to indoor air of different fractions was determined in residential houses (Park et al. 2014).

Simulated exposure scenarios *Scenario 1*
Scenario 1 is based on the calculated PFOA concentrations in air for the period between 1998 and 2012 (decreasing concentrations based on decreasing annual loads, 1998 as the base year). Between 1992 and 1998, a constant air concentration of 77 ng m-3 was assumed for the outer contour and 154 ng m-3 for the inner contour (for details, see Technical Addendum TA-2).

In this scenario, before 1992 and after 2012, the air concentration was 0 ng m-3.

Scenario 2
For the period 1998-2012, scenario 2 is the same as scenario 1. After 2012, the air concentration was 0 ng m-3. Between 1970 and 1998, a constant air concentration of 77 ng m-3 was assumed for the outer contour and 154 ng m-3 for the inner contour.

Scenario 3
For the period 1998 - 2012, scenario 3 is equal to scenario 1. After 2012, the air concentration was 0 ng m-3. Between 1992 and 1997, a constant air concentration of 77 ng m-3 was assumed for the outer contour and for the inner contour of 154 ng m-3. Between 1970 and 1992 a linear increase to 77 ng m-3 (outer contour) resp. 154 ng m-3 (inner contour) in 1992.

Simulated PFOA concentrations in blood serum Technical Addendum 5 contains the detailed results of the simulation of the blood serum PFOA concentration. The results of the simulations are shown in Figure 1 and 2.

Figure 1 shows the result of the model simulations of the expected PFOA level in the serum of local residents in the outer contour over the period 1970 – 2030. These simulations take into account the uncertainty in the emission data in the period prior to 1992 (scenario 1, 2 and 3).

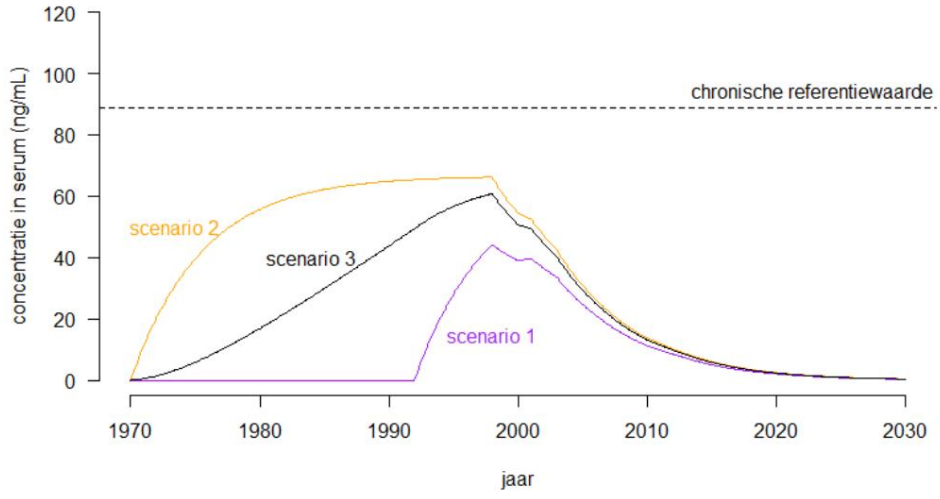

Figure 1 Model simulation of the long-term time course of the PFOA concentration (ng mL-1) in the serum of local residents in the outer contour over the period 1970 – 2030 as a result of inhalation of PFOA.

Dashed line: Lifetime health threshold for PFOA in serum based on chronic liver hypertrophy based on extrapolation from a rat study (89 ng mL-1). Purple line: scenario 1, orange line: scenario 2, black line: scenario 3.

For comparison, the serum level as a result of exposure to PFOA from food and drinking water is 4.4 ng mL-1.

Figure 2 shows the result of the model simulations of the expected PFOA content in the serum of local residents in the inner contour over the period 1970 – 2030. These simulations also take into account the uncertainty in the emission data in the period prior to 1992 (scenario 1, 2 and 3).

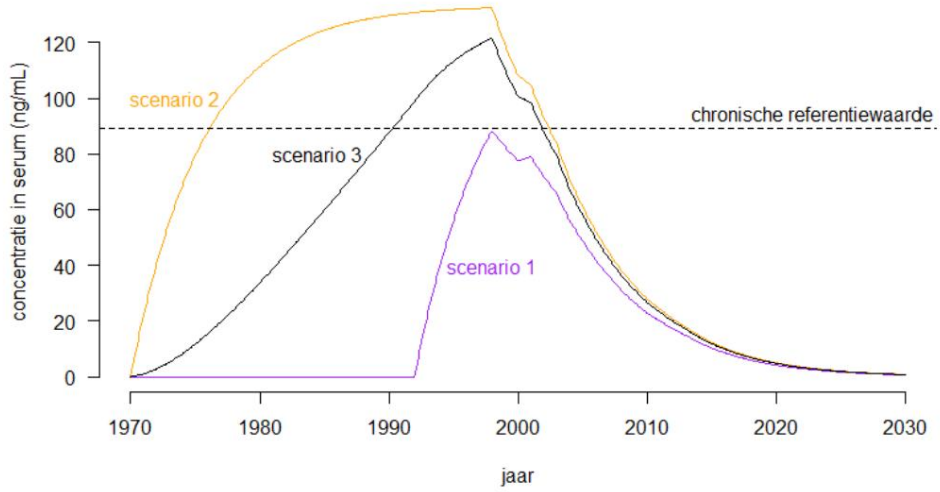

Figure 2 Model simulation of the long-term time course of the PFOA concentration (ng mL-1) in the serum of local residents in the inner contour over the period 1970 – 2030 as a result of inhalation of PFOA.
Dashed line: Lifetime health-based cutoff for PFOA in serum based on chronic liver hypertrophy based on extrapolation from a rat study (89 ng mL-1). Purple line: scenario 1, orange line: scenario 2, black line: scenario 3.

For comparison, the serum level as a result of exposure to PFOA from food and drinking water is 4.4 ng mL-1.

4 Risk assessment

4.1 Liver toxicity

For the outer contour, the simulations show no exceedances of the lifetime health-based limit value for PFOA in serum of 89 ng mL-1. The serum concentrations reach in the period of the highest emission values up to around 45 ng mL-1 in scenario 1 to around 60 -70 ng mL-1 in scenarios 2 and 3. As the figure makes clear, the serum levels from the year 1998 show a continued decline (see Figure 1).

For the inner contour, the simulations show long-term exceedances (up to 25 years) of the lifetime health-based limit value for PFOA in serum of 89 ng mL-1.
The serum concentrations reach in the period of the highest emission values to around 80 ng mL-1 in scenario 1 and to around 110-130 ng mL-1 in scenarios 2 and 3. As the figure makes clear, the serum levels show a decrease from the year 1998 and will be below the lifelong health-based limit value for PFOA in blood serum from the year 2003 (see Figure 2).

4.2 Reproductive Toxicity

For both the outer and inner contour, the health-based limit of 666 ng mL-1 was not exceeded at any time in the period between 1970 and now. The risk of reproductive toxicity is therefore estimated to be low.

4.3 Cancer risk

As indicated above, the calculation of the health-based limit values and the risk assessment is based on the 'burden of proof' for the various effects as found in animal studies and in humans. Based on the available information, liver toxicity and reproductive effects have been identified as the critical effects. For other effects, the burden of proof is limited. This also applies to the possible carcinogenic effect of PFOA. Both animal studies and available epidemiological studies provide “limited evidence” (according to the WHO rating scheme) for a carcinogenic effect by PFOA.

A risk calculation based on the frequency of testes tumors observed in laboratory animals results in an additional risk level of around one in a million per lifetime (for details, see Technical Addendum TA-6).
This corresponds to the Negligible Risk as defined in the Dutch environmental policy. However, epidemiological studies of US residents and workers at Washington Works in the US show a positive association with the incidence of kidney and testicular cancer. For these groups, the exposure was clearly higher than that for Dutch residents as described in the current report. However, the interpretation of this association for the Dutch situation is beyond the scope of the current report.

5 Discussion and conclusion

Health-based limit values To assess a possible health risk, RIVM has derived new health-based limit values based on liver toxicity in semi-chronic animal studies in rats and on reproductive toxicity in a study in mice.

Rodents are extra sensitive to hepatic effects by PFOA due to the presence of the PPAR-alpha receptor. This makes liver toxicity in rodents an extra sensitive criterion for liver damage in humans. There are indications that the PPAR-alpha receptor also plays a role in the reproduction effects as found in the mouse. So also for these effects rodents probably show an extra sensitivity compared to humans.

A study in monkeys and a study in rats are available for the derivation of the limit value for liver effects. Although serum concentrations were reported for all exposure levels in the monkey study, the relationship of these levels to the dose administered is unclear. Therefore, this study was only used to substantiate the development of liver toxicity as the most sensitive effect in laboratory animals. The drawback of the rat study is the increased sensitivity based on the presence of PPAR-alpha receptor. In this study we compensated for this drawback by omitting the usual correction factor for difference in susceptibility between laboratory animals and humans. Therefore, in this assessment, the results of the rat study have been used for the calculation of the health-based limit value.

The limit value derived in this way (89 ng ml-1) is lower than the health-based limit value of US EPA (142 ng ml-1). However, a lifetime limit value derived from the ATSDR limit value for semi-chronic exposure would be lower (21 ng mL-1) .

Exposure calculation The available information on concentrations of PFOA in drinking water in the supply area of the production location Dordrecht indicates that the concentrations are not elevated. The drinking water in question comes from the Meuse (Biesbosch) and deep groundwater from another location. It is known that in the past there have been discharges of waste water containing PFOA on the Merwede (in considerably higher concentrations than now). This may have influenced the groundwater quality north of the Merwede. It cannot be ruled out that the concentrations of PFOA found in drinking water there are caused by the discharge of waste water.

For food, the background exposure to food in the Netherlands in 2009 is assumed. A distribution calculation was performed to estimate the exposure via air of local residents. This resulted in annual mean concentrations in air of the emitted PFOA aerosol for the years 1998-2012. On the basis of available information, concentrations were estimated for the period 1970-1998. Due to the uncertainty of emissions in this period

3 scenarios were calculated for this. In order to also include the higher annual average concentrations close to the source in the calculation, two zones were calculated (inner and outer contour). Around 1992, an emission standard of 14 tons per year temporarily applied.
This risk assessment does not take into account this high annual load for the period 1970 – 1998. If we had also calculated the risks for this maximum scenario, this would logically have led to higher risks. Based on the available information, this maximum scenario does not seem realistic.

Calculated serum concentrations
The calculated concentrations in serum from inhalation are well above background. In comparison, ECHA/RAC (2015a) states a 'typical concentration' of 3.5 ng mL-1 for the general population and 21 ng mL-1 as a 'reasonable worst case' As expected, workers at PFOA production sites are significantly higher levels found (by ECHA/RAC typical concentration 2639 ng mL-1, highest 5630 ng mL-1).

For local residents, air is the main source of exposure to PFOA.
The calculations in these assessments are based on airborne exposure. The exposure to PFOA via food and drinking water of 0.44 ng/kg bw/day results in a steady state serum level of 4.4 ng/ml.

The calculated maximum serum concentrations for the residents of the factory in Dordrecht are 70 ng mL-1 for the outer contour and around 130 ng mL-1 for the inner contour. These levels are in the lower range of levels estimated for the US cohort of residents around the DuPont Parkersburg plant. An important difference with the American situation is that concentrations in drinking water were strongly increased over a relatively large area (up to several thousand ng L-1). This led to significantly higher serum levels in the highest exposed subpopulation. Emmett et al. (2006) report for the year 2002-2004 serum levels of 175-550 ng mL in highly exposed local residents (Inter Quartile Range, IQR).
[1]

Risk for liver hypotrophy For the inner contour, long-term exceedances of the lifetime limit value for PFOA in serum of 89 ng mL-1 are calculated.
Based on Scenario 2, serum concentrations up to around 130 ng mL-1 are calculated in the period of the highest emission and the concentrations are above the lifetime limit value for a period of 25 years. This means that there has been an increased risk for liver hypertrophy during this time. The total excess in terms of body load is significant.

In the American population of residents living near the Washington Works in Parkersburg, population studies were conducted in 2005-2006 into biomarkers for liver damage, the only abnormality being a small elevation of the liver enzyme ALT in the serum (Gallo *et al.,* 2012). In 2002-2004, Emmett *et al.* (2006) found no effect on liver enzymes in a subpopulation of the same population of local residents. The reported serum levels for this population were 175 – 550 ng

mL-1. It should be noted that these American findings were made at a time when emissions and exposure had already decreased and serum concentrations were therefore already decreasing (Winquist et al. 2013).

The available work-toxicological studies (carried out at companies in the US, Belgium and Italy) do not provide a clear picture of liver effects. Elevations of hepatic transaminases or gamma-glutamyl-transferase (GGT) were found in several groups of workers with high PFOA serum levels (>1000 ng/ mL-1) but this was not found in other comparable studies.

Taking into account that the studied populations (residents around the Parkersburg farm, workers in different farms) were clearly more exposed than the Dutch residents, these findings indicate that for the inner contour the risk for liver toxicity in the period of high emission is probably low.

was.

For the inner contour, the calculated serum concentrations for all scenarios have been lower than the health-based limit value since 2002. This means that the calculated current serum concentrations no longer pose a risk.

For the outer contour, no exceedance of the lifetime limit value for PFOA in serum of 89 ng mL-1 has been calculated for the period 1970 -2030 .

Possible reproductive toxicity For both the outer and the inner contour, the health-based limit value of 666 ng mL-1 is not exceeded in the period between 1970 and now. The risk of reproductive toxicity is therefore estimated to be low.

Possible cancer risk
The calculation of the health-based limit values and the risk assessment is based on the 'burden of proof' for the various effects as found in animal studies. Based on the available information, liver toxicity and reproductive effects have been identified as the critical effects. For other effects, the burden of proof is limited. This also applies to the possible carcinogenic effect of PFOA. Both animal studies and available epidemiological studies provide “limited evidence” (according to the WHO rating scheme) for a carcinogenic effect by PFOA.

A risk calculation based on the frequency of testes tumors observed in laboratory animals results in an additional risk level of around one in a million per lifetime. This corresponds to the Negligible Risk as defined in the Dutch environmental policy. However, epidemiological studies of US residents and workers at Washington Works in the US show a positive association with the incidence of kidney and testicular cancer. For these groups, exposure was clearly higher than for the

Dutch residents as described in the current report. The interpretation of this association for the Dutch situation is beyond the scope of the present report.

Conclusion and Recommendations The results of this study point to the possibility of a long-term exceeding of the limit value for exposure to PFOA for residents in the immediate vicinity of the Dupont/Chemours factory in Dordrecht. This situation has resulted in possible adverse effects on the liver. Precise information on the emissions to air in the period 1970 -1998 will provide a more accurate description of the duration of the exceedance. No increased risk for reproductive toxicity has been calculated and an initial calculation does not indicate an increased risk of cancer. The PFOA emission has stopped since 2012 and in this study it is calculated that the current PFOA concentrations in the blood of local residents have fallen below the chronic health limit value.

The exposure of the people living in the vicinity of the factory in Dordrecht and the calculated serum concentrations are lower than those of the people living in the vicinity of the factory in Parkersburg, West Virginia, America.

It is recommended to take measurements of PFOA in individual extraction wells in the intake area of the drinking water abstraction areas north of the Merwede. Specific measures can be taken if certain extraction wells contain higher concentrations.

The current risk assessment does not yet indicate whether health research among local residents is useful. In order to draw a conclusion on this, a further evaluation of all epidemiological information is recommended. This must show whether there are possible further complaints or disorders that require further attention for the residents of DuPont/Chemours in Dordrecht.

In addition, a targeted sample can be taken among local residents to check whether the blood serum values for 2016 are indeed below the health-based limit value.
Studying the epidemiological data and targeted blood tests can lead to a better estimate of the usefulness of health research.

This study did not investigate the risks for employees. Based on the assumption that workers are more exposed than local residents, further research into the risks for workers is recommended.

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Determination of perfluoralkylated substance (PFASs) in drinking water from the Netherlands. Food Add Contam Part A, 32 (12): 2048 – 2057.

Technical addendum

TA-1 Intake from food and drinking water

Exposure to PFOA from Dutch food and drinking water was established in 2009 (Noorlander *et al.,* 2011). This exposure was calculated by statistical modeling of monitoring results of perfluorinated compounds (including PFOA) in Dutch foodstuffs and drinking water and food consumption data. On an individual level, the daily short-term intake of PFOA could be calculated. At the population level, this was the case for lifelong daily intake.

The short-term dietary intake was 112 pg PFOA/kg bw/day. For drinking water this was 138 pg PFOA/kg bw/day.
Drinking water therefore contributed 55% to the combined intake of 250 pg/kg bw/day (based on the used PFOA concentration in drinking water of 9 pg PFOA/g drinking water and a body weight of 70 kg, this corresponds to a daily intake of 1073 , rounded to 1000, g drinking water).

Lifetime daily PFOA intake was estimated to be 0.24 ng/kg bw/day (median) to 0.50 ng/kg bw/day (99 percentile) value.
Assuming a daily intake of 1000 g water (according to food consumption data), a content of 9 pg PFOA/g and a body weight of 70 kg, this comes down to the following dependence on the ingested drinking water concentration:

Long-term intake (median, pg/kg bw/day) 111 + = 1000/70 x Cdrinking water (pg/g water)

Long-term intake (99 percentile, pg/kg bw/day) = 371 + 1000/70 x Cdrinking water (pg/g water)

Based on Noorlander *et al. ,* the median exposure to PFOA from (only) food is therefore 111 pg/kg bw/day.
For the 99 percentile, this is 371 pg/kg bw/day.

Measurements in drinking water in the Dordrecht area give a level from
2.5 ng PFOA L-1 (Evides mail 29-02-2016 to RIVM). If this concentration and a daily drinking water consumption of 2 L (in accordance with WHO (2011) Guidelines for Drinking-Water Quality (fourth edition)) are assumed, then a drinking water exposure of 2500 x 2/70 = 71 pg PFOA/kg calculate lg/day.

Together with the dietary exposure, this corresponds to 71 + 111 = 182 resp. 71 + 371 = 442 pg PFOA/kg bw/day for the median and 99 percentiles for the combined PFOA exposure from food and drinking water.

For the risk assessment, the P99 exposure from food and drinking water is included as a “realistic worst case” case, namely 442 pg PFOA/kg bw/day.

In the drinking water produced from groundwater that is under the influence of the Merwede, measurement data are available from 2014-2015 (Oasen personal communication). These data are presented below, but not included in this study because this drinking water was not supplied to the Dordrecht area.

Table TA-1.1 Measurements in drinking water produced from groundwater under the influence of the Merwede (2014-2015). Data provided by Oasen.

Drinking water production site	Concentration PFOA (minimum – maximum (µg/L) N=number of measurements
A	0,02 - 0,03 N= 7
B	<0,01 - 0,04 N= 7
C	0,01 – 0,03 N= 7

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TA-2 Calculations PFOA air concentrations

Starting points The
following starting points have been used: - The
distribution calculation has been carried out with the calculation model OPS-PRO version 4.4.4. This calculation model was developed by RIVM. It is suitable for calculating the concentrations of a substance in an environment at a (standard) height of 4 m. The distribution of both aerosols and gases can be calculated.

- From literature research, inquiries with Chemours itself and the The 1998 revision permit shows that the PFOA is released as a gas from a drying process in both plants. However, the gas coagulates as it is released and forms aerosols, small particles (Paustenbach *et al.,* 2007 and Shin *et al.,* 2011). This process will continue for some time after the PFOA has been released. The PFOA can also attach to other dust particles that are in the air.

- In the dispersion calculation, the diameter of the particles is assumed as follows: 90% 0 to 1 µm and 10% 1 to 2.5 µm (information Chemours by e-mail dated 13-10-2015). This particle size distribution is very similar to the distribution reported by Paustenbach (Paustenbach *et al.,* 2007).

- The annual load from chimneys L12 . has been calculated (PTFE, the Teflon factory), L20 (FEP factory) and L42 (Viton). The annual average concentrations for the years 1998 up to and including 2003 have been determined, taking into account the meteorology of the relevant year. For the other years, the annual average concentrations have been scaled to annual load.
- The emission characteristics of the chimneys are taken from the 1998 revision permit application. The temperature of chimney 12 was taken from the statement sent by Chemours by e-mail dated 13 October 2015. The emission characteristics used are shown in Table TA 2.1.

- The annual loads for each chimney are shown in Table TA-2.2. These data come from the Electronic Environment Annual Report and/or have been provided by Chemours.
- The distribution is calculated in a grid of 50 by 50 km. In this grid, the concentration is calculated in cells that are each 100 by 100 meters in size. The calculation result therefore does not give the exact concentration at any point, but the average concentration in the relevant grid cell.

Table TA-2.1 Emission characteristics chimney L12, L20 and L42.

Parameter	Chimneys		
	L12 (PTFE)	L20 (FEP)	L42 (Viton)
x coordinate RDM (m) y	109726	109817	109844
coordinate RDM (m) chimney	425865	425858	425831
height (m) temperature (K)	20 323	28 353 Factory hall ambient temperature	21
flow rate (Nm³/hour)	20.000	700	11.000
heat content (MW)	0,252	0,0164	

Annual freight 1998 -2013

Table TA-2-2. Emissions to air PFOA, Chemours

Year	Freight L12 (kg per year)	Freight L20 (kg per year)	Freight L42 (kg per year)	Total
1998	1595	54	500	2149
1999	1682	27	500	2209
2000	2420	612	500	3532
2001	1505	192	125	1822
2002	1876	25	0	1901
2003	415	33	0	448
2004	452	83	0	535
2005	332	46	0	378
2006	276	76	0	352
2007	177	67	0	244
2008	185	79	0	264
2009	148	40	0	188
2010	187	98	0	285
2011	135	60	0	195
2012	85	49	0	134
2013	0	0	0	0

NB. The pink colored cells contain information as obtained from Chemours. The other cells contain information obtained from the Environment Service-ZHZ / Province-ZH.

Concentration Calculations: Results

Outer contour For residents living in the outer contour, the calculation results are shown in Table TA-2.3. The spatial pattern of the calculation results of all grid cells for the year 2000 is shown in Figure TA-2.1. This is the year in which the largest annual freight was reported.

Table TA-2.3 Calculated PFOA emission and the resulting annual average air concentration of PFOA at local residents level (outer contour, see Figure TA-2-1) and the associated inhalatory daily PFOA intake by local residents by inhaling 20 m3 of *air.*

Year	PFOA emission PFOA concentration		Intake
	(kg year-1)	(buitenste contour, max, ng m-3) 33	(living, max, ng day-1) 660
1998 lt	2149		
1998	2149	31	620
1999	2209	32	640
2000	3532	50	1000
2001	1822	23	460
2002	1901	22	440
2003	448	5	100
2003 lt	448	5	100
2004	535	5	100
2005	378	4	80
2006	352	3	60
2007	244	2	40
2008	264	2	40
2009	188	2	40
2010	285	3	60
2011	195	2	40
2012	134	1	20

For the period before 1998 it is only known that the emission of PFOA to air was reduced in 1998 and that the emission in the 1990s is expected to be higher than in the period from 1998 onwards. In the years prior to 1998, it was established that: “In the 1990s, emissions were expected to be higher than in the period from 1998 onwards. In the limited study of the years before 1998, it was established that from 1992 a temporary standard of 14 tons per year applied and that the calculated emission load of less than 5 tons per year was reported” (Memo Milieusdienst Zuid-Holland Zuid, 01 October 2015, PFOA emissions from Chemours and context of the data, Case number 150531).

It can be concluded from this that the PFOA concentration in the air of local residents in the outer contour was higher in the period 1992 – 1998 than in the subsequent period. In the kinetic model simulations it has therefore been assumed as a “worst case” that in this period the annual emission coat amounted to 5000 kg, with a scaled annual PFOA concentration in the air of local residents of 5000/2149 x 33 = 77 ng m-3.

Inner contour As Figure
TA-2.1 shows, the exposure to PFOA at the local residents location closest to the source is approximately 2 times higher than at a location further from the source, such as the outer contour.

The calculation results for residents living in the vicinity of this location are shown in Table TA-2.4.

Table TA-2.4 Calculated PFOA emissions and the resulting annual average air concentration of PFOA at local residents level (inner contour) and the associated inhalatory daily PFOA intake by local residents by inhaling 20 m3 PFOA-containing air.

Year	PFOA emission PFOA concentration (inner contour,	Intake
	(kg year-1)	max, ng m-3) 66 (living, max, ng day-1) 1320
1998 lt	2149	
1998	2149	62 1240
1999	2209	60 1200
2000	3532	100 2000
2001	1822	42 840
2002	1901	41 820
2003	448	9 180
2003 lt	448	11 220
2004	535	13 260
2005	378	9 180
2006	352	8 160
2007	244	5 100
2008	264	6 120
2009	188	4 80
2010	285	6 120
2011	195	4 80
2012	134	3 60

In the kinetic model simulations it has therefore been assumed as a “worst case” that
in the period 1922 – 1998 the PFOA concentration in the air of local residents had a constant level of 5000/2149 x 66 = 154 ng m-3 .

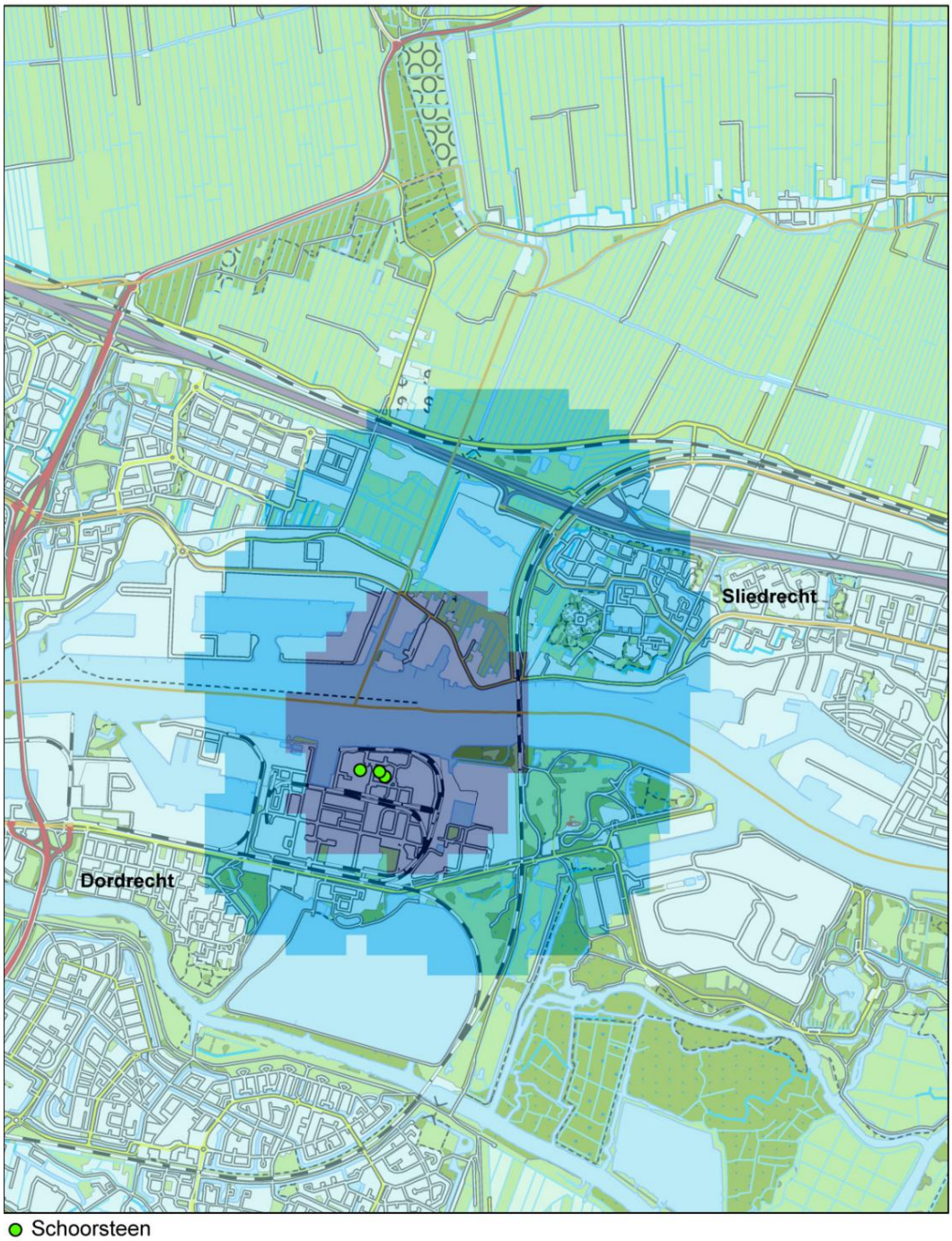

Figure TA-2.1 The calculated annual average PFOA concentration in the open air in 2000 (ng m-3) in the vicinity of DuPont Chemours Netherlands. Contours show the areas in which a minimum concentration has been calculated of 25 (light blue) and 75 ng m-3 (dark blue) respectively. The median concentration to which residents in these areas may be exposed is 50 (light blue) and 100 ng m-3 (dark blue) respectively. . *The calculations must be considered indicative.*

Modelsimulaties: Scenario's

As described earlier, the PFOA emission for 1992 is uncertain. To reflect this uncertainty in calculating the effect on historical exposure on the expected serum levels in 2016, the following three exposure scenarios have been calculated:

Scenario 1
1998-2012: PFOA concentrations in air as calculated. No more emissions after 2012.

Between 1992 and 1997: outer contour 70 ng m-3; inner contour 140 ng m-3. No emission for 1992.

Scenario 2
1998-2012: PFOA concentrations in air as calculated. No more emissions after 2012.

Between 1970 and 1997: outer contour 70 ng m-3; inner contour 140 ng m-3. No emissions before 1970.

Scenario 3
1998-2012: PFOA concentrations in air as calculated. No more emissions after 2012. 1992 – 1997: outer contour 70 ng m-3; inner contour 142 ng m

^{3} . Between 1970 and 1992 increasing linearly to 70 ng m-3 (outer contour) resp. 140 ng m-3 (inner contour) in 1992. Before 1970 none emission.

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TA-3 Derivation of the Assessment Factor for semi chronic ÿ chronic toxicity.

ATSDR derived a subchronic Health Based Guidance Value (HBGV, Nederlands: “gezondheidskundige referentiewaarde”), i.e. “a HBGV relating to an exposure duration between 14 and 365 days”. However, the actual exposure duration for the population living close to the DuPont site may grossly exceed this period and may even be as long as 42 years (1970-2012). It is thus concluded that the exposure duration related to the ATSDR HBGV does not correspond with the actual exposure duration. Below, it is discussed why the study underlying the ATSDR HBGV should be considered as a subchronic guidance value. In addition, an approach to arrive at a chronic HBGV is provided.

ATSDR derived a (chronic) HBGV based on a 6-month study in cynomolgus monkeys *(Macaca fascicularis)* [3]. However, no assessment factor was applied to account for the uncertainty of using a subchronic study as a surrogate for a chronic study.
The 6-months during study is considered a subchronic study. The life span of cynomolgus monkeys is approximately 30 years[4]. According to the EPA[5], EHC[6] and OECD[7] definitions, subchronic exposure is spanning no more than approximately 10 percent of the lifetime of an organism.
Various Assessment Factors (values) are proposed to account for subchonic-to-chronic extrapolation. Here, three overviews of proposed assessment factors are considered:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health
- Falk-Filipsson (2007) Assessment factors—applications in health risk assessment of chemicals[8]
- IPCS, Harmonization Project Document 11, Guidance document on evaluating and expressing uncertainty in hazard characterization[9]

In the ECHA guidance a subchronic-to-chronic assessment factor of 2 is proposed (R8-5). However, the summary of empirically derived assessment factors (R8-19) already shows that for at least 50% of the

[3] Butenhoff J, Costa G, Elcombe C, et al. 2002. Toxicity of ammonium perfluorooctanoate in male Cynomolgus monkeys after oral dosing for 6 months. Toxicol Sci 69:244-257.
[4] Primate factsheets, Wisconsin National Primate Research Center (WNPRC), University of Wisconsin-Madison http://pin.primate.wisc.edu/factsheets/
[5] http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary
[6] www.inchem.org/documents/ehc/ehc/ehc240_chapter4.pdf
[7] Summary of considerations in the report from the OECD expert groups on short term and long term toxicology www.oecd-ilibrary.org/summary-of-considerations-in-the-report-from-the-oecd-expert-groups-on-short-term and-long-term toxicology_5l9kd88xt4r3.pdf?contentType=%252Fns%252FOECDBook%252C%252Fns%252FBook&itemId=%252Fcontent%252Fbook%252F9789264035447-en&mimeType=application%252Fpdf&containerItemId=%252Fcontent%252Fserial%252F20745788&accessItemIds=%252Fcontent%252Fserial%252F20745788
[8] Falk-Filipsson A, Hanberg A, Victorin K, Warholm M and Wallen M (2007). Assessment factors--applications in health risk assessment of chemicals. Environ Res 104, 108-27.
[9] http://www.who.int/ipcs/methods/harmonization/uncertainty_in_hazard_characterization.pdf?ua=1

substances with a subchronic and chronic study available the difference is larger than a factor 2, i.e. when applying a factor of 2 the probability of underestimating the subchronic-chronic differences is at least 50 %.
Moreover, the empirical studies described in the ECHA guidance show that even 10% of the substances require an assessment factor larger than 10 to account for subchronic-chronic differences. Given the results from the empirical derived assessment factors, and because we want exclude the possibility of underestimating the true differences between subchronic and chronic exposure, the factor of two is not considered sufficient.

For the uncertainty distribution related to the subchronic to chronic extrapolation, several studies comparing oral NOAELs from chronic and subchronic toxicity studies were considered relevant by Falk-Filipsson *et al.* and by IPCS. Furthermore, both reviews discuss a (probabilistic) assessment factor based on benchmark ratios, such as that calculated by Bokkers and Slob (2005)10. Based on the 95th percentile of the distribution (covering 95% of the substances compared) obtained in this study, Falk-Filipsson *et al.* propose an assessment factor of 7.
IPCS considers that the reported GM of the oral subchronic to chronic ratios varies between 1 and 2.5, whereas most of them are close to 2.
The width of the distribution varies considerably among the studies, which is not clearly understood, although variability in study design is an important factor. When taking the reported BMD ratios (Bokkers & Slob, 2005) as the most relevant information, the P95/P50 ratio would be 4.
Based on these considerations IPCS proposes a probabilistic subchronic to chronic extrapolation factor with GM = 2, with P95/P50 = 4 [(P05, P95) = (0.5, 8)].
In addition IPCS discusses the oral subchronic to chronic BMD ratios, next to NOAEL ratios (for the same database) which are reported in Bokkers and Slob (2005). IPCS notes that for the BMD ratios, Bokkers & Slob (2005) found a median of 1.7, with a P95/P50 ratio of about 4. The variation in NOAEL ratios was found to be larger, the P95 value being about 15 times higher than the median (P50). However, various other studies reported factors lower than 4, the factor found for the BMD ratios in Bokkers & Slob (2005). This is considered remarkable, as higher values would be expected because (1) they relate to NOAEL ratios, (2) the latter studies do not match end-points, whereas Bokkers & Slob (2005) did, and (3) some of them did not even match species. In contrast, for example, Batke et al. (2011)11 calculated their ratios based on a millimole per kilogram body weight per day scale (oral studies), which can be expected to result in a narrower distribution than using milligrams per kilogram body weight per day, given that molecular masses of commonly used industrial chemicals span a range of 3 – 4 orders of magnitude.

In conclusion, ATSDR used a semi-chronic animal toxicity study to derive its HBGV for intermediate PFOA exposure. To scale this study to a chronic, life-long, toxicity study the application of a deterministic AF of 8 is recommended. This factor is based in the empirically derived

[10] Bokkers BGH and Slob W (2005). A comparison of ratio distributions based on the NOAEL and the benchmark approach for subchronic-to-chronic extrapolation. Toxicol Sci 85, 1033-40.
[11] Batke M, Escher S, Hoffmann-Doerr S, Melber C, Messinger H and Mangelsdorf I (2011). Evaluation of time extrapolation factors based on the database RepDose. Toxicol Lett 205, 122-9.

distribution proposed by IPCS and has a coverage of 95%, i.e. there is a 95% confidence that this factor is sufficiently large to account for the possible subchronic-chronic differences.

TA-4 Kinetic modelling

P.o. exposure (ATSDR)
In deriving its (oral) HBGV, ATSDR (2015) applied the following one compartmental PFOA kinetical model:

$$\frac{dC_s(t)}{dt} = \frac{D \cdot F_{after}}{V_d} - k_{el} C_s(t)$$

with:

Cs(t)	serum concentration (mg L-1) daily
D	external intake (mg kg bw-1 day) p.o. fraction
Fp.o.	absorbed volume of distribution (L kg bw-1)
Vd	elimination rate constant (day-1)
kel	

Considering the external dose as continuous dosing the analytical solution of this differential equation gives:

$$Ct(\,) = \frac{D \cdot F_{after}}{to_{the}\,V_d} \cdot (1 - e^{-k_{el} t})$$

With “steady state”:

$$C_{ss} = \frac{D \cdot F_{p.o.}}{to_{the}\,V_d}$$

Rewriting then gives:

$$D = \frac{C_{ss} \cdot kV_{the} \cdot d}{F_{after}}$$

The latter equation relates the chronic daily intake *D* to its corresponding “steady state” serum concentration *Css.*

Vice versa, given *Css, D* may be calculated. ATSDR applied this approach to calculate the HBGV for PFOA based on serum concentrations as observed in an experimental toxicity study in the cynomolgus monkey.
In this study animals were daily exposed to 0, 3, 10 and 20/30 mg/kg bw PFOA in capsules for 26 weeks, with toxicity evaluated at the end of the study (Butenhoff *et al.,* 2002). Serum collected at week 6 or thereafter was considered to represent “steady state” PFOA concentrations. A BMD analysis with the serum concentration as the independent variable and hepatic toxicity (absolute or relative liver weight) as the dependent variable resulted in a serum concentration of 15.53 µg PFOA/ml based on absolute liver weight as the Point Of Departure (POD) for the calculation of the corresponding daily human exposure from food. In this calculation ATSDR used the following model parameters were: *Fp.o.* = 1, *kel* = *ln2/t1/2* with *t1/2* being 1400 days and *Vd* = 0.2 L kg bw-1. This resulted in *D* = 1.538 µg/kg bw/day. On this exposure an Assessment Factor of 90 was applied, to arrive at the HBGV

of 17 ng PFOA/kg bw/day. The applied AF accounted for dosimetric adjustment (factor: 3), intra human variability (factor: 10) and uncertainty in the database (factor: 3).

Remark
The 1400 day ATSDR half-life of 3.84 years, which was based on the 5-year follow up follow-up of retired workers (Olsen *et al.,* 2007) is higher than PFOA half-lives reported elsewhere, i.e. 2.3 years (Bartell *et al.,* 2010) and 3.3 years (Brede *et al.,* 2010). The latter studies, however, were restricted to a much shorter observation time as the time period in Olsen *et al.*

Inhalatory exposure In concordance with Lorber *et al.* (2011) the daily external inhalatory dosage reads as:

$$D = FCV_{inh} \cdot C_{inh} \cdot F_{inh} / BW$$

with:

C_{inh}	the concentration in inhaled air (mg m-3)
V_{inh}	alveolar ventilation rate (m3 day-1)
F_{inn}	inhalatory fraction absorbed
BW	body weight (kg)

Taking a body weight of 70 kg, F_{inh} = 0.5 (Lorber *et al.,* 2011), V_{inh} = 20 m3 day-1, C_{inh} as provided (Table A-4). To correct C_{inh} for differences in indoor and outdoor air and for the time spent indoors and outdoors as an input term for the kinetic model it was corrected as follows:

In concordance with Park *et al.* (2014):

$$0.6\, C_{indoor} + C_{outdoor}$$

Taking 90% of the time spent indoors and 10 % outdoors then gives a time weighted inhalatory concentration of:

$$C_{inh} = \frac{0.9\ V_{inh}\ 0.6\ 0.1\ C_{outdoor}\ VC_{outdoor}}{0.9\ V_{inh}\ 0.1\ IN_{inh}} \cdot 0.6\ C_{outdoor}$$

Based on observations in the rat, i.e. an absorption rate constant of 1.3 hr-1 (Hinderliter *et al.,* 2006), a daily inhalatory volume of 20 m3 results in a 1 hour uptake fraction of 1-e(-ln2) ·1/1.3 ÿ 0.41 of the inhaled amount of 20/24 x *Cinh.*

HBGV calculations

Butenhoff study POD animal serum concentration: 14 µg mL-1.
Human half-life: 1400 days.
Volume of distribution (human): 0.2 L kg bw-1
Corresponding Equivalent Human semi-chronic Intake: 1.39 ÿg kg bw-1 day-1
AF = 3 x 10
HBGVsemi-chronic: 46.2 ng kg bw-1 day-1
Corresponding “steady state” serum concentration: 467 ng mL-1
AFsemi-chronicÿchronic
= 8 HBGVchronic: 5.8 ng kg bw-1 day-1
Corresponding “steady state” serum concentration: 58.4 ng mL-1

Lau study
POD animal serum concentration: 20 µg mL-1.
Human half-life: 1400 days.
Volume of distribution (human): 0.2 L kg bw-1
Corresponding Equivalent Human semi-chronic Intake: 1.98 ÿg kg bw-1 day-1
AF = 3 x 10
HBGVchronic: 66 of kg bw-1 day-1
Corresponding “steady state” serum concentration: 666 ng mL-1

Perkins study POD animal serum concentration: 7.1 µg mL-1.
Human half-life: 839,5 days.
Volume of distribution (human): 0.17 L kg bw-1
Corresponding Equivalent Human semi-chronic Intake: 1.00 ÿg kg bw-1 day-1
OF = 10
HBGVsemi-chronic: 100 ng kg bw-1 day-1
Corresponding “steady state” serum concentration: 710 ng mL-1
AFsemi-chronicÿchronic
= 8 HBGVchronic: 12.5 ng kg bw-1 day-1
Corresponding “steady state” serum concentration: 89 ng mL-1

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TA-5 Model simulations (inner and outer zone; scenarios 1,2,3)

Outer zone

Year	Outdoor Air Concentration (ng/m3) Scenario 1	Ventilated amount# (ng/year) Scenario 1	Outdoor Air Concentration (ng/m3) Scenario 2	Ventilated amount# (ng/year) Scenario 2	Outdoor Air Concentration (ng/m3) Scenario 3	Ventilated amount# (ng/year) Scenario 3
1970	0	0	77	337260	3	14663
1971	0	0	77	337260	7	29327
1972	0	0	77	337260	10	43990
1973	0	0	77	337260	13	58654
1974	0	0	77	337260	17	73317
1975	0	0	77	337260	20	87981
1976	0	0	77	337260	23	102644
1977	0	0	77	337260	27	117308
1978	0	0	77	337260	30	131971
1979	0	0	77	337260	33	146635
1980	0	0	77	337260	37	161298
1981	0	0	77	337260	40	175962
1982	0	0	77	337260	44	190625
1983	0	0	77	337260	47	205289
1984	0	0	77	337260	50	219952
1985	0	0	77	337260	54	234616
1986	0	0	77	337260	57	249279
1987	0	0	77	337260	60	263943
1988	0	0	77	337260	64	278606
1989	0	0	77	337260	67	293270
1990	0	0	77	337260	70	307933
1991	0	0	77	337260	74	322597
1992	77	337260	77	337260	77	337260
1993	77	337260	77	337260	77	337260
1994	77	337260	77	337260	77	337260
1995	77	337260	77	337260	77	337260
1996	77	337260	77	337260	77	337260
1997	77	337260	77	337260	77	337260
1998	31	135780	31	135780	31	135780
1999	32	140160	32	140160	32	140160
2000	50	219000	50	219000	50	219000
2001	23	100740	23	100740	23	100740
2002	22	96360	22	96360	22	96360
2003	5	21900	5	21900	5	21900

Year	Outdoor Air Concentration (ng/m3) Scenario 1	Ventilated amount# (ng/year) Scenario 1	Outdoor Air Concentration (ng/m3) Scenario 2	Ventilated amount# (ng/year) Scenario 2	Outdoor Air Concentration (ng/m3) Scenario 3	Ventilated amount# (ng/year) Scenario 3
2004	5	21900	5	21900	5	21900
2005	4	17520	4	17520	4	17520
2006	3	13140	3	13140	3	13140
2007	2	8760	2	8760	2	8760
2008	2	8760	2	8760	2	8760
2009	2	8760	2	8760	2	8760
2010	3	13140	3	13140	3	13140
2011	2	8760	2	8760	2	8760
2012	1	4380	1	4380	1	4380

#VentAmount (ng/yr) = airConc [ng/m3] * lung ventilation [m3/yr] * Foutdoor-indoor [-] lung ventilation: 20 m3/dy * 365 dy Foutdoor-indoor: indoor air concentration is a fraction of the outdoor air conc: 0.6

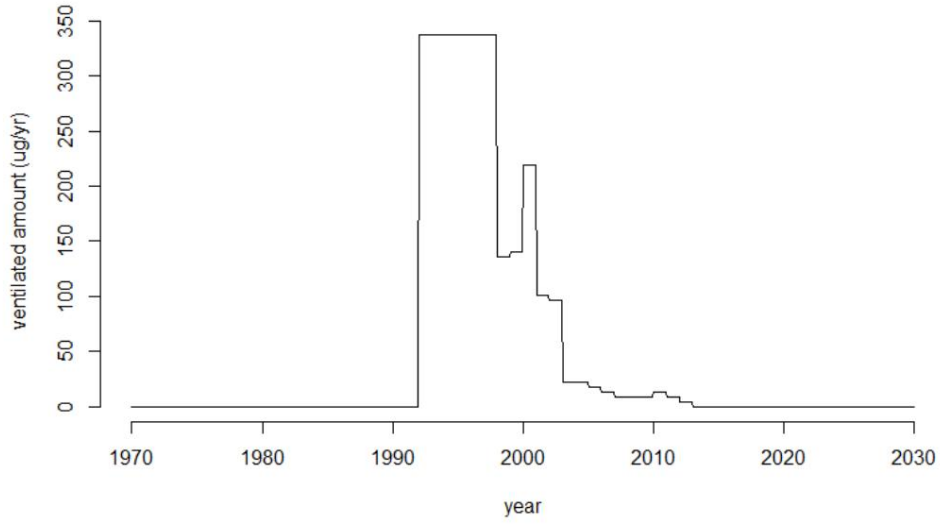

Figure TA-5.1 Scenario 1; simulated dosing regimen based on ventilated amount from indoor air.

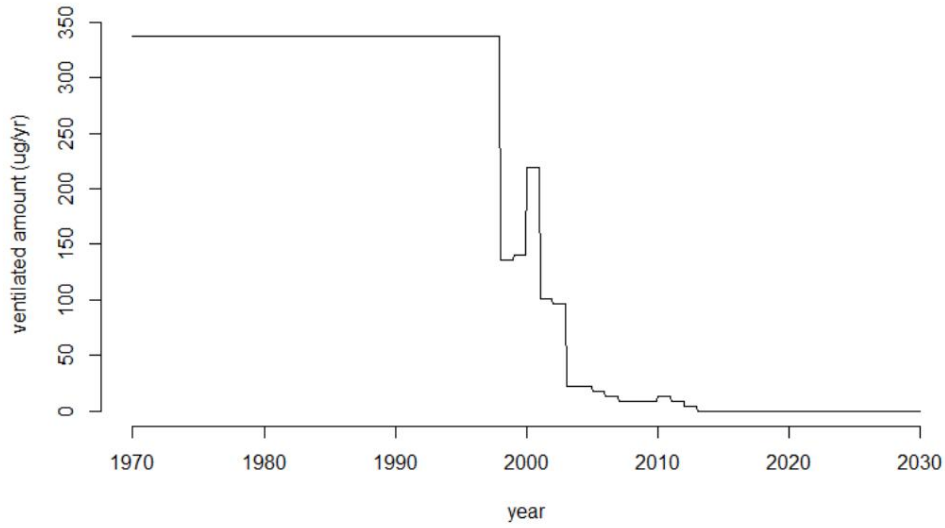

Figure TA-5.2 Scenario 2; simulated dosing regimen based on ventilated amount from indoor air.

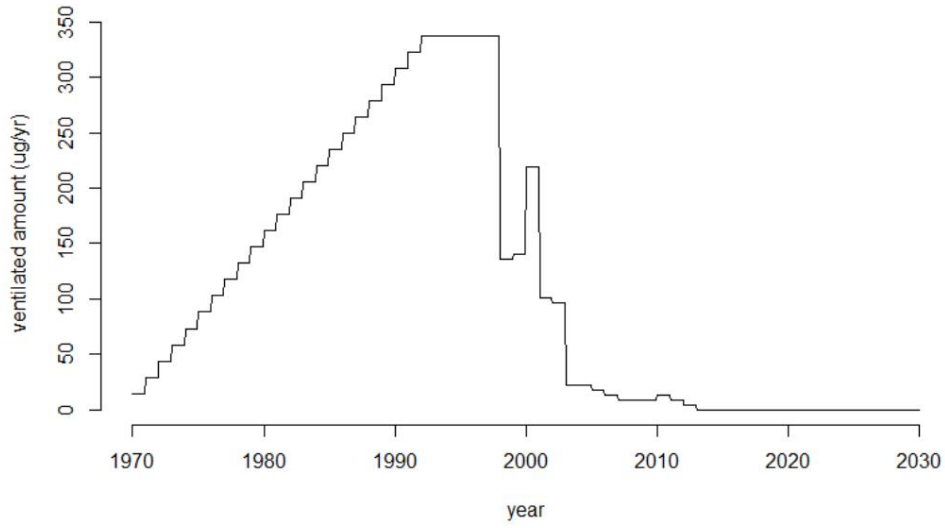

Figure TA-5.3 Scenario 3; simulated dosing regimen based on ventilated amount from indoor air.

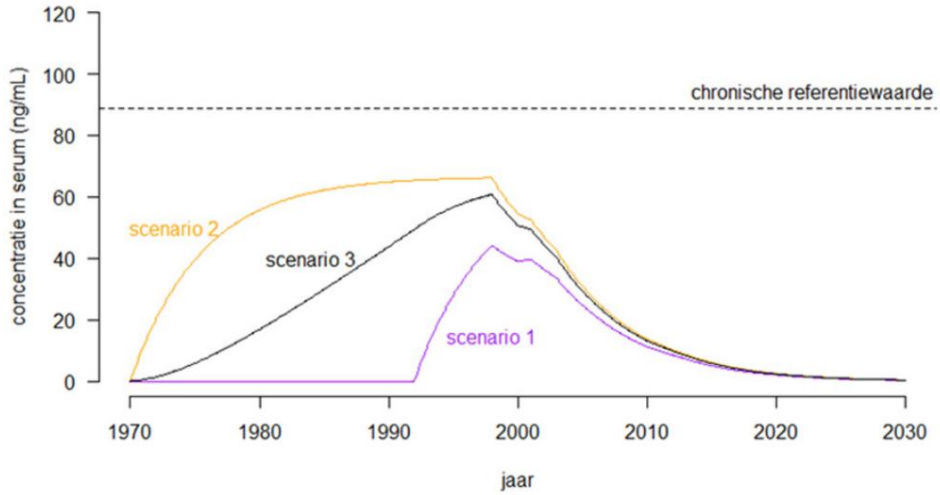

Figure TA-5.4 Scenario 1, 2 and 3; serum concentration (ng mL-1) based on ventilated amount in the outer zone. Dashed line: chronic serum reference value based on extrapolation of hepatic hyperthrophy in the rat (89 ng mL-1). Pink curve: scenario 1, orange curve: scenario 2, black curve: scenario 3.

*Table TA-5.1 Simulated serum concentrations on the first day of each year corresponding to figure TA-5.4. In **bold:** serum concentrations above the chronic HBGV of 89 ng mL-1.*

Year	Serum concentration (ng/mL)		
	Scenario 1	Scenario 2	Scenario 3
1970	0	0	0
1971	0	11.0	0.5
1972	0	20.2	1.4
1973	0	27.9	2.6
1974	0	34.3	4.1
1975	0	39.7	5.9
1976	0	44.1	7.8
1977	0	47.9	9.9
1978	0	51.0	12.1
1979	0	53.6	14.4
1980	0	55.7	16.9
1981	0	57.5	19.4
1982	0	59.1	21.9
1983	0	60.3	24.6
1984	0	61.4	27.2
1985	0	62.2	30.0
1986	0	63.0	32.7
1987	0	63.6	35.5
1988	0	64.1	38.2
1989	0	64.5	41.0
1990	0	64.9	43.9
1991	0	65.2	46.7

Year	Serum concentration (ng/mL)		
	Scenario 1	Scenario 2	Scenario 3
1992	0.5	65.4	49.5
1993	11.5	65.6	52.4
1994	20.6	65.8	54.7
1995	28.2	65.9	56.7
1996	34.6	66.0	58.4
1997	39.9	66.1	59.7
1998	44.0	65.9	60.6
1999	41.2	59.5	55.0
2000	39.1	54.3	50.6
2001	39.6	52.3	49.2
2002	36.3	47.0	44.4
2003	33.4	42.2	40.1
2004	28.5	35.9	34.1
2005	24.5	30.7	29.2
2006	21.0	26.2	24.9
2007	18.0	22.3	21.2
2008	15.3	18.9	18.0
2009	13.0	16.0	15.3
2010	11.2	13.7	13.1
2011	9.8	11.8	11.3
2012	8.4	10.2	9.7
2013	7.2	8.6	8.3
2014	6.0	7.2	6.9
2015	5.0	6.0	5.8
2016	4.2	5.0	4.8
2017	3.5	4.2	4.0
2018	2.9	3.5	3.3
2019	2.4	2.9	2.8
2020	2.0	2.4	2.3
2021	1.7	2.0	1.9
2022	1.4	1.7	1.6
2023	1.2	1.4	1.4
2024	1.0	1.2	1.1
2025	0.8	1.0	0.9
2026	0.7	0.8	0.8
2027	0.6	0.7	0.7
2028	0.5	0.6	0.5
2029	0.4	0.5	0.5
2030	0.3	0.4	0.4

Inner zone

Year	Outdoor Air Concentration (ng/m3) Scenario 1	Ventilated amount# (ng/year) Scenario 1	Outdoor Air Concentration (ng/m3) Scenario 2	Ventilated amount# (ng/year) Scenario 2	Outdoor Air Concentration (ng/m3) Scenario 3	Ventilated amount# (ng/year) Scenario 3
1970	0	0	154	674520	7	29327
1971	0	0	154	674520	13	58654
1972	0	0	154	674520	20	87981
1973	0	0	154	674520	27	117308
1974	0	0	154	674520	33	146635
1975	0	0	154	674520	40	175962
1976	0	0	154	674520	47	205289
1977	0	0	154	674520	54	234616
1978	0	0	154	674520	60	263943
1979	0	0	154	674520	67	293270
1980	0	0	154	674520	74	322597
1981	0	0	154	674520	80	351923
1982	0	0	154	674520	87	381250
1983	0	0	154	674520	94	410577
1984	0	0	154	674520	100	439904
1985	0	0	154	674520	107	469231
1986	0	0	154	674520	114	498558
1987	0	0	154	674520	121	527885
1988	0	0	154	674520	127	557212
1989	0	0	154	674520	134	586539
1990	0	0	154	674520	141	615866
1991	0	0	154	674520	147	645193
1992	154	674520	154	674520	154	674520
1993	154	674520	154	674520	154	674520
1994	154	674520	154	674520	154	674520
1995	154	674520	154	674520	154	674520
1996	154	674520	154	674520	154	674520
1997	154	674520	154	674520	154	674520
1998	62	271560	62	271560	62	271560
1999	60	262800	60	262800	60	262800
2000	100	438000	100	438000	100	438000
2001	42	183960	42	183960	42	183960
2002	41	179580	41	179580	41	179580
2003	9	39420	9	39420	9	39420
2004	13	56940	13	56940	13	56940
2005	9	39420	9	39420	9	39420
2006	8	35040	8	35040	8	35040
2007	5	21900	5	21900	5	21900

Year	Outdoor Air Concentration (ng/m3) Scenario 1	Ventilated amount# (ng/year) Scenario 1	Outdoor Air Concentration (ng/m3) Scenario 2	Ventilated amount# (ng/year) Scenario 2	Outdoor Air Concentration (ng/m3) Scenario 3	Ventilated amount# (ng/year) Scenario 3
2008	6	26280	6	26280	6	26280
2009	4	17520	4	17520	4	17520
2010	6	26280	6	26280	6	26280
2011	4	17520	4	17520	4	17520
2012	3	13140	3	13140 #VentAmount	3	13140

(ng/yr) = airConc [ng/m3] * lung ventilation [m3/yr] * Foutdoor-indoor [-] lung ventilation: 20 m3/dy * 365 dy Foutdoor-indoor: indoor air concentration is a fraction of the outdoor air conc: 0.6

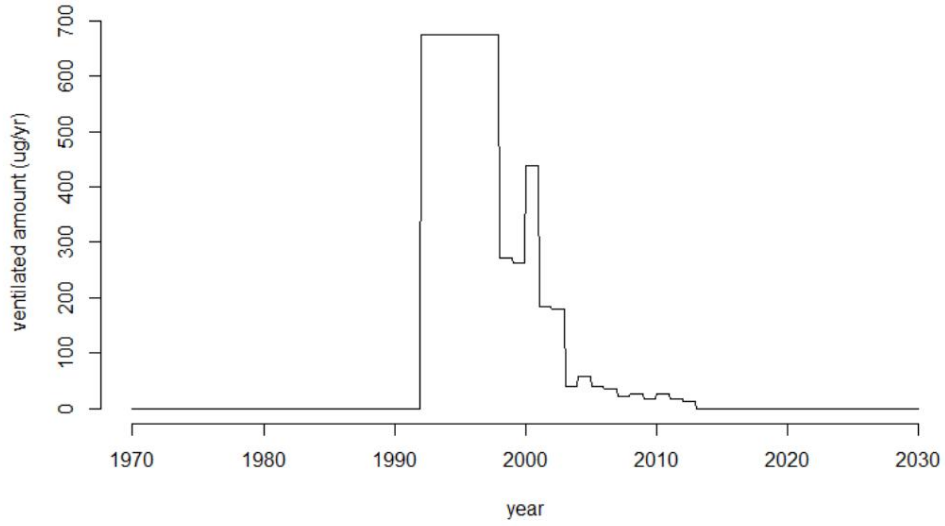

Figure TA-5.5 Scenario 1; simulated dosing regimen based on ventilated amount from indoor air.

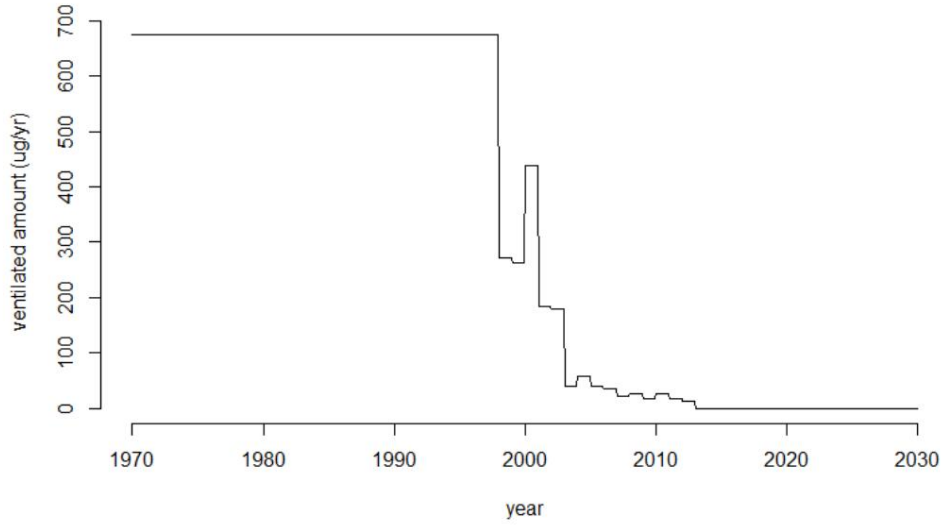

Figure TA-5.6 Scenario 2; simulated dosing regimen based on ventilated amount from indoor air.

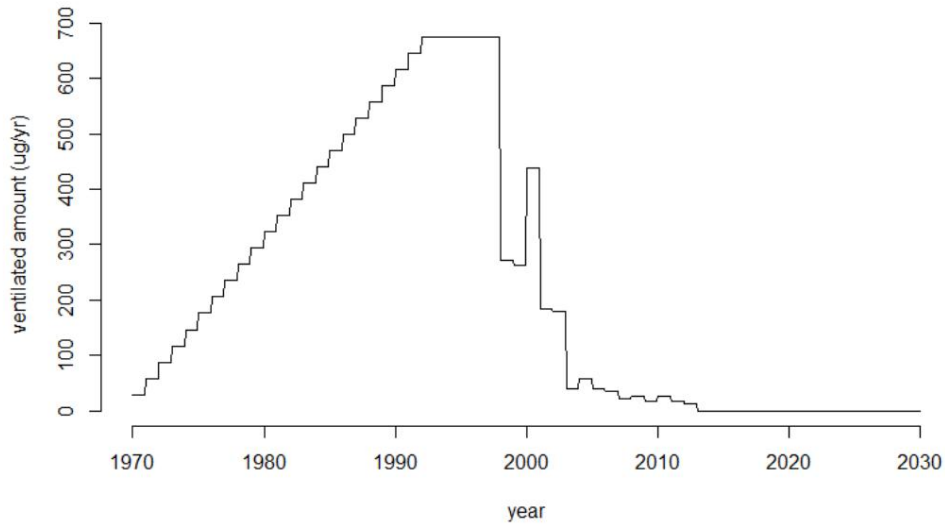

Figure TA-5.7 Scenario 3; simulated dosing regimen based on ventilated amount from indoor air.

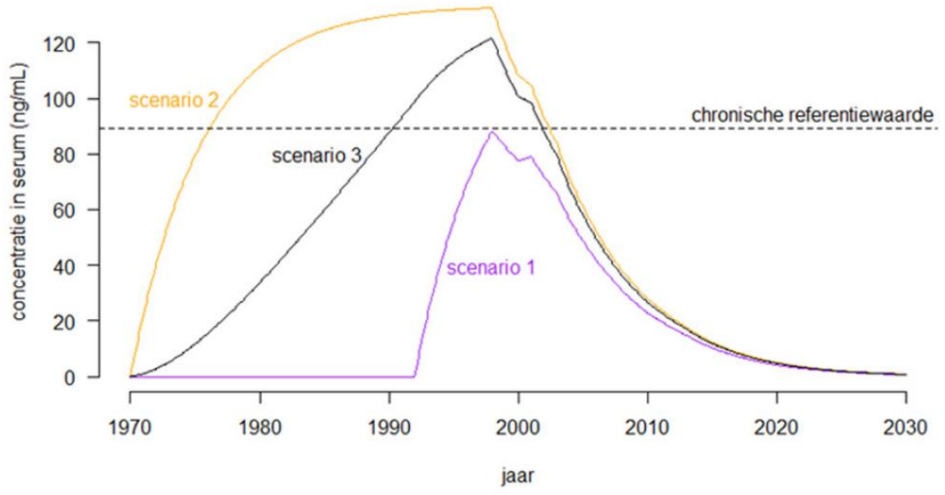

Figure TA-5.8 Scenario 1, 2 and 3; serum concentration (ng mL-1) based on ventilated amount in the inner zone. Dashed line: chronic serum reference value based on extrapolation of hepatic hyperthrophy in the rat (89 ng mL-1). Pink curve: scenario 1, orange curve: scenario 2, black curve: scenario 3.

*Table TA-5.2 Simulated serum concentrations on the first day of each year corresponding to figureTA-5-8. In **bold:** serum concentrations above the chronic HBGV of 89 ng mL-1.*

Year	Serum concentration (ng/mL)		
	Scenario 1	Scenario 2	Scenario 3
1970	0	0	0
1971	0	22.1	1.0
1972	0	40.5	2.8
1973	0	55.8	5.3
1974	0	68.7	8.3
1975	0	79.4	11.7
1976	0	88.3	15.6
1977	0	**95.7**	19.8
1978	0	**102.0**	24.2
1979	0	**107.2**	28.9
1980	0	**111.5**	33.7
1981	0	**115.1**	38.8
1982	0	**118.1**	43.9
1983	0	**120.6**	49.1
1984	0	**122.7**	54.5
1985	0	**124.5**	59.9
1986	0	**125.9**	65.4
1987	0	**127.2**	70.9
1988	0	**128.2**	76.5
1989	0	**129.0**	82.1
1990	0	**129.7**	87.7
1991	0	**130.3**	**93.4**
1992	1.0	**130.8**	**99.1**
1993	22.9	**131.2**	**104.8**
1994	41.2	**131.6**	**109.5**
1995	56.4	**131.9**	**113.4**
1996	69.2	**132.1**	**116.7**
1997	79.8	**132.3**	**119.5**
1998	88.0	**131.9**	**121.2**
1999	82.3	**118.9**	**110.0**
2000	77.6	**108.1**	**100.6**
2001	78.7	**104.1**	**97.9**
2002	71.7	**92.9**	87.7
2003	65.5	83.2	78.9
2004	55.9	70.7	67.1
2005	48.5	60.9	57.9
2006	41.8	52.1	49.6
2007	36.0	44.6	42.5
2008	30.8	37.9	36.2
2009	26.5	32.5	31.0

Year	Serum concentration (ng/mL)		
	Scenario 1	Scenario 2	Scenario 3
2010	22.7	27.7	26.5
2011	19.8	24.0	22.9
2012	17.1	20.6	19.7
2013	14.7	17.6	16.9
2014	12.2	14.7	14.1
2015	10.2	12.2	11.7
2016	8.5	10.2	9.8
2017	7.1	8.5	8.2
2018	5.9	7.1	6.8
2019	5.0	5.9	5.7
2020	4.1	5.0	4.8
2021	3.4	4.1	4.0
2022	2.9	3.4	3.3
2023	2.4	2.9	2.8
2024	2.0	2.4	2.3
2025	1.7	2.0	1.9
2026	1.4	1.7	1.6
2027	1.2	1.4	1.3
2028	1.0	1.2	1.1
2029	0.8	1.0	0.9
2030	0.7	0.8	0.8

TA-6 Risk of Testicular Cancer Based on animal extrapolation

For the scenario with the highest exposure (scenario 2), the calculated average intake level over the period from 1970 to 2012 is equal to 19 ng kg bw-1 day-1. Compared to a unit risk for lifetime exposure of 0.07 per mg kg bw-1 day-1 , this intake level leads to an estimated additional cancer risk of 8.0 x 10-7. This is around the level of one in a million per life, which is defined as Negligible Risk in Dutch environmental policy. For scenarios 1 and 3, the calculated average intake is lower, ie 11 and 12 ng kg bw-1 day-1 respectively (for the period 1992-2012 and 1970-2012 respectively). For these scenarios, the estimated additional cancer risk based on the testes tumors as observed in laboratory animals is below the VR level.

RIVM

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