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

WAGENINGEN UNIVERSITY & RESEARCH

FRONT OFFICE FOOD AND PRODUCT SAFETY

RISK ASSESSMENT OF GenX AND PFOA IN FOOD
PART 1: TOXICITY OF GenX AND PFOA AND INTAKE THROUGH CONTAMINATED FOOD OF ANIMAL ORIGIN

Risk assessment requested by:	Office for Risk Assessment and Research
Risk assessment performed by:	RIVM and RIKILT[1]
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Subject

In the past, the companies DuPont/Chemours in Dordrecht and Custom Powders in Helmond emitted GenX[1] and perfluoro-octanoic acid (PFOA) into the air. The emission of GenX by DuPont/Chemours is ongoing. Consequently, the area around these companies (soil, water and vegetation) has been polluted. In May 2018, the Netherlands Food and Consumer Product Safety Authority (NVWA) took samples (dairy products, egg, fish and silage) in these areas. At that moment, the detection and quantification limits of the analytical method to analyse these compounds were not low enough for performing a risk assessment. In other words, if all concentrations would be below these limit values, the calculated exposure using concentrations at these limit values (worst case) would exceed the health-based guidance value. In that case, a conclusion about a possible health risk cannot be drawn. RIKILT-WUR resolved this analytical issue, and on 10 January 2019 sent the analysed concentrations of GenX and PFOA in dairy products, egg, fish and silage to the Front Office Food and Product Safety (FO).

Questions

Given the GenX and PFOA concentrations in dairy products, egg and fish, the Office for Risk Assessment and Research (BuRO) has asked the FO several questions, which are answered in this FO assessment (Part 1). BuRO has also asked questions related to the GenX and PFOA concentrations in silage. These questions are answered in a separate FO assessment (Part 2). The questions addressed in this Part 1 FO assessment are:

1. Describe the toxicology of GenX and PFOA.
2. Estimate the intake of GenX and PFOA for consumers based on the measured concentrations of GenX and PFOA in dairy products, egg and fish.
3. Perform a risk assessment of GenX and PFOA in contaminated food of animal origin.

[1] GenX refers to hexafluoropropyleneoxide dimer acid (HPFO-DA), or to its ammonium salt, as used in the GenX technology.

Conclusions

1) In 2017, RIVM derived a tentative tolerable daily intake (t-TDI) of 21 ng/kg body weight (bw) per day for GenX, based on an increased albumin/globulin ratio in serum of rats (Janssen, 2017). For PFOA, RIVM derived a TDI of 12.5 ng/kg bw per day based on liver toxicity in rats in 2016 (Zeilmaker et al., 2016).
2) The exposure to GenX and PFOA through the consumption of dairy products (milk, cheese and yoghurt), egg and eel was negligible. A rough, maximum exposure to GenX and PFOA through the consumption of carp was estimated at 5.3 and 1.3 ng/kg bw per day, respectively, based on
   - concentrations in one carp caught in a fish pond in Helmond;
   - a high consumption level of fish from the Dutch National Food Consumption Survey of 2012-2016.
3) GenX and PFOA concentrations in dairy products (milk, cheese and yoghurt), egg, and fish (eel and carp) do not pose a health risk for people living in the environment of both companies.

Question 1: Toxicology of GenX and PFOA

Below the toxicity data underlying the derivation of the tolerable daily intakes (TDI) of GenX and PFOA used to perform a risk assessment (question 3) are described, as well as the recent EFSA evaluation of PFOA (EFSA, 2018b). For a more extended description of the toxicity of both compounds, see Appendix A for GenX and Appendix B for PFOA.

GenX

The chemicals FRD-902 and FRD-903, also known as "GenX chemicals", are the main substances associated with the GenX processing aid technology that enables the production of fluoropolymers. FRD-902 is the dimer ammonium salt (ammonium-2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate; CAS no. 62037-80-3) and FRD-903 is the dimer acid (2,3,3,3-tetrafluoro-2 (heptafluoropropoxy)propanoic acid; CAS no. 13252-13-6) (Figure 1). Under environmental and physical conditions, such as in water or in blood, FRD-902 and FRD-903 dissociate into the ion HFPO-DA (hexafluoropropyleneoxide dimer acid), which is responsible for the observed toxicological effects. In this assessment, the ion HFPO-DA is called GenX.

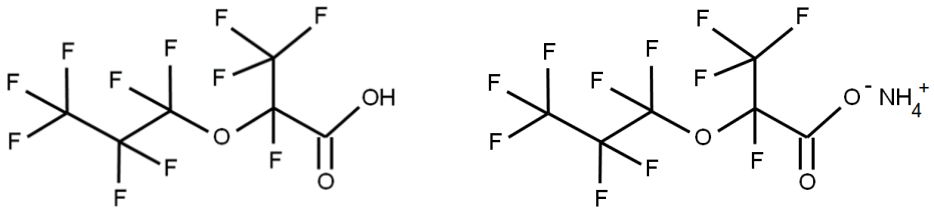

Figure 1. The chemical structure of the acid FRD-903 (left) and the ammonium salt FRD-902 (right)

In 2017, RIVM derived a tentative TDI (t-TDI) of 21 ng/kg bw per day for GenX (Janssen, 2017). This t-TDI was based on an overall no-observed adverse level (NOAEL)[2] of 0.1 mg/kg body weight (bw) per day from a chronic oral study in rats with increased albumin/globulin ratio in serum as the critical effect (Beekman et al., 2016), and the following assessment factors (Janssen, 2017):

- interspecies (for toxicokinetic differences related to metabolic rate): 4
- interspecies (for toxicodynamic differences): 1.8
- intraspecies (standard factor): 10
- extra factor for possible bioaccumulation: 66

[2] The highest dose administered in an animal study at which no adverse effects are observed

PFOA

Perfluoro-octanoic acid (CAS no. 335-67-1; PFOA) and its salts are used as processing aids in the production of fluoro-elastomers and fluoropolymers, with polytetrafluoretheen (PTFE; brand name is 'Teflon') being an important fluoropolymer. In addition, PFOA-related compounds are used as surfactants in non-food applications (in fire-fighting foams, wetting agents and cleaners) and for the manufacture of side-chain fluorinated polymers (used as surface finishes for textiles and apparel, leather, paper and cardboard, paints, lacquers etc.). The chemical structure of PFOA is given in Figure 2.

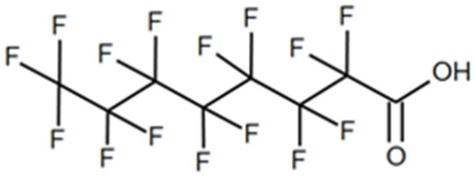

Figure 2. The chemical structure of perfluoro-octanoic acid (PFOA)

In its 2016 risk assessment of PFOA, RIVM concluded that liver effects represented the most sensitive endpoint for PFOA-toxicity (Zeilmaker et al., 2016). According to the approach previously developed for polychlorinated dioxins, which is a group of substances with a high potential for bioaccumulation in humans, RIVM used a quantitative approach to derive a TDI for PFOA based on a critical PFOA blood serum concentration (Zeilmaker et al., 2016). The reason for this is that PFOA belongs to the group of per- and polyfluoroalkyl substances, which has, as dioxins, a high potential to accumulate in humans (EFSA, 2018b).

The TDI was derived from the (mean) NOAEL PFOA concentration of 7.1 µg PFOA/mL in rat from a semi-chronic study by Perkins et al. (2004) using one compartmental modelling to calculate the corresponding chronic human oral dose (Human Equivalent Dose ((HED) of 1000 ng/kg bw per day. The TDI of 12.5 ng/kg bw per day was subsequently derived by dividing this HED by an "overall" assessment factor of 80. This "overall" factor was composed of the following sub-factors:

- Interspecies extrapolation:
  A correction for interspecies differences in kinetics and toxicodynamics was not needed, and therefore the assessment factor was set at 1. Interspecies differences in kinetics were explicitly considered in the derivation of the TDI, and based on mechanistic considerations it was assumed that rats are more sensitive for liver toxicity than humans.
- Intraspecies extrapolation
  In order to correct for intraspecies differences in toxicokinetics and toxicodynamics the default assessment factor of 10 was used.
- Semi-chronic → chronic extrapolation
  The NOAEL was based on a semi-chronic study. To extrapolate the TDI based on semi-chronic exposure to chronic exposure, an assessment factor of 8 was used. This factor was based on an empirically derived distribution for this assessment factor as proposed by the International Programme on Chemical Safety (IPCS) and has a coverage of 95%; there is a 95% confidence that this factor is sufficiently large to account for possible semi-chronic versus chronic differences in toxicity (for technical details, see Zeilmaker et al., 2016, Annex TA-3).

This approach of deriving a TDI is in agreement with the approach used by the US EPA (2016), DWQI (2017) and ATSDR (2018).

EFSA (2018b) has recently re-evaluated PFOA (and perfluoroctane sulfonic acid (PFOS)) and derived a health-based guidance value (HBGV) for both compounds based on health effects from epidemiological studies. For PFOA, the critical effect was an increase in serum total cholesterol. Based on benchmark modelling, EFSA established a tolerable weekly intake (TWI) of 6 ng/kg bw per week for PFOA (equivalent to 0.8 ng/kg bw per

day). PFOA (and PFOS) belong to the group of per- and polyfluoroakyl substances (PFAS). In 2019, EFSA will finalise a scientific opinion on "The risk to human health related to the presence Perfluoroalkylated substances, other than Perfluorooctane sulfonate and Perfluorooctanoic acid, in food" (EFSA-Q-2017-00549, scheduled December 2019)[3], with the possible application of the forthcoming Scientific Committee guidance on combined exposure to multiple chemicals[4]. Until then, EFSA's derived tolerable weekly intake for PFOA (as well as for PFOS) has to be considered provisional.

In general, RIVM follows the HBGVs derived by EFSA. However, in the case of PFOA, RIVM has questioned EFSA's HBGV derivation (EFSA, 2018a)[5]. Given EFSA's ongoing evaluation, RIVM maintains presently its own TDI for PFOA. However, also risk assessments based on this HBGV should be considered provisional until the EFSA evaluation is finalised.

Question 2 and 3: Exposure and risk assessment

Concentration GenX and PFOA in dairy products, egg and fish
GenX and PFOA were analysed in dairy products (milk, cheese and yoghurt), egg and fish sampled near the companies Chemours/DuPont in Dordrecht and Custom Powders in Helmond. Table 1 lists the product concentrations per location as provided by RIKILT-WUR. The majority of the concentrations were below the limit of quantification (LOQ). Only the PFOA concentration in one egg sampled in Dordrecht and that of both compounds in one carp caught in a fish pond in Helmond were above the LOQ (Table 1).

Table 1. Analysed concentrations of GenX and PFOA in dairy products, egg and fish sampled near the companies Chemours/DuPont in Dordrecht and Custom Powders in Helmond

Product and location	Concentration (ng/g)[1]		
	n	GenX	PFOA
Dordrecht			
Dairy products			
Milk[2]	15	<0.10	<0.01
Cheese[2]	1	<0.10	<0.10
Yoghurt[2]	1	<0.10	<0.10
Egg[3]	1	<0.25	0.14
Helmond			
Dairy products			
Milk[2]	2	<0.10	<0.01
Egg[3]	1	<0.25	<0.025
Fish			
Eel (farmed)	1	<0.10	<0.05
Carp	1	4.7	1.3

PFOA: perfluoro-octanoic acid
[1] Samples with concentrations reported as '<' may contain GenX and PFOA, but the concentrations did not exceed the limit of quantification of the analytical method
[2] Cow and one sample of goat in Dordrecht
[3] Chicken

20% TDI concentrations
In September 2018, the FO calculated how low the LOQ for the analysis of GenX and PFOA in animal products should be for performing a risk assessment. For this, GenX and PFOA concentrations for egg, meat (beef) and cow's milk were calculated at which a high consumption of each product would result in an exposure equal to 20% of the TDI of

[3] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2017-00549
[4] https://www.efsa.europa.eu/en/topics/topic/chemical-mixtures
[5] https://www.rivm.nl/en/news/discussion-regarding-health-based-guidance-value-of-pfoa

GenX or PFOA (FO, 2018). The percentage of 20% accounted for the exposure to GenX and PFOA through the consumption of other foods than the product itself. In this present assessment, these concentrations are referred to as '20% TDI concentrations'. No such concentrations were derived for cheese and yoghurt.

These 20% TDI concentrations were calculated using high consumptions of egg, meat (beef) and milk on an arbitrary day among children and adults and corresponding body weights (Table 2) combined with the RIVM TDIs of GenX and PFOA (see question 1) with the following equation:

$$20\%\ TDI\ concentration = \left(\frac{TDI}{(High\ consumption \div Body\ weight)}\right) \div 5 \qquad \text{Equation 1}$$

20% TDI concentration	= Concentration of GenX and PFOA at which a high consumption of a product results in an exposure equal to 20% of the TDI in ng/g
TDI	= Tolerable daily intake of GenX and PFOA in ng/kg bw per day
High consumption	= High consumption of a product in gram per day
Body weight	= Body weight in kg

The 20% TDI concentrations per product that were calculated in this way are listed in Table 3. If the measured concentrations of GenX and PFOA are below these 20% TDI concentrations, a health risk can be excluded. If the measured concentrations are higher, a risk assessment is required to assess possible health risks.

Table 2. High consumptions on an arbitrary day per product used to derive the 20% TDI concentrations for GenX and PFOA

Product	Age (years)	Body weight (kg)	High consumption (gram)
Egg	2 - 6	18.8[1]	65[3]
Meat (beef)	19 - 69	66[2]	210[4]
Milk	2 - 6	18.8	750[5]

bw: body weight; DNFCS: Dutch Food Consumption Survey; TDI: tolerable daily intake
[1] The average body weight of children aged 2 to 6 years in DNFCS 2005-2006 among children within this age range (Ocké et al., 2008).
[2] This body weight is the weight of boys aged 14 to 18 in DNFCS 2007-2010 (van Rossum et al., 2011). The average body weight in this DNFCS for the adult population from which the estimated meat (beef) consumption was obtained (footnote 4 of this table) was about 80 kg. The high consumption per kg bw (210/66 = 3.2 g/kg bw) used to derive the 20% TDI concentrations for meat (beef) was therefore higher than when the average body weight for adults had been used (210/80 = 2.6 g/kg bw). This has resulted in lower (more conservative) 20% TDI concentrations.
[3] The consumed amount of egg was comparable to the 95th percentile consumption of boiled egg in DNFCS 2005-2006 among children aged 2 to 6 and equals about one large egg.
[4] This consumed amount of meat (beef) was equal to the 95th percentile of consumption of meat (beef) by persons aged 19-69 in DNFCS 2007-2010.
[5] This consumed amount of milk was higher than the maximally reported consumption of 520 gram of semi-skimmed milk reported in DNFCS 2005-2006 among children aged 2 to 6.

Table 3. The 20% TDI concentrations for GenX and PFOA per product[1]

Product	20% TDI concentration (ng/g)	
	GenX	PFOA
Egg	1.2	0.7
Meat (beef)	1.3	0.8
Milk	0.1	0.06

PFOA: perfluoro-octanoic acid; TDI: tolerable daily intake
[1] See equation 1 and Table 2
[2] TDI for GenX is 21 ng/kg bw per day and for PFOA 12.5 ng/kg bw per day

Exposure and risk assessment of dairy products, egg and eel
The LOQs of the analytical method were either equal (GenX in milk) or lower (GenX in egg and PFOA in milk and egg) than the 20% TDI concentrations (Table 1 and 3). Assuming that eel is not consumed at higher amounts than meat (beef), also the analytical LOQ of eel was below the corresponding 20% TDI concentration. As the concentrations are all at or below the 20% TDI concentration, these products (milk, egg and eel) are not likely to pose a health risk, even if consumed in combination. The reasons for this are:

1. GenX and PFOA may cause adverse effects if ingested at doses higher than the TDI over a lifelong period. However, the consumed amounts on which the 20% TDI concentrations were based reflect large consumed amounts on an arbitrary day. These amounts overestimate the consumed amounts over a lifelong period, when large consumed amounts of a food will be alternated with lower amounts or days on which these products are not consumed;
2. The 20% TDI concentrations were set in such a way that the exposure to GenX and PFOA would equal 20% of the TDI if analysed concentrations were at these concentrations;
3. Except for GenX in milk, the LOQs used in the analyses were even lower than the 20% TDI concentrations (Table 1 and 3).

To substantiate this further, we performed a rough, worst case exposure assessment. For this, we selected the maximum consumption of milk, eel and eggs as such per kg body weight on one of the two recording days in the Dutch National Food Consumption Survey (DNFCS) of 2012-2016 among persons aged 1 to 79[6] (Table 4). The highest consumed amounts of milk and egg were reported for a 1-year old child and that of eel by an adult aged 59. The adult with the maximum consumption of eel also consumed milk and egg on that specific day. Using the analysed concentration of PFOA in egg (0.14 ng/g) and assuming that the concentrations below LOQ equalled a concentration at the LOQ, the GenX and PFOA intake for these three persons would maximally equal 14% of both TDIs (Table 4). These intakes reflect a possible intake on one day and overestimate the intake expected over a lifelong period, the relevant time period for GenX and PFOA exposure (see above).

For cheese and yoghurt, the analysed concentrations were also below the LOQ (Table 1). For these products, no 20% TDI concentrations were derived for risk assessment (FO, 2018). As the analytical LOQs were only slightly higher than the 20% TDI concentrations' for milk, it is not likely that the analysed levels would have resulted in an intake of GenX and PFOA that would pose a health risk. The consumption of yoghurt and cheese is not likely to exceed 750 gram per day in children aged 2 to 6 (Table 2).

Risk assessment of GenX and PFOA through the consumption of carp
Using the same assumption for carp as for eel, i.e. the 20% TDI concentration for meat is also applicable to carp, the analysed concentrations of GenX and PFOA in carp were above the 20% TDI concentration for meat (beef). We therefore performed a risk assessment for carp to establish if the consumption of this fish could pose a health risk. The carp was caught in a fish pond in the vicinity of Custom Powders in Helmond. The concentrations refer to the concentrations in fish meat.

To assess the risk, we first calculated the exposure to GenX and PFOA using the food consumption data among 4313 individuals aged 1 to 79 of DNFCS 2012-2016. In this survey, individuals, or their caretakers in case of young children, recorded what and how much they consumed on two arbitrary days. As there are no consumption levels of carp in this survey, the consumption of fish was used as a proxy. Fish included all types of

[6] Wateetnederland.nl

Table 4. Maximal consumed amounts per kg body weight for milk, eel and eggs on one of the two recording days in DNFCS 2012-2016

Age (years)	Body weight (kg)	Product	Consumed amount (gram/kg bw)	Concentration (ng/g)		Exposure (ng/kg bw)				Exposure as % of the TDI[1]	
						Per product		On one day			
				GenX	PFOA	GenX	PFOA	GenX	PFOA	GenX	PFOA
1	8.6	Milk	29.9	0.1	0.01	3	0.3	3	0.3	14	2
		Eel	-	0.1	0.05	-	-				
		Egg		0.25	0.14						
59	60	Milk	7.1	0.1	0.01	0.7	0.07	1.4	0.4	7	3
		Eel	5	0.1	0.05	0.5	0.25				
		Egg	0.8	0.25	0.14	0.2	0.1				
1	11.2	Milk	-	0.1	0.01	-	-	2.2	1.3	10	10
		Eel		0.1	0.05						
		Egg	8.9	0.25	0.14	2.2	1.3				

bw: body weight; DNFCS: Dutch National Food Consumption survey; PFOA: perfluoro-octanoic acid; TDI: tolerable daily intake
[1] TDI for GenX is 21 ng/kg bw per day and for PFOA 12.5 ng/kg bw per day

fish, such as salmon, tuna and pangasius. The consumption of crustaceans and fish products, such as fish fingers, was not included as being considered not representative of the amounts in which carp may be consumed. Table 5 lists the mean and high (95th percentile) consumption of fish for different age groups and sex for all days in the survey and for only those days on which the consumption of fish was reported ("consumption days").

Table 5. Mean and high (95th percentile) consumed amounts of fish1 per age group and sex based on DNFCS 2012-2016

Age group (year) + sex	Consumed amount (gram per day)				Percentage consumption days[4]
	All days[2]		Consumption days only[3]		
	Mean	High	Mean	High	
1-3	1.5	14.5	46.5	122	4
4-8	3	24.5	71.5	178.5	5
9-18 man	3	15	73.5	219	5
9-18 female	3.5	37	63.5	141	6
19-50 man	12	88	119	286	10
19-50 female	10	71	91	208	11
51-79 man	18	101	126	301.5	15
51-79 female	15.5	80	97.5	239	16

DNFCS: Dutch National Food Consumption Survey
[1] Based on consumed amounts of all types of fish reported in DNFCS 2012-2016. Consumed amounts of crustaceans and fish products were not included.
[2] Based on all days, irrespective of whether fish was consumed or not. Mean and high (95th percentile) consumed amounts were calculated based on mean consumed amounts across the two consumption days per individual
[3] Based on only the days on which the consumption of fish was reported. Mean and high (95th percentile) consumed amounts were calculated based on consumed amounts per consumption day per individual
[4] Percentage of the days on which consumption of fish was reported.

GenX and PFOA may be harmful when ingested at amounts above the TDI over a lifelong period. Therefore, we should use the consumed amounts of fish that best reflect lifelong consumed amounts of fish for the risk assessment. Based on the information in Table 5, the best estimate for this is the consumed amounts based on 'all consumption days', assuming that individuals are not likely to consume daily fish obtained from the fish pond. We used the high (95th percentile) consumed amounts to estimate the intake of GenX and PFOA to also protect possible high consumers of fish (Table 5).

Based on the analysed concentrations of GenX and PFOA in carp and high consumed amounts of fish per age group and sex, the intake was estimated per age – sex group using the following equation:

$$Intake = \frac{Consumption \times Concentration}{Body\ weight}$$ Equation 2

Intake	= Intake of GenX and PFOA in ng/kg bw per day
Consumption	= Consumption of carp in gram (Table 5)
Concentration	= Concentration of GenX and PFOA in carp in ng/g (Table 1)
Body weight	= Body weight in kg (Table 5)

Using this equation, the maximum intake of GenX and PFOA was estimated at 5.3 ng/kg bw per day for GenX and 1.5 ng/kg bw per day for PFOA, both in men aged 51 to 79 (Table 6). The maximum exposure to GenX and PFOA through the consumption of carp was equal to 25% and 12% of the TDI, respectively. Therefore, the consumption of this specific fish at the analysed concentrations does not pose a health risk for GenX and PFOA.

Table 6. Intake of GenX and PFOA through a high (95th percentile) consumption of fish contaminated with GenX and PFOA at 4.7 and 1.3 ng/g[1], respectively

Age group (year) + sex	High consumption of fish (gram per day)[2]	Body weight (kg)	Intake			
			ng/kg bw per day		% of the TDI[3]	
			GenX	PFOA	GenX	PFOA
1-3	14.5	14.5	4.9	1.4	23	11
4-8	24.5	24.5	4.8	1.3	23	10
9-18; man	15	56.6	1.3	0.4	6	3
9-18; female	37	55.2	3.3	0.9	16	7
19-50; man	88	84.6	4.9	1.4	23	11
19-50; female	71	75.7	4.4	1.2	21	10
51-79; man	101	88.8	5.3	1.5	25	12
51-79; female	80	76.9	4.9	1.4	23	11

bw: body weight; TDI: tolerable daily intake
[1] Concentration analysed in fish meat of carp
[2] High consumption based on all consumption days within the food consumption survey, irrespective of whether fish was consumed (Table 5)
[3] TDI for GenX is 21 ng/kg bw per day and for PFOA 12.5 ng/kg bw per day

Discussion points

- The risk assessment of GenX and PFOA in carp was based on only one concentration per compound. There is no information available about the distribution of concentrations of GenX and PFOA in carp present in the same fish pond, as of other fish present that may be caught for consumption. It is therefore unclear if the analysed concentrations are representative of those in carp and other fish that may be caught in the future or have been caught in the past. Because of this, the intake of GenX and PFOA may be under- or overestimated. Also the number of concentrations of GenX and PFOA analysed in dairy products, egg and eel was limited, except possibly for milk sampled in Dordrecht.
  Due to the absence of consumed amounts of fish by persons fishing in the fish pond, consumed amounts of fish by the general Dutch population were used in the risk assessment. Persons fishing in this fish pond possibly consume fish more frequently than the general population. They may also consume fish in larger amounts when eating fish. By using the consumed amount at the 95th percentile of the consumption distribution, this was partly addressed.
- People living in the vicinity of both companies are not only exposed to GenX and PFOA through the consumption of dairy products, egg and fish. Other relevant sources of exposure in the vicinity of both companies are home grown vegetables, fruits and potatoes, drinking water and air (Mengelers et al., 2018; Boon et al., 2019), and possibly meat (Part 2). In Helmond, also swimming water was identified as a potential source of exposure (Beekman, 2018; Muller & te Biesebeek, 2018). These sources need to be considered to determine whether there is a health risk related to the exposure to these compounds.

Overall conclusion

1) In 2017, RIVM derived a tentative tolerable daily intake (t-TDI) of 21 ng/kg body weight (bw) per day for GenX, based on an increased albumin/globulin ratio in serum of rats (Janssen, 2017). For PFOA, RIVM derived a TDI of 12.5 ng/kg bw per day based on liver toxicity in rats in 2016 (Zeilmaker et al., 2016).
2) The exposure to GenX and PFOA through the consumption of dairy products (milk, cheese and yoghurt), egg and eel was negligible. A rough, maximum exposure to GenX and PFOA through the consumption of carp was estimated at 5.3 and 1.3 ng/kg bw per day, respectively, based on
   - concentrations in one carp caught in a fish pond in Helmond;
   - a high consumption level of fish from DNFCS 2012-2016.

3) GenX and PFOA concentrations in dairy products (milk, cheese and yoghurt), egg, and fish (eel and carp) do not pose a health risk for people living in the environment of both companies.

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Appendix A Toxicity of GenX

The main body of information regarding mammalian toxicity are studies performed with FRD-902. Read-across of the toxicological properties of FRD-902 to FRD-903 is considered justified, because under environmental conditions, such as in water or in blood, both FRD-902 and FRD-903 will dissociate into the ion HFPO-DA (hexafluoropropyleneoxide dimer acid ion), which is responsible for the observed toxicological effects. In this assessment, the ion HFPO-DA is called GenX.

The large majority of the toxicity data is obtained from the REACH registration dossier of FRD-902. Additionally, the original study reports for FRD-902 (which largely comprise the same information as in the REACH registration dossier) and the original study reports for FRD-903, published via the Health & Environmental Research Online (HERO) database of the US EPA, are the main sources of information. Other than that, six scientific publications and two scientific reports are available in the public literature (Beekman et al., 2016; Caverly Rae et al., 2015; Gannon et al., 2016; Li et al., 2019; Rushing et al., 2017; Sheng et al., 2018; US EPA, 2018; Wang et al., 2017).

The REACH registration dossier and the HERO database contain:

- *in vitro* and *in vivo* studies on toxicokinetics,
- *in vitro* and *in vivo* studies on skin irritation/corrosion,
- an *in vivo* study on eye irritation,
- subacute and subchronic oral toxicity studies in rats and mice,
- a chronic oral toxicity/carcinogenicity study in rats,
- *in vitro* and *in vivo* genotoxicity studies,
- an oral prenatal developmental toxicity study in rats,
- an oral reproduction/developmental screening toxicity study in mice.

All studies were performed according to OECD test guidelines, except for the studies covering toxicokinetics. Additional information for GenX is available for:

- immunotoxicity (Rushing et al., 2017),
- half-lives in experimental animals (Gannon et al., 2016),
- carcinogenicity (Caverly Rae et al., 2015),
- *in vitro* liver protein binding (Sheng et al., 2018),
- mode of action (Li et al., 2019; Wang et al., 2017).

No epidemiological studies are available for GenX.

Both GenX and PFOA are part of the subgroup of perfluoroalkyl acids (PFAAs), which belong to a larger group of per- and polyfluoroalkyl substances (PFASs) (OECD 2013; 2015; 2018). Many PFASs can degrade to PFAAs that are their final degradation products under relevant environmental conditions. These PFAAs, both with short- and long chain length, show high persistency due to the bond between carbon and fluorine. This bond is stable and requires high energy input to break (Brendel et al., 2018). Besides that GenX and PFOA show high persistency, the substances show also similarities in toxicological profiles in experimental animals at comparable doses (e.g. carcinogenicity, liver toxicity) as illustrated in this Appendix and Appendix B.

The biokinetics of GenX were studied in rats, mice and monkeys (Gannon et al., 2016). The results indicate that GenX has a lower potential for bioaccumulation compared to PFOA in these species (half-lives between hours and days for GenX and between hours and weeks for PFOA). For other PFASs, such as PFOA, it is known that the human half-life is significantly higher compared to other species, which cannot solely be explained by allometric differences. Whether interspecies differences in terms of bioaccumulation also apply to GenX is uncertain, because half-life data for GenX in humans are lacking. This issue is currently under investigation in a Substance Evaluation under REACH, where more information is requested on the half-life of GenX in humans by performing a human biomonitoring study in volunteering workers at a manufacturing site.

In contrast to the classic lipophilic organic pollutants that primarily bind to fatty tissues, PFASs primarily bind to proteins. The limited data available suggests that GenX binds to fatty acid-binding proteins in the liver (Sheng et al., 2018) and to serum proteins (i.e. albumin) in blood. Although no data are available on a direct interaction of GenX with albumin, toxicokinetic data illustrates that GenX mainly distributes to the liver and the blood. Overall, tissue and serum concentrations are higher in males compared to females, suggesting that females are able to eliminate GenX more effectively. Protein binding may be one of the aspects leading to slower elimination, resulting in a longer half-life in humans. Additionally, it is argued that the half-life of PFOA is longer in humans compared to other species, because of stronger reabsorption from the lumen of the kidney back into the blood by organic anion transporters (OATs) in humans (Yang et al., 2010). No data is available on OAT efficacy for GenX in humans. It is therefore not known what effect GenX has on the functioning of OATs and if resorption of GenX in the lumen of the kidney will occur in humans or not.

Chronic exposure to GenX results in a statistically significant induction of pancreatic acinar cell adenomas/carcinomas and Leydig cell tumours in male rats at 50 mg/kg bw per day, and a statistically significant induction of hepatocellular adenomas and carcinomas in female rats at 500 mg/kg bw per day (Caverly Rae et al., 2015). All genotoxicity tests carried out with GenX (Ames test, *in vitro* mammalian cell gene mutation assay, *in vitro* mammalian cell chromosome aberration test, and *in vivo* micronucleus-test in mice) were negative. In 2016, RIVM (Beekman et al., 2016) concluded that the available mutagenicity studies and mechanistic information indicate a non-genotoxic mode of action for the observed tumours in the 2-year study. There is concern that GenX may be a human carcinogen as well, but data are currently insufficient to conclude on the substance's full carcinogenic potential. Therefore, this issue is currently under investigation in a Substance Evaluation under REACH, where more information is requested on the carcinogenic potential of GenX in mice.

Apart from the tumorigenic response in rats, the main affected organs in rodents resulting from repeated exposure to GenX are the liver, the kidneys, the haematological system, and the immune system. In rodents, GenX consistently caused increases in liver weight, changes in clinical chemistry parameters related to liver toxicity (AST, ALT, ALP), decreased serum cholesterol, liver hypertrophy, and liver microscopical changes (i.e. single cell necrosis and (multi)focal necrosis). Single cell necrosis was observed in male mice at doses as low as 0.5 mg/kg bw per day. Overall, males showed higher sensitivity to the substance compared to females, with liver effects being more severe and occurring at lower doses.

In the kidneys, exposure to GenX resulted in increased kidney weight, kidney hypertrophy, microscopically observed kidney damage, and increased blood urea nitrogen in rodents. These kidney effects generally occur at higher concentrations than the observed liver effects (5 mg/kg bw per day and above), and are more apparent in females compared to males.

Haematological effects include changes in red blood cell parameters (e.g. decreased number of red blood cells, decreased haemoglobin). These changes are overall relatively mild, with parameters not exceeding 10% change from control up to dosages of 50 mg/kg bw per day in a chronic study in rats. However, data from female rats dosed at 1000 mg/kg bw per day under a subchronic exposure regimen illustrate that FRD-902 may promote severe anaemic conditions.

Increased albumin (A) and/or decreased globulin (G), and associated increases in A/G ratio occurred in rodents administered with 1 mg FRD-902/ kg bw per day and above. Decreased globulin and corresponding increases in A/G ratio are considered early signs of potential reduced immune function. Furthermore, Rushing et al. (2017) observed suppression of the T cell-dependent antibody response (TDAR) in females and increased

T lymphocyte numbers (but no suppression of TDAR) in males exposed to the substance at a dose of 100 mg/kg bw per day for 28 days. Additionally, decreased spleen weight was detected in some studies. This suggests that the immune system might be affected upon treatment with GenX, but there is little information available, which hampers full assessment of the immunomodulatory effects of GenX.

With regard to developmental toxicity, GenX crosses the placenta and distributes into the foetus, and causes early deliveries and decreased birth weight in pups without causing severe parental toxicity at 100 mg/kg bw per day. Maternal toxicity includes mortality, lower mean body weight gain and decreased food consumption, decreased gravid uterine weight, higher mean kidney weight, liver hypertrophy, and microscopic changes in the liver at 1000 mg/kg bw per day. Also, at 100 mg/kg bw per day, GenX caused a mean decreased gravid uterine weight and focal necrosis in the liver. RIVM (Beekman et al., 2016) set the NOAEL for developmental toxicity at 10 mg/kg bw per day, based on early deliveries and decreased birth weight in pups.

Information is inconclusive with respect to potential effects to the reproductive system. No effects on reproduction were observed at any of the dose levels tested in a combined reproductive/developmental screening study in mice. In the parental animals, liver effects were observed, in concordance with the effects observed in the subchronic and chronic toxicity studies. Furthermore, F1 animals of both sexes showed decreased mean body weight during the pre-weaning period. The results from this study do not allow for final conclusions regarding the reproductive effects because the highest dose level tested exerted minimal effects in the parental animals. Therefore, information is regarded inconclusive with respect to potential effects to the reproductive system.

Based on the currently available data, FRD-902 does cause serious eye damage, but does not result in skin irritation. Furthermore, FRD-903 was graded as corrosive to the skin in an *in vitro* Corrositex assay. FRD-902 is not considered to be a skin sensitizer. No information is available on respiratory sensitisation. Lastly, no studies are available providing insight into potential endocrine (disrupting) mode of action for GenX, such as *in vivo* modulation of thyroid hormone (T3, T4 and TSH), androgenic/estrogenic effects, or *in vitro* receptor binding studies.

The observed liver effects are suggested to be (at least partly) explained (directly or indirectly) by activation of the peroxisome proliferator-activated receptor alpha (PPARα), a biological pathway mainly responsible for lipid metabolism. This is, amongst others, indicated by treatment-related increases in fatty acid beta oxidation in rodents upon exposure to GenX, and a mechanistic study which showed that many lipid metabolism associated genes were upregulated in mice treated with GenX for 28 days (Wang et al., 2017). Rodents are known to be more susceptible to PPARα mediated liver effects (i.e. hepatocellular hypertrophy and increased liver weight) (Hall et al., 2012) and PPARα mediated formation of liver tumours (Klaunig et al., 2003) than are primates. For PFOA the interaction with PPARα in rodents has been studied extensively (especially many studies using *pparα* knockout or *pparα* humanised mice) and the effects seen in rodents with GenX closely match those seen with PFOA.

It should however be noted in this context that the liver effects for PFOA in rodents have been demonstrated to be in part non PPARα mediated, and whether this also is the case for GenX still needs further inquiry. At least it cannot be excluded that the liver effects as well as the tumorigenic responses are induced by a non-PPARα related mode of action. A recent study has indicated that GenX is able to bind to- and to activate PPARγ (Li et al., 2019), just as PFOA. Moreover, it should also be noted that although rodents are more susceptible than humans, PPARα mediated effects do occur in humans: this is clearly demonstrated by the fact that certain drugs (fibrates) that act via PPARα activation are applied in human medicine as a treatment for cholesterolemia. Based on the above, the hepatic effects as seen in rodents after treatment with GenX and PFOA are considered

relevant for the risk assessment for humans. This is in agreement with RIVM (Beekman et al., 2016; Zeilmaker et al., 2016a), US EPA (2016), DWQI (2017) and ATSDR (2018).

Appendix B. Toxicity of PFOA

Production and use of PFOA have been reduced significantly following the discovery of its wide-spread occurrence in the environment and in humans due to its persistence and its bioaccumulative potential in addition to its toxic potential.

The toxicity and toxicokinetics of PFOA have been studied extensively in experimental animals and in human biomonitoring and epidemiology studies. Comprehensive reviews of these data are provided by US EPA (2016), DWQI (2017), ATSDR (2018) and EFSA (2018b). RIVM has evaluated the toxicity and toxicokinetics of PFOA as part of its risk assessment of the emission of PFOA by the DuPont/Chemours chemical plant in Dordrecht, The Netherlands (Zeilmaker et al., 2016). As a supplement to this assessment, RIVM provided a review specifically of the available epidemiological studies for PFOA (Rijs & Bogers, 2017).

The biokinetics of PFOA and its salts has been studied in rats, mice, monkeys and humans. A remarkably high potential for bioaccumulation in humans has been determined, with an estimated half-life for clearance from human serum as long as 3-4 years. This contrasts with the half-life for PFOA in experimental animals (monkeys, rats, mice), which is only several weeks at the most (11-21 days) (Zeilmaker et al., 2016). As explained in the Appendix on GenX toxicity, in contrast to classic lipophilic organic pollutants (e.g. DDT, dioxins) which accumulate via linking into fat metabolism leading to accumulation in fatty tissues, PFOA primarily bind to proteins. The long half-life of PFOA in humans compared to other species has been hypothesized to be due to stronger reabsorption from the lumen of the kidney back into the blood by organic anion transporters (OATs) (Yang et al., 2010).

Animal toxicity experiments have been carried out using both PFOA and its ammonium salt ammonium pentadecafluorooctanoate (APFO). Since in aqueous environments both PFOA and APFO lead to the presence of perfluorooctanoate as the dominant chemical species the read across from the salt to the acid is considered valid. Animal toxicity studies with orally dosed PFOA of short-term, subchronic and chronic duration are available in multiple species including monkeys, rats, and mice. In addition, developmental toxicity and reproductive toxicity and carcinogenicity were studied in mice and rats. These studies report developmental effects, liver and kidney toxicity, immune effects, and cancer (liver, testicular, and pancreatic). Developmental effects observed in animals include decreased survival, delayed eye opening and reduced ossification, skeletal defects, altered puberty (delayed vaginal opening in females and accelerated puberty in males) and altered mammary gland development.

Human epidemiology data report associations between PFOA exposure and a number of disorders and diseases. The examined populations were workers at PFOA production plants, a high-exposure community population near a production plant in the United States (the C8 cohort) and members of the general population in the United States, Europe, and Asia. In its review of the epidemiological evidence for PFOA, RIVM (Rijs & Bogers, 2017) selected the following effects reported in the available epidemiology studies for further evaluation: increased liver enzymes and liver disease, testicular and kidney cancer, pregnancy-induced hypertension and pre-eclampsia, decreased birth weight, increased serum uric acid concentration, ulcerative colitis, changes in blood lipid concentrations, decreased vaccination response and thyroid disorders. The weight of evidence for an association between PFOA and these effects was concluded to be variable. For some effects inconsistencies were noted, for others the influence of possible confounders could not be ruled and for others the biological significance was doubtful. The evidence for decreased birth weight and increased cholesterol is strongest but even for these effects uncertainty remains about the causality of the observed association (Rijs & Bogers, 2017). Because of the limitations in the available epidemiological evidence, most international organizations do not use these data for quantitative dose response analysis and risk assessment.

In animal studies with PFOA, changes in liver weight and hepatocellular hypertrophy were the most common effects observed with or without other hepatic indicators of adversity. Liver contains the highest levels of PFOA when analysed after test animal sacrifice. The increases in liver weight and hypertrophy as seen in rodent studies may be associated with activation of the cellular peroxisome proliferator-activated receptor α (PPARα). The PPARα response in the liver is known to be greater in rodents than in humans. But increased liver weight and hypertrophy were also observed in monkeys. In its 2016 risk assessment for PFOA, RIVM concluded liver effects to represent the most sensitive endpoint for PFOA-toxicity (Zeilmaker et al., 2016). In the derivation of a health-based guidance value (HBGV) for PFOA, RIVM (Zeilmaker et al., 2016) initially selected a subchronic study in monkeys in which increased liver weight and hypertrophy were seen, but rejected this study upon evaluation due to inconsistencies in the serum PFOA-levels that were reported for the different dose groups. As a replacement a subchronic study in rats (Perkins et al., 2004) was used, which included measurement of the serum PFOA levels. In deriving the HBGV for PFOA, the NOAEL from this rat study was divided by a reduced interspecies factor because of the known higher susceptibility to liver effects by PFOA in rodents compared to humans (for the complete derivation see below).

In reproduction toxicity studies in mice reduced fertility and reduced sperm counts were observed (NOAEL of 2.5 mg/kg bw per day). Developmental toxicity in mice and rats showed decreases in pup weight as the most sensitive effect (NOAEL of 1 mg/kg bw per day). In addition, several developmental toxicity studies in mice showed delayed mammary gland development in female offspring at very low maternal dose levels. The biological significance of this effect is unknown. RIVM noted that other hormone-related parameters in these studies showed no effect and concluded that further research on this possible effect is needed. This effect was therefore not used for deriving an NOAEL.

Rat bioassays showed increased incidences of tumours in liver, testes and pancreas. Epidemiological studies in a population living in the vicinity of a PFOA production plant in the USA and in workers of this plant showed an association between PFOA exposure and testicular cancer and kidney cancer. As stated above, IARC concluded the rat bioassay results to represent limited evidence in experimental animals and the positive associations as seen in the epidemiological studies to represent limited evidence for a carcinogenic effect by PFOA in humans. Available information on PFOA genotoxicity and mechanistic information for the induction of the observed tumours indicates a non-genotoxic mode of action (DWQI, 2017; US EPA, 2016; Zeilmaker et al., 2016). For the derivation of a HBGV for PFOA this means that a threshold in its toxic action is assumed and that a HBGV can be derived via application of the appropriate assessment factors to a selected point of departure in the form of an adequate NOAEL or BMDL.