Attachment A

Proposed Drinking Water Health Advisory Value for GenX: 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoic acid

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ABSTRACT

The widespread occurrence and subsequent environmental concerns of long-chain perfluoroalkyl acids (PFAAs) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) has led to the production and use of alternative polymer processing aids with more environmentally favorable chemical and biological properties. One alternative that has been used successfully is ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate, also known by its trade name *GenX,* and it has been detected in the environment near where it has been used in large quantities. This paper presents an analysis of the currently available toxicity data for GenX for the purpose of deriving a drinking water health advisory value using standard US EPA methodologies. A review of existing data on GenX revealed that a 2-year chronic study with rats provides the best available data on GenX toxicity for deriving a lifetime exposure health advisory. The No Observed Adverse Effect Level (NOAEL) for this study was 1.0 mg/kg/day and was used as the point of departure for deriving the health advisory. Using protective uncertainty factors of 10 for both interspecies and intraspecies and a conservative relative source contribution from water of 20%, a conservative lifetime health advisory value would be 70,000 ng/L for GenX. Furthermore, data on the elimination of GenX from mammals indicate it has a much faster elimination rate in humans compared to PFOA, PFOS and other legacy chemicals with an estimated half-life on the order of a few days at most.

INTRODUCTION

Per- and poly-fluorinated alkyl substances (PFAS) have been produced for over 70 years for use in industrial processes and manufacturing of consumer products (Kissa 2001; Buck 2011, Buck et al. 2015). The widespread use of PFAS has led to their release and detection in the environment (Heydebreck et al. 2015; Sun et al. 2016; Gebbink et al. 2017), most notably the long-chain perfluoroalkyl acids (PFAAs) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Concern over the presence of these longer-chain PFAAs in the environment has led to development of alternative fluorinated substances with more environmentally favorable chemical and biological properties. An important class of these alternatives are the per- and poly-fluorinated ether carboxylic acids (PFECAs) that have replaced ammonium perfluorooctanoate (APFO) as polymer processing aids (Feiring 1994; Buck 2015; Buck et al. 2011; Gordon 2011). Compared to the legacy long chain PFAAs, the shorter chain PFECAs have higher water solubility, much more rapid elimination from biological systems, are less toxic and expected to have very low accumulation in aquatic or terrestrial food webs (Ritter 2010; Buck et al. 2011; Caverly Rae et al. 2015; Gannon et al. 2016; Hoke et al. 2016).

A PFECA that has been used successfully as a polymer processing aid is ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate (EC 700-242-3, CAS 62037-80-3), also known by its trade name *GenX*, that is the conjugate base ammonium salt of the 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoic acid (Fig. 1, CAS 13252-13-6). This dimer acid is both the precursor to the salt in the production of GenX and the environmentally relevant form in water if GenX is released to the environment. The dimer acid form has been referred to as PFPrOPrA,

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hexafluoropropylene oxide dimer acid, HFPO-DA, FRD 903 and as the trade name *GenX*. In this paper, the term *GenX* refers to the environmentally relevant deprotonated acid form of GenX. GenX has received significant attention recently owing to it being detected in the environment near where it has been used in large quantities: Cape Fear River, North Carolina, USA (Sun et al 2016); Parkersburg, West Virginia, USA; Dordrecht, Netherlands (Heydebreck et al. 2015; Gebbink et al. 2017); and Xiaoqing River, Shandong, China (Heydebreck et al. 2015). More specifically, some of the surface and groundwater where GenX has been detected serve as a drinking water source thus raising concern over possible adverse health effects associated with consumption of this water.

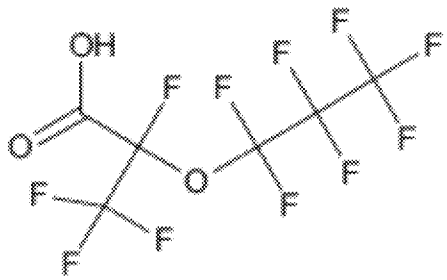

Figure 1. Chemical structure for 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoic acid.

GenX is not subject to proposed or promulgated drinking water regulations, nor is it on the US EPA Chemical Contaminants List (CCL) for unregulated chemicals, but the detection of GenX in North Carolina led to the issuance of a provisional lifetime health goal by the State of North Carolina (NC), USA. The NC provisional health goal was initially set at 71,000 ng/L, then revised to 140 ng/L, and now is subject to review by a Scientific Advisory Board (SAB) to the NC Department of Environmental Quality and NC Department of Health and Human Services, who may further revise the value based on the SAB recommendations (NCDEQ 2018).

This paper presents an analysis of the currently available toxicity data for GenX for the purpose of deriving a drinking water health advisory value (known as a health goal in the State of North Carolina). This paper is not intended to be as comprehensive as an US EPA Health Advisory document, but instead an initial summary and analysis of existing data to inform scientists contemplating further studies to assess exposure and toxicity, and for regulators and the public who may have concern about exposure to GenX and thus are making decisions regarding water use and/or treatment.

In this paper, all available data were treated to the standard methodologies used by the US EPA to derive lifetime drinking water health advisories and then recommend a proposed health advisory value for GenX based on the best available scientific data. This health advisory value is then compared to measured GenX exposures to provide perspective on the margin of exposure (or safety) at locations where GenX has been detected in drinking water sources.

NATURE OF THE CHEMICAL

The acid form of GenX is a liquid and the ammonium salt a white/colorless solid at ambient temperature (20 °C). Both are infinitely soluble in water above the pK_a (2.84) of the acid. The substance has a decomposition point of 150–160°C, a sublimation point of 130–140◦C, a density of 1.7 g/cm^{3}at 20°C, and a low vapor pressure of 0.01 Pa at 20°C (Caverly Rae et al. 2015; Gannon et al. 2016). Due to its high water solubility and negative charge at the pH of natural waters, GenX has a very low organic carbon-normalized adsorption coefficient (K_{oc}) to soil (log K_{oc} = 1.08) and sludge (log K_{oc} = 1.10) (Bloxham, 2008) and thus would not be expected to partition significantly onto environmental particles (e.g., soil, suspended or bedded sediment). This has implications for the fate of the chemical (e.g., it will not accumulate in sediments) and also for environmental sampling conducted to understand GenX fate or estimate exposure (e.g., focus should be on water and there should be little difference in measured values of GenX between whole water and filtered water samples).

In areas of large volume use of GenX, it has been found in soil, surface water, groundwater, and air (Heydebreck et al. 2015; Beekman 2016; Sun et al 2016; Gebbink et al. 2017; NCDEQ 2018), with very low concentrations in vegetables grown very near the GenX source (Mengelers 2018) and preliminary data indicating very low concentrations might be found in sediment (UNCW 2018).

Although detailed environmental fate data are not available at this time, GenX is expected to be relatively persistent in the environment and a biodegradability test indicated GenX was not readily biodegradable and not transformed structurally under the test conditions (Mitsubishi Chemical 2009). Given the high water solubility, GenX is expected to be mobile in the presence of water and thus would be expected to move from soil to groundwater and to surface waters in runoff or effluent discharge. The high water solubility and low volatility would cause any GenX emitted to air to return to the ground or surface water through wet deposition. This same high water solubility and very low K_{oc} would prevent GenX from partitioning strongly to soil or sediment or undergo significant bioaccumulation in aquatic food webs. Preliminary data with oysters exposed to high concentrations of GenX (100,000 ng/L) indicated very little accumulation in the oysters (UNCW 2018). The very high biological elimination rates (see below) would also prevent GenX from accumulating significantly in terrestrial food webs. Documents used by the European Chemicals Agency (ECHA) to review GenX support the above summary by concluding GenX "is unlikely to be a concern for aquatic bioaccumulation" (ECHA 2017a) and "is not a concern for terrestrial bioaccumulation" (ECHA 2017b).

HEALTH EFFECTS ASSESSMENT

The primary toxicological studies for GenX are four oral toxicity studies in rats (28-day subacute, 90-day subchronic, 2-year chronic and carcinogenicity, and a prenatal developmental study) and three oral toxicity studies in mice (28-day subacute study, a 90-day subchronic study, and 70+ day developmental and reproductive toxicity (DART) study). This work is summarized in Table 1 (provided at the end of the document). All seven of these studies followed Good Laboratory

Practices (GLP). Five of these studies were reviewed by the ECHA to assess the toxicity of GenX to humans and all were deemed reliable. The ECHA identified only the 2-year chronic rat study (Craig 2013; Caverly Rae et al. 2015) as the Key Study, with the other studies being adequate as supporting studies only. The ECHA also included two 7-day non-GLP studies that are summarized below but not included in Table 1.

Additional GLP studies were conducted to evaluate acute toxicity, biodistribution/elimination, and genotoxicity. The oral LD50 (rat) was 1,750 mg/kg, the dermal LD50 was >5,000 mg/kg, the inhalation 4-h acute lethal concentration (ALC) was >3.6 mg/L vapor (Buck 2015). Genotoxicity was determined to be negative based on negative results in the following tests: Ames and chromosome aberration *in vitro* studies; and mouse bone marrow, mouse micronucleus, and rat unscheduled DNA synthesis (UDS) *in vivo* studies (Buck 2015).

Some non-GLP work has been published on GenX toxicity by academic researchers. *In vitro* responses (cytotoxicity and protein binding capacity) to GenX with a human liver cell line were investigated, but these data cannot be used directly for deriving a health advisory (Sheng et al. 2018). Immunomodulatory responses (T cell-dependent antibodies) to GenX exposure also were reported, but possible adverse effects were not found until very high doses (100 mg/kg) indicating that GenX is a very weak suppressor of immune function and thus would not be a factor in setting a health advisory value (Rushing et al. 2017).

Two non-GLP 7-day organ toxicity studies were conducted in mice at a single dose of 30 mg/kg/day that were identical except one used the GenX dimer acid (Nabb 2008a) and the other used the GenX dimer salt (Nabb 2008b, note this is also ECHA Study 006). The results were nearly identical: microscopic changes were limited to the liver and the study author indicated it was uncertain if these changes were related to the test substance. The value of these two studies is they demonstrate that the dimer acid and dimer salt are likely to have identical toxicities and thus a read-across (i.e., toxicological equivalency) of the salt to the acid form is justified and is consistent with other analyses of these data (Beekman 2016). This also is consistent with expected behavior, where both the acid and salt would be in the dissociated acid form following absorption and distribution in the test organism.

In the Key Study identified by ECHA, the 2-year chronic and carcinogenicity rat study (Craig 2013; Caverly Rae et al. 2015), the NOAELs were 1 mg/kg/day in males and 50 mg/kg/day in females; with the (more sensitive) NOAEL in the male rat based on observed effects at 50 mg/kg/day. These observed effects are manifested via a rodent-specific response to a PPARα-agonist exposure and thus is very likely a non-human-relevant mode of action (see below). These effects included focal cystic degeneration and necrosis, that study authors described as minimal to mild. These effects were observed only at 50 mg/kg/day (the Lowest Observed Adverse Effect level, LOAEL) in 5/70 animals and this response was not statistically significant. The shorter-term subchronic and subacute rat toxicity studies also reported liver effects that were considered adaptive and reversible responses to repeated chemical exposure that are commonly observed in rodents. In the developmental rat study, maternal toxicity was reported as focal necrosis of the liver at 100 mg/kg/day, and developmental effects were also reported at this high dose. Of

these four studies, the 2-year chronic study resulted in the lowest NOAEL for rats (1 mg/kg/day). Note that this study had no doses between 1 and 50 mg/kg/day (Table 1).

All of the mouse studies were considered by ECHA to be supporting studies only. They were only subchronic or subacute in duration, and they did not reveal any different types of toxicity or modes of action compared to the chronic rat study that might require additional consideration. Mice also have been shown to be less similar to primates than the rat with regard to GenX toxicokinetic behavior (see below).

The Appropriate Toxicity Study Duration for Lifetime Exposure Analysis

The US EPA risk assessment process uses the 1- or 2-year chronic study as the standard for assessing potential adverse health effects for a lifetime exposure duration and allows for subchronic studies to be used "when a chronic study is not available" (US EPA 2014a). For GenX, there is a complete 2-year chronic and carcinogenicity rat study that meets all the criteria established by the US EPA for use in a lifetime exposure analysis and was identified by ECHA as the Key Study (Craig 2013). There is therefore no scientific justification to use the subchronic or subacute studies as a surrogate for the 2-year chronic study, especially when the shorter duration studies do not reveal any different types of toxicity or modes of action that might require additional consideration. Thus, the 2-year chronic study was chosen as the Key Study for setting the proposed health advisory.

Identification of *Adverse Effects*

Since properly designed toxicological studies identify doses at which test substance-related changes occur, decisions must be made on which observed changes are considered *adverse effects* and that also are relevant and representative of human response. Repeated exposure to GenX in rodents is associated with peroxisome proliferator-activated receptor alpha (PPARα) effects, but the lack of human relevance of this pathway (PPARα-dependent toxicity) is very well established (Corton et al. 2017; Felter et al. 2018). Thus, the endpoints of reduced serum lipids, hepatocyte hypertrophy, increased liver weights, and liver tumors in the rodent studies of GenX (Table 1) are not relevant to humans. A strong argument also can be made to treat single-cell necrosis as a non-adverse effect because 1) the effects were minimal-to-mild, 2) were not consistently seen at higher doses or at the lower doses at longer time points, and 3) are therefore likely a result of the adaptive and reversible hypertrophy that is known to be PPARα-dependent and thus not relevant to human health. As the cell enlarges due to the PPARα-dependent hypertrophy, minimal-to-mild single-cell necrosis would be expected. However, a non-PPARα-dependent pathway for single-cell necrosis cannot be ruled out at this time and single-cell necrosis is usually considered adverse when correlative enzyme activation is observed (Thoolen et al. 2010; Maronpot et al. 2010; Hall et al. 2012.) Thus, to be conservative, one could consider the minimal-to-mild single-cell necrosis as an adverse effect in the subchronic/subacute studies.

Use of NOAEL versus Benchmark Dose (BMD) to set Point of Departure (POD)

The US EPA risk assessment process includes an analysis of the dose-response relationship between exposure and adverse health-related outcomes and follows a two-step process: (1) defining a point of departure (POD) and (2) extrapolating from the POD for relevance to human exposure. The NOAEL has been used as the POD for many years, but recognizing the limitations of this approach, the US EPA has adopted an alternative approach called the benchmark dose (BMD) method (US EPA 2012). The BMD method involves statistical modeling of dose-response data and is particularly helpful at incorporating data from multiple related studies and extrapolations near the low end of the exposure range. The BMD analysis results in a BMDL (benchmark dose lower confidence level) that is used as the POD instead of the NOAEL. Not all data sets are amenable to BMD modeling and different models within the BMD software can provide slightly different results. BMD modeling was performed on the data available for GenX using the latest US EPA BMD software (US EPA 2017). A brief summary of this analysis is provided below. BMD analysis was performed on males only because in all studies males were more sensitive than females and would provide the lowest BMDL and POD. A benchmark response (BMR) of 10% extra risk was applied to all dichotomous model types.

The 2-year chronic rat study data (Craig 2013) were not amenable to BMD modeling owing to the lack of observed effects at the lower doses and a wide range between the LOAEL (50 mg/k/day) and NOAEL (1 mg/kg/day), resulting in a best-fit BMDL of 38.2 mg/kg/day (for liver centrilobular necrosis) which is much higher than the NOAEL. Thus, the appropriate POD for the 2-year chronic study is the more conservative NOAEL of 1 mg/kg/day.

For the subchronic mouse studies, the data for male mice were combined for the 90-day subchronic (MacKenzie 2010) and 70+ day DART (Edwards 2010b) studies because the exposure durations were similar, the mice were the same strain (Crl:CD1(ICR)) and single-cell necrosis in the liver was the common adverse but reversible endpoint reported by both studies. These data were amenable to BMD analysis and resulted in a best-fit BMDL of 0.23 mg/kg/day using the multistage model. This model had the second highest p-value (0.9944) and the lowest Akaike's Information Criterion, AIC, value (50.51). The multistage model also resulted in the second lowest BMDL value, where the lowest BMDL value resulted in a very poor fit (p-value 0.0592 and AIC Value 58.40). The multistage model also is the most conservative BMDL that has an acceptable statistical fit (BMDL range was 0.228 – 0.339 mg/kg/day). Although the chronic rat data are the most appropriate and preferred data for setting the POD, the 0.23 mg/kg/day BMDL has a stronger scientific basis for use as the POD than the 0.1 mg/kg/day NOAEL from the subchronic/subacute studies and is used below for comparative purposes.

Uncertainty Factors (UF)

A subchronic-to-chronic UF would not be needed if the 2-year chronic rat study is used to derive the POD. However, if the subchronic study data were used then consideration must be given to the value of this UF. The US EPA states *"A default value of 10 for this UF is applied to the NOAEL/LOAEL or BMDL/BMCL from the subchronic study on the assumption that effects from a*

given compound in a subchronic study occur at a 10-fold higher concentration than in a corresponding (but absent) chronic study" (US EPA 2014b). This condition is not true for GenX, since a complete 2-year chronic rat study is available for GenX (Craig 2013). Moreover, the rationale for using a subchronic-to-chronic UF = 10 is to account for possible effects "*at a 10-fold higher concentration*" in a chronic study (US EPA 2014b). However, in the case of GenX the opposite is true. In the mouse studies, there is no single-cell necrosis progression or higher NOAEL/LOAEL with the longer exposure duration study (90 days) compared to the shorter duration studies (28 days and 70+ days). Thus, the subchronic data do not support the use of a default subchronic-to-chronic UF = 10 or even a UF = 3. Rather, the data support a UF = 1 given that longer duration and higher dose did not demonstrate increased severity or incidence of any adverse endpoints.

The US EPA uses a default interspecies UF = 10 under the assumption that humans may be more susceptible/sensitive to a chemical than the rat or mouse used in the toxicity study, but the US EPA also allows for this 10-fold UF to be reduced if there is evidence that that humans are less sensitive (US EPA 2014c). Although definitive human data are lacking, there is good reason to assume that humans are less sensitive than rats and mice to the reported GenX toxicities (single-cell necrosis in subchronic studies and centrilobular necrosis in chronic study) due to the very strong ***PPARα-dependent*** toxicities that are not relevant in humans. This would justify setting the interspecies UF = 3.

Relative Source Contribution

The health advisory may include a provision to account for other possible sources of GenX besides drinking water (such as food, inhalation, and dermal absorption) by using a relative source contribution (RSC) to apportion exposure to different sources. Given the chemical properties of the environmentally-relevant form of GenX (e.g., highly water soluble) one would not expect significant amounts of GenX in the food of the general population. This is consistent with a recent study in the Netherlands where GenX was measured in vegetable crops grown in private gardens in the vicinity of the Dordrecht Chemours site where GenX is known to have been released to the environment (Mengelers 2018). The study concluded 1) that very low concentrations of GenX were found in some samples very near the site, but these levels did not exceed exposure thresholds and 2) that beyond 1 km distance from the site, consumption of vegetables did not contribute significantly to GenX exposure. Also, as pointed out by the Centers for Disease Control (CDC), GenX is unlikely to be absorbed through the skin (Moore 2017). Finally, due to its high water solubility and low volatility, any GenX emitted to air would return to the ground though wet deposition. This, combined with the very low volatility of GenX, means that inhalation would not contribute significantly to GenX exposure for the general population. Thus, assuming that 100% or nearly 100% of GenX exposure is through drinking water is probably accurate for most people. However, since we do not yet have enough data on all relevant exposure pathways, for the purpose of this paper the more protective assumption that only 20% of GenX exposure is through drinking water will be used until additional data become available. This would set the RSC value for water to be 20% (RSC = 0.2) in the risk equation.

Derivation of Proposed Health Advisory Value for GenX

Using the above discussion as a basis for deriving a health advisory for GenX, three possible values are listed in Table 2 along with the parameters and assumptions used to derive the value. The values listed in green columns are based on the 2-year chronic study in rat and thus are scientifically defensible in matching the lifetime exposure health advisory to the lifetime chronic study in the rat. The value listed in the yellow column is provided for comparative purposes only to show the value one would derive in the absence of the chronic study data (using the BMD method with subchronic data from the mouse as described above). Based on these analyses, a conservative lifetime health advisory value would be 70,000 ng/L for GenX.

Table 2. Alternative health advisory values based on available data, with assumptions listed.

	US EPA Benchmark Dose Method (subchronic)	Lifetime Exposure Assessment (chronic)	Lifetime Exposure Assessment Adjustment 1 (chronic)
Health Advisory (ng/L or ppt)	16,100	70,000	233,300
Population Assumed	Adult Lifetime Exposure	Adult Lifetime Exposure	Adult Lifetime Exposure
Key Study Used	90-day and 70+ day subchronic mouse	2-year chronic rat	2-year chronic rat
Relative Source Contribution for Water	0.2	0.2	0.2
Subchronic-Chronic UF	1	Not applicable	Not applicable
Interspecies UF	10	10	3
Intraspecies UF	10	10	10

All values are based on lifetime exposure to an adult using 70 kg bodyweight and 2.0 L/day drinking water intake that is the standard in many countries and many states within the US. The US EPA has recently updated bodyweight to be 80 kg and drinking water intake to be either 2.4 L/day or 2.5 L/day (US EPA 2015). The values in Table 2 can be adjusted accordingly depending on local standards/rules.

RISK CHARACTERIZATION

Toxicokinetics and Elimination Half-lives

The toxicokinetics of GenX was initially studied in male and female rats that were given either a 10 mg/kg or a 30 mg/kg dose (Gannon 2008). Concentrations of GenX were followed in the plasma of the rats at 14 time points up to 168 hours (Fig. 2) and GenX was measured in the liver and adipose tissues at time of sacrifice (168 hours). Clearance times, defined as the time for 98.4% of the initial GenX concentration in the plasma to be cleared, were 28 hours (10 mg/kg dose) and 22 hours (30 mg/kg dose) for males and 8 hours (10 mg/kg does) and 4 hours (30 mg/kg dose) for females. At 168 hours, the ratio of GenX in liver:plasma for males was 0.64 (10 mg/kg dose) and 0.71 (30 mg/kg dose). The liver:plasma GenX ratio could not be calculated for females because GenX was not detectable in plasma in females after 120 hours and was never detected

in the liver of females at either dose. GenX was never detected in adipose tissue in either males or females at either dose, indicating that GenX is not stored in the fat tissue. Overall, these data show very fast clearance of GenX from rats.

A follow-on study of the absorption, distribution, metabolism, and elimination (ADME) and kinetic behavior of GenX was performed in rats, mice, and cynomolgus monkeys (Gannon et al. 2016). A single dose of GenX was given by oral and intravenous routes of exposure and followed in both plasma and urine. GenX was rapidly and completely absorbed in both rats and mice and then rapidly eliminated in the urine with elimination half-lives of approximately 5 hours in rats and 20 hours in mice. In monkeys, rats, and mice GenX undergoes a rapid, biphasic elimination with a very fast alpha phase and a slower beta phase. The beta phase indicated no potential for accumulation after multiple dosing in rats or monkeys (Gannon et al. 2016), consistent with the earlier study of rats showing no detectable GenX in adipose tissue (Gannon 2008). Both *in vivo* and *in vitro* experiments demonstrated that GenX is not metabolized. This comparative pharmacokinetic study in rats, mice, and monkeys indicated that the rat, and not mice, is more similar to the monkey and the authors concluded that the rat is therefore a more appropriate rodent model than that of the mouse for a pharmacokinetics assessment of GenX behavior in primates (Gannon et al. 2016.) This provides further justification for using the 2-year chronic rat study rather than the short-term mouse studies (Table 1).

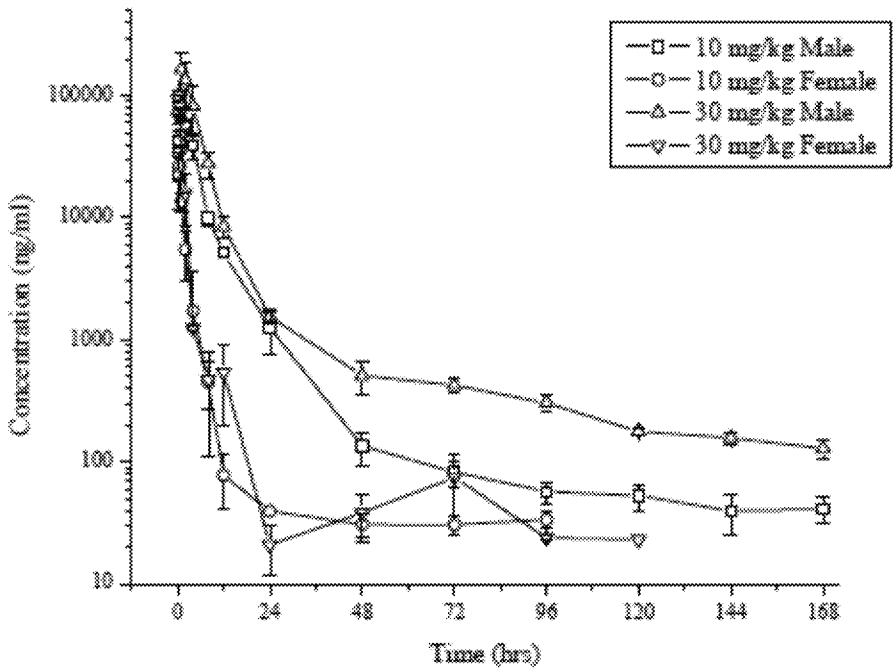

Figure 2. Toxicokinetics of GenX in plasma of male and female rats at two doses (from Gannon 2008). Clearance times (time for 98.4% of initial value to be cleared from the plasma) where 28 hours (10 mg/kg dose) and 22 hours (30 mg/kg dose) for males and 8 hours (10 mg/kg does) and 4 hours (30 mg/kg dose) for females. The ratio of GenX in liver:plasma for males at time of sacrifice (168 hours) was 0.64 (10 mg/kg dose) and 0.71 (30 mg/kg dose). GenX was not detectable in female plasma after 120 hours and was never detected in the liver of females at either dose. GenX was never detected in fat tissue in either males or females at any time. All data are from Gannon 2008.

No estimates for human elimination rates for GenX have been published yet, but values can be estimated from monkey:human elimination rate ratios of other perfluorinated chemicals: PFOA, PFOS and shorter chain fluoropolymers perfluorobutane sulfonate (PFBS) and perfluorobutanoic acid (PFBA). It is likely that the monkey:human elimination rate ratio of GenX would fall between the values of the longer chain PFAS chemicals (PFOA: 66 or 40; PFOS: 16) and the shorter chain PFAS chemicals (PFBS: 7.5; PFBA: 1.9). Using the data from Gannon et al. (2016) for GenX in monkey and a conservative monkey:human ratio of 16 (PFOS) comparison of GenX is made to the legacy compounds PFOA, PFOS and other chemicals regarding elimination rates in humans (Figure 3) using data for humans for the other chemicals (US EPA 2016a, US EPA 2016b, Gannon et al. 2016, Olsen et al. 2007, Bartell et al. 2010, Wang et al 2013.). Clearly GenX has a much faster estimated elimination rate in humans compared to PFOA, PFOS and other legacy chemicals with a half-life range of 4 hours to 6 days depending on which monkey:human elimination rate ratio is used as a surrogate for GenX. The elimination curve for GenX shown in Figure 3 corresponds to a half-life in humans of 1.8 days and is based on the monkey:human elimination rate ratio of 16 for PFOS.

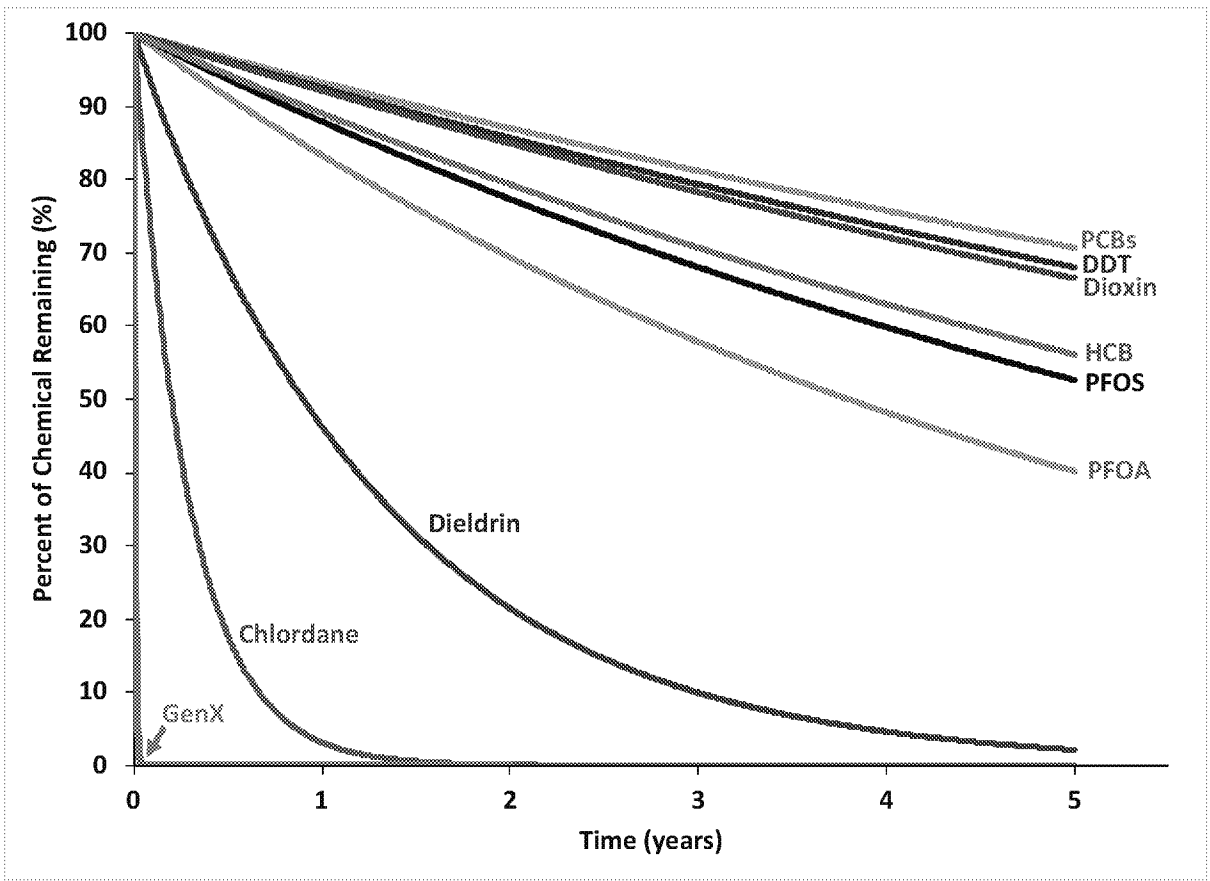

Figure 3. Estimated elimination curves in humans showing percent of various chemicals remaining in the body as a function of time. The elimination curve for GenX is based on a conservative assumption that GenX follows the same monkey:human half-life ratio as PFOS (16). Using the monkey:human ratio for the shorter-chain PFBS (7.5) or PFBA (1.9) would lead to even more rapid loss of GenX in humans. See text for data sources and explanation of estimation method.

Margin of Safety or Exposure: Comparing Measured Water Values of GenX to the Proposed Health Advisory

Recent data on GenX in drinking water from North Carolina, USA are used to provide some perspective on how measured values of GenX compare to the proposed health advisory. A study measuring GenX in tap water from 198 homes potentially affected in NC reported GenX values ranging from non-detectable to nearly 100 ng/L with an average of 45 ng/L (Kotlarz 2018). The highest value measured represents a margin of exposure of greater than 700 compared to the proposed health advisory of 70,000 ng/L. Similar margins of exposure are found for data in the Cape Fear River, NC, USA and in homeowner wells near the source of GenX in that area.

CONCLUSIONS

There is sufficient information to perform a preliminary analysis to provide guidance to scientists, regulators and the public on the potential for adverse health effects associated with exposure to GenX through drinking water. A 2-year chronic study with rats provides the best available data on GenX toxicity for deriving a lifetime exposure health advisory. The NOAEL for this study was 1.0 mg/kg/day and was used as the point of departure for deriving the health advisory. Using protective uncertainty factors of 10 for both interspecies and intraspecies and a conservative relative source contribution from water of 20%, a conservative lifetime health advisory value would be 70,000 ng/L for GenX. Data on the elimination of GenX from mammals indicate its half-life in humans is in the range of 4 hours to 6 days, and most likely at the low end of that range, indicating no potential for significant accumulation in humans. Using data from North Carolina, USA where GenX has been detected in drinking water and drinking water sources, indicates a margin of safety (exposure) in excess of 700 in the most recent tap water sampling. In other words, for a consumer to approach the derived health threshold, they would have to consume 1,400 L of water per day from the most contaminated tap for their entire life.

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Table 1. Summary of Rodent Toxicity Studies. Observations and effects are taken directly from statements of the study authors in the toxicology reports. All studies were conducted under GLP.

Study Reference Regulatory Guideline Species/Study Type Exposure/Duration	Dose (mg/kg/day)	Effects and Observations in Males	Effects and Observations in Females
Key Study Identified by European Chemicals Agency and used in this Study to Derive the Drinking Water Health Advisory Value			
Craig 2013. Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats. (ECHA Study 001) Data also summarized in Caverly Rae et al. 2015 OECD 453 (GLP) Rat/Chronic-Cancer Gavage/2-year	0.1	No adverse effects were observed at this dose	Not applicable, dose not given
	1	**NOAEL**: no adverse effects were observed at this dose	No adverse effects were observed at this dose
	50	**LOAEL**: Increases in focal cystic degeneration, focal necrosis, and centrilobular necrosis of the liver, with associated increases in cytotoxic liver enzymes, and equivocal increases in pancreatic acinar cell tumours and testicular interstitial (Leydig) cell tumours	**NOAEL**: No effects were observed at this dose
	500	Not applicable, dose not given	**LOAEL**: Reductions in body weight, body weight gain, and food efficiency; mild decreases in red cell mass; increases in individual cell necrosis in the liver, hyperplasia and/or inflammation in the nonglandular stomach and tongue; an increase in incidence and severity of microscopic pathology in the kidneys; and an increase in hepatocellular adenomas and carcinomas,
Supporting Study Identified by the European Chemicals Agency and *not used* to Derive the Drinking Water Health Advisory Value			
Haas 2009. A 90-Day Oral (Gavage) Study of H-28548 in Rats with a 28-Day Recovery (ECHA Study 002) OECD 408 (GLP) Rat/Subchronic	0.1	No adverse effects were observed at this dose	Not applicable, dose not given
	10	**NOAEL**: Study authors state that clinical chemistry changes were associated with PPARα activation (decreased cholesterol, decreased globulin, increased albumin, increased A/G ratio); increased liver weights, hepatocellular hypertrophy (reversible); increased kidney weights (not adverse)	No adverse effects were observed at this dose; increased kidney weights (not adverse)
	100	**LOAEL:** Erythrocyte changes associated with regenerative anemia (reversible)	**NOAEL**: Study authors noted that the clinical chemistry changes (decreased cholesterol and globulin) were associated with PPAR-alpha activation

Study Reference Regulatory Guideline Species/Study Type Exposure/Duration	Dose (mg/kg/day)	Effects and Observations in Males	Effects and Observations in Females
Gavage/90-day 4-wk recovery	1000	Not applicable, dose not given	**LOAEL:** Three mortalities (two were associated with treatment); erythrocyte changes associated with regenerative anemia (reversible); additional clinical chemistry changes (lower total protein, bilirubin, and GGT levels; higher A/G ratio); increased liver weights, hepatocellular hypertrophy (reversible)
Supporting Study Identified by the European Chemicals Agency and *not used* to Derive the Drinking Water Health Advisory Value			
Haas 2008a. An Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery (ECHA Study 004) OECD 407 (GLP) Rat/Subacute Gavage/28-day 4-wk recovery	**Study authors state that all test-substance related changes were non-adverse, NOAEL is highest dose administered**		
	0.3	Decreased cholesterol; increased hepatic peroxisomal beta-oxidation (considered reversible)	Not applicable, dose not given
	3	Study authors state that clinical chemistry changes were associated with PPARα (decreased globulin, increased albumin, increased A/G ratio, decreased triglycerides (not significant at other doses)); minimal decreases in red cell mass parameters; increased liver weights and kidney weights; multifocal centrilobular liver hypertrophy (all effects were considered reversible and non-adverse by the study authors)	No adverse effects were observed at this dose
	30	**NOAEL**: increased hepatic microsomal cytochrome P-450 enzyme (considered reversible and non-adverse)	Increased hepatic peroxisomal beta-oxidation (considered reversible and non-adverse)
	300	Not applicable, dose not given	**NOAEL**: Study authors reported that clinical chemistry changes were associated with PPARα activation (decreased globulin, increased albumin, and increased A/G ratio); increased relative liver weights; multifocal centrilobular hypertrophy (all effects reversible and non-adverse)
Supporting Study Identified by the European Chemicals Agency and *not used* to Derive the Drinking Water Health Advisory Value			
Edwards 2010a. An Oral (Gavage) Prenatal Developmental	10	Not applicable, dose not given	**MATERNAL (F0) / FETAL (F1 both genders)**
			F0: **Maternal NOAEL**; no adverse effects were observed at this dose

Study Reference Regulatory Guideline Species/Study Type Exposure/Duration	Dose (mg/kg/day)	Effects and Observations in Males	Effects and Observations in Females
Toxicity Study of H-28547 in Rats OECD 414 (GLP) Rat/Developmental Drinking water/ Gestation Day 6-20			F1: **Developmental NOAEL**; no adverse effects were observed at this dose
	100	Not applicable, dose not given	F0: **LOAEL**: Early deliveries; lower gravid uterine weights; higher liver weights, focal necrosis of liver F1: Reduced mean fetal weights
	1000	Not applicable, dose not given	F0: One mortality; reduced body weight and body weight gains; edematous pancreas (2 females); higher kidney weights, hepatocellular hypertrophy F1: Higher mean litter skeletal variations
Supporting Study Identified by the European Chemicals Agency and *not used* to Derive the Drinking Water Health Advisory Value			
Haas 2008b. An Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery (ECHA Study 005) OECD 407 (GLP) Mouse/Subacute Gavage/28-day 4-wk recovery	0.1	**NOAEL**: increased hepatic peroxisomal beta-oxidation was found at all doses, however study authors indicate this observation was completely reversible and consistent with PPARα agonist and considered non-adverse.	No adverse effects were observed at this dose
	3	Non-adverse effects were PPARα agonist related (increased beta-oxidation in the liver, increased liver weights, hepatocellular hypertrophy, and changes in serum lipids and proteins) or reversible (increased body weights, minimal decreases in red cell mass parameters and increased adrenal weights and adrenal cortical hypertrophy. Adverse effects were single cell necrosis of hepatocytes (4/10; minimal) and correlative increases in hepatic microsomal cytochrome P-450 enzyme content liver enzymes, but both of these also were reversible.	**NOAEL**: Decreased globulin and A/G ratio (reversible); increased liver weights (reversible at 3 mg/kg/day, but not 30 mg/kg/day); changes in liver enzymes, increased hepatic peroxisomal beta-oxidation at doses ≥ 3 mg/kg/day (reversible). All observations considered non-adverse.

Study Reference Regulatory Guideline Species/Study Type Exposure/Duration	Dose (mg/kg/day)	Effects and Observations in Males	Effects and Observations in Females
	30	Increased body weights; increased monocytes and large unstained cells (not associated with other hematological effects), increased albumin (reversible); liver enzymes increased (ALT, AST, SDH, ALKP; all were reversible except SDH), multifocal single cell hepatocellular necrosis (10/10; minimal, reversible), decreased chloride and increased BUN (not associated with correlative microscopic changes); adrenal cortical hypertrophy (reversible); increased mitoses distributed multifocally throughout the liver (reversible)	Liver enzymes increased (ALKP and SDH; reversible); decreased uterine weights (reversible); reversible liver changes: hepatocellular hypertrophy, increased mitoses distributed multifocally throughout the liver, multifocal single cell hepatocellular necrosis; increased number of animals in diestrus stage (likely secondary to systemic stress indicated by adrenal hypertrophy; not observed in recovery group)
Supporting Study Identified by the European Chemicals Agency and *not used* to Derive the Drinking Water Health Advisory Value			
MacKenzie 2010. H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice (ECHA Study 003) OECD 408 (GLP) Mouse/Subchronic Gavage/90-day	0.1	No adverse effects were observed at this dose	Increased monocytes (not observed at higher doses)
	0.5	**NOAEL**: increased liver weights, hepatocellular hypertrophy (reversible and PPARα dependent)	**NOAEL**: No adverse effects were observed at this dose
	5	**LOAEL:** Increased total bile acids and liver enzymes along with increased liver weights, and microscopic changes (increased hypertrophy, single cell necrosis (10/10, minimal), mitotic figures and/or Kupffer cell pigment); increased albumin and total protein, reduced cholesterol, decreased potassium; increased adrenal weights with cortical hypertrophy, increased kidney weight with minimal tubular epithelial hypertrophy, reduced spleen weight (no pathological changes)	**LOAEL:** Increased total bile acids and liver enzymes along with increased liver weights and microscopic changes (increased hypertrophy, single cell necrosis (1/10, minimal), mitotic figures and/or Kupffer cell pigment); increased albumin, decreased bilirubin, decreased potassium
Supporting Study Identified by the European Chemicals Agency and *not used* to Derive the Drinking Water Health Advisory Value			
Edwards 2010b. An Oral (Gavage) Reproduction/ Developmental Toxicity	0.1	**NOAEL**: No adverse effects were observed at this dose	No adverse effects were observed at this dose
	0.5	Hepatocellular hypertrophy (minimal/mild) and increased liver weights; 5 of 24 animals with minimal	**NOAEL**: Hepatocellular hypertrophy (minimal/mild) and increased liver weights

Study Reference Regulatory Guideline Species/Study Type Exposure/Duration	Dose (mg/kg/day)	Effects and Observations in Males	Effects and Observations in Females
Screening Study of H-25848 in Mice		single cell necrosis (versus 1 of 24 in controls) was considered to be test-substance related	
OECD 421 (GLP) Mouse Developmental/ reproductive toxicity Gavage/ F0 males: 70+ days F0 females: 57+ days	5	Various liver lesions including increases in single cell necrosis (24/24 animals 4 minimal, 17 mild and 3 moderate), mitotic figures, and lipofuscin pigment	liver lesions including increases in single cell necrosis (21/24 animals) and focal necrosis, mitotic figures, and lipofuscin pigment **NOAEL for reproductive toxicity**: There were no effects on reproduction (mating, fertility, or copulation indices, number of days between pairing and coitus, and gestation length) at any dose.

NOAEL: No Observed Adverse Effect Level; LOAEL: Lowest Observed Adverse Effect Level; A/G: albumin to globulin; PPARα: Peroxisome proliferator-activated receptor-alpha; RBC: red blood cell; BUN: blood urea nitrogen