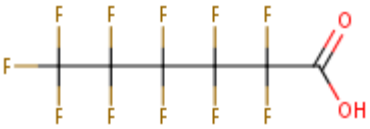
CAS # 307-24-4  	**Perfluorohexanoic acid (PFHxA)** Synonym[1]s: EINECS 206-196-6; NSC 5213; Perfluorohexanoic acid; Undecafluoro-1-hexanoic acid; UNII-ZP34Q2220R **RTECS #[2]:** MO8445000 **EINECS #[3]:** 206-196-6 **Molecular Weight[4]**: 314.0499 **Molecular Formula[5]:** C6-H-F11-O2 **Common Salts:** Sodium perfluorohexanoate, CAS # 2923-26-4 Ammonium perfluorohexanoate, CAS # 21615-47-4
PHYSICAL CHARACTERISTICS	
Primary Use	"*PFHxA is both a degradation product and potential impurity in fluorotelomer-based products and in perfluoroalkane sulfonyl-based electrochemical fluorination products. PFHxA is not generally manufactured and used itself for commercial purposes. PFCAs such as PFHxA were released directly into the environment during the historical manufacture and use (of) per- and poly-fluoroalkyl substances*".[6] "The available information indicates that ammonium PFHxA could be used as a replacement for ammonium perfluorooctanoate in manufacturing fluorotelomers (Wang, et al., 2013)."[7] "Available information indicates that PFHxA, … were in use between 1999 and 2002 in Nordic countries (SPIN)(ENVIRON, 2014)."[8] *"While PFHxA is not generally manufactured and used itself for commercial purposes, there are some known applications of this product."*[9] PFHxA - known occurrences: Breakdown product of stain- and grease-proof coatings on food packaging and household products.[10]
Physical state, odor at room temperature & pressure	Colorless liquid[11]
Melting point; Boiling point	Not found; BP = 157 deg C[12]
Solubility	In water, 15,700 mg/L at ambient temperature[13] Water solubility<<29 mg/L (Solubility of protonated acid would be much lower than that of the anion; PFHxA is a strong acid (pKA <1) that dissociates at environmentally relevant pHs. The anion, PFHx, is highly water soluble [29.5 mg/L @ 25°C] and relatively non-volatile.)(ENVIRON, 2014)[14]
Specific Gravity	Not found

SAFETY/PHYSICAL HAZARDS	
Vapor Pressure	1.98 mm Hg at 25 deg C (est)[15] 264 Pa (exp.)[16] 114-121Pa @ 25 deg C (est)[17]
Flammability	Not found
Flashpoint	Not found
Flammability Rating	Not found
Auto Ignition Point	Not found
Combustion products	Special hazards arising from the substance or mixture: Carbon oxides, Hydrogen fluoride[18]
Explosivity (UEL, LEL, shock sensitive)	Not found
Oxidizer	A molecular entity capable of donating a hydro[ge]n to an acceptor (Bronsted base).[19] Not an oxidizer, as is donating.
Corrosivity	Non-harmonized classification: H290 Met. Corr. 1 (May be corrosive to metals)[20]
pH	Not found
Reactivity	Incompatible materials: Strong oxidizing agents[21]
Viscosity	Not found
Odor Threshold	Not found
Particle size, shape, respirable fraction	Not found
Other physical hazards associated with process: Heat, gases under pressure, noise, vibration, ergonomic hazard	Not found
HEALTH HAZARDS	
Acute Toxicity	
Oral LD_{50}	The acute toxicity of the sodium salt of perfluorohexanoic acid (PFHxA) is considered low with a rat oral LD_{50} > 1,750 mg/kg bw.[22] "In an acute oral toxicity study [indicated directly above] in Crl:CD female rats, the median lethal dose (LD_{50}) of NaPFHx was determined as 1,750–5,000 mg/kg bw, based on 1/4 rats dying in the 1,750 mg/kg bw dose group and 3/3 rats dying in the 5,000 mg/kg bw dose group (Loveless et al., 2009). Female rats were used in this study. The serum clearance of PFHxA is reportedly faster in female rats than male rats. Subsequently systemic concentrations of PFHxA following oral administration were up to four-fold higher for males than females. Male rats might, therefore, be more sensitive to the effects of PFHxA than female rats and the LD_{50} for

	males could be lower. Reactive chemicals in this group, such as the acids and anhydrides, are likely to have higher acute toxicity due to local effects, but data are not available."[23]
Dermal LD_{50}	Not found in RTECS "In an acute dermal toxicity study, conducted according to the Organisation for Economic Co-operation and Development (OECD) test guidelines (TG) for oral acute toxicity, single doses of 2,000 mg/kg bw of the ammonium salt of PFHxA (ammonium PFHx; CAS No. 21615-47-4) was applied to the clipped skins of five male and five female Wistar rats. The test substance was held in contact with the skin with a surgical gauze patch dressing. No mortality occurred. Flat hunched postures were noted for the majority of animals. Based on these results, the LD_{50} of ammonium PFHx (the ammonium salt of PFHxA) was established >2,000 mg/kg bw (Teunissen, 2004a)."[24]
Inhalation LC_{50}	Not found in RTECS
Intraperitoneal LD_{50}	Not found in RTECS
TDLo	Values ranging from 4,500 mg/kg/90D-I to 18,000 mg/kg/90D-I[25]
Chronic or Sub-chronic Toxicity	
IARC rating	Not found in the IARC database
Carcinogenicity	Not found on Prop 65 list[26]; Not found in the CCRIS database "In a two-year oral chronic toxicity/carcinogenicity study (Klaunig et al., 2014), Crl:CD rats were administered PFHxA at 2.5, 15 or 100 mg/kg bw/day (males) and 5, 30 or 200 mg/kg bw/day (females) by gavage for up to 104 consecutive weeks. Several deaths occurred in rats in the highest dose groups, but histopathological evaluations concluded that these deaths were not related to exposure. Treatment-related effects consisted of changes in the specific gravity and pH of urine and slight histological changes such as kidney papillary necrosis and tubular degeneration. The NOAEL was established as 15 mg/kg bw/day for males and 30 mg/kg bw/day for females, based on the pathological effects in the kidney."[27] "The potential carcinogenicity of PFHxA was also investigated in the 24-month chronic toxicity study of rats discussed previously. Overall, about 300 rats receiving treatment with PFHxA were assigned to the 2-year carcinogenicity phase of the study, in addition to a control group of about 50 rats receiving a vehicle control of deionized water. There was no evidence that PFHxA induced tumorigenesis in the 24-month oral gavage study in male or female rats at doses of 2.5, 15, and 100

	mg/kg/day for males and 5, 30, and 200 mg/kg/day for females; thus, NOAELs for neoplasia of 100 mg/kg/day for males and 200 mg/kg/day for females, the highest dosages examined, were identified (Asahi and Daikin-WIL-534009)"(ENVIRON 2014).[28]
Neurotoxicity	Not found in HAZMAP Three studies were identified that addressed neurotoxicity. Loveless and colleagues (2009) noted that clinical signs of systemic toxicity were observed in most rats exposed to acute doses of PFHxA ranging from 175 to 5,000 mg/kg, which included potential signs of neurotoxicity including abnormal gait and ataxia. However, no specific NOAEL or LOAEL is provided for symptoms of systemic toxicity following the acute dosing. The authors further noted no effects on neurobehavioral parameters were observed in the subchronic part of the study involving doses up to 500 mg/kg/day for 90 days. These included a set of neurobehavioral endpoints from functional observations including grip strength and sensory motor function, as well as motor activity assessments. Chengelis et al. (2009b) also reported that no changes in autonomic and central nervous system function or somatomotor activity and behavior patterns were observed following oral doses of 10, 50, or 200 mg/kg/day for 90 days in rats. The authors (Daikin-WIL-534009) noted that no PFHxA-related effects on motor-activity assessments were observed in rats chronically exposed to up to 200 mg/kg/day for 24 months. (ENVIRON 2014)[29] Klaunig et al. 2015 reported FOB (functional observational battery) observations were not affected by PFHxA treatment (data not shown). No statistically significant changes in locomotor activity patterns (total and ambulatory activity counts) or in the pattern of habituation were seen with PFHxA administration. An increase in the number of male rats in the high-dose (100 mg/kg/day) group asleep or lying on their side compared to the control group was noted. In addition, lower mean grip strength was noted in the 5-mg/kg/day treated females. Authors concluded that because of lack of dose response, and no correlating FOB, no neurotoxicity exhibited.[30] See wildlife toxicity below
Developmental/Reproductive Toxicity	Not found on Prop 65 list[31] Details from developmental study re: NaPFHx and reproductive study re: NH_4PFHx available (Dewitt 2015) The reproductive oral toxicity of the ammonium salt of PFHxA in pregnant female mice was investigated by Iwai and Hoberman (2014). PFHxA was administered once daily from gestation day 6 through 18 in

	doses up to 500 mg/kg b. w.[32] Adverse effects occurred only in the 175 mg/kg/d group (*from Phase 2*) and consisted of increased stillborn pups, pups dying on PPD I, and reduced pup weights on PPD I.[33] The maternal and reproductive no observable adverse effect level (NOAEL) of PFHxA ammonium salt was 100 mg/kg/d.[34] Additional details on these studies can also be found in the NICNAS report found in the Special Report box below. "…based on still births and increased postnatal pup mortality and decreased pup body weight and corneal opacity and microphthalmia observed in mice with ammonium salt of PFHxA, a classification for developmental effects is proposed for of short-chain PFCAs,…"[35] See aquatic toxicity and other observable ecological effects below. See avian wildlife toxicity below. ToxServices 2016 assigned PFHxA a score of Moderate for developmental toxicity based on reduced body weight (gain) in a reproductive toxicity study and a developmental toxicity study in rats for the surrogate sodium perfluorohexanoate (Loveless 2009), and reduced pup body weight, increased stillborn pups and/or reduced post-natal survival observed in the absence of apparent maternal toxicity in mice for the surrogate ammonium perfluorohexanoate (Charles River 2011a, Charles River 2012 and Charles River 2011b).[36]

Genotoxicity/Mutagenicity	Not found in the GENETOX database
	
	• Micronucleus (G04048) Completed
	  ○ Rats: Harlan Sprague-Dawley
	  ○ Male Equivocal
	  ○ Female Negative
	• Salmonella (A97455) Completed
	  ○ Negative[37]
	PFHxA did not generate reactive oxygen species or cause DNA damage in human HepG2 cells (Eriksen et al. 2010), and was found not to be genotoxic based on negative results from both the bacterial reverse mutation assay and the in vitro chromosomal aberration assay (Loveless et al. 2009).[38]
	Mulkiewicz *et al.* (2007) evaluated the acute cytotoxicity of among others PFHxA in several *in vitro* assays using eukaryotic cell lines, bacteria and enzymatic assays. The toxicity was in general low and increased with chain length, and the toxicity of PFHxA was about ten times lower than PFOA.[39]
	In an *in vitro* assay with human colon carcinoma (HCT116) cells

	estimated values of EC_{50} decreased with elongation of fluorocarbon chain from PFHxA > PFHpA > PFOA > PFNA etc. The cytotoxicity was rather low but intensified after longer exposure (72 h) (Kleszczynski *et al.* 2007). "NaPFHx was not mutagenic to bacteria or clastogenic in vitro to cultured human lymphocytes under the conditions of the tests (DuPont, 2006a; DuPont, 2006b)."[40]
Endocrine Disruption/Thyroid Effects	Found on TEDX List of Potential Endocrine Disruptors (per Vongpachan et al 2011).[41] The mechanism is a competitive binding to the thyroid hormone plasma transport protein transthyretin (TTR) that will alter/decrease the free thyroxine (T4) in blood. This competitive binding capacity of some poly- and perfluorinated compounds was studied by Weiss *et al.* (2009) with a radio-ligand-binding assay. The binding potency of the fluorinated chemicals was 12-300 times lower than for thyroxine itself and decreased in the order: PFHxS > PFOS/PFOA > PFHxA > PFBS. PFBA and FTOHs had no effect in that assay.[42] See wildlife toxicity below "In the first study (DuPont, 2007a, Loveless et al., 2009), Crl:CD rats were administered sodium salt of PFHxA by gavage for 90 days, at 0, 20, 100 or 500 mg/kg bw/day. No treatment-related clinical signs were observed. … Relative thyroid weight was also significantly increased in female rats at the 500 mg/kg bw/day dose. … Minimal hypertrophy of the thyroid follicular epithelium in the 500 mg/kg dose group was reversible and consistent with the induction of hepatic microsomal enzymes that led to increased biliary excretion of the thyroid hormone T4 (thyroxine), subsequent elevation of thyroid-stimulating hormone (TSH), and the consequent follicular hypertrophy."[43] See other observable ecological effects below. "…PFHxA…had no effect on the protein intrinsic fluorescence…, suggesting no binding or very weak binding of these chemicals with the protein" … "No cell proliferation was found at concentrations up to cytotoxic levels" [pertaining to the activity of PFCs on TR pathway by T-screen assay](Ren 2015).[44] According to the TTR competitive binding assays, the 16 PFASs showed different binding potencies (Table 1). For the ten perfluoroalkyl acids, the K_d (dissociation constant) values decreased from 14.3μM to 60 nM as the carbon chain length increased from C4 to C8 [where PFHxA has a K_d value of 510±184nM]. … perfluoroalkyl acids with carbon chain less than 8C (e.g., PFHxA, PFHxS) did not adequately fill the T4 binding pocket…(Ren 2016).[45]

	Transcriptional effects of PFHxA on thyroid related genes, *Pax 8* and *Hex* were studied (Naile et al 2012).[46] "A significant increase was observed for $\sum_8$PFASs, PFOS, and PFHxS concentrations with age ($p<0.01$). Gender-related differences were found; PFOS, PFHxS, PFBS, and PFOA levels were higher in males ($p<0.05$), and the mean concentration of $\sum_8$PFASs was 1.5 times greater in males (6.02 ng/mL) than in females (4.15 ng/mL). PFOS and $\sum_8$PFASs were significantly negatively correlated with FT3 and FT4 and positively correlated with TSH while PFPeA and PFHxA were significantly positively correlated with TGAb and TMAb in all the samples." PFHxA was detected in 53.0% of the serum of samples. (Li et al 2017c)[47]
Immunotoxicity	
Other organ toxicity	PFHxA is hepatotoxic, … In a 90-day gavage study in rats a NOAEL value for PFHxA of 20 mg/kg bw/day was identified based on effects on the liver and blood parameters (Loveless et al., 2009).[48] "Effects observed in the liver in studies with PFHxA and PFBA were generally mild and reversible."[49] ITC measurement revealed that PFOA/PFNA displayed a moderate affinity for hL-FABP at a 1:1 molar ratio, a weak binding affinity for PFHxS and no binding for PFHxA (Sheng et al 2016).[50]
Skin, Eye and Respiratory Effects	
*Irritant – **S**kin, **E**ye, or **R**espiratory*	Non-harmonized classifications: H311 – Acute Tox. 3 (Toxic in contact with skin).[51] "Ammonium PFHx was considered to be a severe eye irritant in rabbits. As a salt, it is considered to have lower irritation potential than the acids and anhydrides in the group; therefore, in the absence of additional information, classification is considered warranted for all chemicals in this group."[52] "In an acute dermal irritation study, conducted according to the OECD test guidelines, single doses of 0.5 mL of pure ammonium PFHx were applied to the clipped skins of New Zealand White rabbits as a semi-occlusive application (Teunissen, 2004b). Four hours' after application, the dressing was removed and the skin was cleaned of residual substance. Four hours' exposure to 0.5 mL ammonium PFHx resulted in erythema and very slight oedema in the treated skin. However, these effects had resolved within seven days of the exposure. The chemical was considered to be a mild skin irritant."[53]

*Corrosive – **S, E, or R***	Non-harmonized classifications: H314 – Skin Corr. 1B; H318 – Eye Dam. 1[54]
*Permanent Damage – **S, E, or R***	Not found
*Sensitizer– **S** & **R***	Not found in AOEC database "No data are available for the chemicals in this group. Based on data for the analogues, PFOA and its ammonium salt (NICNAS), the chemicals in this group are not considered skin sensitisers."[55]
Asthmagen – Initiator or Exacerbator	Not found in AOEC database One human study examined the association between PFHxA exposure and childhood asthma. The study reported no difference in serum levels (median = 0.2 ng/mL) in children aged 10-15 years with (n = 231) or without (n = 225) asthma, and no dose-response trend (Dong *et al.*, 2013).[56]
Skin Absorption, Kp	Not found
LOAEL	COS-1 cells were transfected with mouse or human PPARα plasmids to investigate the effects of different PFASs on PPARα activation. PFHxA (5-100 µM) caused a significant dose-dependent activation of mouse and human PPARα compared with controls lowest observed adverse effect level (LOAEL, 20 and 10 µM, respectively). … PFNA (mouse, 5 µM; human, 11 µM) and PFOA (6 µM; 16 µM) were most potent at activating PPARα, followed by PFDA (20 µM; human not active), PFHxA (38 µM; 47 µM), PFBA (51 µM; 75 µM), PFHxS (76 µM; 81 µM), PFOS (94 µM; 262 µM) and PFBS (317 µM; 206 µM) (Wolf et al., 2008a).[57] PPARa activity was higher in response to carboxylates compared to sulfonates.[58] "All PFCAs led to increased PPARα and PPARγ activity from exposure concentrations of 30 uM or 100uM, except for PFBA, which did not cause any change in PPARγ activity" (Rosenmai 2016).[59]
NOAEL	In a 90-day gavage study in rats a NOAEL value for PFHxA of 20 mg/kg bw/day was identified based on effects on the liver and blood parameters (Loveless et al., 2009). In another study, in which PFHxA was administered in drinking water, a NOAEL of 50 mg/kg bw/day males and 200 mg/kg bw in females was determined (Chengelis et al., 2009b). This is higher than the NOAEL for PFOA.[60] The Chengelis et al., 2009 study NOAELs were based on liver histopathology and liver weight changes.[61] The reproductive arm of a 90-day toxicological evaluation in which Sprague Dawley rats were administered PFHxA (0, 20, 100 or 500 mg/kg b.w. per day NaPFHx) by oral gavage (see Section 5.2.3) indicated NOAELs of 20 mg/kg b.w. per day (P1 adult males) and 100 mg/kg b.w. per day (F1 pups), based on reduced body-weight parameters. A parallel developmental toxicity study (same doses, GD 6-

	20) indicated a maternal and developmental NOAEL of 100 mg/kg b.w. per day, based on maternal and fetal reduced body weight (Loveless et al., 2009).[62] "A 24-month chronic toxicity study was carried out on rats that received oral doses of 2.5, 15, and 100 mg/kg/day for males and 5, 30, and 200 mg/kg/day for females. There were no PFHxA-related effects on body weight, food consumption, functional observational battery, hematology, serum chemistry, or hormone parameters. However, the authors identified NOAELs of 15 mg/kg/day for males and 30 mg/kg/day for females based on non-neoplastic systemic toxicity observed in the highest dose groups of males and females. These effects involved histological changes in the kidneys of the 200 mg/kg/day female group and lower urine pH values in the 100 mg/kg/day male group (Asahi and Daikin-WIL-534009)"(ENVIRON 2014).[63] (See carcinogenicity section above for study details) "The NOAEL was established as 15 mg/kg bw/day for males and 30 mg/kg bw/day for females, based on the pathological effects in the kidney."[64] "In a health risk assessment of 17 perfluoroalkylated and polyfluoroalkylated substances, Borg et al. (2013) identified various substances, including PFHxA, in serum in the general population and among occupationally exposed individuals in Sweden (<0.22 ng/ml and 24 ng/ml, respectively). They also identified hepatotoxicity NOAELs (external dose: 20 mg/kg bw/day; internal dose: 6.2 µg/ml serum) and reproductive NOAELs (external dose: 100 mg/kg bw/day; internal dose: 11.9 µg/ml serum) based on animal studies." (ENVIRON 2014)[65]
Benchmark Dose Response (BMD)	Russell *et al.* (2013) calculated the benchmark dose (BMD_{10} = 95% lower confidence limit of a dose resulting in a 10% increase in risk) to 13 mg PFHxA/kg b. w. per day.[66]
Toxicokinetics	"In human workers exposed to high concentrations of PFHxA, the apparent elimination half-life ranged between 14 and 49 days, with a geometric mean of 32 days (Russell et al., 2013). During seasonal use of ski wax, which contained an indirect precursor to PFHxA, levels of PFHxA in workers' blood increased during the ski season, then decreased to below the detection limit after exposure ceased. PFOA levels in blood were also monitored and were found at mostly stable concentrations before, during and after the ski season (elevated compared with the general population). These data suggest that PFHxA is cleared from blood more rapidly than PFOA and shortly after exposure ceases (Nilsson et al., 2010)."[67] In a study of human whole blood in cities around the Bohai Sea in

	China, PFHxA was detected in 99% of whole blood samples with a mean concentration of 0.51 ng/mL; ranging from <LOD to 2.23 ng/mL.[68] PFHxA was not metabolized in rat or mouse hepatocytes, nor were any metabolites observed after oral dosing in either rodent species (Gannon *et al.* 2011).[69] "In a study of PFHx absorption, distribution, metabolism, and excretion in mice and rats, Gannon and colleagues (2011) noted that essentially 100% of the dose was eliminated in urine within 24 hours, and that the route and extent of elimination was unchanged after 14 days of daily dosing. PFHx was also not quantifiable in all tissues except skin at time points ranging from 0.5 to 24 hours following dosing."(ENVIRON 2014).[70] "Based on the available information, the chemicals of this group are expected to be rapidly absorbed by the gastrointestinal tract and eliminated mainly in the urine. Elimination of these chemicals is substantially faster in humans than perfluoroalkyls with longer carbon chain lengths (ATSDR, 2009; Russell et al., 2013)."[71] "Toxicokinetics and metabolism studies using the sodium salt of PFHxA (NaPFHx—CAS No. 2923-26-4 (not listed on the AICS)) have been conducted in mice, rats and monkeys following oral and intravenous administration (Chengelis et al., 2009a). … Blood levels of the chemical were higher in males than in females in both mice and rats, probably due to a higher rate of clearance in females. Repeated oral exposure in rats demonstrated that uptake was proportional to dose, and there was no evidence of accumulation. Distribution of the chemical into tissues was examined in rats and mice. PFHxA was detected at low levels in a wide range of tissues and decreased significantly over 24 hours after administration."[72] "In mice, rats and monkeys, NaPFHx was mainly excreted via the urine, with a small percentage (about 10 %) excreted in faeces. Excretion in both male and female rats and mice was rapid and virtually complete, indicating no bioaccumulation (Iwai, 2011). The half-life in male rats was 2–3 times longer than in females. PFHxA was excreted unchanged and no metabolites of PFHxA could be detected in the urine."[73]
Synergistic or Antagonistic Effects	It was also observed that exposure of JEG-3 cells to a *mixture* of the eight PFASs (0.6 µM each) altered/increased cellular lipid pattern (up to 3.4-fold) at concentrations well below those that generate toxicity.[74]

Interactions	... **PFHxA** and PFOA were used as model perfluorinated carboxylic acids (PFCAs) to characterize the major site of PFCA interaction in human sera. Using novel heteronuclear saturation transfer difference nuclear magnetic resonance spectroscopy experiments, human serum albumin (HSA) was identified as the major site of interaction for both PFHxA and PFOA in human sera. Heteronuclear single quantum coherence nuclear magnetic resonance experiments were then performed to interrogate site-specific interactions of PFHxA and PFOA with isolated HSA. **PFHxA** was found to bind specifically to Sudlow's drug-binding site II, whereas PFOA interacted preferentially with Sudlow's drug-binding site I at the lower concentration, with additional interactions developing at the higher concentration. These experiments highlight the utility of nuclear magnetic resonance spectrometry as a tool to observe the in situ interactions of chemical contaminants with biological systems. Both PFCAs displaced the endogenous HSA ligand oleic acid at concentrations lower than observed for the drugs ibuprofen and phenylbutazone, which are established HSA ligands. Interactions between PFCAs and HSA may affect the pharmacokinetics and distribution of fatty acids and certain drugs in the human body and warrant further investigation.[75]
GHS Codes	Non-harmonized classifications: H314 – Skin Corr. 1B; H290 – Met. Corr. 1; H318 – Eye Dam. 1; H301 and H311 – Acute Tox. 3; H330 – Acute Tox. 2[76]; H361d – Cat. 2 – Suspected of damaging the unborn child[77] Aggregated GHS information from 4 notifications provided by 29 companies to the ECHA C&L Inventory. Each notification may be associated with multiple companies. H314 (100%): Causes severe skin burns and eye damage [Danger Skin corrosion/irritation] H335 (10.34%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from all companies. Only Hazard Codes with percentage values above 10% are shown.[78]
Environmental and Human Health Exposure and Risk Values	
RfC/RfD	Not found in EPA IRIS database VTR = 0.32 mg/kg/day, Critical impact/effect: Renal effects (Papillary necrosis and tubular degeneration) Klaunig et al 2015; NOAEL = 30 mg/kg/day (ANSES 2017a)[79]

ATSDR-MRL	Not found on the June 2017 ATSDR Minimal Risk Levels List
Adverse Effect Levels: DNEL, PNEC, PNEL	
Health Based Exposure Limits	
NIOSH-REL/IDLH/Ceiling Limits	Not found in NIOSH Pocket Guide
OSHA-PEL	Not found on OSHA website
ACGIH TLV-TWA	None
TLV-STEL	Not found in NIOSH Pocket Guide
Biomonitoring Action Limits	
Drinking Water Standards	Concentrations found in Drinking Water are indicated in HSDB; There are no set threshold values for the content of PFAS in groundwater / drinking water in Denmark.[80]
Other	In autopsy tissues PFHxA partitioned mostly to the liver and brain (median: 68.3 and 141 ng/g, respectively).[81] Analysis of Spanish human autopsy tissues revealed that the highest concentrations of most PFAS, including PFHxA, were found in lung tissues but the highest PFAS in the brain was PFHxA. PFOS concentration in the brain was less than a third of that (Perez *et al.* 2013). Thus the body half-life of PFHxA seems to be much longer in humans than in experimental animals.[82] PFCAs mimic fatty acids, and specifically PFHxA is attached to a different binding site on serum albumin compared to PFOA; however, PFOA is more strongly bound, and 5-6 PFOA molecules can interact with each albumin molecule (D'eon and Mabury 2010).[83]
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
PBT	As with PFOA, PFHxA is very persistent and is not transformed or degraded by abiotic mechanisms (e.g. hydrolysis and photolysis) or biotic mechanisms in water or soil. Precursors such as fluorotelomers or PFAS with other functional groups attached will undergo primary degradation to PFHxA.[84] On ECHA Public Activities Coordination Tool (PACT) list for PBT; Risk Management Option Analysis is under development[85] Categorized by the Australian government as P, but not B or T.[86] Data on the degradation half-life of PFHxA in soil, sediment, and water are not available. However, based on a read-across from degradation studies of PFOA, PFHxA is likely to be environmentally persistent.[87] Although, the biodegradation of PFHxA has not been directly studied, PFHxA is a metabolite of 6:2 FTOH degradation (Butt et al. 2014).

	Studies of 6:2 FTOH degradation in soil and sediment do not indicate that PFHxA completely mineralizes with a half-life less than the six month criterion listed in Annex D 1 (b) (i).[88] Limited experimental data suggest that PFCAs may react with photochemically-generated hydroxyl radicals in the atmosphere. Taniyasu et al. (2013a) conducted a field study on the photolysis of perfluoroalkyl substances at Mt. Mauna Kea, Hawaii (4200 m). PFHxA concentrations decreased by 0.8% after 106 days of solar irradiation. This suggests that the atmospheric oxidation of PFHxA occurs extremely slowly and is not expected to impact the half-life of PFHxA in the atmosphere.[89] Therefore, it would meet the POP criteria for persistence.
Bioaccumulation	As with PFOA, PFHxA is both hydrophobic and lipophobic, and so does not follow typical pattern of partitioning to fatty tissues and accumulating there. Instead it tends to bind to proteins, so protein-rich tissues such as liver; kidney and blood are their main repositories. Precursors such as fluorotelomers may be partially responsible for the observed bioaccumulation of the acids. [90] There are two mechanistic theories for observed bioaccumulation of perfluoroalkyl acid substances: 1) partitioning to membrane phospholipid (PL) which have higher affinity for charged species than neutral storage lipids; and 2) protein binding (PB) model assumes interactions with proteins, including serum albumin, liver fatty acid binding proteins (L-FABP) and organic anion transporters determine distribution, accumulation and half-lives. Likely that both mechanisms are at work, where the protein component would account for the accumulation in the blood and elimination and reabsorption as mediated by transporter proteins, and phospholipid describing the distribution into tissues where little or no binding occurs (e.g., liver). Increasing bioaccumulation tendency with increasing C chain length could be explained in the PL model by increasing hydrophobicity which decreases elimination rates, For PB model, bioaccumulation is determined based on balance of affinities for albumin, L-FABP and renal transporter proteins.[91] <u>Serum Elimination Half-lives</u>[92]: **Rat:** Male – 1.6 hours; Female – 0.6 hours (concentrated in tissues: bladder, plasma, kidney, liver and skin[93]) **Mouse:** 1 hour[94] (concentrated in tissues: plasma, bladder, liver, kidney, lung, heart[95]) **Monkey:** 14-47 hours[96]

	Human: 32 days** ** The toxicokinetics of perfluorohexanoic acid (PFHxA) has recently been evaluated in human ski waxers (Russell *et al.* 2013). The decline in blood levels after the ski season was used to determine the apparent human blood elimination half-life to 14-49 days with a geomean of 32 days. These calculations assume that PFHxA is eliminated from the body, when it leaves the blood, however, instead PFHxA may be distributed to various organs as it was measured in liver, kidney, bone and brain from some autopsy samples from Spain (Perez *et al.* 2013).[97] The log BCFs of the C4-C7 carboxylic acids were found to be below 1 thus indicating little bioaccumulation potential of these substances in fish. Short chain PFCAs are not considered bioaccumulative according to the regulatory criteria of 1,000–5,000 L/kg.[98] The bioaccumulation of PFOS and other PFAS is higher in the marine environment than in soil.[99] These findings are believed to be valid also for the short-chain perfluorinated carboxylic and sulfonic acids and their salts. According to a number of reports (e.g. Ellis et al. (2004), Butt et al. (2010), Martin et al. (2013)), the acids are not very bioaccumulative in themselves but precursors such as fluorotelomer alcohols and acrylates accumulate and are subsequently transformed in the organs of animals to the corresponding acids, which are retained in the body.[100] Presence in environment and biota: Study of Spanish Jucar river basin, water and biota samples –water conc. 1.44-18.7 ng/L, detected in 40% of samples, non-detect in sediment; non-detect in biota sampled (limits of quantification 0.02-2.26 µg/kg.)(Campo 2016)[101] In a study of groundwater contamination in Uppsala, Sweden found PFHxA in 3 of 6 well areas, with median water concentration 81, 40 and 10 ng/L. (no associated human serum measurements above MDL of 0.3 ng/g)(Gyllenhammar 2015)[102] PFHxA was measured in 11 out of 13 water bodies in the Great Lakes region in a study by Michigan Department of Community Health. Geometric mean concentration from 2 sampling events in 2011 and 2013 ranged in most water bodies from <LOD to 8.43 ng/L. One area, Clark's Marsh, had mean concentration of 922 ng/L. A subset of fish fillet samples from these areas were tested for PFHxA and were below the MDL of 0.5 µg/kg[103] Human: study of 20 individuals at autopsy Catalonia, Spain. Mean concentrations: 180 ng/g ww brain, 115 ng/g liver, 50 ng/g lung, 36 ng/g bone, 6 ng/g kidney. [104] Concentration in brain of PFHxA

	significantly higher than all other PFAS tested. Human breast milk: PFPeA, PFHxA, and PFHpA were detected in higher frequencies, ranging between 67.4% and 81.8%. The concentrations of short carbon-chain PFCAs in breast milk such as PFPeA and PFHxA were the highest ever reported to date, and were comparable to that of PFOS. PFHxA was detected in 70.8% of samples with a mean concentration of 0.047 ng/mL (Kang 2016).[105] Plant bioaccumulation: hydroponic (water only) uptake rate constant k_1 (per day) NA (no good slope fit) in roots, 0.6±0.2 in shoots; elimination half life 0.21 days; (this rapid elimination was similar for all PFAS studied except PFBA, which had 1.83 day half life).[106] Cape Cod groundwater: detected in 50% of 20 private wells sampled, max concentration 2 ng/L. Sampling from other studies and locations, groundwater and surface water, varied from 14 – 110 ng/L.[107] An additional study on the uptake of PFHxA by marine ogliochetes in sediment also determined a BSAF (The Biota-Sediment (or Biota-Soil) Accumulation Factor) of 2.2 to 3.5 g, dw/g, ww, indicating some uptake of PFHxA into sediment dwelling invertebrates (Lasier et al. 2011). … There are currently no regulatory screening criteria for bioaccumulation based on BSAFs in sediment, however typically BSAFs > 1 are associated with a potential for bioaccumulation.[108] Controlled laboratory bioaccumulation experiments with terrestrial worms indicate that BSAF values for PFHxA are greater than 1 g, dw/g, ww (Table 6.5). Although there are no formal criteria for interpreting BSAF values, BSAF values greater than one indicate that PFHxA may accumulate from soil or sediment to invertebrates. BSAFs for a number of terrestrial plants were available in the literature, ranging from 0.3 to 7.7 g, dw/g, ww for plants (Table 6.5).[109] Zhao et al. (2014) performed bioaccumulation studies on PFCAs for earthworm and wheat. PfPeA, PFHxA and PFBS bioaccumulated in earthworms. This could be due to the active ingestion of soil through the gut and the high protein content of the earthworms. The BSAFs of earthworms decreased with increasing soil concentrations, suggesting that the bioaccumulation of PFASs is concentration dependent. Similar result was observed in our previous study (Zhao et al., 2013[110]), which might be caused by the constant binding sites in earthworm and resistant desorption of PFASs from organic matter in soil. Translocation factors (ratio of PFAS concentration in shoots and in roots) of PFCAs

	increased from PFPeA (0.393e0.580) to PFHxA (0.604e1.91), then decreased with increasing chain length from PFHxA to PFOA (0.078e0.122), and were quite constant from PFOA to PFDoA (0.057e0.176)[111]
BCF	**PFHxA** was not found to bioaccumulate in laboratory experiments using rainbow trout (*Onchorynchus mykiss*) with a reported BCF of 0.59(1). According to a classification scheme(2), this BCF suggests the potential for bioconcentration in aquatic organisms is low(SRC).[112] Modelled BCF ~ 0.1 in fish assuming Log BCF:C chain length linear relationship, based on experimentally determined BCF for long chain carboxylic acids in rainbow trout (carcass, liver and blood)[113] Study in muscle tissue of two fish species in Chinese lake determined Log BCF of C4-C7 carboxylic and sulfonic acids all below 1 (little bioaccumulation potential of these substances in fish).[114]
Ecological Toxicity	EC_{50}; Species: *Geitlerinema amphibium* (Blue-green Algae) Exponential Growth Phase BA-13; Conditions: saltwater, static, 20 deg C, pH 7.6-7.8; Concentration: **3.18 mM for 72 hr;** Effect: decreased population growth rate /formulation/[115] 2 other higher values available from this paper in HSDB, species = *Chlorella vulgaris* (Green Algae) and *Skeletonema marinoi* (Diatom) Toxicity tests with rainbow trout, *Daphnia magna*, and the alga (*P. subcapitata*) showed corresponding 50 % effect concentrations of >100 mg/L. Other algae (*S. marinoi* and *G. amphibium*) as well as a marine bacterium were less susceptible to PFHxA with effect concentrations ranging from 998.7 – 1,482 mg/L.[116]
Aquatic Toxicity: LC_{50}, EC_{50}, ErC_{50}, NOAEC/NOEC	Rainbow trout 96 hr LC_{50} >99.2 mg/L[117] Rainbow trout 56 d. NOEC reprod. =10.1 mg/L [118] Algae (*P. subcapitata*) 72 hr ECb_{50} and EcR_{50} >100 mg/L; (Hoke 2012)[119] Algae (*G. amphibium*) 72 h. IC_{50} optical density 999 mg/L (Ding 2013)[120] Algae (*S. Subspicatus*) 72 h. ErC_{50} = 86 mg/L; NOEC=50 mg/L (ENVIRON 2014)[121] *Daphnia magna*: 48 hr LC_{50} = >96.5 mg/L[122] *d. magna*: 48 hr EC_{50} 1,048 mg/L; EC_5 596 mg/L *d. magna:* 21 d. chronic EC_{50} 1,273 mg/L (survival) 776 mg/L per capita no. offspring.[123] General: The acute toxicity decreased with decreasing carbon chain length, but the polymer did not show a dose related effect. In a chronic toxicity test performed with PFHxA, mortality was observed at similar concentrations as in the acute toxicity test, indicating that toxicity did not increase with increasing exposure time. Effects on mortality, reproduction and population growth rate occurred at similar

	concentrations, indicating no specific effect of PFHxA on sublethal endpoints. C4-C6 chemistry is thus less hazardous to daphnids than C7-C8 chemistry.[124] "PFHxA has low toxicity to aquatic species, based on laboratory toxicity data (Table 6.6). A 28-day, chronic study of effects on early life stages of rainbow trout indicated a chronic NOEC greater than 10.1 mg/L – the highest tested concentration in the study (Daikin-2901/001). The chronic NOEC for rainbow trout is at least approximately 100 times higher than the REACH Toxicity criterion, therefore PFHxA would not be considered toxic under REACH PBT criteria. Another prolonged acute study by Martin et al. (2003a) determined a NOEC during a bioaccumulation test where rainbow trout were exposed to low concentrations of PFCAs. No effects to growth rates were observed at the test concentration for PFHxA (0.0017 mg/L). The test concentration is reported as the NOEC in Table 6.6; however the true (bounded) NOEC is greater than the reported NOEC by an unknown amount. Liu et al. (2008) observed a lower NOEC (>628 mg/L) for the algae Scenedesmus obliquus, based on growth rate; however, this was the highest concentration tested and so the true (bounded) NOEC is unknown." (ENVIRON 2014)[125] "Additional acute studies focusing on effects to algae by Latała et al. (2009) result in acute, EC50 values ranging from 999 to 4,032 mg/L for growth inhibition based on biomass. Additionally, Mulkeiwicz et al. (2007) observed an EC50 for inhibition of bioluminescence of marine algae of 1,339 mg/L. These tests were all acute studies using nominal, rather than measured concentrations of PFHxA, therefore are less reliable for use in the toxicity assessment than the Daikin-901/001 and Martin et al. (2003a) studies. The results of the acute studies reviewed indicate PFHxA would be regarded as "practically non-toxic" (EC_{50}/LC_{50} > 100 mg/L) (ECHA 2011)." (ENVIRON 2014)[126] We evaluated the toxicity of PFOA, PFHxA and PFBA on a zebrafish liver cell line and investigated the effects of exposure on cell metabolism. Gross toxicity after 96 h of exposure was highest for PFOA and PFO(-) , while PFHxA and PFBA exhibited lower toxicity …our study revealed that PFASs with shorter carbon chains are less toxic than PFOA, and that exposure to sublethal dosage of PFOA, PFHxA or PFBA affects cell metabolism (Mahapatra et al 2017).[127] While presented as environmentally safe, PFHxA demonstrated that it could affect gene expression patterns in zebrafish embryos when combined to PFOS and PCB126, suggesting that such mixture may increase PCB126 toxicity (Blanc et al 2017).[128]
Wildlife Toxicity: LC_{50}, EC_{50}, ErC_{50},	There is some evidence to suggest that perfluoroalkyl acids (PFAA's)

NOAEC/NOEC	can impact essential endocrine pathways and neurodevelopment in birds and other animals. In a study by Vongphachan *et al.* (2011), PFHxA altered the messenger RNA (mRNA) expression of thyroid hormone (TH)–responsive transcripts in chicken embryonic neuronal (CEN) cells. In a later study, the same research group determined *in ovo* effects of PFHxA exposure (maximum dose *5* 9,700 ng/g egg) on embryonic death, developmental endpoints, tissue accumulation, mRNA expression in liver and cerebral cortex, and plasma TH levels. PFHxA accumulated in the three tissue compartments analyzed as follows: yolk sac > liver > cerebral cortex (Cassone *et al.* 2012).[129]
Breakdown/degradation /combustion products	Results of studies in soil and sediment for 6:2 FTOH demonstrated primary biodegradation with half-lives of less than 2 days. Transformation products such as PFHxA did not degrade appreciably within half a year.[130]
Anaerobic degradation	They are neither biodegradable under aerobic or anaerobic environmental conditions in water or soil.[131]
Aerobic degradation	They are neither biodegradable under aerobic or anaerobic environmental conditions in water or soil.[132]
Other observable ecological effects (e.g. BOD)	In the present study, we assessed the developmental toxicity and teratogenicity of PFCs with different numbers of carbon atoms on Xenopus embryogenesis. An initial frog embryo teratogenicity assay-Xenopus (FETAX) assay was performed that identified perfluorohexanoic (PFHxA) and perfluoroheptanoic (PFHpA) acids as potential teratogens and developmental toxicants. The mechanism underlying this teratogenicity was also investigated by measuring the expression of tissue-specific biomarkers such as phosphotyrosine-binding protein, xPTB (liver); NKX2.5 (heart); and Cyl18 (intestine). Whole-mount in situ hybridization, reverse transcriptase-polymerase chain reaction (RT-PCR), and histologic analyses detected severe defects in the liver and heart following exposure to PFHxA or PFHpA. In addition, immunoblotting revealed that PFHpA significantly increased the phosphorylation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), while PFHxA slightly increased these, as compared with the control. These results suggest that PFHxA and PFHpA are developmental toxicants and teratogens, with PFHpA producing more severe effects on liver and heart development through the induction of ERK and JNK phosphorylation.[133]
Fate and Transport: Aquatic	The shorter chain length acids tend to be more soluble in water and have a lower potential for sorption to particles than the long-chain

	analogues. Thereby, they have a higher potential for aqueous long-transport.[134] Based on a classification scheme (1), log Koc values of 1.63-2.35(2), indicate that **PFHxA** is expected to adsorb to suspended solids and sediment (SRC). A pKa of -0.16(3) indicates **PFHxA** will exist entirely in the anion form at pH values of 5 to 9 and, therefore, volatilization from water surfaces is not expected to be an important fate process(SRC). **PFHxA** is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions (4). According to a classification scheme (5), a reported BCF of 0.59 in rainbow trout (6), suggests bioconcentration in aquatic organisms is low (SRC). Biodegradation data in water were not available (SRC, 2016).[135] Fate data on PFHxA are sparse. PFCAs are degradation products of other PFASs and are not transformed/degraded by hydrolysis or photolysis in water to any appreciable extent.[136]
Fate and Transport: Terrestrial	Based on a classification scheme (1), log Koc values of 1.63-2.35(2), indicate that **PFHxA** is expected to have very high to moderate mobility in soil (SRC). The pKa of **PFHxA** is -0.16(3), indicating that this compound will exist entirely in anion form in the environment and, therefore, volatilization from moist soil surfaces is not expected to be an important fate process(SRC). **PFHxA** is expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 2.0 mm Hg at 25 deg C(SRC), determined from a fragment constant method(4). Biodegradation data in soil were not available (SRC, 2016).[137]
Fate and Transport: Atmospheric	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (1), **PFHxA**, which has an estimated vapor pressure of 2.0 mm Hg at 25 deg C (SRC), determined from a fragment constant method (2), is expected to exist solely as a vapor in the ambient atmosphere. Vapor-phase **PFHxA** is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals(SRC); the half-life for this reaction in air is estimated to be 31 days(SRC), calculated from its rate constant of $5.2X10^{-13}$ cu cm/molecule-sec at 25 deg C(SRC) that was derived using a structure estimation method(2). **PFHxA** does not contain chromophores that absorb at wavelengths >290 nm (3) and, therefore, is not expected to be susceptible to direct photolysis by sunlight (SRC).[138] Fluorotelomers (FTOHs) are volatile and will be transported over long distances via the atmosphere[139]
Factors affecting bioavailability	**See "Interactions" endpoint**
Global Environmental Impacts	

Ozone Depletion Potential (ODP)	Not found
Global Climate Change	Not found
Greenhouse Gas Production	Not found
Acid Rain Formation	Not relevant
Special Reports	
Special Reports	**Short-chain Polyfluoroalkyl Substances (PFAS)** – A literature review of information on human health effects and environmental fate and effect aspects of short-chain PFAS, Environmental project No. 1707, 2015 http://www2.mst.dk/Udgiv/publications/2015/05/978-87-93352-15-5.pdf **Polyfluoroalkyl substances (PFASs) in textiles for children** – Survey of chemical substances in consumer products No. 136, 2015 http://www2.mst.dk/Udgiv/publications/2015/04/978-87-93352-12-4.pdf **Survey of PFOS, PFOA and other perfluoroalkyl and polyfluoroalkyl substances** – Part of the LOUS-review, Environmental project No. 1475, 2013 http://www2.mst.dk/Udgiv/publications/2013/04/978-87-93026-03-2.pdf **Human Health Tier II Assessment for Short chain perfluorocarboxylic acids and their direct precursors,** NICNAS, https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1686 **ToxServices 2016:** Perfluorohexanoic Acid (CAS # 307-24-4) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment. Prepared by: ToxServices LLC, June 3, 2016.

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