


Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

<p>CAS # 375-95-1</p> 	<p>Perfluorononanoic acid Synonym¹s: EINECS 206-801-3; UNII-5830Z6S63M; HSDB 8040 RTECS #²: RA6901000 EINECS #³: 206-801-3 Molecular Weight⁴: 464.0709 Molecular Formula⁵: C9-H-F17-O2</p>
PHYSICAL CHARACTERISTICS	
<i>Primary Use</i>	<p>Long-chain perfluoroalkanecarboxylic acids and their salts are surface-active chemicals (surfactants), which greatly reduce the surface tension (surface energy) of water, aqueous solutions, and organic liquids even at low concentrations. These acids (C₆- C₁₂) and derivatives are used as wetting, dispersing, emulsifying, and foaming agents. /Long-chain perfluoroalkanecarboxylic acids/⁶</p> <p>Breakdown product of stain- and grease-proof coatings on food packaging, couches, carpets.⁷</p>
<i>Physical state, odor at room temperature & pressure</i>	White, solid ⁸
<i>Melting point; Boiling point</i>	MP/range: 68-73°C (154-163°F) ⁹ ; Initial BP and Boiling range = 218°C (424°F) at 987 hPa (740 mmHg) ¹⁰
<i>Solubility</i>	No data available
<i>Specific Gravity</i>	No data available
SAFETY/PHYSICAL HAZARDS	
<i>Vapor Pressure</i>	8.3X10 ⁻² mm Hg at 25 deg C (est) ¹¹
<i>Flammability</i>	No data available
<i>Flashpoint</i>	No data available
<i>Flammability Rating</i>	No data available
<i>Auto Ignition Point</i>	No data available
<i>Combustion products</i>	Hazardous decomposition products formed under fire conditions – Carbon oxides, Hydrogen fluoride ¹²
<i>Explosivity (UEL, LEL, shock sensitive)</i>	No data available
<i>Oxidizer</i>	No data available
<i>Corrosivity</i>	No data available
<i>pH</i>	No data available
<i>Reactivity</i>	Incompatible materials: Bases, Oxidizing agents, Reducing agents ¹³

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

<i>Viscosity</i>	No data available
<i>Odor Threshold</i>	No data available
<i>Particle size, shape, respirable fraction</i>	No data available
<i>Other physical hazards associated with process: Heat, gases under pressure, noise, vibration, ergonomic hazard</i>	No data available
HEALTH HAZARDS	
Acute Toxicity	
<i>Oral LD₅₀</i>	“No studies that determined the acute oral LD ₅₀ of pure PFNA were located. However, Mertens et al. (2010) state that the “approximate lethal dose” (unpublished data, calculated herein as 65 mg/kg) in rats for the Surflon S-111 mixture of PFCs consisting primarily of PFNA (see below) was 2.9-fold lower than the acute LD ₅₀ for PFOA of 198 mg/kg identified by Olson and Anderson (1983).” ¹⁴
<i>Dermal LD₅₀</i>	No data available
<i>Inhalation LC₅₀</i>	“The inhalation LC ₅₀ in male rats (5 or 6 per group) exposed for 4 hours to six concentrations ranging from 67 to 4,600 mg/m ³ of ammonium perfluorononanoate (the ammonium salt of PFNA) as a dust was 820 mg/m ³ ; the lowest dose that caused death was 590 mg/m ³ . Animals were observed for 5-14 days after exposure and deaths occurred earlier with increasing dose (Kinney et al., 1989). As has been observed in animals acutely exposed to PFOA (reviewed in Lau et al., 2007; Post et al., 2012), severe body weight loss occurred in surviving rats of all but the lowest dose group.” ¹⁵
<i>Intraperitoneal LD₅₀</i>	No data available
Chronic or Sub-chronic Toxicity	
<i>IARC rating</i>	Not found
<i>Carcinogenicity</i>	Not found on the Prop 65 list
<i>Neurotoxicity</i>	Not listed in HAZMAP as a neurotoxin “These results suggested that exposure to PFNA elevated the intracellular calcium level and activated the CaMKII signaling pathway, which may aggravate oxidative stress in PC12 cells and lead to cell damage or cell apoptosis (Fang et al 2018).” ¹⁶ “...A total of 282 subjects have completed the PFASs analysis and questionnaire survey. After adjusted for potential confounders, we observed that PFNA is inversely associated with inattention and oppositional defiant disorder of SNAP-IV, and hyperactivity/inattention of SDQ. ...Prenatal exposure to PFNA was found to associate with neurobehavioral symptoms related to ADHD among Asian seven-year-

Updated EHS Summary of Perfluorononanoic acid for the MA
TURA Science Advisory Board Meeting – June 21, 2018

	<p>old children. Further studies are needed to elucidate the causal relationship (Lien et al 2016).”¹⁷</p> <p>“Serum-PFOS and PFHxS concentrations declined over time, whereas PFOA, PFNA, and PFDA tended to increase. No associations were observed between prenatal PFAS concentrations and SDQ scores. However, a two-fold increase in 5-year serum-PFOA, PFNA, and PFDA concentrations was associated with increases in total SDQ scores by 1.03 (95% CI: 0.11, 1.95), 0.72 (95% CI: 0.07, 1.38) and 0.78 points (95% CI: 0.01, 1.55), respectively. For SDQ subscales, significant associations were found in regard to hyperactivity, peer relationship, and conduct problems, as well as internalizing and externalizing problems and autism screening composite scores. Cross-sectional analyses at age 7 years showed possible sex-dimorphic associations between PFAS concentrations and SDQ scores, where girls had consistently positive associations with SDQ scores whereas boys exhibited a pattern of negative or null associations. ... Higher serum PFAS concentrations at ages 5- and 7-years, but not prenatally, were associated with parent-reported behavioral problems at age 7 (Oulhote et al 2016).”¹⁸</p> <p>“Whereas PFHxS, PFOS and PFUnDA aggregated in large hotspots, PFOA, PFNA and PFDA showed a more dispersed distribution pattern. In conclusion, the toxicity of the investigated PFAAs increased with increasing carbon chain length. For molecules with a similar chain length, a sulfonate functional group led to greater toxicity than a carboxyl group (Berntsen et al 2017).”¹⁹</p>
<p><i>Developmental/Reproductive Toxicity</i></p>	<p>In the EU, Sweden has proposed PFNA to be classified as toxic to reproduction²⁰</p> <p>Not found on the Prop 65 list</p> <p>There is evidence based on the RAC opinion on PFNA and its sodium and ammonium salts that these substances meet the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of the REACH Regulation. As a consequence the toxicity criterion of REACH Annex XIII is fulfilled. ... H360Df: May damage the unborn child. Suspected of damaging fertility.²¹</p> <p>ToxPLANET – Notes “Reproductive Effector”</p> <p>Oral, rat: TDLo: 70 mg/kg (2W male); Paternal Effects: Spermatogenesis (including genetic material, sperm morphology, motility, and count); Paternal Effects: Other effects on male²²</p> <p>...PFNA... exposure resulted in significantly altered responses in terms</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

of morphometric, locomotion, and gene expression endpoints, which could be manifested in field exposed teleosts (Jantzen et al 2016a).²³

In boys, prenatal PFNA, and PFDODA were associated with reductions in height at certain ages in childhood, but not with size at birth....Prenatal exposure to long-chain PFCAs may interfere with fetal and childhood growth in girls, and childhood growth in boys (Wang et al 2016a).²⁴

Plasma concentrations of ...perfluorononanoic acid (PFNA) were inversely associated with endometriosis-related infertility, but the associations were attenuated in the sensitivity analyses. (Wang et al 2017).²⁵

We did not find evidence of associations between PFNA and total testosterone or between any of the PFAAs and SHBG. ... Our findings were based on a small study sample and should be interpreted with caution. However, they suggest that prenatal exposure to some PFAAs may alter testosterone concentrations in females (Maisonet et al 2015).²⁶

In a multiple logistic regression with adjustment for age, BMI, parity and gestational age at serum sampling, women with the highest tertile of exposure to perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) in pregnancy had odds ratios for miscarriage of 16.5 (95% CI 7.4-36.6-36.5) and 2.67 (1.31-5.44), respectively, as compared to the lowest tertile (Jensen et al 2015).²⁷

Our results indicate that developmental toxicity of PFNA in mice is comparable to that of PFOS and PFOA, and that these adverse effects are likely common to perfluoroalkyl acids that persist in the body (Das et al 2015).²⁸

...PFNA...were associated with a lower percentage of sperm with coiled tails (Louis et al 2015).²⁹

The results of this study indicate that chronic exposure to PFNA can lead to dysfunction in the HPGL axis and sex hormone synthesis and cause adverse effects on fish reproduction (Zhang et al 2016d).³⁰

No significantly elevated HRs were observed for any PFASs suggesting no association with loss: ..., PFNA (0.86; 0.70, 1.06), ..., PFOS (0.81; 0.65, 1.00), and PFOA (0.93; 0.75, 1.16) (Louis et al 2016).³¹

“...After adjustment for confounding factors, nonsignificant associations between PFASs and reproductive hormone were found except for PFNA with ln(estradiol) ($\beta=0.2060$, 95%CI: 0.0016, 0.4105). When stratified by sex, more significant associations were found in

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

males than in females. Among males, PFASs were negatively associated with $\ln(\text{testosterone})$ level for ... PFNA ($\beta = -0.4233$, 95%CI: -0.6998, -0.1467). ...In conclusion, this study showed higher levels of PFASs coincide with lower testosterone and higher estradiol levels, and more significant associations of PFASs with reproductive hormone were found in males than in females (Zhou et al 2016a)."³²

"In secondary analyses, instead of PFOS, we examined perfluorononanoate (PFNA) [mean (SD): 0.7 (0.4) ng/mL], a PFAS more closely linked to lower BW/GA in our cohort. The best-fit multi-pollutant model included positive two-way interactions between PFNA and both black carbon and smoking (p -interactions = 0.03). ... Concurrent prenatal exposures to maternal smoking, black carbon, and PFOS are additively associated with lower fetal growth, whereas PFNA may attenuate associations of smoking and black carbon with lower fetal growth. It is important to examine interactions between multiple exposures in relation to health outcomes, as effects may not always be additive and may shed light on biological pathways (Rokoff et al 2018)."³³

"The duration of breastfeeding was positively associated with the serum concentrations of \ln -transformed ...PFNA...(all $P < 0.001$). Height at 2 years of age was inversely related to ... PFNA, ... concentrations (adjusted β per \ln unit [95% confidence interval, CI]: -0.48 [-1.40, -0.51] cm ...), after adjusting for age, sex, and midparental height. Weight at 2 years of age was inversely associated with PFNA (adjusted β per \ln unit [95% CI]: -0.32 [-0.48, -0.15] kg), after adjusting for age, sex, and parental BMI. In conclusion, the serum concentrations of PFCs were inversely associated with growth parameters in 2-year-old children (Lee et al 2018)."³⁴

"Perfluorooctane sulfonate (PFOS) and perfluorononanoate (PFNA) were weakly inversely associated with birth weight-for-gestational age z scores (adjusted $\beta = -0.04$ (95% confidence interval (CI): -0.08, 0.01) and adjusted $\beta = -0.06$ (95% CI: -0.11, -0.01) per interquartile-range increase, respectively). PFOS and PFNA were also associated with higher odds of preterm birth (e.g., for highest PFOS quartile vs. lowest, adjusted odds ratio = 2.4, 95% CI: 1.3, 4.4). Adjusting for markers of pregnancy hemodynamics (glomerular filtration rate and plasma albumin), to the extent that they accurately reflect underlying pregnancy physiology, did not materially affect associations. These results suggest that pregnancy hemodynamics may not confound associations with birth outcomes when PFAS are measured early in

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

	<p>pregnancy (Sagiv et al 2018).³⁵</p> <p>“Inverse associations were found between maternal levels of perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA), and birth weight SDS with a change of -0.10 to -0.18 weight SDS for an inter-quartile range (IQR) increase in ng/g PFAA. After birth, weight and length SDS were not significantly associated with maternal PFAA. However, BMI SDS was significantly associated with PFOA, PFNA, and PFHxS at 3 and 4 years of age, and with PFOS at 4 and 5 years of age. If causal, these associations suggest that PFAA affects fetal and childhood body development in different directions (Gyllenhammar et al 2018).³⁶</p> <p>“Median serum PFASs concentrations were PFOS>PFOA>PFHxS>PFNA in prenatal, 3-year, and 8-year children. The covariate-adjusted general linear regression identified positive associations between serum PFOA, PFOS and PFNA concentrations and children's reading scores at ages 5 and 8 years, . . . Prenatal PFOS and PFNA were positively associated with children's reading abilities at age 5 years, but not at age 8 years; 3-year PFOS and PFNA were positively associated with reading scores at age 5 years. . . . Prenatal and childhood serum PFOA, PFOS and PFNA concentrations were positively associated with better children's reading skills at ages 5 and 8 years, but no association was found between serum PFHxS and reading skills (Zhang et al 2018).³⁷</p>
<p><i>Genotoxicity/Mutagenicity</i></p>	<p>We concluded that PFOA and PFNA induced DNA damage and the biomarker of oxidative DNA damage (8-OHdG) could be measured by HPLC-MS/MS. In addition, PFNA produced high level of 8-OHdG at concentrations lower than PFOA, this may indicate that PFNA is more potent genotoxicant for TK6 cells than PFOA (Yahia et al 2016).³⁸</p>
<p><i>Endocrine Disruption</i></p>	<p>Found on TEDX List of Potential Endocrine Disruptors³⁹</p> <p>Maternal serum concentrations of HCB, PFOS and PFOA were associated with increased BMI z-scores and/or overweight risk (i.e. BMI z-score≥85th WHO percentile). No clear association was found for maternal serum-PCBs, p,p'- DDE, PFHxS, PFNA and PFDA. (Karlsen et al., 2017).⁴⁰</p> <p>Overall, this study demonstrated that PFAA mixture could have the potential of multigenerational endocrine disruptors in <i>O. latipes</i> (Lee et al 2017).⁴¹</p> <p>Normal acini maturation was negatively impacted by PFOS, PFNA and PFDA already at the lowest concentration tested (0.6µM). Observed effects included loss of organization of the cell clusters and absence of</p>

Updated EHS Summary of Perfluorononanoic acid for the MA
TURA Science Advisory Board Meeting – June 21, 2018

	<p>a hollow lumen. Overall, this study demonstrated that PFAAs can interfere with cellular events related to normal development of glandular breast tissue through ER-independent mechanisms (Halsne et al 2016).⁴²</p>
<p>Thyroid</p>	<p>Total PFAS exposure level was 2.63-44.7ng/mL in the case group and 2.44- 22.4ng/mL in the control group. Concentrations of serum...perfluorononanoic acid (PFNA, p<0.001), ... were significantly higher in the case group than the control group (Kim et al 2016).⁴³</p> <p>“We also highlighted a negative association between perfluorononanoic acid (PFNA) concentration and TSH in male newborns (p = 0.018) (Dufour et al 2018)”.⁴⁴</p> <p>“PFAS concentrations [PFOA, PFOS, and perfluorononanoate (PFNA)] were inversely associated with TSH levels in TPOAb-positive women only (Preston et al 2018)”.⁴⁵</p> <p>“We found some evidence of a positive association between ...PFNA and TSH levels measured in the blood of boys aged ≥11 years. ...Although there is a small number of studies with comparable data, we found some consistency of a positive association between maternal or teenage male exposure to some PFAS and TSH levels based on the current literature. However, further studies are required to confirm these possible relationships (Ballesteros et al 2017)”.⁴⁶</p> <p>“PFAS levels gradually increased from 2006 to 2013, decreasing thereafter. We found that PFAS levels were higher in male than in female participants and were positively correlated with age. PFASs were not significantly correlated with body mass index, although we observed positive correlations with total cholesterol, low-density lipoprotein cholesterol, and triglycerides and negative correlations with high-density lipoprotein cholesterol. Uric acid and free thyroxine (fT4) also showed positive correlations with major congeners while correlations between thyroid stimulating hormone and PFASs were inconsistent. We demonstrated significant correlations between fT4 and perfluorononanoic acid (PFNA), ... Furthermore, principal component analysis suggested possible differences in disease manifestation based on the congener distribution of PFASs (Seo et al 2018)”.⁴⁷</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

	<p>Hormone Summary – Females Free thyroxine is decreasing with increasing dose.</p> <p>Hormone Summary – Males Free Thyroxine (T4) and TSH are decreasing with increasing dose. See additional information in NTP Tox-97 report.⁴⁸</p>
<p style="background-color: #00FF00; display: inline-block; padding: 2px;">Immunotoxicity</p>	<p>The substance is immunotoxic (Fang et al., 2008)⁴⁹</p> <p>“In ovalbumin (OVA)-induced model of systemic anaphylaxis in the presence of hypothermia, PFNA, PFDA, and PFUnA exacerbated allergic symptoms accompanied by elevation in serum histamine, TNF-α, IgE, and IgG1. Our data indicate that some PFC aggravated high-affinity IgE receptor (FcϵRI)-mediated mast cell degranulation and allergic symptoms. Consequently, the results demonstrated that carbon-chain length of PFC may serve as a factor in allergic inflammation (Lee and Kim 2018).”⁵⁰</p> <p>“The number of reported airways infections were significantly associated with cord blood concentrations of PFASs; ...LRTIs from 0 to 10 years of age with PFOS ($\beta = 0.50$ (0.42-0.57)), PFOA ($\beta = 0.28$ (0.22-0.35)), PFOSA ($\beta = 0.10$ (0.06-0.14)), PFNA ($\beta = 0.09$ (0.03-0.14)) and PFUnDA ($\beta = 0.18$ (0.13-0.23)) concentrations. Neither reduced lung function at birth, asthma, allergic rhinitis, AD nor allergic sensitization were significantly associated with any of the PFASs. ... Although prenatal exposure to PFASs was not associated with atopic or lung manifestations by 10 years of age, several PFASs were associated with an increased number of respiratory tract infections in the first 10 years of life, suggesting immunosuppressive effects of PFASs (Impinen et al 2018).”⁵¹</p> <p>“...A total of 687 children completed a 2-year follow-up visit and had PFASs measurement. AD (atopic dermatitis) was diagnosed in 173 (25.2%) children during the first 24 months. In female children, a log-unit increase in perfluorooctanoic acid (PFOA) was associated with a 2.1-fold increase in AD risk (AOR 2.07, 95% CI 1.13-3.80) after adjusting for potential confounders. The corresponding risk was 2.22 (1.07-4.58) for perfluorononanoic acid (PFNA). ... The highest quartile of PFNA, perfluorodecanoic acid (PFDA) and perfluorohexane sulfonic acid (PFHxS) were associated with AD with AOR (95% CI) being 2.14 (0.97-4.74), 2.14 (1.00-4.57), and 2.30 (1.03-5.15), respectively. ... However, no significant associations were found in male children. ... In addition, the associations between AD with prenatal exposure to PFNA were close to statistical significance (Chen et al 2018).”⁵²</p>

Updated EHS Summary of Perfluorononanoic acid for the MA
TURA Science Advisory Board Meeting – June 21, 2018

	<p>“Together, these results suggest that PFNA exerts toxic effects on lymphoid organs and T cell and innate immune cell homeostasis in mice and that these effects may result from the activation of PPAR-alpha, PPAR-gamma, and the hypothalamic-pituitary-adrenal axis. Interestingly, at the transcriptional level, the nuclear factor-kappa B signaling pathway appears to be uninvolved in the immunotoxic potential of PFNA (Fang et al 2008).”⁵³</p> <p>“The present study demonstrates that PFNA produces immunotoxic effects in both male and female C57BL/6 mice as evidenced by splenic atrophy, decreased splenocyte numbers, and a marked reduction in thymocyte viability. The current study also demonstrates that the effects of PFNA on different leukocyte populations are not uniform. The CD4⁺CD8⁺ double-positive thymocytes were particularly sensitive to PFNA in which the proportion of this population was >95% decreased relative to the entire CD4⁺ thymocyte population in PFNA-treated mice. Interestingly, PFNA also markedly increased serum levels of TNFα in response to LPS in mice. Collectively, the present studies demonstrate that PFNA decreases lymphocyte viability and alters the immune response to LPS in C57BL/6 mice (Rockwell et al 2013).”⁵⁴</p> <p>“The present studies sought to determine whether, and to what degree, the immune system recovered 28 days after PFNA exposure. None of the parameters measured had fully recovered. A few parameters had partially recovered, including decreased spleen size and the decreased ratio of the CD4⁺/CD8⁺ double-positive population in thymus. The majority of effects of PFNA remained unchanged 28 days after exposure, including decreased proportion of intact thymocytes (as determined by FSC vs SSC), alterations in the ratios of immune cell populations in spleen and the CD4⁺, CD8⁺ and double-negative populations in thymus. Notably, PFNA markedly increased the TNFα response to LPS in vivo, and no recovery was evident 28 days after exposure. The effect of PFNA on CD4⁺ T cells, CD8⁺ T cells and CD19⁺ cells was more pronounced in females. The current study demonstrates that a single high dose exposure to PFNA (e.g. as might occur accidentally in an occupational setting) has long-lasting effects on the immune system (Rockwell et al 2017).”⁵⁵</p> <p>Also see Liu and Gin 2018 in the Ecological Toxicity section below</p>
Heart	<p>“When adjusting for multiple comparisons, none of the eight PFASs evaluated were significantly related to left ventricular mass. However, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

	<p>perfluoroundecanoic acid (PFUnDA) were related to relative wall thickness (RWT) in a negative fashion ($p < 0.0021$). Besides being inversely related to RWT, PFNA was also positively related to left ventricular end-diastolic volume (LVEDD) ($p < 0.0021$). ...In this cross-sectional study, several of the PFASs evaluated, especially PFNA, were related to myocardial geometry: a reduction in relative wall thickness and an increase in left ventricular diameter following adjustment for traditional cardiovascular risk factors, suggesting a role for PFASs in cardiac remodeling (Mobacke et al 2018).⁵⁶</p>
<p><i>Liver/Lipid Effects</i></p>	<p>Increases in liver weight and cell size, and decreases in DNA content per mg of liver, were observed for all compounds in WT mice, and were also seen in PPARα-null mice for ...PFNA, ... (Das et al 2017).⁵⁷</p> <p>These results indicate that most of the PFAAs increase liver TG load and promote steatosis in mice (Das et al 2017).⁵⁸</p> <p>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).⁵⁹</p> <p>In summary, all perfluorinated compounds increased cell number, decreased cell size, increased total triglyceride, and altered expression of genes associated with adipocyte differentiation and lipid metabolism (Watkins et al, 2015).⁶⁰</p> <p>“Moreover, PFNA increased free and total cholesterol in mouse liver but not in mouse serum. Furthermore, PFNA increased mRNA expression of sterol transporters, namely Abca1, g1, g5/g8, and steroidogenic acute regulatory protein via PPARα. In conclusion, PFNA produced cholestasis in mouse liver, and the activation of PPARα plays a central role in regulating BA and cholesterol metabolism and transport in mouse serum and liver (Zhang et al 2018a).”⁶¹</p> <p>“While PFASs exposure was associated with a consistent negative relationship with bone health parameters, among four PFASs tested, only PFNA showed a significant negative relationship with bone parameter (β [95% CI], = -72.7 [- 126.0, - 19.6], $p = .010$). PFNA was also associated with raised systolic blood pressure ($p = .008$), low density lipoprotein cholesterol (LDL-C; $p < .001$), and total cholesterol (TC; $p = .014$). ... In this analysis, PFASs were not strongly related to thyroid hormones, 25-hydroxy vitamin D, liver enzymes, or glucose homeostasis. ...PFASs exposure in obese children may play a role in</p>

Updated EHS Summary of Perfluorononanoic acid for the MA
TURA Science Advisory Board Meeting – June 21, 2018

	<p>adverse skeletal and cardiovascular risk profiles (Khalil et al 2018).⁶²</p> <p>“Perfluorohexanoate, perfluoroheptanoate, perfluorooctanoate, perfluorononanoate (PFNA) and perfluorodecanoate induced PPARα activities >2.5-fold compared to controls. The concentration-response relationships were positive for all the tested compounds, except perfluorooctane sulfonate PFOS and FOSA, and were compound-specific, as demonstrated by differences in the estimated slopes. The relationships were steeper for PFCAs with chain lengths up to and including PFNA than for the other studied PFASs (Rosenmai et al 2017).⁶³</p>
<p><i>Diabetes/Obesity</i></p>	<p>“The expression of phospho-glycogen synthase kinase-3 beta (GSK3β, Ser 9) was increased, which explains the augment of hepatic glycogen. Significant increases in hydrogen peroxide (H₂O₂) and malondialdehyde (MDA) were found in the livers of 5mg/kg/d PFNA-treated rats. Thus, exposure to PFNA disordered glucose metabolism via inhibiting hepatic insulin signal pathway, accelerating the output of glucose and increasing glycogen synthesis in the rat liver. Furthermore, the oxidative stress induced by PFNA may be involved in this process (Fang et al 2012).⁶⁴</p> <p>The expressions of protein related to lipid homeostasis, liver X receptor α and apolipoprotein E, were decreased after PFNA administration. Exposure to PFNA also increased the activity of serum alanine aminotransferase in diabetic rats. ... this study discloses that exposure to PFNA impacts on enzymes and proteins related to liver lipid metabolism and lead to obvious accumulation of lipid in the liver of diabetic rats, which may be responsible for hepatotoxicity of this compound in individuals with diabetes mellitus (Fang et al, 2015).⁶⁵</p> <p>However, ... PFNA, ... showed a potential protective effect against glucose intolerance and the risk of diabetes (Su et al 2016).⁶⁶</p> <p>“PFHxS and PFNA concentrations were associated with impaired glycemic status in metabolically vulnerable pregnant women and might further enhance the risk of developing GDM (gestational diabetes mellitus)(Jensen et al 2018).⁶⁷</p> <p>“Furthermore, diabetes was not related to PFOS, PFHxS and PFNA, regardless of gender (He et al 2018).⁶⁸</p> <p>“In women, comparing the highest to the lowest tertiles of PFAS</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

	concentrations, the multivariate-adjusted mean weight regain (SE) was ... 4.7 (0.9) versus 2.5 (0.9) kg for perfluorononanoic acid (PFNA) (Ptrend = 0.006); ... When further adjusted for changes in body weight or thyroid hormones during the first 6 months, results remained similar. Moreover, higher baseline plasma PFAS concentrations, especially for PFOS and PFNA, were significantly associated with greater decline in RMR during the weight-loss period and less increase in RMR during the weight regain period in both men and women (Liu et al 2018).” ⁶⁹
Skin, Eye and Respiratory Effects	
<i>Irritant – Skin, Eye, or Respiratory</i>	Skin Irrit. 2; Eye Irrit. 2A; STOT SE 3; H315, H319, H335 ⁷⁰
<i>Corrosive – S, E, or R</i>	Corrosive as concentrated acid; pKa = -0.21 ⁷¹
<i>Permanent Damage – S, E, or R</i>	
<i>Sensitizer– S & R</i>	
<i>Asthmagen – Initiator or Exacerbator</i>	Not found in AOEC Database as of 01/04/18
<i>Skin Absorption, Kp</i>	
<i>LOAEL</i>	12,400 ng/ml – pregnant mice (Das et al., 2015); 11,500 ng/ml – male mice (Wang et al, 2015) ⁷²
<i>NOAEL</i>	
<i>Benchmark Dose Response (BMD)</i>	Benchmark Dose Modeling for 10% Increase in Liver Weight in Pregnant Mice from Das et. Al (2015) – Table 10 in NJ 2015 document ⁷³
<i>Toxicokinetics</i>	a. PFNA is present in human blood of the general population b. Elimination half-lives are > 1.7 years c. Human elimination half-lives seem to be the longest amongst the available mammalian data, whereas the elimination half-lives in laboratory mammals vary highly depending on the study conditions (ECHA 2015). ⁷⁴
<i>Metabolites</i>	
<i>Synergistic or Antagonistic Effects</i>	
Environmental and Human Health Exposure and Risk Values	
<i>RfC/RfD</i>	Not found in IRIS as of 12/14/17
<i>ATSDR-MRL</i>	Not found on June 2017 MRL list as of 01/04/18
<i>Adverse Effect Levels: DNEL, PNEC, PNEL</i>	
Health Based Exposure Limits	
<i>NIOSH-REL/IDLH/Ceiling Limits</i>	Not found
<i>OSHA-PEL</i>	Not found
<i>ACGIH TLV-TWA</i>	Not found
<i>TLV-STEL</i>	Not found
<i>Biomonitoring Action Limits</i>	

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

<i>Drinking Water Standards</i>	NJ: Drinking Water Quality Institute recommends that the Department propose and adopt an MCL of 13 ng/L for PFNA in drinking water. ⁷⁵
<i>Other</i>	Mechanism of Action information in HSDB On SIN List (reason for inclusion): This substance has persistent, bioaccumulative and toxic properties, has been detected in human blood, in dolphins, seals and polar bears. Substance is concluded to be a PBT and Reprotoxic substance SVHC by ECHA Member State Committee. ⁷⁶
ENVIRONMENTAL & ECO-SYSTEM HAZARDS (Bulk of information cited UNEP 2015a and UNEP 2015b)	
PBT	No photodegradation tested under relevant environmental conditions; 100 % after 12 h (irradiated with a xenon-mercury lamp under oxygen) by use of persulfate ion (S ₂ O ₈ ²⁻) in water (Hori 2005). No hydrolysis tested under relevant environmental conditions; 100% (by use of S ₂ O ₈ ²⁻) after 6 h in 80°C water. (Hori 2008) Reaction products were mainly F ⁻ and CO ₂ ; short chain PFCAs were minor reaction products (ECHA 2015). ⁷⁷
Bioaccumulation	<p>“Due to its expected notable water solubility, PFNA is, like the other PFCAs, expected to quickly be excreted via gill permeation. Furthermore, PFNA is present mainly in protein rich tissues like blood and liver (OECD, 2006; Kelly et al. 2009). Hence, bioconcentration in gill breathing organisms and the accumulation in lipids is not the most relevant endpoint to consider. Field studies show that air-breathing organisms are more likely to bioaccumulate PFNA and other PFCAs compared to water breathing organisms. Therefore, the numerical bioaccumulation (B) criterion defined in the REACH regulation Annex XIII (sections 1.1.2 and 3.2.2(a)) is not suitable to assess the bioaccumulation potential of PFNA (ECHA 2015).”⁷⁸</p> <p>The bioaccumulation data on PFNA in environmental species, in laboratory mammals and in humans is consistent with the data on other long-chain perfluorinated carboxylic acids, such as PFOA. a. Recent models to explain the substantial bioaccumulation of PFCAs take into account the observed pattern of animal tissue distribution, the relationship between chain length and bioaccumulation and the species and gender-specific variation in elimination half-life.⁷⁹ To conclude, taken all available information together in a weight-of-evidence approach, the elimination half-lives from humans and other mammals show that PFNA bioaccumulates. The available field data also</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

indicate that bioaccumulation and trophic magnification occur in certain food webs in the environment. The data on PFNA are in line with the expected regular pattern of fate properties of the already assessed PFOA and C11-C14-PFCAs. Therefore it is considered that the B criterion of REACH Annex XIII is fulfilled. Whether the vB criterion is fulfilled has not been assessed.⁸⁰

There is evidence that PFNA preferentially bioaccumulates in air-breathing mammals, including endangered species and humans

- a. BMFs range from 1.4 – 24 based on estimated whole body values
 - b. TMFs range from 2.9 to 9.88 referring to either whole body measurements or estimated whole body values
3. PFNA does not seem to consistently accumulate in water breathing animals
- a. No experimental BCFs are available for PFNA. For the closest structural analogues BCFs range from 4.0 to 27 (PFOA) and from 450 to 2,700 (PFDA)
 - b. Whole body BAFs range from 0 to 3,981
 - c. Whole body BMFs range from 0.13 to 5.3 whereas most of the data are below 1
 - d. Whole body TMFs range from [0.33 to 2.1] in aquatic piscivorous food webs⁸¹

Presence in air breathing mammals:

PFNA was identified in female beaver tissues (liver, subcutaneous adipose and peritoneum) in a range from 1.50 to 6.61ngg(-1) ww (Surma et al, 2015).⁸²

Presence in marine mammals:

“Juveniles (dolphins) had significantly higher levels of PFOS and PFNA than adults in both species, suggesting growth dilution as they approach maturity (Lynch et al 2018).”⁸³

Presence in humans:

The geometric mean concentrations (and P95 values) for ...PFNA (perfluorononanoic acid) in the serum of 755 Spanish adults, 0.96 (2.44) µg/L, (Bartolome et al 2017).⁸⁴

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

“...perfluorononanoate (PFNA) ... found in 99% of the participants. ... Median concentrations were: ...PFNA 0.50 ng/mL.... Median of PFASs sum concentration (Σ PFAS) was 10.7 ng/mL, the concentration range was 2.6-200.8 ng/mL. Intake of fat fish, fish liver, seagull eggs, reindeer meat and drinks with sugar were the main dietary predictors of several PFASs. Intake of junk food (pizza, hamburger, sausages) was positively associated with PFNA, intake of canned food was positively associated with PFHxS (Averina et al 2018).”⁸⁵

“We detected PFOS, PFOA, PFHxS, and PFNA in all children at concentrations similar to those of NHANES 2013-2014 adolescents and adults, suggesting prevalent exposure to these PFAS or their precursors among U.S. 3-11 year old children, most of whom were born after the phase out of PFOS in the United States in 2002 (Ye et al 2018).”⁸⁶

“After a month of nursing, the concentrations of PFOS, PFOA, perfluorononanoic acid (PFNA), and Σ PFAS significantly increased. This could be due to changes in the dietary and behavior patterns of the mothers after the first month of lactation. ... Certain types of diet (e.g. consuming snacks and milk) and eating-out frequency were significantly associated with increasing levels of PFAS (Lee et al 2018a).”⁸⁷

“Serum levels of perfluorohexane sulfonic acid (PFHxS), perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) were significantly higher in the subjects with MetS. Logistic regression results showed that concentration of PFNA in serum was associated with 10.9-fold [95% confidence interval (CI), 2.00-59.1] increased risk of MetS. Moreover, increased serum PFNA concentrations were associated with high blood pressure [both for systolic and diastolic blood pressure (SBP and DBP); odds ratio (OR) 7.52 (95%CI, 1.34-42.1) for SBP and 7.27 (95%CI, 1.17-45.1) for DBP], hypertriglyceridemia [13.2 (95%CI, 2.34-74.2)] and obesity [13.3 (95%CI, 2.38-74.4)], respectively (Yang et al 2018).”⁸⁸

“Diet accounted for a low of 18.6% of the total explained variance in

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

	<p>the adjusted levels of NPFOA and a high of 72.3% for PFNA (Jain 2018).”⁸⁹</p> <p>Phytoaccumulation – PFHpA, PFOA, PFNA and PFBS were taken up by yam root, maize cob and sugarcane stem (Dalahmeh et al 2018).⁹⁰</p>
BAF	<p>BAFs range from 0 to 3981⁹¹</p> <p>BAFs: [biota]/[water]</p> <p>Phytoplankton (whole): 1680 (Loi et al, 2011)</p> <p>Lake trout (whole): 3981 (Furdui et al, 2007)</p> <p>European chub (various tissues): 39 – 630 (Labdie and Chevreuril, 2011)</p> <p>Atlantic croaker (whole): not detected (Houde et al 2006)</p> <p>5 different marine fish (whole): 705-2800 (Houde et al 2006)</p> <p>5 different marine fish (whole) 59-197 (Loi et al, 2011)</p> <p>Biota-sediment accumulation factor (BSAF) for benthic-dwelling worm downstream from 2 WWTP in California varied from 83-149 (lipid normalized) 0.64 – 0.83 (non-lipid normalized). Use results with caution, as PFNA does not enrich in lipids. (Higgins et al, 2007)⁹²</p>
BCF	<p>PFNA does not seem to consistently accumulate in water breathing animals; No experimental BCFs are available for PFNA. For the closest structural analogues BCFs range from 4.0 to 27 (PFOA) and from 450 to 2700 (PFDA)⁹³</p>
BMF	<p>There is evidence that PFNA preferentially bioaccumulates in air-breathing mammals, including endangered species and humans</p> <p>a. BMFs range from 1.4 – 24 based on estimated whole body values⁹⁴</p> <p>Whole body BMFs range from 0.13 to 5.3 whereas most of the data are below 1⁹⁵</p>
Ecological Toxicity	<p>PFNA was also the compound producing the greatest levels of oxidative stress, both in zebrafish and TLT cells. Additionally, in both biological systems, it showed a much stronger effect on mixtures in comparison to the others PFCs tested in this work (Rainieri et al 2017).⁹⁶</p> <p>This study demonstrates that acute, embryonic exposure (5 days) to individual PFASs result in significant biochemical and behavioral changes in young adult zebrafish 6 months after exposure. These three</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

PFASs have long term and persistent impacts following short term embryonic exposure that persists into adulthood (Jantzen et al 2016).⁹⁷

The observed dose-response PFAS-induced effects were to some extent related to their cytotoxicity: the EC₅₀-values of most influential PFAS treatments increased (PFOS < PFNA < PFOA << PFBS), and higher-doses of these chemicals induced a larger impact. Major spectral alterations were mainly attributed to DNA/RNA, secondary protein structure, lipids, and fatty acids. Finally, PFOS and PFOA caused a decrease in A6 cell numbers compared to controls, whereas PFBS and PFNA did not significantly change cell population levels. Overall, this work highlights the ability of PFASs to alter A6 cells, whether forming monolayers or differentiated into dome structures, and the potential of PFOS and PFOA to induce cell death (Gorrochategui et al 2016).⁹⁸

All three PFCs commonly resulted in a decrease in total body length, increased *tfc3a* (muscle development) expression and decreased *ap1s* (protein transport) expression at 5dpf, and hyperactive locomotor activity 14 dpf. All other endpoints measured at both life-stage time points varied between each of the PFCs. PFOS, PFNA, and PFOA exposure resulted in significantly altered responses in terms of morphometric, locomotion, and gene expression endpoints, which could be manifested in field exposed teleosts (Jantzen et al 2016a).⁹⁹

Acute toxicity was greater for PFOS in zebrafish; however, it was greater for PFNA in TLT cells. PFNA was also the compound producing the greatest levels of oxidative stress, both in zebrafish and TLT cells. Additionally, in both biological systems, it showed a much stronger effect on mixtures in comparison to the others PFCs tested in this work. Mixture studies in zebrafish showed that acute toxicity depended on the concentration and that the mixture was far more toxic than the individual compounds (Rainieri et al 2017).¹⁰⁰

These findings suggest that PFNA affected the development of zebrafish embryos at relatively low concentrations (Liu et al, 2015).¹⁰¹

This study demonstrates that acute, embryonic exposure (5days) to individual PFASs result in significant biochemical and behavioral

Updated EHS Summary of Perfluorononanoic acid for the MA
TURA Science Advisory Board Meeting – June 21, 2018

	<p>changes in young adult zebrafish 6 months after exposure. These three PFASs have long term and persistent impacts following short term embryonic exposure that persists into adulthood (Jantzen et al, 2016).¹⁰²</p> <p>“We found that exposure to PFASs could lead to reduced hemocyte cell viability and suppress immune function by up to 50% of normal performance within the experimental exposure range. The results indicate that PFASs have an immunotoxic potential and thus could pose severe health risks to aquatic organisms. The reported immunotoxicity is likely to result from the compounds' direct and indirect interactions with the hemocyte membrane, and therefore likely to affect the functionality of these cells. The immunotoxic response was found to be related to the organism's burden of PFASs, and was reversible when the compounds were removed from the test organisms (Liu et al 2018a).”¹⁰³</p> <p>“Earthworms were exposed to spiked soil for 21 days. Concentrations of these compounds in earthworms after 21-d exposure ranged from below detection to 127 mg kg⁻¹ wet weight with the rank order of PFNA > PFHxS > PFHpA > PFBS; no mortality of earthworms was observed in all treatments including controls, except PFBS at 1,000 µg kg⁻¹ and all PFASs at 100,000 µg kg⁻¹. The highest weight loss (29%) was observed for earthworms exposed to PFNA at 100,000 µg kg⁻¹, which was significantly different from all other treatments except PFHpA at 100,000 µg kg⁻¹ (Karnjanapiboonwong et al 2018).”¹⁰⁴</p>
<p>Aquatic Toxicity: LC₅₀, EC₅₀, ErC₅₀, NOAEC/NOEC</p>	
<p>Mammalian Toxicity: LC₅₀, EC₅₀, ErC₅₀, NOAEC/NOEC</p>	
<p>Wildlife Toxicity: LC₅₀, EC₅₀, ErC₅₀, NOAEC/NOEC</p>	
<p>Breakdown/degradation /combustion products</p>	
<p>Anaerobic degradation</p>	
<p>Aerobic degradation</p>	
<p>Other observable ecological effects (e.g. BOD)</p>	<p>“All PFASs were found to interact with the bilayer by incorporation, indicating PFAS ability to accumulate once ingested or taken up by organisms. The interactions were observed to increase with chain length and vary with the functional group as SO₂NH₂(FOSA)>SO₂O-(PFOS)>COO-(PFNA). The PFAS hydrophobicity, which is strongly</p>

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

	<p>correlated with perfluorocarbon chain length, was found to strongly influence the interactions. Longer chain PFASs showed higher tendency to penetrate into the bilayer compared to the short-chain compounds. The incorporated PFASs could for all substances but one (PFNA) be removed from the lipid membrane by gentle rinsing with water (2mLmin⁻¹). Although short-chain PFASs have been suggested to be the potentially less bioaccumulative alternative, we found that in high enough concentrations they can also disturb the bilayer (Nouhi et al 2018).”¹⁰⁵</p>
Fate and Transport: Aquatic	
Fate and Transport: Terrestrial	
Fate and Transport: Atmospheric	
Transport Issues	
<i>Factors affecting bioavailability</i>	
Global Environmental Impacts	
<i>Ozone Depletion Potential (ODP)</i>	
<i>Global Climate Change</i>	
<i>Greenhouse Gas Production</i>	
<i>Acid Rain Formation</i>	
Special Reports	
<i>EU</i>	<p>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</p> <p>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</p> <p>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</p>

Notes on chemical research: Not found in NIOSH Pocket Guide; CCRIS; GENETOX;

¹ www.expub.com; Chemical Identity Page for Perfluorononanoic acid.

² www.expub.com; RTECS for Perfluorononanoic acid.

³ www.expub.com; Chemical Identity Page for Perfluorononanoic acid.

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

- ⁴ U.S. National Library of Medicine, ChemIDplus, a Toxnet Database, entry for “Perfluorononanoic acid.”, accessed online at: <https://chem.sis.nlm.nih.gov/chemidplus/rn/startswith/375-95-1>
- ⁵ U.S. National Library of Medicine, ChemIDplus, a Toxnet Database, entry for “Perfluorononanoic acid.”, accessed online at: <https://chem.sis.nlm.nih.gov/chemidplus/rn/startswith/375-95-1>
- ⁶ **HSDB 2018:** [Siegemund G et al; Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2012). NY, NY: John Wiley & Sons; Fluorine Compounds, Organic. Online Posting Date: June 15, 2000] **PEER REVIEWED** Record for Perfluorononanoic Acid, CASRN: 375-95-1, Accessed online, 1/13/17, <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~P5vudW:1>
- ⁷ NTP: Testing Status of Perfluorononanoic Acid M040049, Accessed online: <https://ntp.niehs.nih.gov/testing/status/agents/ts-m040049.html>
- ⁸ **Sigma-Aldrich 2018:** SDS for Perfluorononanoic acid, revised February 15, 2017. Accessed online: <https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=91977&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D375-95-1%26interface%3DCAS%2520No.%26N%3D0%2B%26mode%3Dpartialmax%26lang%3Den%26region%3DUS%26focus%3Dproduct>
- ⁹ Sigma-Aldrich 2018, page 4.
- ¹⁰ Sigma-Aldrich 2018, page 4.
- ¹¹ **HSDB 2018:** [US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Jan, 2011. Available from, as of Jul 26, 2012: <http://www.epa.gov/oppt/exposure/pubs/episuitedi.htm> **PEER REVIEWED** Record for Perfluorononanoic Acid, CASRN: 375-95-1, Accessed online, 1/13/17, <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~P5vudW:1>
- ¹² Sigma-Aldrich 2018, page 5.
- ¹³ Sigma-Aldrich 2018, page 5.
- ¹⁴ **NJ 2015:** New Jersey Drinking Water Quality Institute – Health Effects Subcommittee. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). June 22, 2015. Accessed online, 2/21/17: <http://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf>.
- ¹⁵ **NJ 2015:** New Jersey Drinking Water Quality Institute – Health Effects Subcommittee. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). June 22, 2015. Accessed online, 2/21/17: <http://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf>.
- ¹⁶ **Fang 2018:** Fang X, et al. Elevation of intracellular calcium and oxidative stress is involved in perfluorononanoic acid-induced neurotoxicity. *Toxicology and Industrial Health*. 2018 Mar; **34(3)**: 139-145.
- ¹⁷ **Lien 2016:** Lien GW, et al. Perfluoroalkyl substances in cord blood and attention deficit/hyperactivity disorder symptoms in seven-year-old children. *Chemosphere* **156** (2016) 118-127.
- ¹⁸ **Oulhote 2016:** Oulhote Y, et al. Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances. *Environment International* **97** (2016) 237-245.
- ¹⁹ **Berntsen 2017:** Bernsten HF, et al. Time-dependent effects of perfluorinated compounds on viability in cerebellar granule neurons: Dependence on carbon chain length and functional group attached. *NeuroToxicology* **63** (2017) 70-83.
- ²⁰ **Danish EPA 2015a:** Danish Environmental Protection Agency. Polyfluoroalkyl substances (PFASs) in textiles for children. Survey of chemical substances in consumer products No. 136, 2015. Page 82. Accessed online at: <http://www2.mst.dk/Udgiv/publications/2015/04/978-87-93352-12-4.pdf>
- ²¹ **ECHA 2015:** European Chemicals Agency, (2015). Member State Committee Support Document for Identification of Perfluorononanoic Acid and Its Sodium and Ammonium Salts As Substances of Very High Concern Because of Their Toxic For Reproduction and PBT Properties. Available online at: <https://echa.europa.eu/documents/10162/48ae5fe3-9436-4a10-a533-ed642b92ce47>.
- ²² **ToxPlanet 2017:** RTECS®: Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health, Cincinnati, OH. ToxPlanet, a division of Timberlake Ventures, Inc.

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

- Cornelius, NC. 2017. Specifically, *Toxicology Letters*. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1977- 190,224,2009.
- ²³ **Jantzen 2016a**: Jantzen CE, et al. PFOS, PFNA, and PFOA sub-lethal exposure to embryonic zebrafish have different toxicity profiles in terms of morphometrics, behavior and gene expression. *Aquat Toxicol*. 2016 Jun;**175**:160-70.
- ²⁴ **Wang 2016a**: Wang Y, et al. Prenatal Exposure to Perfluorocarboxylic Acids (PFCAs) and Fetal and Postnatal Growth in the Taiwan Maternal and Infant Cohort Study. *Environ Health Perspect*. 2016 Nov;**124**(11):1794- 1800.
- ²⁵ **Wang 2017**: Wang B, et al. Perfluoroalkyl substances and endometriosis-related infertility in Chinese women. *Environ Int*. 2017 May;**102**:207-212.
- ²⁶ **Maisonet 2015**: Maisonet M, et al. Prenatal Exposure to Perfluoroalkyl Acids and Serum Testosterone Concentrations at 15 Years of Age in Female ALSPAC Study Participants. *Environ Health Perspect*. 2015 Dec;**123**(12):1325-30.
- ²⁷ **Jensen 2015**: Jensen TK, et al. Association between perfluorinated compound exposure and miscarriage in Danish pregnant women. *PLoS One*. 2015 Apr 7;**10**(4):e0123496. Erratum in PLoS One. 2016;11(2):e0149366.
- ²⁸ **Das 2015**: Das KP, et al. Developmental toxicity of perfluorononanoic acid in mice. *Reprod Toxicol*. 2015 Jan;**51**:133-44.
- ²⁹ **Louis 2015**: Louis GM, et al. Perfluorochemicals and human semen quality: the LIFE study. *Environ Health Perspect*. 2015 Jan;**123**(1):57-63.
- ³⁰ **Zhang 2016d**: Zhang W, et al. Zebrafish reproductive toxicity induced by chronic perfluorononanoate exposure. *Aquat Toxicol*. 2016 Jun;**175**:269-76.
- ³¹ **Louis 2016**: Louis GM, et al. Preconception perfluoroalkyl and polyfluoroalkyl substances and incident pregnancy loss, LIFE Study. *Reprod Toxicol*. 2016 Oct;**65**:11-17.
- ³² **Zhou 2016a**: Zhou Y, et al. Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status. *Environment International*. 2016 Sep; **94**:189-195.
- ³³ **Rokoff 2018**: Rokoff LB, et al. Cumulative exposure to environmental pollutants during early pregnancy and reduced fetal growth: the Project Viva cohort. *Environmental Health*. 2018 Feb 20; **17**(1): 19.
- ³⁴ **Lee 2018**: Lee YA, et al. The serum concentrations of perfluoroalkyl compounds were inversely associated with growth parameters in 2-year old children. *The Science of the Total Environment*. 2018 Jul 1; **628-629**: 226-232.
- ³⁵ **Sagiv 2018**: Sagiv SK, et al. Early-Pregnancy Plasma Concentrations of Perfluoroalkyl Substances and Birth Outcomes in Project Viva: Confounded by Pregnancy Hemodynamics? *American Journal of Epidemiology*. 2018 Apr 1; **187**(4): 793-802.
- ³⁶ **Gyllenhammar 2018**: Gyllenhammar I, et al. Perfluoroalkyl acid levels in first-time mothers in relation to offspring weight gain and growth. *Environmental International*. 2018 Feb; **111**: 191-199.
- ³⁷ **Zhang 2018**: Zhang H, et al. Prenatal and childhood perfluoroalkyl substances exposures and children's reading skills at ages 5 and 8 years. *Environmental International*. 2018 Feb; **111**: 224-231.
- ³⁸ **Yahia 2016**: Yahia D, et al. 8-Hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage induced by perfluorinated compounds in TK6 cells. *Environ Toxicol*. 2016 Feb;**31**(2):192-200.
- ³⁹ TEDX: Search for 375-95-1, Accessed online, 1/13/17, <http://www.endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/chemicalsearch?sname=&x=52&y=17&action=search&sall=1&searchfor=any&scas=375-95-1&searchcats=all>
- ⁴⁰ **Karlsen 2017**: Karlsen M, et al. Early-life exposures to persistent organic pollutants in relation to overweight in preschool children. *Reprod Toxicol*. 2017 Mar;**68**:145-153.
- ⁴¹ **Lee 2017**: Lee JW, et al. Multi-generational xenoestrogenic effects of Perfluoroalkyl acids (PFAAs) mixture on *Oryzias latipes* using a flow-through exposure system. *Chemosphere*. 2017 Feb;**169**:212-223.

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

- ⁴² **Halsne 2016:** Halsne R, et al. Effects of perfluorinated alkyl acids on cellular responses of MCF-10A mammary epithelial cells in monolayers and on acini formation in vitro. *Toxicol Lett.* 2016 Sep 30; **259**:95-107.
- ⁴³ **Kim 2016:** Kim DH, et al. Perfluoroalkyl substances in serum from South Korean infants with congenital hypothyroidism and healthy infants--Its relationship with thyroid hormones. *Environ Res.* 2016 May; **147**:399- 404.
- ⁴⁴ **Dufour 2018:** Dufour P, et al. Association between organohalogenated pollutants in cord blood and thyroid function in newborns and mothers from Belgian population. *Environmental Pollution* (Barking, Essex: 1987). 2018 Mar 23; **238**:389-396.
- ⁴⁵ **Preston 2018:** Preston EV, et al. Maternal Plasma per- and Polyfluoroalkyl Substance Concentrations in Early Pregnancy and Maternal and Neonatal Thyroid Function in a Prospective Birth Cohort: Project Viva (USA). *Environmental Health Perspectives.* 2018 Feb 27; **126** (2): 027013.
- ⁴⁶ **Ballesteros 2017:** Ballesteros V, et al. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. *Environmental International* **99** (2017) 15-28.
- ⁴⁷ **Seo 2018:** Seo SH, et al. Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. *Environment International.* 2018 Apr; **113**:149-161.
- ⁴⁸ **NTP TOX-97:** Perfluorohexanoic acid (307-24-4), Perfluorooctanoic acid (335-67-1), Perfluorononanoic acid (375-95-1), Perfluorodecanoic acid (335-76-2), WY-14643 (50892-23-4). Chemical Effects in Biological Systems (CEBS). Research Triangle Park, NC (USA): National Toxicology Program (NTP). Accessed 06-11-2018. <https://manticore.niehs.nih.gov/cebssearch/publication/TOX-97>.
- ⁴⁹ **Danish EPA 2015a:** page 82.
- ⁵⁰ **Lee and Kim 2018:** Lee JK and Kim SH. Correlation between mast cell-mediated allergic inflammation and length of perfluorinated compounds. *Journal of Toxicology and Environmental Health, Part A.* 2018; **81**(9) 302-313.
- ⁵¹ **Impinen 2018:** Impinen I, et al. Prenatal exposure to perfluoroalkyl substances (PFASs) associated with respiratory tract infections but not allergy- and asthma-related health outcomes in childhood. *Environmental Research* **160** (2018) 518-523.
- ⁵² **Chen 2018:** Chen Q, et al. Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study. *Environmental Health: A Global Access Science Source.* 2018 Jan 17; **17**(1): 8.
- ⁵³ **Fang 2008:** Fang X, et al. Immunotoxic effects of perfluorononanoic acid on BALB/c mice. *Toxicological Sciences*, 2008, **105**:312-321.
- ⁵⁴ **Rockwell 2013:** Rockwell CE, et al. Acute Immunotoxic Effects of Perfluorononanoic Acid (PFNA) in C57BL/6 Mice. *Clin Exp Pharmacol.* 2013; **Suppl 4**:S4-002.
- ⁵⁵ **Rockwell 2017:** Rockwell CE, et al. Persistent alterations in immune cell populations and function from a single dose of perfluorononanoic acid (PFNA) in C57B1/6 mice. *Food and Chemical Toxicology* **100** (2017) 24-33.
- ⁵⁶ **Mobacke 2018:** Mobacke I, et al. Circulation levels of perfluoroalkyl substances and left ventricular geometry of the heart in the elderly. *Environmental International* 2018 Apr 2; **115**:295-300.
- ⁵⁷ **Das 2017:** Das KP, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. *Toxicology.* 2017 Mar 1; **378**:37-52.
- ⁵⁸ **Das 2017:** Das KP, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. *Toxicology.* 2017 Mar 1; **378**:37-52.
- ⁵⁹ **Sheng 2016:** Sheng N, et al. Interaction of perfluoroalkyl acids with human liver fatty acid-binding protein. *Arch Toxicol.* 2016 Jan; **90**(1):217-27.
- ⁶⁰ **Watkins 2015:** Watkins AM, et al. The effects of perfluorinated chemicals on adipocyte differentiation in vitro. *Mol Cell Endocrinol.* 2015 Jan 15; **400**:90-101.
- ⁶¹ **Zhang 2018a:** Zhang Y, et al. Alteration of Bile Acid and Cholesterol Biosynthesis and Transport by Perfluorononanoic Acid (PFNA) in Mice. *Toxicological Sciences* **162**(1) 1 March 2018, 225-233.

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

- ⁶² **Khalil 2018:** Khalil N, et al. Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8-12 year old children: A pilot study. *Environmental Research* 2018 Jan; **160**: 314-321.
- ⁶³ **Rosenmai 2017:** Rosenmai AK, et al. Relationship between peroxisome proliferator-activated receptor alpha activity and cellular concentration of 14 perfluoroalkyl substances in HepG2 cells. *Journal of Applied Toxicology* 2018; **38**: 219-226.
- ⁶⁴ **Fang 2012:** Fang X, et al. Exposure of perfluorononanoic acid suppressed the hepatic insulin signal pathway and increases serum glucose in rats. *Toxicology*; **294**: 109-115.
- ⁶⁵ **Fang 2015:** Fang X, et al. Perfluorononanoic acid disturbed the metabolism of lipid in the liver of streptozotocin-induced diabetic rats. *Toxicol Mech Methods*. 2015;**25(8)**:622-7.
- ⁶⁶ **Su 2016:** Su, et al. Home produced eggs: An important pathway of human exposure to perfluorobutanoic acid (PFBA) and perfluorooctanoic acid (PFOA) around a fluorochemical industrial park in China. *Environment International* **101** (2017) 1-6.
- ⁶⁷ **Jensen 2018:** Jensen RC, et al. Perfluoroalkyl substances and glycemic status in pregnant Danish women: The Odense Child Cohort. *Environment International* **116** (2018) 101-107.
- ⁶⁸ **He 2018:** He X, et al. PFOA is associated with diabetes and metabolic alteration in US men: National Health and Nutrition Examination Survey 2003-2012. *The Science of the Total Environment*. 2018 Jun 1; **625**: 566-574.
- ⁶⁹ **Liu 2018:** Liu G, et al. Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: A prospective study. *PLoS Medicine* **15(2)**: e1002502.
- ⁷⁰ Sigma Aldrich SDS for – Revised 02/15/17, Accessed online, 12/20/17;
<https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=91977&brand=SI&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D375-95-1%26interface%3DCAS%2520No.%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DUS%26focus%3Dproduct>
- ⁷¹ HSDB: [SPARC; pKa/property server. Ver 3. Jan, 2006. Available from, as of July 9, 2012: <http://archemcalc.com/sparc/> **PEER REVIEWED**
- ⁷² **NJ 2015:** New Jersey Drinking Water Quality Institute Health Effects Subcommittee. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). Page 72. June 22, 2015. Accessed online: <http://www.nj.gov/dep/watersupply/pdf/pfna-health-effects.pdf>.
- ⁷³ **NJ 2015:** New Jersey Drinking Water Quality Institute – Health Effects Subcommittee. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). June 22, 2015. Page 74. Accessed online, 2/21/17: <http://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf>.
- ⁷⁴ **ECHA 2015:** European Chemicals Agency, (2015). Member State Committee Support Document for Identification of Perfluorononanoic Acid and Its Sodium and Ammonium Salts As Substances of Very High Concern Because of Their Toxic For Reproduction and PBT Properties. Available online at: <https://echa.europa.eu/documents/10162/48ae5fe3-9436-4a10-a533-ed642b92ce47>. Pages 7-8.
- ⁷⁵ **NJ 2015a:** New Jersey Drinking Water Quality Institute. Maximum Contaminant Level Recommendations for Perfluorononanoic Acid in Drinking Water: Basis and Background. Page 4. July 1, 2015. Accessed online: <http://www.nj.gov/dep/watersupply/pdf/pfna-recommend-final.pdf>.
- ⁷⁶ <http://sinlist.chemsec.org/chemical/375-95-1>.
- ⁷⁷ **ECHA 2015:** Page 13. ECHA references for decomposition with persulfate studies: Hori H, Nagaoka Y, Murayama M, Kutsuna S. (2008) Efficient Decomposition of Perfluorocarboxylic Acids and Alternative Fluorochemical Surfactants in Hot Water. *Environ. Sci. Technol.* **42**: 7438-7443. And Hori H, Yamamoto A, Hayakawa E, Taniyasu S, Yamashita N, Kutsuna S, Kiatagawa H, Arakawa R. (2005) Efficient decomposition of environmentally persistent perfluorocarboxylic acids by use of persulfate as a photochemical oxidant. *Environ. Sci. Technol.* **39**: 2383-2388.
- ⁷⁸ **ECHA 2015:** Page 46.
- ⁷⁹ **ECHA 2015:** Page 47.
- ⁸⁰ **ECHA 2015:** Page 8.

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

- ⁸¹ **ECHA 2015:** Page 8, 29, 47.
- ⁸² **Surma 2015:** Surma M, et al. Determination of perfluorinated sulfonate and perfluorinated acids in tissues of free-living European beaver (castor fiber L.) by d-SPE/ micro-UHPLC-MS/MS. *Ecotoxicol Environ Saf.* 2015 Oct;**120**:436-44.
- ⁸³ **Lynch 2018:** Lynch JM, et al. Feasibility of using the National Marine Mammal Tissue Bank for retrospective exploratory studies of perfluorinated alkyl acids. *Science of the Total Environment* **624** (2018) 781-789.
- ⁸⁴ **Bartolome 2017:** Bartolome M, et al. Perfluorinated alkyl substances in Spanish adults: Geographical distribution and determinants of exposure. *Sci Total Environ.* 2017 Jun 17;**603-604**:352-360.
- ⁸⁵ **Averina 2018:** Averina M, et al. Perfluoroalkyl substances in adolescents in northern Norway: Lifestyle and dietary predictors. The Tromso study, Fit Futures 1. *Environmental International* 2018 May; **114**:123-130.
- ⁸⁶ **Ye 2018:** Ye X, et al. Per- and polyfluoroalkyl substances in sera from children 3 to 11 years of age participating in the National Health and Nutrition Examination Survey 2013-2014. *International Journal of Hygiene and Environmental Health.* 2018 Jan; **221(1)**:9-16.
- ⁸⁷ **Lee 2018a:** Lee S, et al. Perfluoroalkyl substances (PFASs) in breast milk from Korea: Time-course trends, influencing factors, and infant exposure. *Science of the Total Environment.* 2018 Jan 15; **612**:286-292.
- ⁸⁸ **Yang 2018:** Yang Q, et al. Association of serum levels of perfluoroalkyl substances (PFASs) with the metabolic syndrome (MetS) in Chinese male adults: A cross-sectional study. *Science of the Total Environment* **621** (2018) 1542-1549.
- ⁸⁹ **Jain 2018:** Jain RB. Contribution of diet and other factors to the observed levels of selected perfluoroalkyl acids in serum among US children aged 3-11 years. *Environmental Research.* 2018 Feb; **161**:268-275.
- ⁹⁰ **Dalahmeh 2018:** Dalahmeh S, et al. Per- and polyfluoroalkyl substances (PFASs) in water, soil and plants in wetlands and agricultural areas in Kampala, Uganda. *Science of the Total Environment* **631-632** (2018) 660-667.
- ⁹¹ **ECHA 2015:** Page 8.
- ⁹² **ECHA 2015:** page 20, referencing Higgins CP, McLeod PB, MacManus-Spencer LA, Luthy RG. (2007) Bioaccumulation of perfluorochemicals in sediments by the aquatic oligochaete *Lumbriculus variegatus*. *Environ. Sci. Technol.* **41**: 4600-4606.
- ⁹³ **ECHA 2015:** Page 8.
- ⁹⁴ **ECHA 2015:** Page 8.
- ⁹⁵ **ECHA 2015:** Page 8. Referenced BMF and TMF studies include Martin 2004, Houde 2006, Butt 2008, Tomy 2009, Kelly 2009, Xu 2014.
- ⁹⁶ **Rainieri 2017:** Rainieri S, et al. Toxic effects of perfluorinated compounds at human cellular level and on a model vertebrate. *Food Chem Toxicol.* 2017 Jun;**104**:14-25.
- ⁹⁷ **Jantzen 2016:** Jantzen CE, et al. Behavioral, morphometric, and gene expression effects in adult zebrafish (*Danio rerio*) embryonically exposed to PFOA, PFOS, and PFNA. *Aquat Toxicol.* 2016 Nov;**180**:123-130.
- ⁹⁸ **Gorrochategui 2016:** Gorrochategui E, et al. Perfluoroalkylated Substance Effects in *Xenopus laevis* A6 Kidney Epithelial Cells Determined by ATR-FTIR Spectroscopy and Chemometric Analysis. *Chem Res Toxicol.* 2016 May 16;**29(5)**:924-32.
- ⁹⁹ **Jantzen 2016a:** Jantzen CE, et al. PFOS, PFNA, and PFOA sub-lethal exposure to embryonic zebrafish have different toxicity profiles in terms of morphometrics, behavior and gene expression. *Aquat Toxicol.* 2016 Jun;**175**:160-70.
- ¹⁰⁰ **Rainieri 2017:** Rainieri S, et al. Toxic effects of perfluorinated compounds at human cellular level and on a model vertebrate. *Food Chem Toxicol.* 2017 Jun;**104**:14-25.
- ¹⁰¹ **Liu 2015:** Liu H, et al. Toxic effects of perfluorononanoic acid on the development of Zebrafish (*Danio rerio*) embryos. *J Environ Sci (China).* 2015 Jun 1;**32**:26-34.

Updated EHS Summary of Perfluorononanoic acid for the MA TURA Science Advisory Board Meeting – June 21, 2018

¹⁰² **Jantzen 2016:** Jantzen CE, et al. Behavioral, morphometric, and gene expression effects in adult zebrafish (*Danio rerio*) embryonically exposed to PFOA, PFOS, and PFNA. *Aquat Toxicol.* 2016 Nov; **180**:123-130.

¹⁰³ **Liu & Gin 2018:** Liu C, et al. Immunotoxicity in Green Mussels Under Perfluoroalkyl Substance (PFAS) Exposure: Reversible Response and Response Model Development. *Environmental Toxicology and Chemistry* **37(4)**, 1138-1145, 2018.

¹⁰⁴ **Karnjanapiboonwong 2018:** Karnjanapiboonwong A, et al. Perfluoroalkylsulfonic and carboxylic acids in earthworms (*Eisenia fetida*): Accumulation and effects results from spiked soils at PFAS concentrations bracketing environmental relevance. *Chemosphere.* 2018 May; **199**: 168-173.

¹⁰⁵ **Nouhi 2018:** Nouhi S, et al. Interactions of perfluoroalkyl substances with a phospholipid bilayer studied by neutron reflectometry. *Journal of Colloid and Interface Science.* 2018 Feb 1; **511**:474-481.