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TECHNICAL SUPPORT DOCUMENT: INTERIM SPECIFIC GROUND WATER QUALITY CRITERION FOR CHLOROPERFLUOROPOLYETHER CARBOXYLATES

(CAS Numbers 220182-27-4, 220207-15-8, 330809-92-2, and 329238-24-6)

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NOTE: *Information that is not publicly available, including confidential business information (CBI) and other non-public information, is redacted throughout the document.*

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ABBREVIATIONS

ADONA — 4,8-dioxa-3H-perfluorononanoate; a replacement for PFOA

A/G — albumin/globulin

ALP — alkaline phosphatase

ALT — alanine aminotransferase

APFO — ammonium perfluorooctanoate, the ammonium salt of PFOA

ARG1 — arginase 1

AST — aspartate aminotransferase

AUC — area under the curve

BMD — Benchmark Dose

BMDL — lower 95% confidence limit on the Benchmark Dose

BMR — Benchmark Response

CAS # — Chemical Abstract Service Number

CBI — Confidential Business Information

CI – confidence interval

ClPFPECA — chloroperfluoropolyether carboxylate

Cl-PFESA — chlorinated perfluorinated alkyl ether sulfonates

6:2 Cl-PFESA — 6:2 chlorinated polyfluoroalkyl ether sulfonate; F53B major component

8:2 Cl-PFESA — 8:2 chlorinated polyfluoroalkyl ether sulfonate, F53B minor component

Cmax — maximum observed serum or plasma concentration

DWQI — New Jersey Drinking Water Quality Institute

EFSA — European Food Safety Authority

FOIA — Freedom of Information Act

FT3 — free triiodothyronine

FT4 — free thyroxine

GAC — granular activated carbon

GGT — gamma-glutamyl transferase

GOT1 — aspartate aminotransferase 1

GSTα — glutathione-S-transferase alpha

Hb — hemoglobin

Hct — hematocrit

HDL — high-density lipid cholesterol

HED — Human Equivalent Dose

HFPO-DA — hexafluoropropylene oxide-dimer acid; GenX

HFPO-TA — hexafluoropropylene oxide-trimer acid

HFPO-TeA — hexafluoropropylene oxide-tetramer acid

IgG — immunoglobulin G

IgM — immunoglobulin M

ISGWQC — Interim Specific Ground Water Quality Criterion

ISGWQS — Interim Specific Ground Water Quality Standard

IRIS — USEPA Integrated Risk Information System

LD50 — lethal dose to 50% of animals

LDL — low-density lipid cholesterol

LOAEL — Lowest Observed Adverse Effect Level

MCHC — mean corpuscular hemoglobin concentration

MCL — Maximum Contaminant Level

miRNA-122 — microRNA-122

NAFLD – non-alcoholic fatty liver disease

NaPFO — sodium perfluorooctanoate; sodium salt of PFOA

NHANES — National Health and Nutrition Examination Survey

NJDEP — New Jersey Department of Environmental Protection

NOAEL — No Observed Adverse Effect Level

NTP — National Toxicology Program

5’NT/CD73 — Ecto-5’-nucleotidase

PFAS — per- and polyfluoroalkyl substances

PFBA — perfluorobutanoic acid

PFBS — perfluorobutane sulfonate

PFHxA — perfluorohexanoic acid

PFHxA — perfluorohexane sulfonate

PFOA — perfluorooctanoic acid

PFOS — perfluorooctane sulfonate

PFO3OA — perfluoro-3,5,7-trioxaoctanoic acid

PFO4DA — perfluoro-3,5,7,9- tetraoxadecanoic acid

PFO5DoA — perfluoro-3,5,7,9,11- pentaoxadodecanoic acid

PFNA — perfluorononanoic acid

PFPECA — perfluoropolyether carboxylates

PSA – prostate serum antigen

PFUnDA — perfluoroundecanoic acid

POD — point of departure

POET — point of entry treatment

PPAR — peroxisome proliferator activated receptor

PQL – Practical Quantitation Level

PVDF – polyvinylidene fluoride

RBC — red blood cell

RfD — Reference Dose

RSC — Relative Source Contribution

SDS — Safety Data Sheet

SDH — sorbitol dehydrogenase

SLS — sodium lauryl sulfate

STOT — short term systemic toxicity

Tmax — time to Cmax

TRH — thyrotropin releasing hormone

TSH — thyroid stimulating hormone

UF — uncertainty factor

USEPA — United States Environmental Protection Agency

SUMMARY

An Interim Specific Ground Water Quality Criterion (ISGWQC) was developed for the chloroperfluoropolyether carboxylates (ClPFPECAs) used and discharged at the Solvay facility in West Deptford, NJ. ClPFPECAs occur as mixtures of congeners of different carbon and oxygen chain lengths. They are reported to be bioaccumulative in humans with a half-life of 2.5-3 years, similar to other bioaccumulative PFAS such as perfluorooctanoic acid (PFOA). ClPFPECAs are associated with numerous health endpoints in occupationally exposed workers, including increased serum lipids and liver enzymes, decreased immunoglobulins, changes in endocrine parameters, and others. The toxicological database for ClPFPECAs includes acute oral and dermal studies and repeated dose oral studies of up to 13 weeks duration in rats. No information on developmental, reproductive, immune system, or carcinogenic effects is available.

The oral rat LD50s reported for ClPFPECAs are lower than for PFOA, indicating that ClPFPECAs are more acutely toxic than PFOA in rats. Effects of ClPFPECAs in repeated dose studies included liver toxicity, decreases in red blood cell (RBC) parameters, and neurobehavioral effects, among others. Male rats were more sensitive to ClPFPECA toxicity than female rats, presumably because female rats rapidly excrete the 8-carbon congener that is the predominant congener in the ClPFPECA mixtures used in toxicity studies. Hepatic effects of ClPFPECAs were dependent on dose and exposure duration, suggesting that effects would occur at lower doses and/or would be more severe with chronic exposure. Comparison of data from studies of the same duration in the same rat strain reveals that ClPFPECAs are more potent in causing increased relative liver weight than PFOA and perfluorononanoic acid (PFNA).

Effects in male rats in the 13-week study were identified as the most sensitive toxicological endpoints. Increased relative liver weight, decreases in RBC parameters, and hepatocellular micro- and macrovesicular vacuolation likely due to steatosis were identified as endpoints that are sensitive, adverse or precursor to adverse, and relevant to humans, and these three endpoints were considered for Reference Dose (RfD) development. A lower confidence limit on the benchmark dose (BMDL) of 0.05 mg/kg/day, which is identical to the No Observed Adverse Effect Level (NOAEL) of 0.05 mg/kg/day for the endpoint, was developed for increased relative liver weight. Because the data for decreased RBC parameters and hepatocellular micro- and macrovesicular vacuolation did not support BMD modeling, the Lowest Observed Adverse Effect Level (LOAEL) of 0.05 mg/kg/day for these effects was used as the point of departure (POD). The PODs of 0.05 mg/kg/day for all three endpoints were converted to Human Equivalent Doses (HEDs) of 0.000833 mg/kg/day (833 ng/kg/day) with a toxicokinetic adjustment factor of 60 based on the ratios of ClPFPECA half-lives in humans (3 years) and rats (18.3 days). Uncertainty factors (UFs) appropriate for each endpoint were applied to this HED to derive RfDs for each of the three endpoints. These include UFs to protect sensitive human subpopulations, account for toxicodynamic differences between humans and experimental animals, extrapolate to a NOAEL when the POD is a LOAEL, protect for chronic exposure, and account for the incomplete toxicology database for the ClPFPECAs (e.g., no data on developmental, reproductive, or immune system toxicity).

The RfD of 0.28 ng/kg/day for increased relative liver weight, which incorporates a total UF of 3000, was selected as the basis for the ISGWQC. The RfDs for decreases in RBC parameters and hepatocellular macro- and microvesicular vacuolation were not supportable because the total UF exceeded the maximum recommended UF of 3000. Default assumptions for adult drinking water consumption and the default Relative Source Contribution (RSC) factor of 20% were applied to derive an ISGWQC of 1.9 ng/L. The NJDEP Ground Water Quality Standards regulations specify that ISGWQC "shall be rounded to one significant digit". As such, the ISGWQC is rounded to 2 ng/L (0.002 ug/L).

INTRODUCTION

Establishment of Interim Specific Ground Water Quality Criterion (ISGWQC) and Interim Specific Ground Water Quality Standard (ISGWQS) for ClPFPECAs

The New Jersey Ground Water Quality Standards (GWQS) regulations at N.J.A.C. 7:9C-1.7(c)(2) allow for the New Jersey Department of Environmental Protection (NJDEP) to establish an Interim Specific Ground Water Quality Criterion (ISGWQC) for a constituent not listed in the GWQS at N.J.A.C. 7:9C by providing notice and access to the supplemental information used in its derivation. An ISGWQC is a health-based criterion intended to be protective for chronic (lifetime) exposure through drinking water. NJDEP incorporated the ISGWQC into the GWQS to allow NJDEP and other parties to respond to environmental threats in a timely manner. The GWQS regulations state that, after establishing an ISGWQC, NJDEP shall replace it with a specific criterion as soon as reasonably possible by rule.

NJDEP has determined that it is appropriate to establish an ISGWQC and an Interim Specific Ground Water Quality Standard (ISGWQS) for chloroperfluoropolyether carboxylates (ClPFPECAs)[1]. ClPFPECAs are per- and polyfluoroalkyl substances (PFAS) that have been used as processing aids and discharged to the environment by the Solvay Specialty Polymers U.S.A.[2] (Solvay) facility in West Deptford, NJ. Development of an ISGWQC for the ClPFPECAs used by Solvay in West Deptford was requested of the NJDEP Division of Science and Research by the NJDEP Site Remediation Program under N.J.A.C 7:9C. An ISGWQC is intended to be protective for lifetime cancer risk at the one in one million (10^{-6}) risk level and for any adverse non-cancer effects resulting from chronic (lifetime) exposure. The human health risk assessment approaches used to develop the ISGWQC for the ClPFPECAs generally follow USEPA risk assessment guidance and are consistent with the approaches used by NJDEP to develop previous ISGWQC for other contaminants including PFAS.

As discussed in detail below, the available health effects data for ClPFPECAs indicate that they cause toxicity at low doses in laboratory animals, and that they are associated with numerous

[1] Throughout this document, unless otherwise stated, "ClPFPECAs" refers to the ClPFPECAs discussed in *Nomenclature and Physical/ Chemical Properties* below.
[2] Referred to as "Solvay" throughout this document.

health effects and are highly bioaccumulative in humans. ClPFPECAs have been detected in ground water, including private wells, in the vicinity of the West Deptford at estimated concentrations of up to several hundred parts per trillion (ng/L; McCord et al., 2020). Additional private wells, as well as public water systems, in this vicinity have not yet been tested for ClPFPECAs and are potentially impacted. NJDEP has determined that, based on this information, an ISGWQS for ClPFPECAs is needed in order to protect public health and the environment.

NJDEP establishes an ISGWQS upon posting it to the "Table of Interim Specific Ground Water Quality Criteria (ISGWQC), Interim Practical Quantitation Levels (PQLs), and Interim Specific Ground Water Quality Standards (ISGWQS) for Constituents in Class II-A Ground Water" on the NJDEP Ground Water Quality Standards website. A PQL is the lowest concentration of a constituent that can be reliably achieved among laboratories within specified limits of precision and accuracy (i.e., the lowest level that can be quantified) during routine laboratory operating conditions. In general, interim PQLs are developed for contaminants with ISGWQCs, and the higher of the ISGWQC and the interim PQL serves as the ISGWQS. This ensures that the ISGWQS is set at a level at which the contaminant can be reliably measured.

As allowed in appropriate circumstances under the GWQS regulations at N.J.A.C. 7:9C-1.9(c), NJDEP is proceeding with the establishment of an ISGWQS for ClPFPECAs even though a PQL for ClPFPECAs has not been developed at this time. This document provides the basis for the ISGWQC (i.e., the health-based criterion) for ClPFPECAs.

Sources of information on ClPFPECAs[3]

[redacted]

In 2019, NJDEP (2019) issued a Directive that required Solvay and other companies that use PFAS to provide information on "replacement"[4] PFAS used in New Jersey including their "toxic characteristics." As discussed in *Nomenclature and Chemical/Physical Properties* below,

[3] Publicly available versions of the Safety Data Sheets and toxicology studies mentioned here are posted at https://www.nj.gov/dep/dsr/pfas-alternative.htm

[4] These compounds were not technically "replacements" because Solvay started using them before phasing out use of Surflon. This is discussed on Page 7-8 below.

Solvay provided Safety Data Sheets (SDSs) for ClPFPECA products with three different Chemical Abstract Service Numbers (CAS #s) in response to the Directive.

The SDSs state that the ClPFPECAs are classified as Category 1 for specific target organ systemic toxicity (STOT) from repeated dose exposure. This category includes "substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated or prolonged exposure."[5] (SCHC-OSHA Alliance, 2017). The Toxicological Information sections of the SDSs state that the liver is a target organ for repeated dose ingestion toxicity of the ClPFPECAs, and that the No Observed Effect Level (NOEL) for liver toxicity in oral 28-day rat studies is <0.3 mg/kg/day.

After learning from the SDSs that repeated dose toxicity data are available, NJDEP requested that Solvay provide all available toxicology studies on the ClPFPECAs and other PFAS replacements used at the West Deptford facility. In response to NJDEP's request, Solvay provided the studies listed in Appendix 1, all of which are unpublished contract laboratory study reports. These studies were initially provided as CBI, but they were later made publicly available by Solvay with the trade names of the substances that were tested redacted. The studies that were provided include the toxicology studies reviewed below including studies of acute oral and dermal toxicity, half-life, and repeated dose [7-day, 4-week, and 13-week] toxicity in rats; dermal irritation in rabbits; skin sensitization in guinea pigs; and mutagenicity in bacteria. Ecological toxicity studies in zebrafish, *Daphnia magna*, and *Scenedesmus subspicatus* were also submitted but were not reviewed herein.

Additional information on the ClPFPECAs used by Solvay is extremely limited. No peer-reviewed publications related to human or animal toxicokinetics or toxicity were found in a PubMed search of chemical names and CAS #s for the ClPFPECAs. A peer-reviewed publication (EFSA, 2010) states that bacterial and mammalian genotoxicity studies of ClPFPECAs submitted to the European Food Safety Authority (EFSA) by Solvay Solexis Italy were negative. The studies mentioned in EFSA (2010) include the mouse lymphoma forward mutation and Chinese hamster ovary chromosomal aberration assays, which were not provided to NJDEP by Solvay. Additionally, a document (Solvay, 2019a) that provides information on blood serum ClPFPECA levels, human half-life of ClPFPECA, and associations of ClPFPECAs with health endpoints in workers with occupational exposure to ClPFPECAs was submitted by Solvay to USEPA. This document was posted by USEPA (2020a) in response to a Freedom of Information Act (FOIA) request for information on the health effects of these substances.

A few publications that mention ClPFPECAs and/or provide information on them regarding topics other than health effects are available. Wang et al. (2013) present the chemical structure of

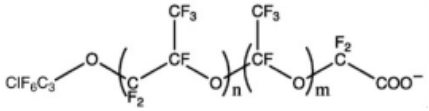
[5] "Substances are classified as in Category 1 for specific target organ toxicity (repeated exposure) on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or, (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations." (SCHC-OSHA Alliance, 2017)

ClPFPECAs and the CAS # for the free anion (329238-24-6), labeled as "Solvay's product," and Gomis et al. (2015) modeled the physical/chemical properties and environmental fate of two ClPFPECAs with this CAS #, as well as other PFAS replacements. Two recent publications, McCord et al. (2020) and Washington et al. (2020), report on the environmental occurrence of ClPFPECAs and other PFAS near the Solvay facility in West Deptford, NJ.

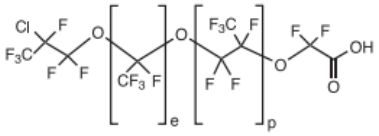
Nomenclature and Chemical/Physical Properties

ClPFPECAs used at the Solvay facility in West Deptford, NJ, are formulated as mixtures of ClPFPECA congeners (also called oligomers) that differ in the number of ethyl and propyl groups that they contain. The general structure of the ClPFPECA congeners, as presented by Wang et al. (2013), Washington et al. (2020), and [redacted] is shown in the box below. In the structures below, the ethyl and propyl groups are designated as "m and n" by Wang et al. (2013), "e and p" by Washington et al. (2020), and [redacted]

- Wang et al. (2013):



- Washington et al. (2020):



[redacted]

As noted by Washington et al. (2020), isomers of ClPFPECAs can have an "alternative terminal structure of the $ClCF_2CF(CF_3)O^-$ group" and/or the relative positions of the ethyl and propyl groups can be reversed.

The CAS #s for the ClPFPECAs used by Solvay refer to mixtures of congeners of different chain lengths of the same chemical form (e.g., free anion, sodium salt, ammonium salt), and there are no CAS #s for the individual congeners. According to information provided by Solvay, ClPFPECA products with three different CAS #s were used as processing aids in the production of fluoropolymers at the Solvay facility in West Deptford, NJ. Additionally, Wang et al. (2013) and EFSA (2010) provide a CAS # for the free anion form of the ClPFPECAs. The different forms (e.g., salts) of the ClPFPECAs designated by different CAS #s all convert to the same free anion form in the environment and in the body.

The CAS #s for the different forms of the ClPFPECAs are:

- 220182-27-4 - Ethyl ester, hydrolyzed (liquid*; Solvay SDS)
- 220207-15-8 - Ethyl ester, hydrolyzed, sodium salt (solid**; Solvay SDS)
- 330809-92-2 - Hydrolyzed, ammonium salts (solid**; SDS)
- 329238-24-6 - Free anion (CAS # published by EFSA, 2010; Wang et al., 2013)

*Based on Safety Data Sheet (SDS) and information from toxicity studies (below).
**Based on information from toxicity studies (below); SDSs are for solutions of the solid.

Solvay provided SDSs for products with the first three CAS #s listed above.

- In the SDS for CAS # 220182-27-4 (Solvay, 2016a), the chemical name is given as: "1-propene, 1,1,2,3,3,3-hexafluoro-, telomer with chlorotrifluoroethene, oxidized, reduced, Et ester, hydrolyzed." This substance is stated to be a liquid of ≥ 99.9% purity, pH 2.0 as aqueous solutions, practically insoluble in water, with boiling point range of 180-250° C, decomposition temperature of >250° C, and density of 1.6-1.8 g/cm^3. It is stated that no data are available for other physical and chemical properties.

- Two SDSs are provided for CAS #220207-15-8. They are for ≥20 - <25% (Solvay, 2016b) and ≥50 - <60% (Solvay, 2019b) solutions of this substance. The chemical name is given as: "1-propene, 1,1,2,3,3,3-hexafluoro-, telomer with chlorotrifluoroethene, oxidized, reduced, Et ester, hydrolyzed, sodium salt." The pH of these solutions is stated to be pH 8.0-13.0, and they are stated to be completely miscible in water with decomposition temperature >250° C. It is stated that no data are available for other physical and chemical properties.

- Two SDSs are also provided for CAS #330809-92-2. They are for ≥10 - <25% (Solvay, 2019c) and ≥30 - <40% (Solvay, 2019d) solutions of this substance. The chemical name is given as: "1-propene, 1,1,2,3,3,3-hexafluoro-, telomer with chlorotrifluoroethene, oxidized, reduced, hydrolyzed, ammonium salts." The pH of these solutions is stated to be pH 7.0-10.0, and they are stated to be soluble in water with decomposition temperature >250° C. The density of the ≥10 - <25% solutions is stated to be 1.04 g/cm^3. It is stated that no data are available for other physical and chemical properties.

Nomenclature used by Solvay, Wang et al. (2013), and Washington et al. (2020) for the ClPFPECA congeners is shown in Table 1 below. [redacted] These congeners, and low levels of other congeners with 7 carbon and 4 oxygen atoms, 11 carbon and 6 oxygen atoms, and 12 carbon and 6 oxygen atoms that are not shown in the table below, were detected in environmental media in the vicinity of Solvay's West Deptford, NJ, facility by Washington et al. (2020).

Table 1: Nomenclature for ClPFPECA congeners

Solvay nomenclature	*Wang et al. (2013) Nomenclature*	*Washington et al. (2020) Nomenclature (e,p)*	*Molecular Formula (Anion Form)*	*Molecular Mass*
N2	n=1, m=0	0,1	$C_8ClF_{14}O_4$	461.9340
M3	n=1, m=1	1,1	$C_{10}ClF_{18}O_5$	577.9225
N3	n=2, m=0	0,2	$C_{11}ClF_{20}O_5$	627.9193
M4	n=2, m=1	1,2	$C_{13}ClF_{24}O_6$	742.9000
N4	n=3, m=0	0,3	$C_{14}ClF_{26}O_6$	793.9046
N5	n=4, m=0	0,4	$C_{17}ClF_{32}O_7$	907.9364

[redacted]

[redacted]

Table 2. [redacted]

[redacted]

[redacted]

Table 3: [redacted]

[redacted]

Finally, Gomis et al. (2015) used modeling approaches to estimate the octanol:water and air:water partition coefficients (K_{OW} and K_{AW}) of two ClPFPECAs (the 0,2 and 1,1 congeners, using the Washington et al., 2020 nomenclature), as well as PFOA, PFOS, and several other replacement PFAS. The predicted log K_{OW} and log K_{AW} values for the ClPFPECAs were similar but slightly greater than the predicted values for PFOS.

Production and Use

No information on the annual amounts of the ClPFPECAs produced or used worldwide was identified.

EFSA (2010) indicates that Solvay's ClPFPECA products are used as processing aids in the production of fluoropolymers used in food processing equipment, food contact articles, and anti-stick coatings on cooking utensils.

According to information provided to NJDEP by Solvay, ClPFPECAs are manufactured outside of the U.S. and used at the Solvay facility in West Deptford, NJ, as processing aids in the manufacture of fluoropolymers including polyvinylidene fluoride (PVDF).

Although Solvay has described the ClPFPECAs as "replacements" for the long-chain PFCAs (e.g., PFNA, PFOA, perfluoroundecanoic acid [PFUnDA, C11]) that were phased out through a voluntary agreement with USEPA (undated), information provided to NJDEP by Solvay shows that ClPFPECAs were used in West Deptford prior to the beginning of the voluntary phaseout of long-chain PFCAs in 2010, and well before the voluntary phaseout agreement was first publicized in 2006.

[redacted]

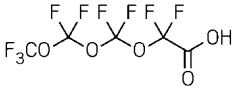
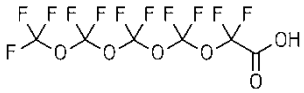
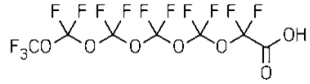
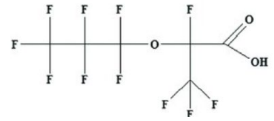
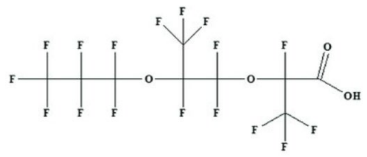
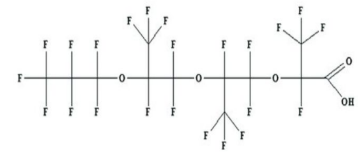
Tables provided by Solvay of annual use and discharge to air and water (kg/year) for ClPFPECA substances with each of the three CAS #s, as well as for another type of PFAS replacement, the perfluoropolyether dicarboxylic acids with CAS # 69991-62-4, are found in Appendix 2. In summary, the tables show annual usage (in kg/year) from 1996 to 2018 of ClPFPECAs with each of the three CAS #s mentioned above at the Solvay facility in West Deptford, NJ (Exhibit G of Solvay 4/17/19 letter to NJDEP). Specifically, use of ClPFPECAs (e.g., <50 kg/year for CAS # 220207-15-8) began in 1996. For ClPFPECAs with CAS # 220207-15-8, annual use from 2003-2009, before the voluntary phaseout began in 2010, was 1681-4507 kg/year, similar to annual use from 2010-2018 (1421-4679 kg/year). Use of ClPFPECAs with CAS # 220182-27-4 from 2005-2009, prior to the beginning of the voluntary phaseout, was 193-1064 kg/year, while only

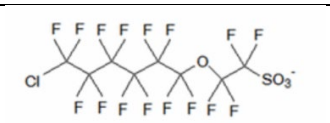
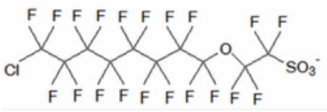
11 kg was used in 2010 and none was used in subsequent years. In contrast, ClPFPECAs with CAS # 330809-92-2 were used during a few years prior to the voluntary phaseout, while 7703-12,549 kg/year were used from 2010-2018. [redacted]

Other perfluoroether alkyl acids

Chemical structures and chemical formulas for other perfluoroether alkyl acids, including perfluoropolyether carboxylates (PFPECAs) and chlorinated perfluorinated alkyl ether sulfonates (ClPFESAs), are shown in Table 4. Because of their structural similarities to ClPFPECAs, information relevant to health effects of these PFAS is informative in the evaluation of human health risks of ClPFPECAs. Information related to these PFAS is summarized in the relevant sections (e.g., *Biomonitoring, Toxicokinetics, Human Epidemiology, Animal Toxicology, Mode of Action*) below.

Table 4. Perfluoroether alkyl acids that are structurally related to ClPFPECAs

PFAS	***Structure***	***Formula (anion form)***	***Comments***
Perfluoropolyether carboxylates (PFPECAs)			
PFO3OA		$C_5HF_9O_5$	Structurally similar to ClPFPECAs but not chlorinated.
			Byproducts of industrial processes; discharged into Cape Fear (NC) River used as drinking water source (Kotlarz et al., 2020).
PFO5DoDA		$C_7HF_{13}O_7$	
Hexafluoropropylene oxide-dimer acid (HFPO-DA; GenX)		$C_6F_{11}O_3$	Structurally similar to ClPFPECAs but not chlorinated. Replacements for PFOA.
Hexafluoropropylene oxide-trimer acid (HFPO-TA)		$C_9F_{17}O_4$	
Hexafluoropropylene oxide-tetramer acid (HPFO-TeA)		$C_{12}F_{23}O_5$	

6:2 Cl-PFESA (F-53B, major component)		$C_8F_{16}ClSO_4$	Structures are similar to ClPFPECAs, except that they are sulfonates rather than carboxylates and monoethers rather than polyethers. PFOS replacements widely used in China (Munoz et al., 2019).
8:2 Cl-PFESA (F-53B, minor component)		$C_{10}F_{20}ClSO_4$	

GUIDANCE AND STANDARDS DEVELOPED BY USEPA AND OTHER STATES

Guidance values or standards for ClPFPECAs have not been developed by USEPA or other states. To the Department's knowledge, this document is the first review of information relevant to human health risks of ClPFPECAs in the environment. Furthermore, NJDEP is not aware of information on use of ClPFPECAs in the United States other than in New Jersey.

ENVIRONMENTAL SOURCES, FATE, AND OCCURRENCE

Information on the environmental occurrence of ClPFPECAs outside of New Jersey is very limited. ClPFPECAs with the chemical structure provided by Wang et al. (2013) were detected in a river downstream of a fluoropolymer production plant in Italy (Mazzoni et al., 2015).

The tables of annual ClPFPECA usage at the Solvay facility in West Deptford, NJ (Appendix 2), mentioned above also provide the estimated amounts (kg/year) of ClPFPECAs that were discharged to air and water annually from 1996-2018 for each of the three CAS #s provided by Solvay. [redacted] The substance with CAS # 330809-92-2 was estimated to have been discharged to air and water in the highest amounts (up to 2318 kg/year to air and 8377 kg/year to water).

The following information about wastewater at the Solvay facility was provided by the NJDEP Site Remediation Program: Solvay uses contaminated source water (groundwater from its site) for both organic and inorganic processes at its facility. Solvay discharges industrial wastewater from its organic processes to the local wastewater treatment facility (Gloucester County Utilities Authority [GCUA]), and, through GCUA, Solvay indirectly discharged untreated wastewater containing ClPFPECAs to the Delaware River from 1996-2017. Since GCUA does not use treatment such as granular activated carbon (GAC) that can be used to reduce or remove perfluoroalkyl acids (e.g., PFOA, PFOS, PFNA) and would also likely reduce or remove

ClPFPECAs, it is assumed that the ClPFPECAs present in Solvay's wastewater that was sent to GCUA are/were discharged to the Delaware River in the GCUA effluent. Since 2017, the ClPFPECA levels in the wastewater from Solvay's organic processes have likely been reduced and potentially eliminated, since Solvay has informed NJDEP that treatment (dual ion exchange resin and dual GAC filters) had been installed to treat wastewater discharged to GCUA from the fluoropolymer process. The groundwater used in the inorganic processes is highly likely to be contaminated with ClPFPECAs and is minimally treated. As such, it is likely that ClPFPECAs are present in the inorganic process wastewater that is directly discharged to the Delaware River and in the biosolids generated during treatment of the inorganic wastewater. The biosolids from the inorganic processes are disposed of in local non-hazardous landfills.

A collaborative research project between NJDEP and the USEPA Office of Research and Development has evaluated the occurrence of PFAS in environmental media in Southwestern New Jersey. As part of this project, ten ClPFPECA congeners were identified using non-target analysis in soil samples in the vicinity of the Solvay facility in West Deptford, NJ, with the geographic distribution of ClPFPECA congeners of various chain lengths suggesting air emissions from the Solvay facility as the likely source (Washington et al., 2020). ClPFPECAs were also detected in surface water and ground water, including private wells, in this area. In these studies, concentrations of ClPFPECA congeners were estimated because analytical standards were not available. The 8-carbon congener designated as 0,1 by Washington et al. (2020) was the predominant congener in surface water, and it was the only congener detected in ground water (McCord et al., 2020). Estimated ClPFPECA concentrations of up to several hundred nanograms per liter (based on abundance ratio with labeled PFNA) were found in private wells. Other components of the NJDEP/USEPA study evaluated the occurrence of PFAS including ClPFPECAs in vegetation and sediment, and reports and publications on these components are forthcoming.

The effectiveness of point of entry treatment (POET) units for removal of ClPFPECAs was evaluated in six private wells that had POETs (granular activated carbon [GAC] or ion exchange) due to PFNA contamination (McCord et al., 2020). ClPFPECA concentrations were reduced by 99% by the POETS (both GAC and ion exchange) in these wells.

An additional ongoing research project is evaluating levels of PFAS, including ClPFPECAs, in recreationally caught fish from waterbodies near Solvay. Preliminary data from this study indicate that ClPFPECAs are present in these fish and that the congener distribution in fish differs from the distribution in surface water with the congeners that predominate in fish being longer chain than those that predominate in surface water. Additionally, semi-quantitative analysis of surface water and fish liver from the same location indicated that ClPFPECAs were an order of magnitude more bioaccumulative than PFOS in white perch liver. Additional data from this study are expected to become available in the near future (Robuck et al., 2021; A. Robuck, Icahn School of Medicine at Mount Sinai, personal communication).

SOURCES OF HUMAN EXPOSURE

Numerous potential sources of human exposure to ClPFPECAs have not yet been fully characterized. As mentioned above, ClPFPECAs were detected in private wells in the vicinity of Solvay's West Deptford facility, and levels in some of these wells are estimated to be several hundred ng/L (McCord et al., 2020). Public water supply wells and additional private wells in this area have not been tested for ClPFPECAs. Therefore, drinking water is a likely source of human exposure that requires further investigation.

As discussed above, ClPFPECAs have also been detected in recreationally caught fish from waterbodies near Solvay. Consumption of these fish and other wildlife species from this vicinity is another potential source of human exposure that requires further investigation.

ClPFPECAs have been detected in soil, vegetation, and sediment in the Solvay vicinity (unpublished data from NJDEP/EPA study). They have also been discharged to air by Solvay and to the Delaware River directly by Solvay and indirectly by GCUA. Finally, biosolids from the Solvay facility containing ClPFPECAs could have potentially been applied to agricultural land, where uptake into crops could occur, and/or used as cover at landfills, where transfer to leachate could occur. Direct and/or indirect potential human exposure is possible from all of these media.

As discussed in the *Human Biomonitoring* section below, occupational exposure at two ClPFPECA manufacturing facilities outside of the United States resulted in blood serum ClPFPECA levels as high as >14 µg/ml (ppm) (Solvay, 2019a). ClPFPECAs persisted in the workers' blood with an estimated half-life of 2.5-3 years.

The ClPFPECAs used by Solvay were approved by EFSA (2010) for use in the production of fluoropolymers used in food contact materials. Migration to food of the residual ClPFPECAs in the food contact materials is a potential route of human exposure, although exposure through this pathway is expected to be minimal (EFSA, 2010).

HUMAN BIOMONITORING

ClPFPECAs

The only human biomonitoring data that have been identified are from occupationally exposed workers in two facilities outside of the U.S. where ClPFPECAs are manufactured (Solvay, 2019a). The workers were exposed to the sodium and ammonium salts of ClPFPECAs (USEPA, 2020b). At the first facility, ClPFPECA levels were measured in blood serum from 65 to 443 workers each year between 2011 and 2019. Data for each year is reported separately. Median serum levels ranged from 136 to 448 ng/ml (ppb), mean serum levels were between 343 and 1169 ng/ml, and the maximum serum level reported was 14,386 ng/ml. At the second facility, serum levels were measured in 46 to 134 workers each year between 2013 and 2019. Median

serum levels ranged from 20 to 110 ng/ml, mean serum levels were between 72 and 259 ng/ml, and the maximum serum level reported was 2,213 ng/ml. As discussed in *Toxicokinetics* below, the half-life of ClPFPECAs in these workers was reported as 2.5-3 years.

Other perfluoroether alkyl acids

Biomonitoring data for perfluoropolyether carboxylates (PFPECAs) and chloroperfluoroether sulfonates (PFPESAs) demonstrate that these perfluoroether alkyl acids are bioaccumulative in humans.

Kotlarz et al. (2020) evaluated blood serum levels of newly identified PFAS in more than 300 residents of Wilmington, NC whose surface water source of drinking water had been contaminated by discharge from an industrial facility approximately 80 miles upstream. Several PFPECAs that are structurally similar to ClPFPECAs except that they are not chlorinated were detected in residents' blood serum approximately five months after exposure through drinking water ended. Specifically, PFO4DA (perfluoro-3,5,7,9- tetraoxadecanoic acid, $C_6HF_{11}O_6$), PFO5DoA (perfluoro-3,5,7,9,11-- pentaoxadodecanoic acid, $C_7HF_{13}O_7$), and PFO3OA (perfluoro-3,5,7-trioxaoctanoic acid, $C_5HF_9O_5$) were detected at >0.1 ng/ml in 99%, 88%, and 28% of serum samples, with median levels of 2.5, 0.3, and 2.7 ng/ml (ppb), respectively. To NJDEP's knowledge, this study provided the first evidence that long-chain perfluoropolyether carboxylates are bioaccumulative in humans. In contrast, hexafluoropropylene oxide-dimer acid (HFPO-DA, GenX), a short-chain perfluoroether carboxylate with 6 carbons and one ether oxygen, was not detected in the blood serum of any study participants, although it was present at considerable levels in their drinking water.

As discussed in *Toxicokinetics* (below), preliminary data from Kotlarz et al. (2020) indicate that the human half-lives of the two longer-chain PFPECAs that were detected in almost all serum samples, PFO4DA and PFO5DoA, are <6 months and approximately 1 year, respectively. In contrast, as mentioned above, the human half-life of the Cl-PFPECAs was reported as 2.5 to 3 years.

6:2 Cl-PFESA (6:2 chlorinated polyfluoroalkyl ether sulfonate, $C_8F_{16}ClSO_4$) and 8:2 Cl-PFESA (8:2 chlorinated polyfluoroalkyl ether sulfonate, $C_{10}F_{20}ClSO_4$) are PFAS that are components of F53B, a PFOS replacement used primarily in China. They are structurally similar to ClPFPECAs in that they are chlorinated ether acids, but they are sulfonates rather than carboxylates and are monoethers rather than polyethers. 6:2 Cl-PFESA is consistently detected in human blood serum in residents of China (Duan et al., 2020; Jin et al., 2020a; Liu et al., 2020; Pan et al., 2017; Yao et al., 2020, Xie et al., 2021, Liu et al., 2021), and 8:2 Cl-PFESA is also detected, although less frequently (Duan et al., 2020; Xie et al., 2021, Liu et al., 2021).

The U.S. Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES) biomonitoring for PFAS in blood serum of U.S residents included 6:2 Cl-PFESA for the first time in 2017-18 (CDC, 2021). It was found at the detection limit (0.100 ng/ml) in the 95th percentile of the total population, and at the same or similar levels in most racial/ethnic

groups (Mexican Americans and all Hispanics – 0.100 at 95th percentile; non-Hispanic blacks - 0.100 ng/ml at 90th and 95th percentiles; non-Hispanic whites- not detected at 95th percentile; [values are geometric means]). The maximum level detected in any of these subgroups was 0.200 ng/ml. However, it was detected more frequently and at higher levels in Asians (0.200 ng/ml at 75th percentile; 1.00 ng/ml at 90th percentile; 2.30 ng/ml at 95^{th} percentile; maximum – 10.9 ng/ml). The source of the more frequent detections and higher serum levels in Asians is unknown. These detections could potentially result from exposure to 6:2 Cl-PFPFESA while in Asia or from other sources such as consumption of foods contaminated with 6:2 Cl-PFESA that are imported from Asia.

Human developmental exposures to PFESAs occur both *in utero* and through breast milk. 6:2 and 8:2 ClPFESA were detected in matched maternal:umbilical cord blood samples, with a higher rate of transfer to cord blood for 8:2 Cl-PFESA (Cai et al., 2020; Chen et al., 2017; Pan et al., 2017; Xu et al., 2019). 6:2 Cl-PFESA and 8:2 Cl-PFESA were also found in 100% and 24%, respectively, of 54 placenta samples from Hunan, China (Lu et al., 2021). Additionally, both PFESAs were detected in breast milk from several locations in China, but not in breast milk from Sweden (Awad et al., 2020; Jin et al., 2020b).

TOXICOKINETICS

An important point relevant to the toxicokinetics of the ClPFPECAs used by Solvay in New Jersey is that they differ from replacement PFAS introduced by other companies (e.g., HPFPO-DA [GenX] and perfluorobutane sulfonate [PFBS]) in regard to their much longer half-lives. These other replacements are short-chain PFAS with 4 to 6 carbons, and they have shorter half-lives and are less bioaccumulative in humans and laboratory animals than the phased-out long-chain perfluoroalkyl acids (e.g., PFOA, PFOS) that they replace. In contrast, the ClPFPECAs, which have 8 or more carbons and several ether oxygens, are not-short chain, and their human half-life has been reported as several years, similar to the half-lives of the phased out long-chain perfluoroalkyl acids.

Human

ClPFPECAs

Biomonitoring was conducted on workers with occupational exposure to ClPFPECAs at two facilities located outside of the United States from 2011-2019. At the first facility, ClPFPECAs were measured in serum from 65 to 443 workers each year, and at the second facility, there are serum data for 46 to 134 workers each year. Based on data from 424 workers whose serum ClPFPECA levels were measured in both 2018 and 2019, the human half-life of ClPFPECAs was reported as 2.5 to 3 years (Solvay, 2019a).

The half-life of ClPFPECAs of 2.5-3 years in occupationally exposed workers is similar to the half-life of PFOA of approximately 2.3 years (Bartell et al., 2010). Since PFOA accumulates from drinking water to blood serum in a ratio of >100:1 in individuals with average daily

drinking water ingestion (reviewed in DWQI, 2017), ClPFPECAs are also expected to bioaccumulate to blood serum from drinking water at a generally similar ratio.

It is well established that other long-chain PFAS with long human half-lives are transferred from the mother to the fetus. Additionally, exposures to infants from drinking water contaminated with long-chain PFAS from prepared formula and, even more so, through maternal transfer to breast milk, are much higher than in older individuals (Post et al., 2017; Goeden et al., 2019). Furthermore, as discussed in *Human Biomonitoring* above, ClPFESAs, which are structurally related to ClPFPECAs, have been found in human cord blood, placenta, and breast milk. Therefore, while there are no data on maternal transfer of ClPFPECAs to the fetus or through breast milk, such exposures to infants through these pathways are highly likely.

Other perfluoroether alkyl acids

In the study of Wilmington, NC residents previously exposed to newly identified PFAS through drinking water discussed in the *Biomonitoring* section (above), Kotlarz et al. (2020) measured the decline in serum PFAS levels over a 6-month period in a subset (n=44) of study participants. Serum levels of PFO4DA and PFO5DoA declined by 65% and 28% respectively in samples taken 6 months apart. These data suggest preliminary half-life estimates of less than 6 months for PFO4DA and approximately 1 year for PFO5DoA, much shorter than the reported ClPFPECA half-life of 2.5-3 years.

Available data suggest that ClPFESAs are very slowly excreted in humans, as indicated by the estimated mean and median human half-lives for 6:2 ClPFESA of 15.3 and 18.5 years, respectively (Shi et al., 2016). It is noted that these estimated half-lives are more than twice the median and mean half-lives for PFOS of 6.7 and 7.7 years that were estimated in the same study.

Laboratory animals

ClPFPECAs

Only one toxicokinetic study of ClPFPECAs in laboratory animals was identified. This study was intended to determine the half-life of ClPFPECAs in rats after oral exposure (RTC, 2006). It was conducted as a satellite component of the 4-week rat toxicology study reported in RTC (2006), and it used the same test substance as the 4-week toxicology study. As also stated in the summary of the 4- week study (RTC, 2006) below, the test material was CAS # 33089-92-2, the ClPFPECA ammonium salt. [redacted]

The individual ClPFPECA congeners in the test material and rat blood serum were analyzed using methods described in RTC (2006). The congener content of the test material reported in RTC (2006) is shown in Table 5 below, and the total of the percentages of the five congeners reported is 101%.

A single oral dose of 2 mg/kg (the high dose in the 4-week study) of the ClPFPECA test substance was administered to 9 male and 9 female rats. Plasma levels of the five ClPFPECA

congeners were measured at nine time points (0, 2, 4, 6, 8, 24, 48, 168, and 216 hours after dosing). The blood samples were taken from three subsets of rats, each consisting of 3 males and 3 females, in alternating fashion, such that the first set of 6 rats was sampled at 0, 6 and 24 hours, another set of 6 rats was sampled at 2, 8, and 48 hours, and the third set of 6 rats was sampled at 4, 48, and 168 hours.

RTC (2006) states that the Cmax (maximum observed plasma concentration), Tmax (time to Cmax), t1/2 (half-life), AUC (area under the concentration-time curve over the time course of the study) and AUCinf (theoretical AUC until infinite time) were calculated using "standard non-compartmental analysis." The half-lives reported by RTC (2006) for each congener in males and females are shown in Table 5 below, and the reported values for Cmax, AUC, and AUCinf are shown in Appendix 3.

Plasma levels of most congeners declined slowly, if at all, in both males and female rats over the time course of the study, and it is stated that the half-life values were "obtained by extrapolation as no decrement of test item fraction plasma levels were observed at 216 hours [9 days] post-dose." However, this general statement does not apply to the more rapid excretion of N2, the 8-carbon congener, in females as discussed below.

Table 5. Half-lives of ClPFPECA congeners in male and female rats (RTC, 2006)

Wang et al. (2013) Nomenclature	*Washington et al. (2020) Nomenclature (e,p)*	***Solvay nomenclature***	*Molecular Formula*	*Percent*	*Half-life (hours/days)*	
					M	*F*
n=1, m=0	0,1	N2	$HC_8ClF_{14}O_4$	48.7	481/20.0	39/1.6
n=1, m=1	1,1	M3	$HC_{10}ClF_{18}O_5$	9.5	544/22.6	2185/91.0
n=2, m=0	0,2	N3	$HC_{11}ClF_{20}O_5$	23.5	454/18.9	763/31.8
n=2, m=1	1,2	M4	$HC_{13}ClF_{24}O_6$	11.6	385/16.0	346/14.4
n=3, m=0	0,3	N4	$HC_{14}ClF_{26}O_6$	7.7	201/8.4	160/6.7

In males, the reported half-lives for the N2 (8-carbon), M3 (10-carbon), N3 (11-carbon), and N4 (13-carbon) congeners were generally similar (16.0-22.6 days) while the reported half-life for the longest-chain congener (N4, 14-carbon) was shorter, 8.4 days. In females, the reported half-lives for N3 (11-carbon) of 31.8 days, M4 (13-carbon) of 14.4 days, and N4 (14-carbon) of 6.7 days were generally similar to the half-life values for these congeners in males of 18.9, 16.0, and 8.4 days, respectively. However, the half-life of M3 (10-carbon) in females of 91 days was reported to be much longer than the half-life for this congener in males and for all other congeners in males and females. The basis for the determination of the very long female half-life for M3 in females is unclear since the plasma concentration over time in females for M3 follows a similar pattern as for N3 and M4, as shown in graphs provided in RTC (2006).

Notably, the plasma concentration of congener N2 (8-carbon) in females clearly declined over time during the study, with plasma levels at 168 and 216 hours (7 and 9 days) that were 2-3% of

those at Tmax at 2 hours after dosing. Accordingly, the half-life of congener N2 in females was calculated as 39 hours (1.6 days), much shorter than for N2 in males or for the other congeners in males and females. The rapid excretion of the 8-carbon congener in female rats is consistent with similarly short half-lives in female, as compared to male, rats for other PFCAs, including PFOA and PFNA (DWQI, 2015; DWQI, 2017).

The relative percentages of congeners were provided for the ClPFPECA test substances used in the three repeated dose rat toxicology studies discussed in *Animal Toxicology* below (7-day [RTC, 2007], 4-week [RTC, 2006], 13-week [RTC, 2016]). In these test substances, N2 (8-carbon) was the congener present at the highest concentration (48.7% in the 7-day and 4-week studies; 37.1% in the 13-week study). The proportion of N2 in both test substances was more than twice as high as for the next most prevalent congener, N3 (23.5% in the 7-day and 4-week studies; 18.2% in the 13-week study). As discussed in detail in *Animal Toxicology* below, the mixtures of ClPFPECA congeners tested in the repeated dose rat studies were less toxic in females than males, consistent with the lower toxicity in female, as compared to male, rats in repeated dose studies of PFOA and PFNA (DWQI, 2015; DWQI, 2017). Taken together, these data strongly suggest that congener N2 (8-carbon) is a major contributor to the toxicity of the ClPFPECA congener mixtures in the repeated dose studies. This conclusion is important because the N3 congener was the only congener detected in ground water, including private wells, and it was also the predominant congener detected in surface water, in a study of ClPFPECAs in water in the vicinity of Solvay's New Jersey facility (McCord et al., 2020). N3 was also one of the predominant congeners, based on average concentration, and was the most widely dispersed congener in a study of ClPFPECAs in soil in the vicinity of Solvay's New Jersey facility (Washington et al., 2020).

Other perfluoroether alkyl acids

Guo et al. (2019) studied the toxicity and bioaccumulation in male mice of three PFPECAs detected in the Cape Fear River, the drinking water source for Wilmington NC. The PFECAs studied were PFO2HxA, PFO3OA, and PFO4DA, which have 4, 5 or 6 carbons and 2, 3 or 4 -O-CF_2- groups, respectively. In male mice dosed with the PFECAs at 0.4, 2, or 10 mg/kg/day for 28 days, serum levels at a given dose and the liver:serum ratio increased with chain length. In contrast to PFOA, which bioaccumulated in liver in this study, the liver:serum ratio was <1 for all three of these PFPECAs.

A recent study (Chen et al., 2021) reported half-lives in male mice given a single intravenous dose of 10 ug/kg of 24 hours for PFO4DA and 43 days for its larger homologue, PFO5DoA (7 carbons, four [-O-CF_2-] groups). After 140 days of daily gavage dosing with 2 or 10 µg/kg/day PFO4DA and PFO5DoA, serum levels of PFO5DoA were about 20 times higher than for PFO4DA at each dose. In this study, which was of longer duration than Guo et al. (2019), both compounds accumulated in liver, with liver concentrations of PFO4DA and PFO5DoA that were 7- and 41-fold higher, respectively, than serum concentrations after dosing with 10 µg/kg/day. As discussed in *Biomonitoring* above, both of these PFAS were detected in the blood serum of most residents of a community exposed to them through drinking water (Kotlarz et al., 2020).

HEALTH EFFECTS IN HUMANS

Clinical parameters were evaluated in the occupationally exposed workers whose blood serum was biomonitored for ClPFPECAs (Solvay, 2019a). It was stated that the following endpoints were evaluated: hematology parameters, and clinical chemistry parameters including ALT, ALP, GGT, blood urea nitrogen, creatinine, uric acid, amylase, cholesterol, triglycerides, Apo-A and Apo-B lipoproteins, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free-thyroxine (FT4) testosterone, estradiol, prostate serum antigen (PSA), glucose, and C-reactive protein.

Although numerical data were not provided, numerous statistical associations of blood serum ClPFPECA levels with health endpoints were reported. Many of these associations are consistent with effects of ClPFPECAs and/or other PFAS in animal toxicology studies and/or epidemiological studies (DWQI, 2015; DWQI, 2017; DWQI, 2018). Specifically, associations were reported for increased serum ClPFPECA levels and increases in triglycerides, albumin, albumin/globulin (A/G) ratio, and FT3, and for increased ClPFPECA levels and decreases in alpha-2-globulins, immunoglobulin G (IgG), immunoglobulin M (IgM), and estradiol. Additional associations were reported for serum ClPFPECA levels and increased TSH and prostate serum antigen (PSA), a marker for prostate cancer risk, with the qualification that associations for these endpoints are based on less data than for the other endpoints. Positive associations were also reported for ClPFPECA serum levels and serum lipids, ALT, GGT and apolipoprotein B, and it was stated that these associations may have been confounded by co-exposure to PFOA. However, because the full report, including data tables, for this study has not been provided by Solvay, it is not possible to evaluate the validity of the statements regarding small sample size and potential confounding by PFOA.

LABORATORY ANIMAL TOXICOLOGY STUDIES

The following mammalian toxicology studies are available for ClPFPECAs: three dermal irritation studies in rabbits (RBM, 1998a; RTC, 2002a; RTC 2002b), one dermal sensitization study in guinea pigs (RBM, 1998b), five acute dermal studies in rats (RBM, 1996a; RBM, 1998c; RBM, 1998d; RTC, 2002c; RTC, 2002d), ten acute oral rat studies (RBM, 1996b; RBM, 1998e; RBM, 1998f; RBM, 1998g; RBM, 1998h; RBM, 1998i; RBM, 1998j: RTC, 2002c; RTC, 2002d, RTC, 2003), one 7-day oral study in rats (RTC, 2007), one 4-week oral study with a 2 week recovery period in rats (RTC, 2006), and one 13-week oral study with an 8 week recovery period in rats (RTC, 2016). No inhalation studies are available. Publicly available versions of all of these studies are posted at https://www.nj.gov/dep/dsr/pfas-alternative.htm

These toxicology studies were conducted on ClPFPECA substances consisting of multiple ClPFPECA congeners in varying proportions. Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx [redacted] The percentages of individual congeners in the substances tested are available for the repeated dose (7-day, 4-week, and 13-week) oral studies, but they are not available for the dermal studies or the acute oral studies.

It should be noted that the CAS # of the ClPFPECA substance that was tested in each study refers to the chemical form of the ClPFPECA congeners (e.g., ethyl ester, sodium salt, ammonium salt) in the substance. All of these forms dissociate to the same ClPFPECA anions in the environment and biological systems, and the ClPFPECAs with different CAS #s are therefore considered to be toxicologically equivalent.

All of the studies were conducted at contract toxicology laboratories in Italy, and there are no peer-reviewed journal publications for any of these studies. All of the dermal and acute oral studies were sponsored by Ausimont, the 7-day and 4-week studies were sponsored by Solvay Solexis, and the 13-week study was sponsored by Solvay Specialty Polymers Italy.
There are no data for ClPFPECAs on reproductive, developmental, or chronic toxicity/carcinogenicity, or for specific toxicological effects known to be sensitive endpoints for other PFAS (e.g., immunotoxicity, mammary gland development). As mentioned above, with the exception of the three acute dermal studies that were conducted in rabbits and the skin sensitization test that was conducted in guinea pigs, all of the studies were conducted in rats, and there are no data from mice or non-human primates (i.e., monkeys).

Toxicological data for ClPFPECAs from mice would be informative since mice (male and female) are more sensitive than rats to several other PFAS (e.g., HPFO-DA [GenX], PFOA). Furthermore, as is also the case for several other long-chain PFAS (ITRC, 2020), the ClPFPECA substances tested were less toxic in female rats than male rats, and the 8-carbon ClPFPECA congener, the most prevalent ClPFPECA congener in the substances tested, is much more rapidly excreted in female rats than in male rats (see *Toxicokinetics*, above, and this section, below). In contrast to rats, the other long-chain PFAS are slowly excreted in both male and female mice, and this is likely also true for the 8-carbon ClPFPECA congener. Because long-chain PFAS are also slowly excreted in humans, female mice are therefore considered to be a better model for human toxicity than female rats.

Dermal studies

Dermal irritation
Three dermal irritation studies were conducted in rabbits. In the first study (RTC, 1998a), the ClPFPECA substance that was tested was reported to be corrosive; the undiluted liquid ClPFPECA product was tested in a single rabbit in this study. No dermal irritation or reaction was reported in two later rabbit studies of ammonium salt and sodium salt ClPFPECA substances apparently in more diluted (5% or 20% solution) form (RBM, 2002a, RBM, 2002b). The dermal irritation studies are summarized below:

RBM (1998a): The test substance was CAS # 220182-27-4 (ethyl ester form) as a colorless liquid, purity >99%. [redacted] Dermal irritation was evaluated in one male New Zealand White rabbit. The test substance was applied to three areas (~6 cm^2) of skin, with fur clipped, and it was removed by wiping the skin at the end of the 3 minute, 1-hour, and 4-hour exposure periods. The skin was

observed immediately and 24 hours after the 3-minute and 1-hour exposures, and 1 and 24 hours after the 4-hour exposure.

No dermal effects were observed immediately after the 3-minute exposure, very slight erythema and severe edema occurred immediately after the 1-hour exposure, and slight erythema and severe edema were seen 1 hour after the 4-hour exposure. For all exposure durations, diffuse eschar (dead tissue that is cast off from the surface of the skin) formation and severe edema were observed 24 hours after exposure. Based on these results, the substance was classified as "corrosive for the skin."

RTC (2002a) and RTC 8835-005 (2002b): The test substances were CAS # 33089-92-2 (ammonium salt), 5% in water, purity 90% [redacted] and CAS # 220207-15-8 (sodium salt), 20% in water, purity >90%, respectively. In both studies, dermal irritation was evaluated in three female New Zealand White rabbits. The test substance was applied to skin with fur clipped with a 2.5 cm x 2.5 cm gauze square moistened with 0.5 ml of the test substance and removed with water after 4 hours of exposure. The treated area was examined 1, 24, 48, and 72 hours after dosing. No dermal irritation or other dermal reaction was observed in either study.

Dermal sensitization

One skin sensitization study in male Dunkin Hartley albino guinea pigs (RBM, 1998b) was reported. The test substance was CAS # 220207-15-8 (sodium salt), as a white wax/solid, purity >99%. [redacted]

Preliminary tests (n=2 for each test) were conducted to determine the highest concentration that causes mild irritation for the induction component of the main study and the highest concentration that is not irritating for the booster and challenge exposure (dermal application after sensitization) component of the main sensitization study. Intradermal injection of 0.1 ml of concentrations $\geq$ 0.2% caused eschar formation, and a concentration of 0.1% caused slight erythema, during the 48 hour post-injection observation period. Dermal application of gauze patches with 0.3 ml of concentrations of $\leq$ 50% for 24 hours did not cause irritation during the 48 hour post-exposure observation period. Based on these results, a concentration of 0.1% in water was used for induction by intradermal injection, and a concentration of 50% was applied dermally for the booster and challenge components.

The sensitization test included 10 treated and 5 control animals. In the induction phase of the study, three pairs of intradermal injections (0.1 ml) were given to each animal in areas of the skin with fur clipped as follows: 1:1 mixture of Freund's complete adjuvant (FCA):water; 0.1% test substance (treated) or water (controls); 1:1 mixture of 0.1% test substance (test group) or water (controls):FCA).

Five days after the injections, 0.5 ml of 10% sodium lauryl sulfate (SLS) in Vaseline oil was applied to an area of the skin with fur clipped as a booster to create local irritation and increase

dermal permeability of the test substance to be applied the next day. The following day, 0.3 ml of a 50% solution of the test substance in water (treated) or water (controls) was applied for 48 hours to the area of skin to which SLS had been applied.

In the challenge phase of the study, 20 days after the study began, 0.2 ml of 50% solution of test article in water or water were applied with a gauze pad for 24 hours to skin with fur clipped on the left and right flanks, respectively, of the test group and control animals. The skin was examined for reactions 24 and 48 hours after exposure ended.

Severe dermal reactions were observed in all treated animals after dermal application of the booster dose one day after SLS application. Five of the 10 treated animals died on days 13-15 (7-9 days after the booster dose). The animals that died were anorexic, dehydrated, and emaciated, with decreased body weight. They exhibited hunched posture and piloerection for several days prior to death.

In contrast, the dermal challenge dose on Day 20, which was not preceded by dermal SLS application to increase skin permeability, did not cause mortality or dermal reactions in the 5 surviving treated animals. Therefore, the study authors concluded that severe toxicity occurred after the booster dose because SLS increased the dermal permeability of the test substance. Since dermal application of the challenge dose did not cause a positive reaction, the study authors concluded that the test substance "did not appear to possess sensitizing capacity," with the qualification that the sensitization test was performed on the limited number of surviving animals.

Acute dermal toxicity

Five acute dermal toxicity studies in rats are available (RBM, 1996a; RBM, 1998c; RBM, 1998d; RTC, 2002c; RTC, 2002d). In the three RBM studies, the ClPFPECA substances were tested in undiluted form, while 5% or 20% solutions of the ClPFPECAs were tested in the two later RTC studies. It should be noted that the stated doses in the studies of the solutions are doses of the solutions, not the ClPFPECA substances. Endpoints evaluated in all five studies included mortality during an observation period of at least 14 days after dosing, body weight, clinical signs, and gross pathology; organ weights and microscopic pathology were not evaluated.

The dermal LD50s in male rats for undiluted ClPFPECA substances with two different CAS #s were estimated as 115 mg/kg (RBM, 1996a) and 600 mg/kg (RBM, 1998c). In another study of a substance with the third CAS # (RBM, 1998d), the dermal lethal dose to 50% of animals (LD50) was estimated as 2000 mg/kg in female rats and >2000 mg/kg in males. In both studies of solutions of ClPFPECAs (RTC, 2002c; RTC, 2002d), the dermal LD50s of the solutions were >2000 mg/kg in both males and females. In several of the acute dermal toxicity studies, erythema, edema, and/or eschar occurred at site of application. Macroscopic pathology changes in internal organs in some studies (described in detail below) indicate that dermal absorption and systemic toxicity occurred after dermal exposure. Most of the macroscopic pathology changes

that were reported in one or more acute dermal toxicity studies were also reported in the acute oral studies (see below), including pale liver, decreased spleen size, decreased thymus size, congestion of the renal medulla, and changes in the gastrointestinal tract.

The studies of acute dermal toxicity are summarized below:

RBM (1996a): The test material was CAS # 220182-27-4 (ethyl ester) as a colorless liquid. [redacted] Sprague Dawley rats (5 per sex at the low dose; 5 males at the other doses) were dosed with 25, 100, 200, or 1000 mg/kg of the test material by application to a 6x5 cm area (~10% of body surface) of dorsal skin with fur clipped. The test material was wiped off after a 24-hour exposure period, and the animals were observed for 14 or 16 additional days.
There was no mortality at 25 mg/kg, 3 of 5 animals died on days 10-12 at 100 mg/kg, and all animals died on days 14-16 at 200 mg/kg and days 7-10 at 1000 mg/kg. The dermal LD50 was calculated as 115 mg/kg (95% confidence interval (CI): 74-176 mg/kg).

Body weight was decreased in all animals that died. In animals that survived until sacrifice, body weight was decreased on day 8 and increased between day 8 and terminal sacrifice. Clinical signs (hunched posture, piloerection, sedation, and/or ataxia) were observed in all dosed groups and became more severe with increasing dose. Local skin reactions including erythema and/or edema and eschar were occurred at all doses.

A gross pathology examination was performed on all animals, including those that died during the study and those that survived until the study ended. In the rats surviving until end of study, spleen size was decreased in one male at 25 mg/kg and both surviving males at 100 mg/kg. No changes were reported in the other surviving males or females at 25 mg/kg. Of the 13 rats in the 100, 200, and 1000 mg/kg groups that died prior to end of study, most (10/13) had decreased spleen size, changes in the stomach and/or intestine, and/or congestion of the renal medulla (7/13). Additionally, many had pale liver (6/13), congestion of the lungs (6/13), and/or congestion of the thymus (5/13), and thymus size was decreased in one animal.

RBM (1998c): The test material was CAS # 33089-92-2 (ammonium salt) as a white solid. [redacted] Sprague Dawley rats (5 per males at the three lower doses; 5 per sex at the highest dose) were dosed with 200, 500, 1000, or 2000 mg/kg of the test material by application to a 6x5 cm area (~10% of body surface) of dorsal skin with skin clipped. The test material was wiped off after a 24-hour exposure period, and the animals were observed for 14 or 16 additional days.

There was no mortality at 200 mg/kg, 2 of 5 animals died on at 500 mg/kg, 4 of 5 died at 1000 mg/kg, and all animals died at 2000 mg/kg. The dermal LD50 was calculated as 600 mg/kg (95% CI: 414-871 mg/kg).

Body weight was not affected at 200 and 500 mg/kg, and it was decreased at 1000 and 2000 mg/kg. No clinical signs occurred at 200 mg/kg. At 500, 1000, and 2000 mg/kg, clinical signs included hypoactivity, piloerection, hunched posture, pale skin and mucosae, and hypothermia. No local reactions were observed at the three lower doses, and erythema and edema occurred at 2000 mg/kg.

A gross pathology examination was performed on all animals, including those that died during the study and those that survived until the study ended. In the rats surviving until the end of study, there were no changes at 200 mg/kg and increased liver size was observed at 500 mg/kg. In the 16 rats that died prior to the end of the study, most had decreased spleen size (11/16) and congestion of the renal medulla (9/16). At 500 and 1000 mg/kg, the liver sized was increased in most (5/6) of the rats that died, and all rats (10/10) at 2000 mg/kg had pale livers.

In RBM (1998d), the test substance was CAS # 220207-15-8 (sodium salt) as a white wax solid, purity >99%. [redacted] Male and female Sprague Dawley rats (5/sex) were dosed with 2000 mg/kg of the test material by application to a 6x5 cm area (~10% of body surface) of dorsal skin with fur clipped. The test material was wiped off after a 24-hour exposure period, and the animals were observed for 14 additional days.

There was no mortality in males, and 2 of 5 females died on days 13 and 14. No LD50 was calculated by the study authors, and they reported 20% mortality of total animals (males plus females, n=10). However, since 2 of 5 (40%) of females died, the dermal LD50 in females was close to 2000 mg/kg.

Body weight was decreased in females and growth was slowed in males. At 8 days after dosing, the average body weight loss in females was 19%, with greater loss (average 28%) in the two females that died a few days later. Clinical signs including piloerection and hunched posture were observed in females starting on days 8-9 through day 13.

Gross pathology examination found stomach congestion and ulcer, congestion of renal medulla, and pale liver in one of the two females that died, and pale liver and decreased spleen size in the other one. No changes were reported in the animals that survived until sacrifice on day 14.

RTC (2002c): The test material was CAS # 220207-15-8 (sodium salt) as 20% in water, purity >90%. [redacted] Male and female Sprague Dawley rats (5/sex) were dosed with 2000 mg/kg of the test material by application to dorsal skin with fur clipped, an area that was at least 10% of total body surface. Since the ClPFPECAs were present at 20% in the test material, the actual dose of ClPFPECAs was 400 mg/kg. The test material was washed off with water after a 24-hour exposure period, and the animals were observed for 14 additional days.

One female died on day 14, and the dermal LD50 was reported as >2000 mg/kg (of the test material), which is equivalent to >400 mg/kg of the ClPFPECAs that were tested.
Body weight was decreased in 2/5 males by up to 10% and in 4/5 females by up to 37% during the course of the study. The only clinical signs observed were dark staining around eyes in males on the day of dosing, and hunched posture and thin appearance in one female on the last day of the study. Local reactions including erythema and/or desquamation at the treated site were reported on days 4 through 14. No changes were noted during the gross pathological examinations.

RTC (2002d): The test material was CAS # 330809-92-2 (ammonium salt), 5% in water, purity >90%. [redacted] Male and female Sprague Dawley rats (5/sex) were dosed with 2000 mg/kg of the test material by application to dorsal skin with fur clipped, an area that was at least 10% of total body surface. Since the ClPFPECAs were present at 5% in the test material, the actual dose of ClPFPECAs was 100 mg/kg. The test material was washed off with water after a 24-hour exposure period, and the animals were observed for 14 additional days.

There was no mortality during the study. Therefore, the dermal LD50 was >2000 mg/kg for the test material, or >100 mg/kg for the ClPFPECAs in the test material.

Body weight was decreased in only one female by 9%. The only clinical sign observed was urogenital staining in 1 male, and the only local reaction was erythema in one female on days 6 through 9. No changes were noted during the gross pathological examinations.

Oral studies

Acute oral studies
Ten acute oral rat studies are available (RBM, 1996b; RBM, 1998e; RBM, 1998f; RBM, 1998g; RBM, 1998h; RBM, 1998i; RBM, 1998j; RTC, 2002c; RTC, 2002d; RTC, 2003). The seven RBM studies tested ClPFPECA substances in undiluted form, while the three later RTC studies used solutions of the ClPFPECAs (concentrations not provided in RTC, 2002c and RTC, 2002d; 5% solution in RTC, 2003). The stated doses in the studies of the solutions are doses of the solutions, not doses of the ClPFPECA substances. Endpoints evaluated in all five studies included mortality during an observation period of at least 14 days after dosing, body weight, clinical signs, and gross pathology. Organ weights and microscopic pathology were not evaluated.

The oral rat LD50 values from the acute oral studies of the ClPFPECAs are shown in Table 6. Calculated oral LD50 values in male and female rats range from 39 mg/kg to 100 mg/kg (RBM, 1996b; RBM, 1998e; RBM, 1998f; RBM, 1998i; RBM, 1998j), and oral LD50s were estimated in two other studies as 120 mg/kg (RBM, 1998g; RBM, 1998h). Oral LD50 values in rats for

PFOA were 470-1800 mg/kg and for HFPO-DA (GenX; a 6 carbon perfluoroether replacement for PFOA) were 1730 to >3000 mg/kg, as also shown in Table 6. Comparison of the oral LD50 values for these three PFAS indicates that ClPFPECAs are approximately 5 to 50 times more acutely toxic than PFOA after oral exposure to rats, and approximately 20 to 60 times more acutely toxic than HFPO-DA in rats after oral exposure.

[redacted]

Several macroscopic pathology changes were reported in one or more animals in multiple acute oral studies (see summaries of individual studies below). These changes including pale liver (8 of 10 studies); decreased spleen size (7 of 10 studies), congestion of the renal medulla (7 of 10 studies), changes in the gastrointestinal tract (5 of 10 studies), and decreased thymus size (4 of 10 studies).

Table 6. Oral rat LD50 values for ClPFPECAs, PFOA, and HFPO-DA (GenX)

Citation	*LD50 (mg/kg/day)*	*Chemical form tested*	*Comments*
ClPFPECAs			
RBM (1996b)	39 (M & F)[a]	Ethyl ester, hydrolyzed (CAS # 220182-74-4)	
RBM (1998e)	83 (M)[b]	Hydrolyzed, ammonium salt (CAS #330809-92-2)	
RBM (1998f)	100 (M) [b]	Ethyl ester, hydrolyzed, sodium salt (CAS # 220207-15-8)	
RBM (1998g)	120 (M) [b,c]	Ethyl ester, hydrolyzed, sodium salt (CAS # 220207-15-8)	----
RBM (1998h)	120 (M) [b,c]	Hydrolyzed, ammonium salt (CAS #330809-92-2)	
RBM (1998i)	68 (M) [b]	Ethyl ester, hydrolyzed, sodium salt (CAS # 220207-15-8)	
RBM (1998j)	68 (M) [b]	Hydrolyzed, ammonium salt (CAS #330809-92-2)	
RTC (2002e)	Not determined	Ethyl ester, hydrolyzed, sodium salt (CAS # 220207-15-8)	Test materials were solutions of ClPFPECAs, concentrations not provided. Because doses of ClPFPECAs are unknown, LD50s for the ClPFPECAs cannot be determined.
RTC (2002f)	Not determined	Ethyl ester, hydrolyzed, sodium salt (CAS # 220207-15-8)	
RTC (2003)	>100 (M)[d] >10 - <100 (F)[d]	Hydrolyzed, ammonium salt (CAS #330809-92-2)	Test material was 5% solution of the ClPFPECAs in water. The doses stated in the study reports are for the aqueous solution, not the ClPFPECAs. Doses of ClPFPECAs were determined based on 5% of aqueous solutions.
PFOA (cited in Kennedy et al., 2004)			
Griffith and Long (1980)	680 (M); 430 (F)	Ammonium salt	
DuPont (1981a)	470 (M); 482 (F)	Not specified	
DuPont (1981b)	478 (M)	Not specified	
Hazleton (1997)	1800 (M); 600 (F)	Not specified	----
HPFO-DA (GenX)			
DuPont (1963)	>5000, <7500 (M)	Ammonium salt	
DuPont (1996)	>3400, <5000 (M)	Ammonium salt	
DuPont (2007)	3129 (F)	Ammonium salt	
DuPont (2008a)	1730 (M); 1750 (F)	Acid form	
DuPont (2008b)	1750 (M)	Ammonium salt	

[a] LD50 is based on data from males and females in lowest dose group, and males only in 4 higher dose groups. Mortality occurred in females but not males in the lowest dose group.

[b] Males and females were included in lowest dose group; males only in higher dose groups. Because there was no mortality in lowest dose group, LD50 is based on data from males.

[c] LD50 was estimated.

[d] LD50 was not stated in study report. Values shown are highest dose at which there was no mortality and/or lowest dose at which mortality occurred, based on ClPFPECAs as 5% of the aqueous test solution.

The available acute oral studies are summarized below:

RBM (1996b): The test material was CAS # 220182-27-4 (ethyl ester) as a colorless liquid. [redacted] Sprague Dawley rats were dosed with the undiluted test material by oral gavage at volumes that delivered the intended dose. There was no control group, and the doses and numbers of animals per group were 25 mg/kg (5 per sex), 50, 75, 100, and 200 mg/kg (5 males/group). The animals were observed for 14 days after dosing, except the 50 mg/kg group which was observed for 22 days. In general, mortality occurred earlier as dose increased. At 25 mg/kg, there was no mortality in males and mortality in 2/5 (40%) of females, and at 50 mg/kg, there was mortality in 4/5 (80%) animals (males). The study report states that there was 100% mortality at 75 mg/kg, but subsequent tables show mortality of 4/5 rats in this group, with one rat surviving until sacrifice on day 14. All rats died at 100 and 200 mg/kg. The LD50 was calculated as 39 mg/kg (95% CI: 27-55 mg/kg). (Note: In the study report, the LD50 is stated as 38.74 mg/kg and was rounded to 38 mg/kg.)

Clinical signs generally occurred earlier with increasing dose. Piloerection and hunched posture occurred in 3 of 5 males and 3 of 5 females at 25 mg/kg, and in all animals at $\geq$ 50 mg/kg. At 100 and 200 mg/kg, sedation also occurred in all animals. Other clinical signs not listed here were noted in one or more rats dosed with $\geq$ 50 mg/kg. Body weight was decreased in all rats. In the 25 mg/kg rats that survived until the end of the study, body weight was decreased at day 8, and it began to increase by day 14. In the single surviving 50 mg/kg rat, body weight was decreased on days 8 and 14, and it began to increase by day 21.

Gross pathology examination was performed on all animals. In the 18 male rats in the 50-200 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (9/18); congestion of renal medulla (11/18), decreased spleen size (10/18), congestion of the lungs (10/18), congestion of the thymus (7/18), and decreased thymus size (1/18). Additionally, changes in the intestine (thinning walls, congestion, and/or catarrhal content) and/or stomach (thinning walls, erosion, and/or congestion) occurred in most animals. All of these changes were also observed in one or more of the males that survived until the end of the study, with most occurring in 1/5 (20%) of the low dose (25 mg/kg) group. In the females dosed with 25 mg/kg, similar changes were seen in the two rats that died before the end of the study, as follows: congestion of the kidney medulla (2/2); stomach and intestinal changes (2/2); pale liver (1/2); and thymus congestion (1/2), while no changes were seen in the three rats that survived until sacrifice on day 14.

RBM (1998e): The test material was CAS # 33089-92-2 (ammonium salt) as a white solid. [redacted]
Sprague Dawley rats were dosed with the test material in water by oral gavage. There was no control group, and the doses and numbers of animals per group were 53 mg/kg (5 per sex), and 82 and 128 mg/kg (5 males/group). The animals were observed for 14 days after dosing.

At 53 mg/kg, there was no mortality in males or females. At 82 mg/kg, there was mortality of 3/5 (80%) animals, and all rats died at 128 mg/kg. The oral LD50 was calculated as 83 mg/kg (95% CI: 69-100 mg/kg).

There were no notable clinical signs at 53 mg/kg. Piloerection, hunched posture, and sedation or hypoactivity occurred at 82 and 128 mg/kg. The study report states that there was no effect on "body weight growth" at 53 mg/kg, and it was stated that decreased body weight or slowed growth occurred at 82 and 128 mg/kg. However, there was no control group for use as a comparison for these effects.

Gross pathology examination was performed on all animals. In the 8 male rats in the 82 and 128 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (8/8), congestion of renal medulla (6/8), decreased spleen size (5/8), stomach congestion (5/8). No changes were observed in the male and female rats in the 53 and 82 mg/kg groups that survived until sacrifice on day 14.

RBM (1998f): The test material was CAS # 220207-15-8 (sodium salt) as a white solid, purity >99%. [redacted] Sprague Dawley rats were dosed with the test material in water by oral gavage. There was no control group, and the doses and numbers of animals per group were 82 mg/kg (5 per sex), and 102 and 128 mg/kg (5 males/group). The doses were stated to have been selected based on a preliminary study. The animals were observed for 14 days after dosing.

At 82 mg/kg, there was no mortality in males or females. At 102 mg/kg, there was mortality in 2/5 (40%) animals (males), and all rats died at 128 mg/kg. The oral LD50 was calculated as 100 mg/kg (95% CI: 92-108 mg/kg).

Clinical signs included piloerection and hunched posture in males in all dose groups and sedation or hypoactivity at 128 mg/kg. No notable clinical signs were observed in the females at 82 mg/kg. Body weight was decreased following dosing in all males, and body weight gain was slowed in the females that were included in the 82 mg/kg group. These changes occurred primarily in the first week after dosing.

Gross pathology examination was performed on all animals. In the seven male rats in the 102 and 128 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (6/7), decreased spleen size (5/7), and congestion of renal medulla (1/7). No notable changes were observed in the male or female rats in the 82 and 102 mg/kg groups that survived until sacrifice on day 14.

RBM (1998g): The test substance was CAS # 220207-15-8 (sodium salt) as a white powder, purity >99%. [redacted] Sprague-Dawley rats were dosed with test material by

oral gavage in water. There was no control group, and the doses and numbers of animals per group were 90 mg/kg (5 per sex), and 126 and 162 mg/kg (5 males/group). The doses were stated to have been selected based on a preliminary study. The animals were observed after dosing for 14 days (90 mg/kg females, 162 mg/kg males) or 21 days (90 and 126 mg/kg males) after dosing.

At 90 mg/kg, there was no mortality in males or females. At 126 mg/kg, there was mortality in 3/5 (60%) animals, and all rats died at 162 mg/kg. The oral LD50 was estimated as 120 mg/kg. Clinical signs included piloerection in females at 90 mg/kg, hypoactivity, piloerection, and hunched posture in males in all dose groups; and abdominal dilatation in one 126 mg/kg day male. Body weight was decreased following dosing in all males, and body weight gain was slowed in females (90 mg/kg). These changes occurred primarily in the first week after dosing. Gross pathology examination was performed on all animals. In the eight male rats in the 126 and 162 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (6/8), decreased spleen size (4/8), congestion of renal medulla (2/8), pale kidneys (1/8), and congestion and/or erosion of stomach (3/8). No notable changes were observed in the male or female rats in the 90 and 126 mg/kg groups that survived until sacrifice on day 14 or 21.

RBM (1998h): The test substance was CAS # 330809-92-2 (ammonium salt) as a white powder, purity >99%. [redacted] Sprague Dawley rats were dosed with test material by oral gavage in water. There was no control group, and the doses and numbers of animals per group were 90 mg/kg (5 per sex), and 126 and 162 mg/kg (5 males/group). The doses were stated to have been selected based on a preliminary study. The animals were observed after dosing for 14 days (90 mg/kg females, 162 mg/kg males) or 21 days (90 and 126 mg/kg males) after dosing.

At 90 mg/kg, there was no mortality in males or females. At 126 mg/kg, there was mortality in 3/5 (60%) animals, and all rats died at 162 mg/kg. The oral LD50 was estimated as 120 mg/kg. Clinical sign included piloerection in females (90 mg/kg), and hypoactivity, piloerection, and hunched posture in males in all dose groups. Sedation occurred in the highest dose group (126 mg/kg). Body weight was decreased following dosing in all dose groups.

Gross pathology examination was performed on all animals. In the 8 male rats in the 126 and 162 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (7/8), decreased spleen size (5 /8), congestion of renal medulla (4/8), congestion of the testes (4/8), changes in the stomach (4/8), and changes in the intestine (3/8). No notable changes were observed in the male or female rats in the 90 and 126 mg/kg groups that survived until sacrifice on day 14 or 21.

RBM (1998i): The test material was CAS # 220207-15-8 (sodium salt) as a white gummy substance, purity >99%. [redacted] Sprague-Dawley rats were dosed with test material by oral gavage in water. There was no control group, and the doses and numbers of animals per

group were 45 mg/kg (5 per sex), and 63, 81, and 145 mg/kg (5 males/group). The doses were stated to have been selected based on a preliminary study. The animals were observed for 14 days after dosing.

At 45 mg/kg, there was no mortality in males or females. At 63 and 81 mg/kg, there was mortality in 2/5 (40%) and 4/5 (80%) animals, respectively, and all rats died at 145 mg/kg. The oral LD50 was calculated as 68 mg/kg (95% CI: 59-78 mg/kg).

Clinical signs included piloerection and hunched posture in all dose groups, and hypoactivity in the higher dose groups (81 and 145 mg/kg). Body weight was decreased or body weight gain was slowed in all dose groups following dosing.

Gross pathology examination was performed on all animals. In the 11 male rats in the 63, 81, and 145 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (9/11), congestion of renal medulla (3/11, all were in high dose group), intestinal changes (3/11), congestion of thymus (2/11), decreased spleen size (1/11), and congestion of lungs (1/11). No notable changes were observed in the male or female rats that survived until sacrifice on day 14.

RBM (1998j): The test material was CAS # 330809-92-2 (ammonium salt) as a white powder, purity >99%. [redacted] Sprague Dawley rats were dosed with test material by oral gavage in water. There was no control group, and the doses and numbers of animals per group were 45 mg/kg (5 per sex), and 63, 81, and 145 mg/kg (5 males/group). The doses were stated to have been selected based on a preliminary study. The surviving animals (see below) were observed for 14 days (45 mg/kg males) or 21 days (45 mg/kg females; 63 and 81 mg/kg males) after dosing.

At 45 mg/kg, there was no mortality in males or females. At 63 and 81 mg/kg, there was mortality in 2/5 (40%) and 4/5 (80%) animals, respectively, and all rats died at 145 mg/kg. The oral LD50 was calculated as 68 mg/kg (95% CI: 59-78 mg/kg).

Clinical signs included piloerection and hunched posture in all dose groups, and hypoactivity in the higher dose groups (81 and 145 mg/kg). Body weight was decreased or body weight gain was slowed in all dose groups following dosing.

Gross pathology examination was performed on all animals. In the 11 male rats in the 63, 81, and 145 mg/kg groups that died prior to the end of the study, the following changes were noted: pale liver (8/11), congestion of renal medulla (2/11), stomach changes (3/11), congestion of thymus (1/11), and congestion of lungs (1/11). No notable changes were observed in the male or female rats that survived until sacrifice on day 14.

RTC (2002e): The test material was CAS # 220207-15-8 (sodium salt) as a solution in colorless liquid, concentration not stated, purity >90%. [redacted]

[redacted] Sprague Dawley rats were dosed with test material diluted in water by oral gavage. There was no control group. The doses of the test material were 300 mg/kg and 2000 mg/kg, and each of the two doses were tested in two groups of 3 female rats. Since the concentration of ClPFPECAs in the test material was not provided, the doses of ClPFPECAs are unknown. The animals were observed for 14 days after dosing.

There was no mortality in rats dosed with 300 mg/kg of the test material, and all rats dosed with 2000 mg/kg died on days 10-11. Since the doses of ClPFPECAs are not known, the LD50 cannot be determined.

There were no clinical signs in rats dosed with 300 mg/kg of the test material. Clinical signs in rats given 2000 mg/kg of the test material included hunched posture, thin appearance, reduced activity, and piloerection. The study report states that there were no unexpected changes in body weight in the 300 mg/kg group. However, it is noted that there was no control group for comparison during the study. Body weight was decreased "markedly" in all 2000 mg/kg rats. Gross pathology examination was performed on all animals. No pathological changes were noted in the 300 mg/kg groups at scheduled sacrifice. In the 2000 mg/kg groups, all of which died early, no changes were observed in 3/6 animals. The spleen and thymus size were decreased in 2/6, the uterus was enlarged and filled with clear fluid in 1/6, and 1/6 had abnormal stomach contents.

RTC (2002f): The test material was CAS # 220207-15-8 (sodium salt) as per publicly available information from Solvay, purity >90%, as a solution in colorless liquid with concentration not stated. It is noted that the *Test Item* section of the report provides an incorrect CAS # (CAS # 330809-92-2, which is the ammonium salt). [redacted] Sprague-Dawley rats were dosed with test material diluted in water by oral gavage. There was no control group. The doses of the test material and numbers of animals per group were 200 mg/kg (3 per sex), and 2000 mg/kg (3 males). Since the concentration of ClPFPECAs in the test material was not provided, the doses of ClPFPECAs are unknown. The animals were observed for 14 days after dosing.

There was no mortality in males or females dosed with 200 mg/kg of the test material, and all males dosed with 2000 mg/kg of the test material died on days 2-3. Since the doses of ClPFPECAs are not known, the LD50 cannot be determined.

There were no clinical signs at 200 mg/kg of the test material. At 2000 mg/kg of the test material, reduced activity, piloerection, ataxia, difficulty breathing, and pronation were observed. The study report states that there were no unexpected changes in body weight during the study. However, the body weight of each of the 3 females dosed with 200 mg/kg of the test material decreased between days 8 and 15.

Gross pathology examination was performed on all animals. No pathological changes were noted in either the animals that died prior to the end of the study or the animals that survived until scheduled sacrifice on Day 14. Staining of the skin and/or fur around the muzzle or in the in urogenital area was observed in the high dose males that died prior to the end of the study.

RTC (2003a): The test material was CAS # 330809-92-2 (ammonium salt) as a 5% solution in colorless liquid, purity >90%. [redacted] Sprague Dawley rats were dosed with test material diluted in water by oral gavage. There was no control group. The doses of the test material and numbers of animals per group were 200 and 2000 mg/kg (3 per sex per dose). Since the concentration of ClPFPECAs in the test material was 5%, the doses of ClPFPECAs were 10 and 100 mg/kg. The animals were observed for 14 days after dosing.

There was no mortality in males or females dosed with 200 mg/kg test material, equivalent to 10 mg/kg ClPFPECAs, or in males dosed with 2000 mg/kg test material containing 100 mg/kg, equivalent to 100 mg/kg ClPFPECAs. There was mortality in 2/3 (67%) females dosed with 2000 mg/kg test material (100 mg/kg ClPFPECAs). An LD50 was not reported.

There were no clinical signs in low dose males or females. In high dose males and females, clinical signs included reduced activity and piloerection. Additionally, ataxia, hunched posture, and semi-closed eyes were noted in females.

The study authors stated that there were no unexpected changes in body weight at 200 mg/kg or in 2/3 males at 2000 mg/kg. However, there was no control group for comparison. Loss of body weight was noted in all females and one male at 2000 mg/kg.

Gross pathology examination was performed on all animals. No pathological changes were noted in the 200 mg/kg males or females, the 2000 mg/kg males, or the two 2000 mg/kg females that died prior to the end of the study (while noting that cannibalization of one of these occurred). In the 2000 mg/kg female that survived until scheduled sacrifice, the following changes were observed: small and pale thymus, swollen and pale spleen, pale liver, multiple abnormal areas of the lung described as pale with dark pinpoints, pale and edematous pancreas, pale mesenteric lymph nodes, and abnormal contents of abdominal cavity.

<u>Repeated Dose Oral Studies</u>

Note: Because only one 7-day study (RTC, 2007), one 4-week study with 2 week recovery period (RTC, 2006), and one 13-week study with 8 week recovery period (RTC, 2016) were available, these studies are referred to as the "7-day study", "4-week study", and "13-week study" (without citations) below.

Overview of oral repeated dose studies

There was no mortality in the repeated dose studies (7-day; 4-week with 2 week recovery period; 13-week with 8 week recovery period) with the exception of the death of one female in the low dose (0.3 mg/kg/day) group in the 4-week study, stated to likely not be treatment related.

In the 7-day and 4-week studies, body weight was significantly decreased at the end of dosing in both sexes in the high dose groups (10 mg/kg/day and 2 mg/kg/day, respectively). In the 4-week study, body weight remained decreased in both sexes at the end of the 2 week recovery period. In both studies, food consumption was somewhat reduced in the high dose groups. In contrast, there were no effects on body weight or food consumption at doses up to 0.3 mg/kg/day in the 13-week study.

Hepatic toxicity was the most sensitive and consistent toxicological effect in the repeated dose studies, and it is a well-established and sensitive effect of PFAS in general (ITRC, 2020). Treatment-related hepatic effects of ClPFPECAs include increased absolute and relative liver weight, increased levels of serum liver enzymes, hepatocellular hypertrophy, hepatocellular necrosis, and micro- and macrovesicular vacuolation stated to likely be associated with steatosis. Most of these effects persisted until the end of the recovery period in the 4-week and 13-week studies (Table 7). While no mode of action information (other than negative genotoxicity studies) is available for ClPFPECAs, ClPFPECAs are associated with increased serum levels of liver enzymes in humans (Solvay, 2019a), and mode of action evaluations for other PFAS have concluded that their hepatic effects in rodents should be considered relevant to humans (DWQI, 2015; DWQI, 2017; DWQI, 2018).

Female rats are less sensitive than males to the hepatic effects of ClPFPECAs, likely due to the rapid excretion by female rats of the 8-carbon congener, which is the congener present at the highest percentage in the ClPFPECA substances tested in the repeated dose studies. The lower toxicological potency of the ClPFPECA mixtures in females, as compared to males, provides strong evidence that the 8-carbon contributes substantially to the toxicity of the mixture.

Data from the 7-day, 4-week, and 13-week studies indicate that the hepatic effects of ClPFPECAs are both dose and duration dependent (Table 7 and 8). For example, relative liver weight increased with dose in both males and females in all three studies. Additionally, the incidence and/or magnitude of hepatic effects was greater at the same or similar dose in studies of longer duration. For example, hepatocellular necrosis and increased serum alkaline phosphatase (ALP) levels occurred at 0.3 mg/kg/day in males in the 13-week study but not at the same dose in the 4-week study (Table 7). Similarly, serum levels of three liver enzymes were increased in males at 2 mg/kg/day in the 4-week study but not at the same dose in the 7-day study (Table 7). Additionally, the increase in relative liver weight was greater at a given dose as exposure duration increased (Tables 7 and 8). For example, relative liver weights at 2.5 mg/kg/day in the 7-day study were 143% and 111% of controls in males and females, respectively, while at a slightly lower dose, 2 mg/kg/day, in the 4-week study, there were greater increases of 230% and 165% of controls in males and females, respectively. Similarly, at 0.3

mg/kg/day, relative liver weights were 117% and 102% of controls in males and females, respectively, in the 4-week study, while there were greater increases of 178% and 129% of controls in males and females, respectively, in the 13-week study.

The 4-week study of ClPFPECAs (RTC, 2006) and the 4-week NTP (2019) studies of PFOA and PFNA conducted by NTP (2019) were both conducted in Harlan Sprague Dawley rats. Comparison of data from these studies, which were all of the same duration and in the same rat strain, demonstrates that a given administered dose of ClPFPECAs caused a greater increase in relative liver weight than the same or slightly higher administered doses of PFOA or PFNA in both male and female Harlan Sprague Dawley rats (Table 9). For example, relative liver weight was 230% of the control value in male rats dosed with ClPFPECAs at 2 mg/kg/day, while it was lower, 139% and 186% of the control values, in males at a slightly higher dose, 2.5 mg/kg/day, of PFOA and PFNA, respectively. Similarly, relative liver weight was 165% of the control value in female rats exposed to ClPFPECAs at 2 mg/kg/day (RTC, 2016), while it was not increased in females exposed to a much higher dose of PFOA, 6.25 mg/kg/day, and the increase was lower (121%, 135%, and 147% of the control values, respectively) in female rats exposed to similar and higher doses of PFNA (1.56, 3.12, and 6.25 mg/kg/day). Also shown in Table 9, hepatocellular necrosis occurred in male rats at similar frequencies from comparable doses of ClPFPECAs and PFNA, but it did not occur in male rats treated with PFOA in these studies.

Comparison of data for hepatic toxicity in studies of male rats with 4 weeks (RTC, 2006) or 13 weeks (RTC, 2016) of exposure to ClPFPECAs with another 4-week studies of PFOA in male and female rats (Griffith and Long, 1980) and a 4-week and 13-week study in male rats (Perkins et al., 2004) is more uncertain because the strains of rats used in these PFOA studies (Chr-CD and CR CD:BR, respectively) differed from the strain used in the ClPFPECA studies (Harlan Sprague-Dawley). That being said, the doses that caused toxicity in the 4-week and 13-week studies of the ClPFPECAs were lower than the doses of PFOA that caused toxicity in the rat studies of the same duration.

Table 7: Hepatic toxicity of ClPFPECAs in repeated dose studies in rats[a]

Dose (mg/kg/day)		7-day study		4-week study				13-week study			
				End of dosing		After 2 week recovery		End of dosing		After 8 week recovery	
		M (4)[b]	F (4)	M (5)	F (5)	M (5)	F (5)	M (10)	F (10)	M (5)	F (5)
0.05	↑ Relative Wt.[c]							104	100	101	99
	↑ serum enzymes							--- [d]	---	---	---
	Hepatocellular hypertrophy[e]							---	---	---	---
	Necrosis[e]							---	---	---	---
	Vacuolation[e,f]							9/10 (90%)	---	4/5 (80%)	
0.1	↑ Relative Wt.							118**	101	107	106
	↑ serum enzymes							---	---	ALT[g]	---
	Hepatocellular hypertrophy							10/10 (100%)	---	———	---
	Necrosis							---	1/10 (10%)	---	---
	Vacuolation							6/10 (60%)	---	3/5 (60%)	---
0.3	↑ Relative Wt.			117**	102			178***	129***	133**	129**
	↑ serum enzymes			---	---			ALP*	---	ALT[g]	
	Hepatocellular hypertrophy			4/5 (80%)	---			10/10 (100%)	10/10 (100%)	4/5 (80%)	---
	Necrosis			---	---			2/10 (20%)	---	2/5 (40%)	---
	Vacuolation			---	---			---	3/10 (30%)	3/5 (60%)	---
0.8	↑ Relative Wt.			157**	116 **						
	↑ serum enzymes			Not significant at p<0.05; ~8-fold ALT, ~3-fold AST in 2/5 animals	---						
	Hepatocellular hypertrophy			5/5 (100%)	---						
	Necrosis			1/5 (20%)	---						
	Vacuolation			---	---						
2	↑ Relative Wt.			230**	165**	252**	171**				
	↑ serum enzymes			ALP* ALT** AST*	---	ALP**	---				
	Hepatocellular hypertrophy			5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)				
	Necrosis			2/5 (40%)	---	1/5 (20%)	---				
	Vacuolation			---	---	---	---				
2.5	↑ Relative Wt.	143**	111								
	↑ serum enzymes	---	---								
	Hepatocellular hypertrophy	*Histopathology not evaluated*									
	Necrosis										
	Vacuolation										
5	↑ Relative Wt.	168**	117								
	↑ serum enzymes	---	---								
	Hepatocellular hypertrophy	*Histopathology not evaluated*									
	Necrosis										
	Vacuolation										
10	↑ Relative Wt.	180**	147*								
	↑ serum enzymes	ALT** AST**	---								
	Hepatocellular hypertrophy	*Histopathology not evaluated*									
	Necrosis										
	Vacuolation										

[a] Doses were not evaluated in cells shaded in gray.
[b] Number of animals is in parentheses
[c] Percent of control value
[d] "---" indicates that effect did not occur.
[e] Incidence data shown; none of the histopathological changes shown were reported in the control groups in these studies.
[f] Vacuolation was described as "steatotic vacuolar degeneration, micro and/or macro-vesicular vacuolation."
[g] Dose-related increase, not significant at p< 0.05

*p<0.05; **p<0.01; ***p<0.001

Table 8. Increased relative liver weight in repeated dose rat studies at end of dosing

Dose (mg/kg/day)	% of control	
7-day study		
	Males	Females
0	100	100
2.5	143**	111
5	168**	117
10	180**	147*
4-week study		
	Males	Females
0	100	100
0.3	117**	102
0.8	157**	116**
2	230**	165**
13-week study		
0	100	100
0.05	104	100
0.1	118***	101
0.3	178***	129***

*p<0.05, **p<0.01, ***p<0.001

Table 9. Comparison of hepatic toxicity of ClPFPECAs, PFOA, and PFNA in 28-day studies in Harlan Sprague Dawley rats[a]

Dose (mg/kg/day)	Endpoint	ClPFPECAs (RTC, 2006)		PFOA (NTP, 2019)[b]		PFNA (NTP, 2019)[b]	
		M (5)	F (5)	M (10)	F (10)	M (10)	F (10)
0.3	Relative Wt. (% of control)	117[c]	102				
	Hepatocellular hypertrophy[d]	4/5 (80%)	---				
	Necrosis[d]	---	---				
	Cytoplasmic alterations[d]	---	---				
	Vacuolation[d]	---	---				
0.625	Relative Wt. (% of control)			116[c]		123 [c]	
	Hepatocellular hypertrophy			6/10 (60%)		7/10 (70%)	
	Necrosis			---		---	
	Cytoplasmic alterations			4/10 (40%)		10/10 (100%)	
	Vacuolation			---		---	
0.8	Relative Wt. (% of control)	157 [c]	116 [c]				
	Hepatocellular hypertrophy	5/5 (100%)	---				
	Necrosis	1/5 (20%)	---				
	Cytoplasmic alterations	---	---				
	Vacuolation	---	---				
1.25	Relative Wt. (% of control)			128[c]		160 [c]	
	Hepatocellular hypertrophy			10/10 (100%)		10/10 (100%)	
	Necrosis			---		1/10 (10%)	
	Cytoplasmic alterations			6/10 (60%)		10/10 (100%)	
	Vacuolation			---		6/10	
1.56	Relative Wt. (% of control)						121[c]
	Hepatocellular hypertrophy						---
	Necrosis						---
	Cytoplasmic alterations						5/10 (50%)
	Vacuolation						---
2	Relative Wt. (% of control)	230 [c]	165[c]				
	Hepatocellular hypertrophy	5/5 (100%)	5/5 (100%)				
	Necrosis	2/5 (40%)	---				
	Cytoplasmic alterations	---	---				
	Vacuolation	---	---				
2.5	Relative Wt. (% of control)			139[c]		186 [c]	
	Hepatocellular hypertrophy			10/10 (100%)		10/10 (100%)	
	Necrosis			---		5/10 (50%)	
	Cytoplasmic alterations			10/10 (100%)		10/10 (100%)	
	Vacuolation			---		9/10 (90%)	
3.12	Relative Wt. (% of control)						135[c]
	Hepatocellular hypertrophy						2/10
	Necrosis						---
	Cytoplasmic alterations						10/10 (100%)
	Vacuolation						---
5	Relative Wt. (% of control)			147[c]		NA[e]	
	Hepatocellular hypertrophy			10/10 (100%)		10/10 (100%)	
	Necrosis			---		9/10 (90%)	
	Cytoplasmic alterations			10/10 (100%)		10/10 (100%)	
	Vacuolation			---		---	
6.25	Relative Wt. (% of control)				100		147 [c]
	Hepatocellular hypertrophy				---		10/10 (100%)
	Necrosis				---		---
	Cytoplasmic alterations				---		10/10 (100%)
	Vacuolation				---		---

[a] Doses were not evaluated in cells shaded in gray.
[b] Higher doses (M – 10 mg/kg/day; F – 12.5, 25, 50, 100 mg/kg/day) are not shown because they are above the range of the doses used in the ClPFPECA study.
[c] $p<0.01$
[d] Incidence data shown; none of the histopathological changes shown were reported in the control groups in these studies.
[e] Data not provided due to high mortality rate.

In addition to increased relative liver weight, relative weights of several other organs were affected in both the 7-day and 4-week ClPFPECA studies. Decreased relative spleen and thymus weight and increased relative kidney and testes weight were reported in males and/or females in both studies. Other changes reported in only one of the three repeated dose studies were decreased relative heart weight (7-day study, females), increased relative thyroid, brain, and epididymides weight (4-week study, males), and increased relative uterus weight (13-week study after 8-week recovery).

Histopathological evaluations were not performed in the 7-day study. Histopathological changes in organs other than the liver in the 4-week and 13-week studies included aggregation of alveolar macrophages in the lung and atrophy of the thymus in both sexes in the 4-week study, hypertrophy of thyroid follicular cells and in the pars distalis of the pituitary in males in the 13-week study, and colloid depletion of the seminal vesicles in both studies.

Changes in several clinical chemistry parameters (other than serum liver enzymes, discussed above) occurred in males and/or females in at least two of the three repeated dose studies. These include decreased cholesterol in all three studies, decreased triglycerides in 4-week and 13-week studies (not evaluated in 7-day study), increased urea and decreased creatinine in all three studies, and increased A/G ratio in the 7-day and 4-week studies.

Dose-related decreases in red blood cell (RBC) parameters (RBC count, hemoglobin [Hb], hematocrit [Hct]) in both sexes, and increased mean corpuscular hemoglobin concentration (MCHC) in males only, were reported at 2 mg/kg/day at the end of the 2 week recovery period in the 4-week study; lower dose groups were not included in the recovery period in the 4-week study. In contrast, these parameters were not affected at the end of the dosing period in the 4-week study

Decreased RBC count, Hb, and Hct, and increased MCHC, also occurred in males, but not in females, at the end of dosing in the 13-week study. In general, the magnitude of these changes did not increase with dose, and they were significant ($p<0.01$) at the low dose (0.05 mg/kg/day) and the high dose (0.3 mg/kg/day) but not at the mid dose (0.1 mg/kg/day). Hematology parameters were not evaluated after the recovery period in the 13-week study.

The changes in RBC parameters in rats exposed to ClPFPECAs are notable because numerous other PFAS (e.g., perfluorobutanoic acid [PFBA], perfluorohexanoic acid [PFHxA], PFOA, PFNA, PFBS, perfluorohexane sulfonate [PFHxS], PFOS, 4,8-dioxa-3H-perfluorononanoate [ADONA], and HFPO-DA [GenX]) also cause decreases in RBC parameters (e.g., RBC count, Hb, Hct), as reviewed in ITRC (2020). Conversely, in the 7-day study, a dose-related increase in RBC count, Hb, Hct occurred in males and was significant at the two highest doses, 5 and 10 mg/kg/day, and in females at the highest dose.

Other hematological changes included increased prothrombin time in males in the 7-day study and in the 4-week study at the end of dosing and after recovery, while prothrombin time was

decreased in males and females in the 13-week study. Additionally, changes in numbers of specific types of white blood cells (absolute and/or relative) in males in the 7-day and 4-week studies, and females in the 13-week study were reported, but these effects were inconsistent in magnitude and as to the type(s) of cell affected.

Neurobehavioral tests were performed at the end of dosing and at the end of the recovery period in the 4-week and 13-week studies. Changes in grip strength occurred in both sexes in both studies. At the end of dosing in the 4-week study, there was a dose-related decrease in grip strength in males (35%, 57%, and 60% at 0.3, 0.8, and 2 mg/kg/day, respectively) and decreases of 27% and 26%, respectively, at the two higher doses in females. This endpoint was not affected in the high dose (2 mg/kg/day) males and females after the 2-week recovery period. At the end of dosing in the 13-week study, grip strength was increased by 46% in males at both the mid and high dose (0.1 and 0.3 mg/kg/day), with females unaffected. At the end of the 8-week recovery, grip strength was decreased at all three dose levels by up to 50% in males and 25% in females. There were no effects on motor activity at the end of dosing or recovery in the 4-week study. In the 13-week study, there were no effects at the end of dosing or in females at the end of recovery. However, the increases in motor activity in males at the end of recovery of up to 53% in the high dose group were not statistically significant. No effects were reported for tests of reaction to stimuli in males or females at the end of dosing or recovery in the 4-week or 13-week studies.

The individual oral repeated dose studies are summarized below:

7-Day Study (RTC, 2007): The test substance was CAS # 33089-92-2 (ammonium salt) as a white solid, purity 100%. [redacted] The batch number was 90409/86-I. This is same batch number as in the 4-week study (RTC, 2006), and RTC (2006; Vol. II, p. 173) provides the congener content of this batch, as shown in Table 10.

Table 10. Nomenclature and congener content of ClPFPECA mixture used in 7-day and 4-week rat studies (congener content provided in RTC, 2006).

Wang et al. (2013) Nomenclature	*Washington et al. (2020) Nomenclature (e,p)*	***Solvay nomenclature***	*Molecular Formula*	*Percent*
n=1, m=0	0,1	N2	$HC_8ClF_{14}O_4$	48.7
n=1, m=1	1,1	M3	$HC_{10}ClF_{18}O_5$	9.5
n=2, m=0	0,2	N3	$HC_{11}ClF_{20}O_5$	23.5
n=2, m=1	1,2	M4	$HC_{13}ClF_{24}O_6$	11.6
n=3, m=0	0,3	N4	$HC_{14}ClF_{26}O_6$	7.7

Study design

The purpose of this study was stated to be an evaluation of the toxicity of the test material for dose selection for subsequent studies. Sprague Dawley rats, approximately 4 weeks old (4 per sex/dose) were dosed with 0, 2.5, 5.0, or 10 mg/kg/day of the test substance in water for 7-days

by oral gavage, and controls were dosed with water. Hematological, clinical chemistry, and coagulation parameters were evaluated in blood samples taken at the end of the dosing period. Animals were sacrificed one day after the last dose, and a gross pathology evaluation was performed. Histopathological examination was not conducted.

Results

Mortality: All rats survived until scheduled sacrifice, and no clinical signs were noted during the study.

Body weight: At the end of dosing and at terminal sacrifice, body weights were significantly reduced in the high dose group compared to controls by 15% and 16% in males ($p<0.01$) and 12% and 14% in females ($p<0.05$), respectively. Food consumption in the high dose group was slightly lower than in controls.

Hematology: Changes in hematological parameters included a dose-related statistically significant ($p<0.05$) increase in RBC, Hb, and Hct in 5 and 10 mg/kg/day males; statistically significant ($p <0.05$) increases in these endpoints in high dose females; and increased prothrombin time ($p<0.05$) in 10 mg/kg/day males. Additionally, in males, there were dose-related increases in neutrophils and monocytes, and a dose-related decreased in lymphocytes, that were significant at the high dose (10 mg/kg/day) at $p<0.05$, $p<0.01$, and $p<0.05$, respectively.

Clinical chemistry: Clinical chemistry changes were as follows:

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) - increased by 158% ($p<0.01$) and 74% ($p<0.01$), respectively, in males at 10 mg/kg/day.
- Bilirubin - increased by 688% ($p<0.01$) in males and 369% ($p<0.01$) in females at 10 mg/kg/day.
- Cholesterol - dose-related decrease in males and females significant at 5 mg/kg/day ($p<0.05$ – males; $p<0.01$ -females) and 10 mg/kg/day ($p<0.01$); triglycerides were not reported).
- Urea - dose-related increase in significant at 5 mg/kg/day ($p<0.05$) in males and 10 mg/kg/day in males and females ($p<0.01$ – males; $p<0.05$ - females).
- Creatinine - dose-related decrease significant at 5 and 10 mg/kg/day ($p<0.05$) in females.
- Total protein and globulin - decreased at 10 mg/kg/day ($p<0.01$) in males; dose-related decreases in total protein ($p<0.05$ at 10 mg/kg) and globulin ($p<0.05$ at 5 mg/kg/day; $p<0.01$ at 10 mg/kg/day) in females.
- A/G ratio - dose-related increase significant ($p<0.01$) at 5 mg/kg/day in males and 10 mg/kg/day ($p<0.01$) in females.
- Chloride - statistically significant increase at 10 mg/kg/day in males.
- Calcium and sodium - statistically significant decreases at 10 mg/kg/day in males.

Organ weight: There were statistically significant changes in absolute organ weight and/or organ weight relative to body weight (i.e., relative organ weight) in both males and females.

Effects on relative organ weights included:

- Relative liver weight - dose-related increase in both sexes, significant ($p<0.01$) at all doses in males and at 10 mg/kg/day ($p<0.05$) in females.
- Relative spleen weight - decrease which was dose-related in males and significant at 10 mg/kg/day in both sexes (males - $p<0.05$; females - $p<0.01$).
- Relative thymus weight - dose-related decrease, that was significant ($p<0.01$) at 10 mg/kg/day in males; non-significant decrease at 10 mg/kg/day in females.
- Relative kidney and testes weights - increased ($p<0.01$) at 10 mg/kg/day in males
- Relative heart weight - dose-related decrease, significant ($p<0.05$) at 10 mg/kg/day in females.

Macroscopic pathology: A gross pathology examination was performed at terminal sacrifice, but histopathological examination was not conducted. The liver was pale in all 10 mg/kg/day males (n=4) and females (n=4), and this change was also observed in 1 of 4 females in each of the other dose groups including the control group. Dark areas or dark coloration of the stomach occurred in 2 of 4 males and 2 of 4 females at 10 mg/kg/day. Red or dark color of the lungs was noted in 1 of 4 females at 5 mg/kg/day, and 1 of 4 males and 2 of 4 females at 10 mg/kg/day. Dark pituitary occurred in 3 of 4 females at 10 mg/kg/day.

Conclusions

The study authors concluded that toxicity occurred at 5 and 10 mg/kg/day. They stated that a dose of 2.5 mg/kg/day was "reasonably tolerated," with "minor" effects, primarily in males. Based on these conclusions, they recommended that 2.5 mg/kg/day could be used as the high dose in a study of longer duration.

4-week study with 2 week recovery period (RTC, 2006): The test substance was CAS # 33089-92-2 (ammonium salt) as a white solid, purity 100%. [redacted] The batch number was 90409/86-I. This is same batch number as in the 7-day study (RTC, 2007). As mentioned above, RTC (2006 - Vol. II, p. 173) provides the congener content of this batch, as shown in Table 10.

Study design

Sprague Dawley rats, approximately 4 weeks old were dosed with 0, 0.3, 0.8, or 2 mg/kg/day of the test substance in water for 28 days by oral gavage; the controls were dosed with water. The control and 2 mg/kg/day groups included 10 males and 10 females, with 5 per sex sacrificed at the end of the dosing period and 5 per sex (the recovery group) sacrificed 14 days later. A toxicokinetic study was conducted in an additional group of 9 males and 9 females given a single oral gavage dose of 2 mg/kg. The results of the toxicokinetic study are discussed in the *Toxicokinetics* section of this document.

Before, immediately after, and 1 hour after (and 2 hours after, for the first 10 days of dosing) each daily dose, the animals were observed for reaction to treatment. Additionally, an assessment of clinical signs and a neurotoxicity evaluation was performed on each animal before treatment began and weekly during the study. Reactivity to sensory stimuli, grip strength, and motor activity were evaluated during week 4 of the treatment period and week 2 of the recovery period.

Body weight was measured on the first day of treatment, weekly during the study, and at terminal sacrifice. Food consumption was measured each week during the study period. Urinalysis was performed on overnight urine samples from individual rats collected at the end of the 4-week treatment period and the 2-week recovery period. Hematological, clinical chemistry, and coagulation parameters were measured in blood samples that were also taken at the end of the 4-week treatment period and 2-week recovery period.

At sacrifice after the last dose and at the end of the recovery period, organs were weighed and gross pathology evaluations were conducted. Histopathological evaluations were performed at the end of dosing on the liver, lungs, and thymus, and on any tissues with abnormalities, in all dose groups. Histopathological evaluation was performed on a longer list of tissues in the control and 2 mg/kg/day (high dose) groups, and any animals that died during the treatment period. Histopathological examination was also performed on the liver, lungs, and thymus of the control and high dose (2 mg/kg/day) recovery groups.

Results

Mortality: One female in the 0.3 mg/kg/day group died on day 23 of treatment. This animal had not exhibited clinical signs during the study.

Clinical signs and neurotoxicity: No clinical signs were observed after daily dosing during the study. No effects related to treatment were found during the more detailed weekly evaluations of clinical signs and neurotoxicity parameters.

Grip strength was reduced at the end of the 4-week dosing period in both sexes. In males, there was a dose-related reduction in grip strength, with decreases of 35%, 57%, and 60% compared to controls in the 0.3, 0.8, and 2 mg/kg/day groups, respectively. In females, grip strength was reduced by 27% at 0.8 mg/kg/day and 26% at 2 mg/kg/day. There was no effect on grip strength in the 2 mg/kg/day males or females at the end of the 2-week recovery period. No effects were noted in the tests for reaction to stimuli or in the test of motor activity in either sex at the end of dosing or at the end of the recovery period. It is noted that no statistical analysis was presented for any of these parameters.

Body weight: Body weight was significantly reduced ($p<0.01$) at 2 mg/kg/day in males on day 22 of dosing and at the end of dosing (day 29) and at terminal sacrifice in both sexes. On day 29, body weight was reduced by about 20% in males and about 10% in females. At the end of the 2

week recovery period, body weight was still decreased in the 2 mg/kg/day group ($p<0.01$) by 25% in males and 9% in females compared to controls. Food consumption was reduced in 2 mg/kg/day males during the dosing and recovery periods.

Hematology: Hematological effects in males at the end of the 4-week dosing period included increased prothrombin time at 0.3 mg/kg/day ($p<0.05$) and 2 mg/kg/day ($p<0.01$), decreased neutrophils, statistically significant ($p<0.05$) only at 0.3 mg/kg/day, and increased basophils at 2 mg/kg/day ($p<0.01$). No changes in RBC-related parameters were observed. There were no hematological effects in females at the end of the dosing period.

At the end of the 2-week recovery period, RBC parameters were affected in 2 mg/kg/day males and females. RBC count, Hb, and Hct were decreased in both sexes ($p<0.05$ for all, except $p<0.01$ for hematocrit in males). Additional effects in males only were increased mean corpuscular hemoglobin concentration ($p<0.01$) and increased prothrombin time ($p<0.05$). These changes were discounted by the study authors as "incidental and of not toxicological significance" because they were observed only during the recovery period. However, these effects are relevant and should not be discounted. They also occurred at much lower doses, only in males, during the 13-week study (RTC, 2016). Furthermore, numerous other PFAS (e.g., PFBA, PFHxA, PFOA, PFNA, PFBS, PFHxS, PFOS, ADONA, and HFPO-DA [GenX]) have also been found to cause these effects in rats, as reviewed in ITRC (2020).

Clinical chemistry and urinalysis: Clinical chemistry changes indicative of liver damage were noted in males in the 2 mg/kg/day group, as well as in some animals in the 0.8 mg/kg/day group at the end of the dosing period. Statistically significant effects in 2 mg/kg/day males included increases in ALP ($p<0.05$), ALT (3-fold increase; $p<0.01$), AST ($p<0.05$), and bilirubin ($p<0.01$). While the increases in these parameters were not statistically significant in 0.8 mg/kg/day males, 2 of 5 animals had increases in ALT of ~8-fold and AST of ~3-fold. In females, liver enzymes were not affected, and bilirubin was decreased in all dose groups with significance at 0.8 mg/kg/day ($p<0.01$) and 2 mg/kg/day ($p<0.05$).

Other clinical chemistry changes at the end of the dosing period were as follows: In males, cholesterol was decreased at 0.3 mg/kg/day ($p<0.01$) and 0.8 mg/kg/day ($p<0.05$), and triglycerides were decreased at 0.8 mg/kg/day ($p<0.01$). These endpoints were not affected in females. Urea was increased at 2 mg/kg/day ($p<0.05$) in both sexes, and creatinine was decreased ($p<0.05$) at this dose in females. In males, total protein was decreased at all doses, with significance at 0.3 mg/kg/day ($p<0.05$) and 2 mg/kg/day ($p<0.01$), albumin was decreased at all doses with significance at 0.3 mg/kg/day ($p<0.05$). In males, there were non-significant dose-related increases in the A/G ratio at all doses, and this endpoint was significantly increased ($p<0.05$) in females at 2 mg/kg/day. Additionally, inorganic phosphate was decreased in a dose-related manner in males with significance at 0.8 mg/kg/day ($p<0.05$) and 2 mg/kg/day ($p<0.01$), and it was also decreased in females at 2 mg/kg/day ($p<0.05$). Finally, glucose was increased at 2 mg/kg/day ($p<0.01$) in females.

At the end of the 2 week recovery period, the following clinical chemical changes were noted at 2 mg/kg/day: increased ALP ($p<0.01$) in males, decreased AST and bilirubin ($p<0.01$) in females, increased cholesterol ($p<0.01$) in males, decreased triglycerides ($p<0.01$) in both sexes, increased urea ($p<0.01$) in males, decreased creatinine ($p<0.01$) in both sexes, decreased total protein ($p<0.05$) and globulin ($p<0.01$) in males, increased albumin ($p<0.05$) in females, increased A/G ratio in males ($p<0.01$) and females ($p<0.05$), and increased glucose ($p<0.05$) in females.

There were no treatment-related changes in urinalysis parameters at the end of the dosing period or at the end of the recovery period.

Organ weights: There were statistically significant changes in absolute organ weight and/or organ weight relative to body weight (i.e., relative organ weight) in both males and females, and some of these changes persisted until the end of the 2 week recovery period. Effects on relative organ weights are summarized here. There was a dose-related increase in relative liver weight in both sexes which was significant ($p<0.01$) at all doses in males and at 0.8 and 2 mg/kg/day ($p<0.01$) in females; relative liver weight remained increased in 2 mg/kg/day males and female ($p<0.01$) at the end of the recovery period. Kidney weight was increased in a dose-related fashion in males, with significance ($p<0.01$) at 0.8 and 2 mg/kg/day, and it was increased compared to controls at 2 mg/kg/day males and females ($p<0.01$) at the end of recovery. There was a dose-related decrease in spleen weight in both sexes, with significance in males at 2 mg/kg/day ($p<0.01$), and in females at 0.8 mg/kg/day ($p<0.05$) and 2 mg/kg/day ($p<0.01$); absolute, but not relative spleen weight, remained decreased at 2 mg/kg/day in both sexes at the end of recovery. Additional changes were observed only in males. Thymus weight was decreased ($p<0.05$) at 2 mg/kg/day, with absolute, but not relative, weight decreased ($p<0.05$) at the end of recovery. Relative weights of the epididymides ($p<0.05$), testes ($p<0.01$), and thyroid ($p<0.05$) were increased at 2 mg/kg/day, with the increase in testes weight remaining at the end of recovery ($p<0.01$). Relative brain weight was increased at 2 mg/kg/day at the end of treatment ($p<0.05$) and recovery ($p<0.01$), while noting that absolute brain weight was increased ($p<0.05$) at the end of recovery.

Macroscopic pathology: A gross pathology examination was performed in the animal that died during the dosing period and at terminal sacrifice. The 0.3 mg/kg/day female that died before dosing ended had two ruptured areas in the liver, pale lungs, red thymus with multiple dark pinpoint areas, an enlarged uterus filled with clear fluid, and dark red fluid in the abdominal cavity. The study authors concluded that this death was not treatment related.
In rats sacrificed at the end of the dosing period, 2 of 5 males at 0.8 mg/kg/day, and 3 of 5 males and 1 of 5 females at 2 mg/kg/day, had pale livers; in some of these animals, the liver was swollen. Additionally, thymus size was decreased in 2 of 5 males at 2 mg/kg/day. In the 2 mg/kg/day male recovery group, 2 of 5 had enlarged livers, 2 of 5 had reduced thymus size, 2 of 5 had transparent seminal vesicles, and 2 of 5 had dilatation of the renal pelvis. In 2 mg/kg/day recovery group females, 2 of 5 had abnormal red areas in the thymus.

Microscopic pathology: Histopathological changes in the liver occurred in both males and females. Hepatocellular hypertrophy occurred in 4 of 5 males at 0.3 mg/kg/day, all (5/5) males at 0.8 mg/kg/day, and all (5/5) 2 mg/kg/day males and females at the end of the dosing period. This effect persisted, occurring in all (5/5) 2 mg/kg/day males and females at the end of the 2 week recovery period. Additionally, hepatocytic necrosis in 1 of 5 males at 0.8 mg/kg/day and 2 of 5 males at 2 mg/kg/day, and chronic hepatic inflammation in 1 of 5 males at 2 mg/kg/day, occurred at the end of dosing. Hepatocytic necrosis was also found in 1 of 5 males at the end of recovery. Although the study authors stated that the necrosis and inflammation in the liver were considered to be "spontaneous" and "unspecific" (i.e., not treatment-related), it is concluded herein that these changes are treatment-related since they increased in a dose-related fashion and co-occurred with increases in serum liver enzymes that are indicators of liver damage.

Additional histopathological changes at 2 mg/kg/day at the end of dosing included aggregation of alveolar macrophages in the lungs of 4 of 5 males and 2 of 5 females; colloid depletion in the seminal vesicles in 3 of 5 males; and atrophy of the thymus in 3 of 5 males and 2 of 5 females. Atrophy of the thymus also occurred in 1 of 5 males at the end of recovery.

Conclusions
The study authors concluded that effects occurred at all doses (≥0.3 mg/kg/day) in males, and that most effects were not reversible 2 weeks after the end of dosing with 2 mg/kg/day had ended. In females, no effects occurred at 0.3 mg/kg/day, while effects were seen at 0.8 and 2 mg/kg/day. Based on these results, they concluded that males were more sensitive to the test substance than females. As discussed in the *Toxicokinetics* section, the 8-carbon congener, which is the congener present at the highest percentage in the ClPFPECA mixture tested in this study, was excreted much more rapidly in females than in males. Additionally, in females, the 8-carbon congener was excreted much more rapidly than the other four congeners. The lower toxicity of the ClPFPECA mixture in females as compared to males in this study and the 13-week study (RTC, 2016) discussed below strongly suggest that the 8-carbon congener is a major contributor to the toxicity of the ClPFPECA mixture. It is noted that a similar analysis that considered relative excretion rates in male and female rats of PFNA and other PFAS (e.g., PFUnDA) in the Surflon mixture tested by Stump et al. (2008) and Mertens et al. (2011) similarly indicated that PFNA was the major contributor to the observed toxicity (DWQI, 2015).

The authors of RTC (2006) determined that no NOAEL could be identified in males. The LOAEL in males in this study was therefore 0.3 mg/kg/day, which was the lowest dose. In females, the authors identified a NOAEL of 0.3 mg/kg/day. The LOAEL is therefore 0.8 mg/kg/day.

13-week study with 8 week recovery period (RTC, 2016): The test material was CAS # 33089-92-2 (ammonium salt) as a white solid, purity 100%. [redacted] The batch number was 90409/86-11. The congener content of the test material is shown in Table 11. It is noted that this is a draft report. The final report was not provided to NJDEP, and it was not included in the

documents posted by USEPA (2020b) in response to a FOIA request for health effects information on the ClPFPECAs.

Table 11. Nomenclature and congener content of ClPFPECA mixture used in the 13-week rat study (RTC, 2016)

Solvay nomenclature	*Wang et al. (2013) Nomenclature*	*Washington et al. (2020) Nomenclature (e,p)*	*Molecular Formula*	*Percentage*[a]
N2	n=1, m=0	0,1	$HC_8ClF_{14}O_4$	37.1
M3	n=1, m=1	1,1	$HC_{10}ClF_{18}O_5$	7.3
N3	n=2, m=0	0,2	$HC_{11}ClF_{20}O_5$	18.2
M4	n=2, m=1	1,2	$HC_{13}ClF_{24}O_6$	5.9
N4	n=3, m=0	0,3	$HC_{14}ClF_{26}O_6$	9.1
N5	n=4, m=0	0,4	$HC_{17}ClF_{32}O_7$	1.3

[a] The sum of the percentages of the 6 congeners shown is 78.9%. RTC (2016) states that "the remaining 20% are lighter acids, ketones, neutral substances."

Study design

Sprague Dawley rats (15 per sex/dose group), approximately 4 weeks old, were dosed daily with 0, 0.05, 0.1, or 0.3 mg/kg/day of the test substance in water for a minimum of 13 weeks by oral gavage; the controls were dosed with water. In each dose group, 10 males and 10 females were sacrificed at the end of the dosing period, and 5 per sex per dose group (the recovery groups) were sacrificed 8 weeks later.

Prior to the first dose and each day during the dosing period, the animals were observed and any clinical signs were noted. Additionally, an assessment of clinical signs and a neurotoxicity evaluation was performed on each animal before treatment began and weekly during the study. It is stated that in the study report that reactivity to sensory stimuli (auditory, visual, proprioceptive), grip strength, and motor activity were evaluated during week 12 or 13 of the treatment period and week 8 of the recovery period. However, no data on reaction to sensory stimuli appear to be reported.

Body weight was measured on the first day of treatment, weekly during the study, and at terminal sacrifice. Food consumption was measured each week during the study period.
An ophthalmic examination of both eyes of each animal was performed before treatment, and in the control and 0.3 mg/kg/day groups during week 13 of dosing.

Hematological, clinical chemistry, and coagulation parameters were measured in blood samples that were taken at the end of the 13-week treatment period, and clinical chemistry evaluation was performed at the end of the 8-week recovery period.

At sacrifice after the last dose and at the end of the recovery period, organs were weighed and gross pathology evaluations were conducted. Histopathological evaluations were performed at

the end of the 13-week dosing period on the liver from females; the liver, thyroid, and pituitary from males, on "all abnormalities" in all dose groups; and on a longer list of tissues in the control and 3 mg/kg/day (high dose) groups. At the end of the 8-week recovery period, histopathological examination was performed on the livers in females in all dose groups and the liver, thyroid, and pituitary from males in all dose groups.

Amendments to the study protocol
The study protocol was amended several times. The first two amendments were clarifications that did not affect the data to be collected, while the third amendment removed evaluations that would have provided additional information on liver toxicity, including the lowest dose and earliest time point at which there are changes in biomarkers of liver damage and the mechanism through which the liver damage occurs.

According to the original protocol, blood samples for additional studies related to the mechanism of hepatic toxicity were to be collected from each animal prior to dosing, during the dosing period at the end of weeks 1, 4, 8, and 13, and possibly at the end of the 8 week recovery period. These samples were to be analyzed for a panel of liver injury biomarkers (arginase 1 [ARG1], aspartate aminotransferase 1 [GOT1], glutathione-S-transferase alpha [GSTα], Ecto-5'-nucleotidase [5'NT/CD73], and sorbitol dehydrogenase [SDH]) and for microRNA-122 (miRNA-122), stated to be "a well known liver injury biomarker, in order to supply additional information on mechanisms of hepatic toxicity." In the original protocol, the evaluation of these parameters would have been performed in a "stepwise" manner, based on a "Decision Tree" approach included in the protocol. This Decision Tree approach was designed to identify the lowest dose and the earliest time point at which these parameters are affected in males and females.

The third revision to the protocol occurred after the study and data evaluation were completed. It is dated December 13, 2016, one day before the date of the draft report. The revision states that the sponsor (Solvay) had requested that the liver injury panel biomarker panel and miRNA-122 evaluations included in the original protocol not be conducted and that the sections of the protocol about these evaluations be deleted. The revision states that the blood samples that had been collected for those evaluations from each animal at the end of weeks 1, 4, 8, and 13 would be "eliminated within 3 months of the Final Report."

Results

Mortality: There was no mortality during the study.

Clinical signs and neurotoxicity: No clinical signs that were considered to be treatment related were seen in the observations after each daily dose during the study.

No effects that were considered toxicologically significant by the study authors were observed during the more detailed weekly evaluations that included neurotoxicity parameters. The study

report states that the mean number of rearing animals was reduced at some time points in 0.3 mg/kg/day (high dose) males and females, and that this observation was not considered to be toxicologically relevant. The data tables in RTC (2016) show that the number of animals with rearing behavior was significantly ($p<0.05$, 0.01, or 0.001) decreased in males at 0.3 mg/kg/day at 6 of 13 weeks (weeks 1, 3, 5, 7, 8, and 13) during the dosing period. The number was also decreased in one of the lower dose groups on weeks 1 and 13. In females, rearing was significantly decreased at 0.1 and/or 0.3 mg/kg/day at 5 of the 13 weeks, with substantial but non-significant decreases on several other weeks. In the weekly evaluations during the 8 week recovery period, there were no significant effects on rearing in males and only a few significant values in females.

RTC (2016) states that there were no treatment-related effects on the tests of sensory reaction (i.e., reaction to sensory stimuli and grip strength) at the end of dosing or at the end of recovery. However, these statements do not appear to be accurate because data were not reported for the tests of reaction to sensory stimuli and there were statistically significant changes in grip strength in treated groups.

On day 78 (week 12), grip strength was significantly increased ($p<0.01$) in males at 0.1 and 0.3 mg/kg/day; there was no effect in females. While not statistically significant, grip strength was decreased at the end of the recovery period at 0.05, 0.1, and 0.3 mg/kg/day by 27%, 50%, and 46%, respectively, in males and 11%, 9%, and 25%, respectively, in females.

There were no effects on motor activity during the dosing period, but at the end of recovery, there were non-significant increases in males at 0.05, 0.1, and 0.3 mg/kg/day of 30%, 28%, and 53%, respectively.

Body weight and food consumption: There were no effects on body weight, body weight gain, or food consumption during the study.

Ophthalmic parameters: No ophthalmic effects were observed in the evaluation at the end of the dosing period.

Hematology: Hematological parameters were evaluated at the end of the dosing period. At the end of the dosing period in males, effects on RBC-related parameters in males were similar to effects in males at the end of the 2 week recovery in the 4-week study, as follows: RBC count was decreased at 0.05 mg/kg/day ($p<0.05$), 0.1 mg/kg/day (not significant), and 0.3 mg/kg/day ($p<0.01$). Hb and Hct were decreased, and mean corpuscular hemoglobin concentration was increased, at 0.05 mg/kg/day ($p<0.01$), 0.1 mg/kg/day (not significant), and 0.3 mg/kg/day ($p<0.01$). The magnitude of the changes in RBC-related parameters did not increase with dose. There was also a dose-related decrease in absolute and relative number of eosinophils that was significant at 0.1 mg/kg/day ($p<0.05$) and 0.3 mg/kg/day ($p<0.01$). Prothrombin time was decreased at 0.1 mg/kg/day ($p<0.05$) and 0.3 mg/kg/day (not significant).

The authors of the study report stated that these changes were "of no toxicological relevance" because of their "minimal severity and/or absence of dose relation." However, these effects are relevant and should not be discounted. They also occurred in males and females after the 2 week recovery period in the 4-week study (RTC, 2006). Furthermore, numerous other PFAS (e.g., PFBA, PFHxA, PFOA, PFNA, PFBS, PFHxS, PFOS, ADONA, and HFPO-DA [GenX]) have also been found to cause these effects in rats, as reviewed in ITRC (2020). It is noted that, although RBC parameters were decreased in both sexes at the end of the 2 week recovery period in the 4-week study, a hematology evaluation was not performed at the end of the recovery period in the 13-week study.

There were fewer changes in females, as follows: RBC count was increased only at 0.1 mg/kg/day ($p<0.05$), absolute and relative number of neutrophils was increased at 0.05 and 0.1 mg/kg/day ($p<0.05$, except $p<0.01$ for relative number at 0.1 mg/kg/day), relative numbers of lymphocytes ($p<0.05$) and eosinophils ($p<0.001$) were decreased at 0.1 mg/kg/day only, and prothrombin time was decreased ($p<0.01$) at 0.3 mg/kg/day.

Clinical chemistry: At the end of the dosing period, the liver enzyme ALP was increased ($p<0.05$) in males at 0.3 mg/kg/day. However, most data for GGT and bilirubin, which are also indicators of liver damage, were excluded because invalid values were obtained. In females, AST and bilirubin were decreased ($p<0.01$) at 0.3 mg/kg/day, and some GGT data were excluded. In males, cholesterol was decreased at all doses (0.05 and 0.1 mg/kg/day, $p<0.01$; 0.3 mg/kg/day, $p<0.05$). Triglycerides were decreased at all doses in males (0.05 mg/kg/day, not significant; 0.1 mg/kg/day, $p<0.01$; 0.3 mg/kg/day, $p<0.05$), and they were increased ($p<0.05$) at 0.3 mg/kg/day in females. Glucose was decreased in males at 0.05 mg/kg/day ($p<0.05$) and increased ($p<0.05$) in females at 0.3 mg/kg/day. Urea was increased ($p<0.01$) only in males at 0.3 mg/kg/day, and creatine was decreased ($p<0.01$) in males at 0.05 mg/kg/day and in females at all doses (0.05 mg/kg/day, $p<0.05$; 0.1 and 0.3 mg/kg/day, $p<0.01$). Calcium was increased in males at 0.1 mg/kg/day ($p<0.01$) and in both sexes at 0.3 mg/kg/day ($p<0.05$). Finally, total protein and albumin were increased in females at 0.1 mg/kg/day ($p<0.01$) and 0.3 mg/kg/day ($p<0.05$).

In males at the end of the 8-week recovery period, ALT was increased in a dose-related fashion, although not statistically significant, by 77% at 0.1 mg/kg/day and 159% at 0.3 mg/kg/day. The dose-related decrease in triglycerides in males observed at the end of the dosing period persisted throughout the recovery period ($p<0.05$ at 0.05 and 0.1 mg/kg/day; $p<0.01$ at 3 mg/kg/day). Creatinine was decreased at all dose in males (0.05 mg/kg/day, $p<0.05$; 0.1 mg/kg/day, $p<0.01$; 0.3 mg/kg/day, $p<0.05$), and it was also decreased at 0.05 mg/kg/day ($p<0.05$) in females. Calcium remained increased at 0.3 mg/kg/day in males ($p<0.01$), and total protein and albumin were decreased in males only at 0.1 mg/kg/day ($p<0.05$).

Organ weights: At the end of the dosing period, absolute and relative liver weights were increased in a dose-related manner at all doses in males, and at 0.3 mg/kg/day in females. In males, the increase in relative liver weight was not significant at 0.05 mg/kg/day, but it was significant ($p<0.001$) at 0.1 and 0.3 mg/kg/day. The increased relative liver weight in females at

0.3 mg/kg/day was also significant ($p<0.001$). Absolute and relative liver weight remained increased at the end of the recovery period at 0.3 mg/kg/day in both males and females ($p<0.01$). In females, relative uterus weight was also increased at 0.1 and 0.3 mg/kg/day ($p<0.05$) at the end of recovery.

Macroscopic pathology: Gross pathology findings that are potentially related to treatment were reported in the liver in males and the thymus in females. The liver was increased in size in 6/10 males at 0.3 mg/kg/day, and it was described as swollen in 2/10 males at 0.1 mg/kg/day and 9/10 males at 0.8 mg/kg/day; swollen liver was also reported in 1/10 females at 0.3 mg/kg/day. No changes in the liver were reported at the end of the recovery period.

Thymus size was described as small in 1/10 females at 0.3 mg/kg/day at the end of dosing, and in 0/5, 4/5, 1/5, and 3/5 females in the control, 0.05, 0.1, and 0.3 mg/kg/day groups, respectively, at the end of recovery. Despite the large percentage of treated females with small thymus at the end of recovery, no change in the absolute or relative weight of the thymus was reported.

Microscopic pathology: Histopathological changes were found in the livers of both sexes, and the thyroid, pituitary, and seminal vesicles of males.

At the end of the dosing period, hepatocellular hypertrophy occurred in all (10/10) males at 0.1 mg/kg/day and all males and females (10/10) at 0.3 mg/kg/day. The study report notes that this effect was more severe in males at 0.3 mg/kg/day than at the lower dose, 0.1 mg/kg/day, or in females at 0.3 mg/kg/day This effect persisted through the 8 week recovery period in 4/5 males at 0.3 mg/kg/day. Hepatocytic necrosis was found at the end of dosing in 2/10 males at 0.3 mg/kg/day and 1/10 females at 0.1 mg/kg/day, and at the end of recovery in 2/5 males at 0.3 mg/kg/day. Micro- and macrovesicular hepatocytic vacuolation, described as "most like [sic] consistent with fatty change" (i.e., steatosis) was reported at the end of dosing in 9/10 males at 0.05 mg/kg/day and 6/10 males at 0.1 mg/kg/day, and in 3/10 females at 0.3 mg/kg/day. This change was also seen at the end of recovery in 0/5, 4/5, 3/5, and 3/5 males at 0, 0.05, 0.1, and 0.3 mg/kg/day, respectively. Additionally, clear cell focus/foci in the liver was reported in 1/10 males at 0.3 mg/kg/day at the end of dosing.

Regarding the histopathological changes in the liver, the pathology report and the conclusions of the study report state that: "Hepatocellular hypertrophy may be considered an adaptive and reversible change that does not compromise functional integrity, in particular in all treated females and probably in males dosed at 0.05 and 0.1 mg/kg/day. On the other hand, in the presence of hepatic degenerative changes such as hepatocytic necrosis and/or steatotic vacuolar degeneration, micro and/or macro-vesicular vacuolation, observed in the high dose males and still present after 8 weeks of recovery, the liver pathology may be considered adverse." However, this statement does not appear to be accurate or complete since hepatocytic necrosis also occurred in a female at 0.1 mg/kg/day at the end of the dosing period.

Additionally, micro- and/or macrovesicular vacuolation, concluded to likely be due to steatosis, occurred not only in 3/10 females at the end of dosing and 3/5 males after recovery at the high dose (0.3 mg/kg/day), but also at 0.05 mg/kg/day in 9/10 males at the end of dosing and 4/5 males at the end of recovery, and at 0.1 mg/kg/day in 6/10 males at the end of dosing and 3/5 males at the end of recovery. As discussed above, RTC (2016) concludes that this effect is indicative of hepatic degeneration (i.e., toxic and adverse). The human relevance and adversity of this effect are further discussed in the subsection on *"Selection of studies, endpoints, and data for dose-response evaluation"* in the *Development of Reference Dose* section below.

Follicular cell hypertrophy of the thyroid occurred in 8/10 males at 0.1 mg/kg/day, and this thyroid change as well as basophilic cell hypertrophy of the pars distalis of the pituitary occurred in all (10/10) males at 0.3 mg/kg/day at the end of dosing period. Each of these changes occurred in 1/5 males at 0.3 mg/kg/day at the end of recovery.

RTC (2016) states that the effects on the thyroid and pituitary occur as a compensatory response to increased metabolic breakdown of thyroid hormones resulting from hepatic microsomal enzyme induction. It is stated that the decrease in thyroid hormone levels causes increased secretion of thyrotropin releasing hormone (TRH) from the hypothalamus, which stimulated the pituitary to release thyroid stimulating hormone (TSH) and caused pituitary hypertrophy. The hypertrophy of the thyroid follicular cells is stated to result from stimulation by TSH to increase production and release of the thyroid hormones, T3 and T4. However, no evidence is presented to support these conclusions. For example, levels of TSH and thyroid hormones (T3, T4) were not measured in this study. Additionally, the study report states that it is "well known" that thyroid follicular cell and pituitary hypertrophy are secondary to hepatocellular hypertrophy. Additionally, the two citations (Hall et al., 2012; Zabka et al., 2011) provided by the study authors do not support the conclusion that thyroid and pituitary hypertrophy can be assumed to be secondary to hepatocellular hypertrophy. Hall et al. (2012) cites Zabka et al. (2011) as its only example of this phenomenon. Zabka et al. (2011) reports on this process as a novel observation during toxicity studies conducted as part of the safety assessment of a drug, and its abstract states that "effects on the pituitary gland following hepatic enzyme induction-mediated hypothyroidism have not been reported previously." Furthermore, the changes in thyroid or pituitary histopathology reported in the 13-week study of the ClPFPECAs have not been reported in studies of other PFAS that included histopathological evaluations, and specific studies of the mechanism of thyroid effects of other PFAS show that they do not occur through the mechanism presented here (Chang et al., 2008; Ramhøj et al., 2020).

Additionally, colloid depletion in the seminal vesicles, was observed at 0.3 mg/kg/day in 3/10 males at the end of dosing and 1/5 males at the end of recovery.

Conclusions

RTC (2016) concludes that "possible treatment-related effects" occurred in males at 0.3 mg/kg/day, and "with minor extent" in females at 0.3 mg/kg/day and in both sexes at 0.1 mg/kg/day. The report further concludes that "no changes that could be considered adverse"

were found in males or females at 0.05 mg/kg/day or females at 0.1 mg/kg/day. RTC (2016) concluded that the NOAEL in this study was 0.05 mg/kg/day in males and 0.1 mg/kg/day in females.

The conclusion that the NOAEL was 0.05 mg/kg/day and the LOAEL was 0.1 mg/kg/day in males does not appear to be valid because micro- and macrovesicular hepatocytic vacuolation, stated to likely be associated with steatosis, was not reported in control groups but occurred at 0.05 mg/kg/day in 9/10 males at the end of dosing and 4/5 males at the end of the recovery period. As discussed above, micro- and/or macrovesicular vacuolation associated with steatosis is considered to be an adverse effect. Additionally, triglycerides, cholesterol, and creatinine were decreased in males at 0.05 mg/kg/day and the effects on triglycerides and creatinine persisted to the end of recovery. Furthermore, RBC parameters (RBC, Hb, Hct) were significantly decreased in males at 0.05 mg/kg/day. Based on the information above, it is concluded herein that the LOAEL in males in this study was 0.05 mg/kg/day, and no NOAEL was identified.

Because increased liver weight, hepatocellular hypertrophy, and vacuolation were reported at 0.3 mg/kg/day but not at $\leq$0.1 mg/kg/day in females, it is concluded herein that, as stated in the study report, the NOAEL in females was 0.1 mg/kg/day and the LOAEL was 0.3 mg/kg/day. However, it is noted that hepatic necrosis occurred in 1/10 (10%) of females at 0.1 mg/kg/day. While formal historical control data for hepatic necrosis in Harlan Sprague Dawley rats were not located, the incidence of hepatic necrosis in a 2-year chronic study in female Harlan Sprague Dawley rats which included interim sacrifice at several time points was 0/10 at 14 weeks, 0/10 at 31 weeks, 0/8 at 53 weeks, and 1/53 (1.9%) at 2 years (Hailey et al., 2005). These data suggest that the necrosis observed in the female rat in the 0.1 mg/kg/day dose group may have been treatment related. Additionally, the macroscopic pathology examination reported a small thymus in 4/5 females at 0.05 mg/kg/day, and in 1 or 3 of the 5 animals in each of the higher dose group, but not in the control group, at the end of recovery.

Toxicology studies of other perfluoroether alkyl acids

Available data suggest that longer chain PFPECA analogues are more toxic than HFPO-DA (GenX) which has 6 carbons and one ether oxygen. These larger analogues include hexafluoropropylene oxide-trimer acid (HFPO-TA; 9 carbons, 2 ether oxygens) and hexafluoropropylene oxide-tetramer acid (HFPO-TeA; 12 carbons, 3 ether oxygens). In mouse studies, HFPO-TeA was more hepatotoxic than HFPO-DA (Wang et al., 2017), and HFPO-TA was more hepatotoxic than PFOA (Sheng et al., 2018).

Guo et al. (2019) studied the toxicity and bioaccumulation of three PFPECAs found in the Cape Fear River, the drinking water source for Wilmington NC, in male mice. PFO2HxA, PFO3OA, and PFO4DA had 4, 5 or 6 carbons, including 2, 3 or 4 -O-CF_2- groups, respectively. As discussed in the *Toxicokinetics* section above, serum levels at a given dose and the liver:serum ratio increased with chain length in this series of PFPECAs. Only the largest and most

bioaccumulative PFPECA, with 6 carbons and 4 such groups (PFO4DA), caused increased liver weight after dosing with 0.4, 2, or 10 mg/kg/day for 28 days.

After oral gavage dosing with 10 µg/kg/day for 140 days, PFO4DA and PFO5DoA (7 carbons, 4 -O-CF_2- groups) caused increases in body weight, relative liver weight, and serum glucose, triglycerides and free fatty acids, as well as biochemical changes in the liver consistent with reduced glycolysis in male mice. Dosing with 2 µg/kg/day did not cause these effects (Chen et al., 2021).

6:2 ClPFESA caused liver toxicity in a study of male mice (Zhang et al., 2018). After dosing with 0.04, 0.2, or 1 mg/kg/day for 56 days, relative liver weight was increased at 0.2 and 1 mg/kg/day. Also, at 1 mg/kg/day, serum levels of the liver enzymes ALT and ALT were increased, and serum lipids levels were also affected, with increased triglycerides and low density lipoprotein (LDL) and decreased high density lipoprotein (HDL). Hepatic lipid accumulation was a more sensitive endpoint, with increased levels of total cholesterol and triglycerides in liver at all doses ($\geq$ 0.04 mg/kg/day). In a study of reproductive toxicity of 6:2 ClPFESA in male mice that used the same doses and exposure duration as Zhang et al. (2018), relative weights of epididymides and testis decreased at the highest dose, 1 mg/kg/day. However, there were no histopathological changes in these organs, and hormone levels, sperm counts, fertility, and expression of several testicular genes were not affected (Zhou et al., 2018). In male and female mice exposed to 0, 1, 3, or 10 µg/L in drinking water for 10 weeks, 6:2 ClPFESA accumulated in the small and large intestine, and exposure to 10 µg/L, but not the lower doses, damaged the gut barrier, and caused inflammation of the colon (Pan et al., 2019).

MODE OF ACTION

ClPFPECAs

Genotoxicity

As is generally the case for other PFAS (ITRC, 2020; DWQI, 2015; DWQI, 2017; DWQI, 2018), negative results were reported in the genotoxicity studies of ClPFPECAs that were identified for review.

Three reports of bacterial mutagenicity studies of ClPFPECAs were provided to NJDEP by Solvay (RBM, 1998k; RTC, 2003b; RTC, 2003c). All of these studies were conducted at contract toxicology laboratories in Italy and were sponsored by Ausimont. The test substances were as follows: CAS # 220182-27-4 (ethyl ester), [redacted] in RBM (1998k); CAS # 220207-15-8 (sodium salt), [redacted] in RTC (2003b); and CAS # 330809-92-2 (ammonium salt), [redacted] in RTC (2003c). All three studies tested the ClPFPECAs with and without metabolic activation (with liver S9 from rats induced with phenobarbital and beta-naphthoflavone) in the same five strains of bacteria: *Salmonella typhimurium* TA 1535, TA 1537, TA 98, and TA 100, and *Escherichia coli* WP2 uvrA$^-$. In RBM (1998k), two independent mutagenicity studies were performed in triplicate of ClPFPECAs at up

to 1500 µg/ plate, after preliminary studies that determined that higher concentrations were cytotoxic. RTC (2003a) and RTC (2003b) used identical protocols in which ClPFPECAs at up to 5000 µg/ plate were tested in triplicate with and without a 30-minute preincubation step. ClPFPECAs were negative for mutagenicity at all concentrations and test conditions in these studies.

Additionally, EFSA (2010) is a peer-reviewed publication that provides a scientific opinion on the safety evaluation of the substances with CAS No. 329238-24-6 for use in food contact materials. EFSA (2010) states that the substance was negative for mutagenicity in bacteria (presumably referring to one of the studies provided by Solvay described above) and in mammalian cells (L5178 tk+/tk- mouse lymphoma forward mutation assay), and that it was also negative for chromosomal aberrations (clastogenicity) in Chinese hamster ovary cells. However, no citations were provided for the bacterial mutagenicity, mouse lymphoma forward mutation, or Chinese hamster ovary cell assays, and the latter two studies were not provided to NJDEP by Solvay. Therefore, it was not possible to evaluate the conclusions presented by EFSA (2010) about these studies.

Mode(s) of action for systemic effects

Other than the genotoxicity studies mentioned above, no *in vitro* or *in vivo* mode of action studies for ClPFPECAs were identified. For example, no *in vitro* or *in vivo* studies of activation of peroxisome proliferator activated receptors (PPARs) or other nuclear receptors, such as have been conducted for other PFAS, were identified (DWQI, 2015; DWQI, 2017; DWQI, 2018).

As discussed elsewhere in this document, hepatic effects are the most sensitive toxicological endpoints for ClPFPECAs in the studies that were reviewed herein (while noting that there are no data on several effects of interest including developmental and reproductive toxicity, immunotoxicity, and carcinogenicity). Hepatic effects in rats included increased relative liver weight, increased serum levels of liver enzymes, hepatocellular hypertrophy, hepatocellular necrosis, and hepatocellular vacuolation concluded to likely be due to steatosis (Table 7), and ClPFPECAs were associated with increased serum liver enzymes in occupationally exposed workers. As such, the mode of action for hepatic effects of ClPFPECAs is of interest.

It is noted that the original protocol for the 13-week rat study (RTC, 2016) included evaluation of blood samples taken at several time points during the dosing period and at the end of the 8 week recovery period for specific biomarkers stated to be indicative of the mechanism of action for hepatic toxicity. As discussed above, hepatic effects occurred at very low doses in this study, with a LOAEL of 0.05 mg/kg/day and no NOAEL identified in males. The additional biomarkers that were to have been evaluated included arginase 1 (ARG1), aspartate aminotransferase 1 (GOT1), glutathione-S-transferase alpha (GSTα), Ecto-5'-nucleotidase (5'NT/CD73), and sorbitol dehydrogenase (SDH), as well as microRNA-122 (miRNA-122), which was stated to be "a well known liver injury biomarker". Although blood samples for evaluation of these biomarkers were collected as planned, the protocol was amended immediately before finalization of the study report at the request of the sponsor (Solvay

Specialty Polymers Italy) to delete the sections that discussed these evaluations, and the evaluations were not performed.

Other perfluoroether alkyl acids

Several perfluoroether and perfluoropolyether carboxylates (PFPECAs) that are classified as hexafluoropropyl acids (HFPO-DA, HFPO-TA, and HFPO-TeA) caused estrogenic effects in zebrafish (Xin et al., 2019). Additionally, several PFPECAs of various chain lengths (PFO3OA, PFO4DA, PFO5DoDA), as well as PFOS, decreased thyroid hormone levels in developing zebrafish embryos, leading to thyroid hormone-dependent malformations of the swim bladder (Wang et al., 2020).

Toxicity and bioaccumulation of 6:2 ClPFESA in zebrafish has been observed in several studies. Endpoints that have been reported include bioaccumulation in larvae and adults (Wu et al., 2019a, b), hepatoxicity (Shi et al., 2019a; Wu et al., 2019b), reproductive toxicity in a two-generation study (Shi et al., 2018), disruption of cardiac development (Shi et al., 2017), and thyroid toxicity from developmental exposures to environmentally relevant concentrations (Deng et al., 2018) and in unexposed offspring after exposure of the parental generation (Shi et al., 2019b). Additionally, Tu et al. (2019) reported that 6:2 Cl-PFECA was more bioaccumulative and caused disruption of metabolism in zebrafish at lower concentrations than PFOA.

DEVELOPMENT OF ISGWQC

Consideration of human epidemiological data

The limited information on health effects of ClPFPECAs in humans (Solvay, 2019) is insufficient to use as the basis for quantitative risk assessment. That being said, Solvay (2019a) reports that ClPFPECAs are highly bioaccumulative, with a half-life for elimination of 2.5-3 years, similar to the half-life of PFOA and PFNA. Solvay (2019a) also reports associations of ClPFPECA exposure with an unusually large number of health endpoints including increased levels of serum lipids, liver enzymes, prostate serum antigen (PSA), TSH and FT3, and decreased serum levels of alpha-2-globulins, the immunoglobulins IgG and IgM, and estradiol. Most of these changes are consistent with the toxicological effects of ClPFPECAs and/or other PFAS in laboratory animals and/or health effects of other PFAS in epidemiological studies (DWQI, 2015; DWQI, 2017; DWQI, 2018). This information suggests a need for caution about human exposures to ClPFPECAs and supports the use of a public health protective approach in developing an ISGWQC based on animal toxicology data.

Weight of evidence for carcinogenicity

N.J.A.C 7:9C stipulates that ISGWQC be based on a one in one million lifetime (10-6) cancer risk level for carcinogens and no adverse effects from lifetime ingestion for non-carcinogens. No information is available regarding the carcinogenic potential of ClPFPECAs as relevant human epidemiological studies or chronic carcinogenicity bioassays in laboratory animals have not been conducted. Therefore, the ISGWQC is based on non-carcinogenic effects (i.e., a Reference Dose [RfD]).

Development of Reference Dose

Selection of studies, endpoints, and data for dose-response evaluation

Non-carcinogenic toxicological effects that are sensitive, well established, adverse or a precursor to adverse effect(s) and considered relevant to humans are appropriate for consideration as the basis for RfD development. The most sensitive toxicological effects (i.e., effects that occurred at the lowest dose) in the available toxicology studies were observed in male rats in the 13-week study (RTC, 2016). This is the longest duration study of ClPFPECAs that was identified for review, and 13 weeks of exposure to rodents is considered to be subchronic. Male rats were more sensitive than females in this study, presumably (as discussed above) due to the rapid excretion of the 8-carbon congener, the predominant congener in the ClPFPECA mixture tested, in females. The three toxicological effects selected for dose-response evaluation were increased relative liver weight, decreased RBC parameters (RBC count, Hb, and Hct), and incidence of hepatocellular micro- and macrovesicular vacuolation likely due to steatosis. Each of these endpoints is discussed below:

Data for increased relative liver weight in male rats in the 13-week study (RTC, 2016) was selected for dose-response evaluation. Increased relative liver weight is a well-established and sensitive endpoint for PFAS in general (ITRC, 2020; Bil et al., 2021), and this effect was consistently reported in all three studies of ClPFPECAs in which organ weights were measured, including the 13-week study (RTC, 2013) and the two shorter duration repeated dose studies of ClPFPECAs (7-day, RTC, 2007; 4-week, RTC, 2006). Evaluation of the data from the three repeated dose studies indicates that the magnitude of increased relative liver weight caused by ClPFPECAs increases with both dose and exposure duration, and that it is accompanied by and/or progresses to effects indicative of liver damage including increased serum levels of liver enzymes, hepatocellular necrosis, and vacuolation indicative of steatosis (Tables 7 and 8).

There is no information to suggest that the increased relative liver weight caused by ClPFPECAs in rats is not relevant to humans, and detailed mode of action evaluations of other PFAS, including PFOA (DWQI, 2017), PFOS (DWQI, 2018), PFNA (DWQI, 2015), and HFPO-DA (GenX) (USEPA, 2018), have concluded that increased relative liver weight caused by these PFAS in rodents is relevant to humans. In the 13-week study (RTC, 2016), relative liver weight was increased in males in a dose-related fashion, with statistically significant increases at the two higher doses (0.1 and 0.3 mg/kg/day), but not at the lowest dose, 0.05 mg/kg/day. Therefore, the NOAEL and LOAEL for increased relative liver weight were identified as 0.05 mg/kg/day and 0.1 mg/kg/day, respectively.

Data for decreases in RBC parameters (RBC count, Hb, Hct) in male rats in the 13-week study (RTC, 2016) were the second data set selected for dose-response evaluation. These effects were also observed in the 4-week study at the end of the 2-week recovery period, but not at the end of the dosing period (RTC, 2006). Decreases in these RBC parameters are well established effects of PFAS, as numerous other PFAS (e.g., PFBA, PFHxA, PFOA, PFNA, PFBS, PFHxS, PFOS,

ADONA, and HFPO-DA[GenX]) also cause decreases in these same three parameters (ITRC, 2020). There is no information to suggest that decreases in RBC parameters caused by ClPFPECAs in rats are not relevant to humans, and such hematological changes are considered to be adverse or precursors to adverse effects as they are indicative of anemia or can progress to anemia. It is notable that these hematological effects in a chronic rat study (Sibinski, 1987) were a primary basis for the previous NJDEP (2007) drinking water guidance value for PFOA (published as Post et al., 2009), which was based on review of toxicology studies discussed in USEPA (2005). In the 13-week study (RTC, 2016), statistically significant decreases in RBC parameters (RBC count, Hb, Hct) occurred in males at 0.05 mg/kg/day, the lowest dose tested. Therefore, the LOAEL for decreased RBC parameters was identified as 0.05 mg/kg/day, and a NOAEL was not identified.

Data for the incidence of micro- and macrovesicular hepatocellular vacuolation in male rats in the 13-week study (RTC, 2016) were the third dataset selected for dose-response evaluation. This is a sensitive endpoint, as it occurred at the lowest dose in males in the 13-week study. In the 13-week study, micro- and macrovesicular vacuolation occurred in treated rats at the end of dosing in both males and females and after the 8-week recovery period in males, and it was not reported in control animals. However, this effect was not reported in the 4-week study (RTC, 2006), the only other study that included histopathological evaluation, possibly because it occurs only after a longer exposure to ClPFPECAs.

RTC (2016) concludes that micro- and macrovesicular hepatocellular vacuolation caused by ClPFPECAs was likely caused by steatosis, and that it is indicative of hepatic degeneration (i.e., toxic and adverse). Relevant to this topic, Das et al. (2017) found that other bioaccumulative PFAS (PFOA, PFNA, and PFHxS) cause hepatic steatosis in mice and that PFNA and PFHxS caused this effect in both PPAR-alpha null and wild type mice. Das et al. (2017) also review numerous other studies also reporting that these PFAS cause hepatic steatosis and triglyceride accumulation in rodents. Das et al. (2017) state that "steatosis [in the liver] is the first step in a continuum of chemical-induced adverse effects that, under chronic exposure conditions, include steatohepatitis, fibrosis, impaired liver function, and cancer," and further note that the USEPA Integrated Risk Information System (IRIS) assessments for several chemicals use hepatic steatosis as the critical effect (Kaiser et al., 2012). Consistent with animal toxicology data, there is growing evidence that bioaccumulative PFAS are associated with biomarkers of non-alcoholic fatty liver disease (NAFLD) in humans (Bassler et al., 2019; Jain and Ducatman, 2019; Cave, 2020; Steenland et al., 2020). Based on the information discussed above, micro- and macrovesicular hepatocellular vacuolation caused by ClPFPECAs is considered adverse and relevant to humans. In the 13-week study (RTC, 2016), micro- and/or macrovesicular vacuolation was not reported in control groups but occurred at 0.05 mg/kg/day in 9/10 males at the end of dosing and 4/5 males after the recovery period. Therefore, the LOAEL for hepatocellular micro- and macrovesicular vacuolation in males was identified as 0.05 mg/kg/day, and a NOAEL was not identified.

Determination of Points of Departure (PODs) for toxicological endpoints selected for dose-response evaluation

The first step in dose-response analysis is identification of a Point of Departure (POD), which is the dose within or close to the dose range used in the study from which extrapolation begins. As described below, if a Benchmark Dose can be developed, it is preferred for use as the POD. If BMD modeling does not give an acceptable fit to the data, the NOAEL (or LOAEL, if a NOAEL is not identified) is used as the POD. The BMD modeling presented below was performed using USEPA BMD Software Version 3.2.

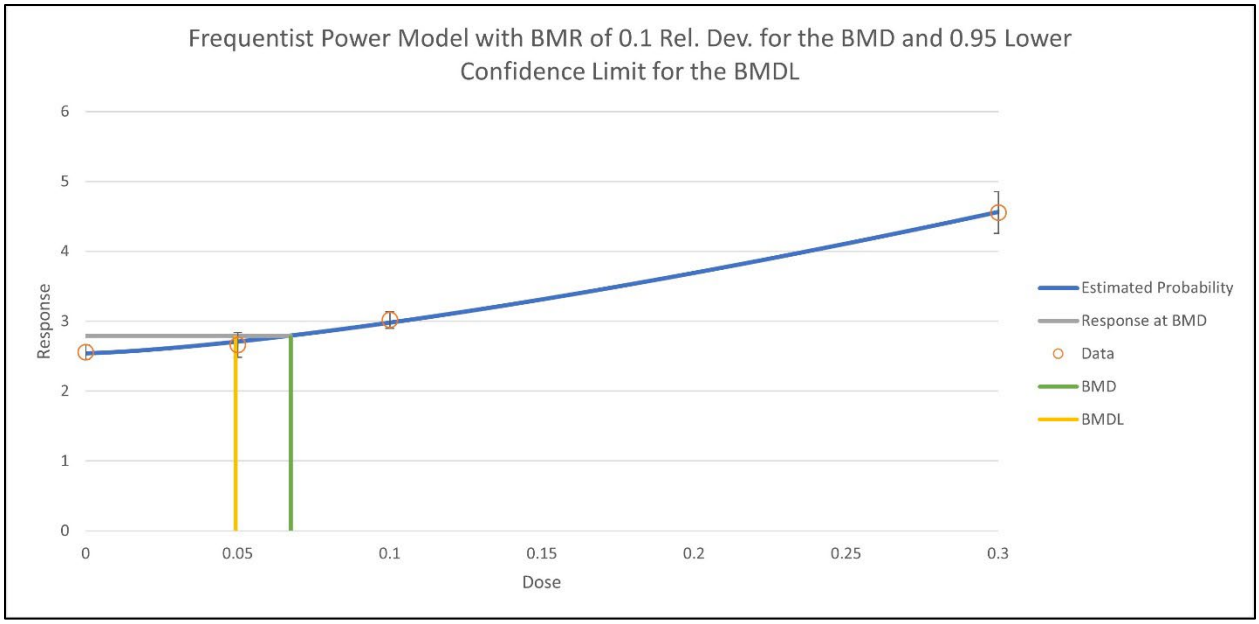
Relative liver weight: BMD modeling for a 10% change in relative liver weight, consistent with the Benchmark Response (BMR) for relative liver weight used in previous New Jersey PFAS risk assessments (DWQI, 2015; DWQI, 2017), was performed for the most sensitive dataset, males in the 13-week study. For comparison purposes, BMD modeling was also performed for the datasets from females in the 13-week study (RTC, 2016) and for data for males and females in the 4-week study (RTC, 2006). Because one or more restricted models fit each dataset, BMD modeling with unrestricted models was not performed, in accordance with USEPA BMD guidance (USEPA, 2012). The data used for BMD modeling, the recommended models, and the 95% lower confidence levels of the BMDs (BMDLs) for a 10% change for each dataset are shown in Table 12, and the complete output from the BMD modeling is found in Appendix 4.

Both recommended models (power model – lognormal, and power model-normal, non-constant) provided the same BMDL of 0.05 mg/kg/day for males in the 13-week study (RTC, 2016). The graphical results for those models are shown in Figure 1. This BMDL is identical to the NOAEL for this effect in males in the 13-week study. As expected, the BMDL for males in the 13-week study was lower than the BMDLs from the other datasets in which the effect occurred at higher doses (Table 12). Therefore, the **BMDL of 0.05 mg/kg/day** was selected as the POD for relative liver weight.

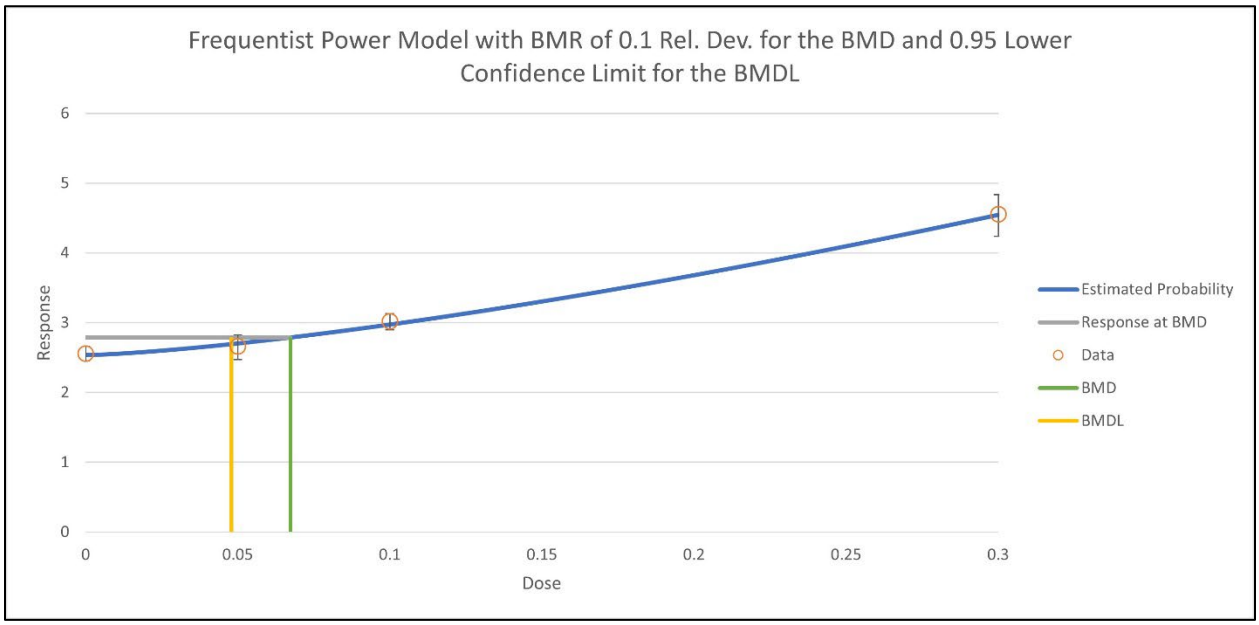
Table 12: Data and BMDLs for increased relative liver weight in rats exposed to ClPFPECAs

Dose (mg/kg/day)	*n*	*Relative liver weight (% of body weight)*		*Recommended models and BMDLs (mg/kg/day) for 10% change** *(recommended BMDLs are in **bold**)*
		Mean	*Standard Deviation*	
4-week study (RTC, 2006) - Males				
0	5	2.665	0.132	Power model (lognormal): BMDL = 0.14 Power model (normal, constant): BMDL = 0.14 (Presented for comparison purposes only)
0.3	5	3.130	0.109	
0.8	5	4.182	0.194	
2	5	6.138	0.141	
4-week study (RTC, 2006) - Females				
0	5	2.646	0.097	Power model (lognormal, constant) noted as potentially appropriate: BMDL = 0.45 (Presented for comparison purposes only)
0.3	5	2.686	0.088	
0.8	5	3.065	0.143	
2	5	4.360	0.275	
13-week study (RTC, 2016) - Males				
0	10	2.5581	0.14453	**Power model (lognormal): BMDL = 0.05** **Power model (normal, non-constant): BMDL = 0.05**
0.05	10	2.6592	0.24788	
0.1	10	3.0176	0.16510	
0.3	10	4.5567	0.41626	
13-week study (RTC, 2016) - Females				
0	10	2.4105	0.14366	Polynomial degree 2 model (lognormal): BMDL = 0.13 Polynomial degree 3 model (normal, non-constant): BMDL = 0.15 (Presented for comparison purposes only. Additionally, it was noted that both of these models may overfit the data, especially considering that there is only an increase at the highest dose.)
0.05	10	2.4041	0.19974	
0.1	10	2.4431	0.09994	
0.3	10	3.1082	0.27397	

*As discussed in the text, data from male rats in the 13-week study (RTC, 2016) were identified as the most sensitive and appropriate dataset for dose-response evaluation. Data and BMDL results for the 4-week study and for females in the 13-week study are presented for comparison purposes only.



NORMAL



LOGNORMAL

Figure 1. Graphical results for recommended BMD models for increased relative liver weight

Hematological effects: RBC parameters (RBC count, Hb, HCT) were decreased in males in the 13-week study. As shown in Table 13, these changes were statistically significant at the low dose (0.05 mg/kg/day, $p<0.05$) and the high dose (0.3 mg/kg/day, $p<0.01$), but they were not statistically significant at the mid dose (0.1 mg/kg/day). BMD modeling with a BMR of 1 standard deviation, as recommended in USEPA (2012a) BMD guidance, from both restricted and

unrestricted models indicated that none of the models fit the data; complete BMD modeling output is found in Appendix 4. In accordance with USEPA (2012a) BMD guidance, the **LOAEL of 0.05 mg/kg/day** was selected as the POD since a BMDL could not be developed.

Table 13: Red blood cell parameters in male rats in 13-week study (RTC, 2016)

Dose (mg/kg/day)	*n*	*RBC Count (x 10^6/µL)*		*Hemoglobin (g/dL)*		*Hematocrit (%)*	
		Mean	*Standard Deviation*	*Mean*	*Standard Deviation*	*Mean*	*Standard Deviation*
0	10	8.904	0.3868	15.01	0.652	47.09	2.660
0.05	10	8.485*	0.2559	14.41*	0.285	43.83**	1.293
0.1	10	8.743	0.3177	14.78	0.439	45.79	1.714
0.3	10	8.111**	0.3707	14.30**	0.573	43.55**	1.940

*p<0.05; **p<0.01.

Micro- and macrovesicular hepatocellular vacuolation: BMD modeling was not performed for the dataset for this effect in male rats in the 13-week study (RTC, 2016) because the dose-response curve is non-monotonic, with the highest incidence at the low dose (0.05 mg/kg/day – 9/10), with decreasing incidence at the middle and high doses (0.1 mg/kg/day – 6/10; 0.3 mg/kg/day – 0/10). In contrast, other hepatic effects indicative of liver toxicity occurred at the two higher doses, but not at the low dose, suggesting that hepatocellular vacuolation is part of a progression of adverse hepatic effects caused by ClPFPECAs. In accordance with USEPA (2012a) BMD modeling guidance, the **LOAEL of 0.05 mg/kg/day** was selected as the POD since a BMDL could not be developed.

Interspecies dosimetric adjustment

Because ClPFPECAs are excreted much more rapidly in rats than in humans, the same administered dose results in a much higher internal dose (i.e., body burden) in humans than in rats. Serum ClPFPECA levels were not measured in any of the available toxicity studies, and the PODs in male rats from the 13-week study identified above are based on administered doses to rats (mg/kg/day). To account for the much higher internal dose from a given administered dose in humans as compared to rats, the PODs from the rat studies were converted to human equivalent doses (HEDs) by adjusting for the ratio of ClPFPECA half-lives in humans and male rats. This approach using the ratio of human:rodent half-lives to determine HEDs has been used in the development of toxicity factors (RfDs and cancer slope factors) for other PFAS including for short-term Reference Doses for PFOA and PFOS (USEPA, 2009), PFOA cancer slope factor (DWQI, 2017), and chronic and subchronic PFBS Reference Doses (MDH, 2020; USEPA, 2021).

The ClPFPECA substance tested in the 13-week study is a mixture of ClPFPECA congeners, and the internal dose of each congener at steady state is proportional to its half-life (assuming constant volume of distribution). The half-life used for the interspecies dosimetric adjustment is therefore the percentage-weighted average of the half-lives in male rats for each of the five ClPFPECA congeners reported in RTC (2006); see Table 5 in *Toxicokinetics* above. The percentages of six congeners in the ClPFPECA mixtures used in the 13-week study, as reported

in RTC (2016), are shown in Table 14. The total of the percentages of these six congeners is 78.9%, and RTC (2016) states that "the remaining 20% are lighter acids, ketones, neutral substances." Half-lives for five of the six congeners are reported in RTC (2006), as shown in Table 5 in *Toxicokinetics* above. The congener for which a half-life was not reported, N5, was present at a much lower percentage (1.3%) than the other five congeners (5.9 to 37.1%). The total percentages of the five congeners with reported half-lives is therefore 77.6% (78.9% minus 1.3%). The percentage-weighted average half-life of 18.3 days was calculated from the percentage and half-life data for each congener (Table 14) and the total percentage of the five congeners with half-life data (77.6%) as follows, where d = days:

$$\frac{(0.371 \times 20.0\ d) + (0.073 \times 22.6\ d) + (0.182 \times 18.9\ d) + (0.059 \times 16.0\ d) + (0.091 \times 8.4\ d)}{0.776} = 18.3\ d$$

Table 14. Percentages and half-lives of ClPFPECA congeners in ClPFPECA substance tested in 13-week study (RTC, 2016)

Wang et al. (2013) Nomenclature	*Washington et al. (2020) Nomenclature (e,p)*	***Solvay nomenclature***	*Molecular Formula*	*Percent (RTC, 2016)*	*Half-life in male rats (hours/days; RTC, 2007)*
n=1, m=0	0,1	N2	$HC_8ClF_{14}O_4$	37.1	481/20.0
n=1, m=1	1,1	M3	$HC_{10}ClF_{18}O_5$	7.3	544/22.6
n=2, m=0	0,2	N3	$HC_{11}ClF_{20}O_5$	18.2	454/18.9
n=2, m=1	1,2	M4	$HC_{13}ClF_{24}O_6$	5.9	385/16.0
n=3, m=0	0,3	N4	$HC_{14}ClF_{26}O_6$	9.1	201/8.4
n=4, m=0	0,4	N5	$HC_{17}ClF_{32}O_7$	1.3	Not reported

The human half-life for ClPFPECAs reported in Solvay (2019a) is 2.5 to 3 years. As a public health protective choice and because limited information on the data used to develop this half-life range are available, the human half-life is assumed to be the higher end of this relatively narrow range, 3 years (1095 days).

The ratio of the human and male rat half-lives (1095 days/18.3 days) is 60. As discussed above, the POD for all three toxicological endpoints selected for dose-response evaluation was 0.05 mg/kg/day. The human dose corresponding to the POD in male rats of 0.05 mg/kg/day (i.e., the HED) is (0.05 mg/kg/day)/60 = **0.000833 mg/kg/day or 833 ng/kg/day.**

Application of uncertainty factors to HEDs

RfDs considered for use in ISGWQC development were developed by application of uncertainty factors (UFs) to the HEDs corresponding to the PODs for effects in rats that were developed above. The choice of uncertainty factors was consistent with current USEPA IRIS guidance (USEPA, 2002; USEPA, 2012b) and previous risk assessments developed by NJDEP. The UFs address specific factors for which there is uncertainty about the relationship of the HEDs derived

from the rat PODS to the protection of sensitive human subpopulations over a lifetime of exposure. UFs are generally applied as factors of 1 (no adjustment), 3 or 10, with 3 and 10 representing 0.5 and 1.0 log-unit. Because individual UFs represent log-units, the product of two UFs of 3 is taken to be 10. Consistent with USEPA guidance (EPA, 2002).

The five UFs shown below were considered. USEPA (2002) recommends that the total UF not exceed 3000 since a higher UF indicates that the level of uncertainty is too great to support RfD development. USEPA (2002) further notes that the maximum recommended total UF of 3000 applies only to the five UFs listed below and that it does not apply to other adjustment factors such as the interspecies toxicokinetic adjustment derived above.

$UF_{intraspecies}$ – To account for the potential greater sensitivity of sensitive human subpopulations than the average human population. A full value of 10 is typically applied unless the endpoint is based on human data that include sensitive sub-populations.

$UF_{subchronic}$ – Applied when a subchronic study is used to account for potential effects at lower doses with chronic exposure.

$UF_{interspecies}$ – Applied when animal data are used to address the potentially greater sensitivity of humans than animals. Two factors of 3 each (i.e., one half on a log scale of the full default UF of 10) are normally applied to account for toxicokinetic and toxicodynamic differences. For ClPFPECAs, the interspecies toxicokinetic difference is accounted for with the ratio of half-lives in humans and rats. A UF of 3 (rather than a full value of 10) is therefore used to account for potential toxicodynamic differences between rodents and humans.

UF_{LOAEL} – Applied when a LOAEL is used to estimate the corresponding NOAEL, when no NOAEL is identified in the study under consideration. A UF_{LOAEL} of 1 is used (i.e., no adjustment) when a BMDL is used since the BMDL is considered to be an estimate of the NOAEL.

$UF_{database}$ – To account for potentially more sensitive effects, target organs, populations, or life stages that have not been fully evaluated. Examples of such database gaps include lack of data on reproductive, developmental, or immune system effects, as well as lack of sufficient data for any specific effects that have been identified for the contaminant being evaluated or related contaminants.

RfD for increased relative liver weight

HED = 833 ng/kg/day (BMDL)

$UF_{intraspecies}$ = 10. The default value of 10 was used to account for potentially more sensitive human subpopulations.

$UF_{interspecies}$ = 3. To account for interspecies toxicodynamic differences as discussed above.

$UF_{subchronic}$ = 10. The study was subchronic, and no chronic studies are available. The magnitude of this effect at a given dose increased with exposure duration in a series of three studies with different durations (7-day, 4-week, 13-week). Additionally, other endpoints for hepatic toxicity occurred at a given dose in studies of longer duration, but not at the same dose in shorter duration studies.

UF_{LOAEL} = 1. No adjustment was made because a BMDL is used.

$UF_{database}$ = 10. There are no data on reproductive, developmental, or immunotoxic effects, either for standard endpoints or for specific effects identified as sensitive endpoints for other PFAS (e.g., effects on mammary gland development). Additionally, more sensitive effects (i.e., endpoints with a lower LOAEL) including adverse histopathological changes in the liver and decreases in hematological parameters related to erythrocytes have been identified for ClPFPECAs.

UF_{Total} = 3000

Reference Dose = 833 ng/kg/day / 3000 = 0.28 ng/kg/day

Reference Dose for decreases in RBC-related parameters (RBC count, Hb, Hct)

HED = 833 ng/kg/day (LOAEL)

$UF_{interspecies}$ = 10. The default value of 10 was used to account for potentially more sensitive human subpopulations.

$UF_{intraspecies}$ = 3 – To account for interspecies toxicodynamic differences as discussed above.

$UF_{subchronic}$ = 10 – The study was subchronic, and no chronic studies are available. The effects on RBC parameters that occurred at a given dose in this study did not occur at the same dose in a study of shorter exposure duration.

UF_{LOAEL} = 3 – A LOAEL is used, and no NOAEL was identified. The magnitude of the effect was relatively small, although statistically significant.

$UF_{database}$ = 10 – There are no data on reproductive, developmental, or immunotoxic effects, either for standard endpoints or for specific effects identified as sensitive endpoints for other PFAS (e.g., effects on mammary gland development).

UF_{Total} = 10,000

RfD = 833 ng/kg/day / 10,000 = 0.083 ng/kg/day

This RfD is not supportable since the total UF exceeds the maximum UF of 3000 recommended by USEPA (2002), and it is therefore not recommended for use in the ISGWQC.

Hepatocellular micro- and macrovesicular vacuolation

HED = 833 ng/kg/day (LOAEL)

$UF_{interspecies}$ = 10. The default value of 10 was used to account for potentially more sensitive human subpopulations.

$UF_{intraspecies}$ = 3 – To account for interspecies toxicodynamic differences as discussed above.

$UF_{subchronic}$ = 10 – The study was subchronic, and no chronic studies are available. This effect occurred at a given dose in this study, but it did not occur at the same dose in a study with shorter exposure duration.

UF_{LOAEL} = 10 – A LOAEL is used, and no NOAEL was identified. The highest incidence (90%) occurred at the lowest dose, and there is no information on the shape of the dose-response curve below the LOAEL.

$UF_{database}$ = 10 – There are no data on reproductive, developmental, or immunotoxic effects, either for standard endpoints or for specific effects identified as sensitive endpoints for other PFAS (e.g., effects on mammary gland development).

UF_{Total} = 30,000

RfD = 833 ng/kg/day / 30,000 = 0.028 ng/kg/day

This RfD is not supportable since the total UF exceeds the recommended maximum total UF of 3000 recommended by USEPA (2002). Additionally, as discussed in DWQI (2017), the application of a LOAEL-to-NOAEL UF lacks scientific support because the dose-response curve is non-monotonic, with the highest incidence at the low dose and decreasing incidences at the middle and high dose. In contrast, other hepatic effects indicative of liver toxicity occurred at the two higher doses, but not at the low dose, suggesting that hepatocellular vacuolation is part of a progression of adverse hepatic effects caused by ClPFPECAs. Therefore, this RfD is not recommended for ISGWQC development.

Selection of RfD

The RfD of 0.28 ng/kg/day for increased relative liver weight in male rats is selected for use in derivation of the ISGWQC. This RfD is based on a BMDL for this sensitive and well-established effect of ClPFPECAs and other PFAS which has been determined to be indicative of adversity and relevant to humans (DWQI, 2015; DWQI, 2017).

The PODs and HEDs for the other two candidate RfDs based on decreases in RBC parameters and hepatocellular micro- and macrovesicular vacuolation were identical numerically to the POD for increased relative liver weight. However, they were based on LOAELs rather than BMDLs, and the total UF, which includes a UF for extrapolation from a LOAEL to a NOAEL, exceeds the maximum recommended UF of 3000. Additionally, the dose-response curve for hepatocellular vacuolation was non-monotonic, and extrapolation from a LOAEL to a NOAEL for such dose-response curves by applying a UF lacks scientific support. Therefore, these RfDs are not recommended for use in ISGWQC development.

Application of exposure factors

The ISGWQC is derived from the RfD of 0.28 ng/kg/day by application of current New Jersey and USEPA default assumptions for chronic drinking water exposure (USEPA, 2015; DWQI, 2020), as shown in the equation below. The rationale for the choice of these exposure factors is provided below.

$$\frac{0.28 \text{ ng/kg/day} \times 80.0 \text{ kg} \times 0.2}{2.4 \text{ L/day}} = 1.9 \text{ ng/L } (0.0019 \text{ µg/L})$$

Where:

0.28 ng/kg/day = Reference Dose
80.0 kg = assumed adult body weight
0.2 = Relative Source Contribution from drinking water
2.4 L/day = assumed adult drinking water intake

The NJDEP Ground Water Quality Standards regulations specify that ISGWQC "shall be rounded to one significant digit." As such, the ISGWQC is rounded to 2 ng/L (0.002 ug/L).

Selection of assumptions for drinking water intake and body weight

The adult body weight and drinking water intake used to develop the ISGWQC for ClPFPECAs are the default assumptions for New Jersey ISGWQCs, GWQC, and Health-based Maximum Contaminant Levels (MCLs) because they are based on chronic (lifetime) drinking water exposure. It must be emphasized that, while adult exposure assumptions were used, the potential for higher-than-adult exposure to ClPFPECAs in the developing fetus and especially in infants via contaminated drinking water is of particular concern. Although there is no information on developmental effects of ClPFPECAs, developmental toxicity is generally a sensitive endpoint for long-chain PFAS with long human half-lives such as ClPFPECAs, and it is therefore likely to also be a sensitive endpoint for ClPFPECAs.

As discussed in *Toxicokinetics* above, it is well established that bioaccumulative PFAS are transferred to the fetus from the pregnant mother and to nursing infants through breast milk. Concentrations of bioaccumulative PFAS such as PFOA, PFOS, and PFNA in breast milk are similar to or higher than in the mother's drinking water source (Fromme et al., 2010; Post et al., 2012; DWQI, 2017; Post et al., 2017; Goeden et al., 2019). As discussed in *Human*

Biomonitoring, ClPFESAs, which are structurally related to ClPFPECAs, are detected in human umbilical cord blood, placenta, and breast milk. Additionally, infants consume several times more fluid (breast milk or formula) than older individuals on a body weight basis, Therefore, exposures to bioaccumulative PFAS are much higher in infants than in older individuals, particularly from breast milk but also from formula prepared with contaminated drinking water. Consistent with this information, serum levels of bioaccumulative PFAS (e.g., PFOA, PFOS, PFNA) in nursing infants increase by several-fold in the first few months after birth (Fromme et al., 2010). While there are no data on maternal transfer of ClPFPECAs to the fetus or through breast milk, the information discussed above indicates a high likelihood of developmental exposure to ClPFPECAs via contaminated drinking water that is similar as for other bioaccumulative PFAS.

Because the fetus and infant are sensitive subpopulations for the developmental effects of PFAS, USEPA and some states have based their drinking water guidelines for PFAS on drinking water ingestion rate for lactating women or infants, which are higher than the default adult rate (Post, 2020). New Jersey (DWQI, 2017; DWQI, 2018) recognized the importance of the higher exposures and susceptibility in the fetus and infant when developing ground water and drinking water standards for PFOA, PFOS, and PFNA, but used the default adult ingestion rate rather than a higher rate for infants or lactating women because of toxicokinetic considerations. Specifically, as stated in Post (2020), the NJ DWQI (DWQI, 2017; DWQI, 2018) and NJDEP concluded that the RfDs for bioaccumulative PFAS "are based on steady-state serum levels resulting from several years of exposure, while the higher ingestion rates in infants and lactating women apply to time periods that are much shorter than needed to reach steady state."

To address the higher exposures to PFAS from drinking water during critical developmental periods, the Minnesota Department of Health (Goeden, 2019) recently published a toxicokinetic model to predict early life drinking water exposures to bioaccumulative PFAS. This model considers transplacental fetal exposure via maternal ingestion of contaminated water, exposure to infants through breastmilk or formula prepared with contaminated water, and exposure through ingestion of contaminated water from early childhood through adulthood. This model was not available during the development of the New Jersey groundwater and drinking water standards for PFOA, PFOS, and PFNA. However, it has been used instead of the standard approach (i.e., based on a defined drinking water ingestion rate) for the development of recent drinking water guidelines for bioaccumulative PFAS (e.g., PFOA, PFOS, PFNA, PFHxS) by several states including Minnesota, Michigan and New Hampshire (reviewed in Post, 2020). Use of this model to develop the ISGWQC for ClPFPECAs would be a scientifically supportable and public health protective approach if all of the PFAS-specific factors (e.g., human half-life, placental transfer ratio, breastmilk transfer ratio) needed for the model were available for ClPFPECAs. However, while the human half-life for ClPFPECAs is available (Solvay, 2019a), the placental and breastmilk transfer ratios for ClPFPECAs are unknown.

Selection of Relative Source Contribution (RSC) factor

A Relative Source Contribution (RSC) factor that accounts for non-drinking water exposure sources (e.g., food, soil, air, consumer products) is used by the NJDEP, USEPA, and other states in the development of health-based drinking water and ground water concentrations based on non-carcinogenic effects (i.e., RfDs). The RSC is intended to prevent total exposure from all sources from exceeding the RfD (Post, 2020; USEPA, 2000).

When sufficient chemical-specific information on non-drinking water exposures is not available, a default RSC of 0.2 (20%) is used (i.e., 20% of the RfD is allocated to drinking water and 80% is allocated to other sources). When sufficient chemical-specific exposure data are available, a less stringent chemical-specific RSC may be derived, with floor and ceiling RSC values of 20% and 80% (USEPA, 2000).

There are insufficient data to develop a chemical-specific RSC for ClPFPECAs, and the default value of 0.2 is therefore used in the ISGWQC. Relevant to non-drinking water exposure sources, as discussed in *Sources of Human Exposure*, humans are potentially exposed to ClPFPECAs from multiple non-drinking water sources. ClPFPECAs have been detected in soil, vegetation, sediment, [redacted] in the vicinity of the Solvay facility in West Deptford, NJ. They have also been discharged by Solvay to air and, directly and indirectly, to the Delaware River. Additionally, biosolids containing ClPFPECAs may have been applied to agricultural land, where they could potentially be taken up by crops or livestock.

Additionally, as discussed above, the ISGWQC is based on an adult drinking water exposure. The default RSC of 20%, while not explicitly intended for this purpose, also partially accounts for the higher exposures through breast milk or formula prepared with drinking water that are expected to occur when drinking water is contaminated with ClPFPECAs. These considerations were also discussed with regard to the choice of the default RSC of 0.2 (20%) for New Jersey's ground water and drinking water standards for PFOA and PFOS (DWQI, 2017; DWQI, 2018; Post, 2020).

DISCUSSION OF UNCERTAINTIES

The uncertainty factors applied in the development of the Reference Dose are intended to account for uncertainties associated with inter-individual and inter-species susceptibility to the toxicity of ClPFPECAs, lack of data on chronic exposure, and lack of data on important toxicological endpoints including developmental, reproductive and immune system effects. Specific uncertainties associated with the ISGWQC for ClPFPECAs are discussed below.

- An uncertainty in the risk assessment of ClPFPECAs is that they occur as mixtures of ClPFPECA congeners, including in the products used by Solvay in New Jersey, in the ClPFPECA substances tested in toxicology studies, and in soil and other environmental media. Relevant to this point, the 8-carbon ClPFPECA congener that was found in New Jersey ground water including private wells was the most prevalent ClPFPECA congener

in the ClPFPECA substances tested in the repeated dose toxicity studies reviewed herein. As discussed above, evaluation of the data on relative half-lives and toxicity of the 8-carbon congener in male and female rats supports the conclusion that the 8-carbon congener contributes substantially to the toxicity of the ClPFPECA substances that were tested. This conclusion decreases the uncertainty associated with use of toxicity data for a mixture of congeners to address ground water contamination primarily by the 8-carbon congener.

- Without additional toxicological data on endpoints for which there are data gaps, it is not possible to definitively determine whether the ISGWQC for ClPFPECAs is sufficiently protective. A major uncertainty regarding human health risks of ClPFPECAs is that there are no toxicological data for developmental, reproductive, immune system, or carcinogenic effects, all of which are sensitive endpoints for other bioaccumulative PFAS. The application of the database uncertainty factor is intended to account for the lack of data on the non-carcinogenic effects mentioned above, but it does not account for lack of data on carcinogenicity.

- Without additional toxicological data from species other than the rat, it is not possible to definitively determine whether the ISGWQC for ClPFPECAs is sufficiently protective. ClPFPECAs are particularly potent in rats as compared to other bioaccumulative PFAS such as PFOA and PFNA. However, mice are more sensitive than rats to several PFAS including PFOA, PFNA, PFOS, and HFPO-DA (GenX), and there is a high likelihood that this is also true for ClPFPECAs. The interspecies uncertainty factor is intended to account for this uncertainty.

  Furthermore, as is also the case for several other PFAS, the 8-carbon ClPFPECA congener, which is the most prevalent congener in the ClPFPECA substances tested in the toxicology studies and in water near Solvay's West Deptford facility, is much more rapidly excreted in female rats than in male rats. In contrast to female rats, such PFAS are slowly excreted in female mice, and this is likely also true for the 8-carbon ClPFPECA congener. Because PFAS are also slowly excreted in humans, female mice are a better model for human toxicity of PFAS that are rapidly excreted in female rats.

- Without additional data on toxicokinetics and health effects in humans, it is not possible to definitively determine whether the ISGWQC for ClPFPECAs is sufficiently protective. Bioaccumulative PFAS (e.g., PFOA, PFOS) are associated with human health effects at very low exposure levels, including exposure levels prevalent in the general population even without additional exposure from contaminated drinking water. As such, the DWQI (DWQI, 2017; DWQI, 2018) concluded that additional exposure to these PFAS from drinking water may potentially pose some risk of health effects. For this reason, it cannot be definitively concluded that lifetime exposure to drinking water guideline levels based on animal toxicology data is protective of sensitive subpopulations with a margin of exposure.

This conclusion also appears to be potentially applicable to ClPFPECAs. No studies of health effects associated with ClPFPECAs in the general population or in communities with drinking water exposure are available, and the data supporting the human half-life estimate of 2.5-3 years are also not available. However, the available information on estimated half-life and health-related endpoints in occupationally exposed workers is notable in regard to the long half-life and the number of clinical parameters associated with exposure (as compared to similar occupational studies of long-chain perfluoroalkyl acids such as PFOA, PFNA, and PFOS). Many of the biomarkers that were associated with ClPFPECA exposure (e.g., increased serum liver enzymes and lipids, decreased serum immunoglobulins, changes in TSH, thyroid hormones, and estradiol) are relevant to toxicological effects of ClPFPECAs and other PFAS and/or are consistent with effects observed in epidemiological studies of other PFAS.

- Without information on maternal transfer of ClPFPECAs to breast milk, it is not possible to definitively determine whether the ISGWQC for ClPFPECAs is sufficiently protective for exposures to infants. As discussed above, levels of other bioaccumulative PFAS (e.g., PFOA) are higher in breast milk than in the maternal drinking water source, and exposures to breast fed infants to such PFAS are up to several fold higher than maternal exposures related to the same drinking water source.

- Uncertainties about the human relevance of effects seen in animals are inherent to all risk assessments based on animal data. As discussed above, the available information indicates that the effects of ClPFPECAs observed in experimental animals are relevant to humans for the purposes of risk assessment.

- Available information indicates that some of the target organs for toxicity of ClPFPECAs (e.g., liver) are also target organs for other PFAS including PFOA and PFNA. Therefore, toxicological interactions may occur when there is co-exposure to ClPFPECAs and other PFAS. Although PFOA and PFNA are known to occur in ground water and drinking water in the area of New Jersey impacted by ClPFPECA contamination, the potential for additive toxicity of ClPFPECAs and other PFAS was not considered in development of the ISGWQC.

ISGWQC RECOMMENDATION

The recommended ISGWQC for ClPFPECAs is 2 ng/L (0.002 µg/L), which is rounded to one significant figure from 1.9 ng/L.

CITATIONS

[redacted]

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Appendix 1: List of documents submitted to NJDEP by Solvay on PFAS "replacements" used at Solvay facility in West Deptford, NJ.
(*Notes: Publicly available versions of all of these studies are posted at https://www.nj.gov/dep/dsr/pfas-alternative.htm. CAS # 69991-62-4 is not a ClPFPECA; it is the CAS # for another type of PFAS, dicarboxylic acid polyethers, used by Solvay in West Deptford, NJ.*)

Attachment A to K. Brown's Letter of November 14, 2020 -- *Updated December 3, 2020 to Add Certain CAS Numbers per NJDEP Request*
Documents referred to in DEP's September 1, 2020 Letter as to which Solvay Specialty Polymers USA, LLC agrees to waive CBI with tradenames redacted

Title	Relevant CAS Number for Toxicology Reports	Source	Date of Source
Table Listing West Deptford Replacement Surfactants Safety Data Sheets		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Cover Page for Safety Data Sheets: CAS 220207-15-8		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Safety Data Sheet: CAS 220207-15-8 (revision 10/21/16)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Safety Data Sheet: CAS 220207-15-8 (revision 04/12/2019)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Cover Page for Safety Data Sheets: CAS 330809-92-2		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Safety Data Sheet: CAS 330809-92-2 (revision 04/12/2019) (Concentration (%): > = 30 < 40)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Safety Data Sheet: CAS 330809-92-2 (revision 04/12/2019) (Concentration (%): > = 10 < 25)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Cover Page for Safety Data Sheet: CAS 69991-62-4 (revision 04/06/2017), (replaced with revision 11/4/2020)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Safety Data Sheet: CAS 69991-62-4 (revision 04/06/2017) (replaced with revision 11/4/2020)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Cover Page for Safety Data Sheet: CAS 220182-27-4 (revision 10/21/2016)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Safety Data Sheet: CAS 220182-27-4 (revision 10/21/2016)		Solvay Response to NJDEP Directive, Exhibit H	17-Apr-19
Table Listing Attachments C-1 to C-11 in Response to Items 5 and 6 in June 11, 2019 NJDEP Letter		Solvay Response to NJDEP June 11, 2019 Letter, Attachment C	25-Jun-19
Acute Dermal Toxicity Study in Rats (March 1998)	220207-15-8	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-1	25-Jun-19
Acute Oral Toxicity Study in Rats (October 1998)	220207-15-8	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-2	25-Jun-19
Acute Oral Toxicity Study in Rats (October 1998)	220207-15-8	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-3	25-Jun-19
Skin Sensitization Test in Guinea-Pigs (April 1998)	220207-15-8	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-4	25-Jun-19
Acute Oral Toxicity Study in Rats (March 1998)	220207-15-8	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-5	25-Jun-19
Acute Oral Toxicity Study in Rats (October 1998)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-6	25-Jun-19
Acute Oral Toxicity in Rats (October 1998)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-7	25-Jun-19
Acute Oral Toxicity in Rats (March 1998)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-8	25-Jun-19
Acute Dermal Toxicity Study in Rats (March 1998)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-9	25-Jun-19
4 week Oral Toxicity Study in Rats, Followed by a 2 Week Recovery Period, Volume I of II (October 2006)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-10a	25-Jun-19

4 Week Oral Toxicity Study in Rats, Followed by a 2 Week Recovery Period, Volume II of II (October 2006)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-10b	25-Jun-19
13-Week Oral Toxicity Study in Rats, Followed by a 8 Week Recovery Period (Draft dated December 14, 2016)	330809-92-2	Solvay Response to NJDEP June 11, 2019 Letter, Attachment C-11	25-Jun-19
Exhibit A Summary Table of Additional Toxicology Studies		Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A	12-Aug-19
330809-92-2: Bacterial Mutation Assay (No. 8837-008)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-1	12-Aug-19
330809-92-2: Acute Dermal Irritation Study in the Rabbit (No. 8835-006)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-2	12-Aug-19
330809-92-2: Acute Dermal Toxicity Study in the Rat (No. 8833-006)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-3	12-Aug-19
330809-92-2: Acute Toxicity to Zebra Fish in 96-Hour Semi Static Test (No. 842902)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-4	12-Aug-19
330809-92-2: Acute Toxicity to Daphnia Magna in a 48-Hour Immobilization Test (No. 842904)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-5	12-Aug-19
330809-92-2: Toxicity to Scenedesmus Subspicatus in a 72-Hour Algal Growth Inhibition Test (No. 842906)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-6	12-Aug-19
330809-92-2: Acute Oral Toxicity Study in Rats (Acute Toxic Class Method) (No. 9563- 003)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-7	12-Aug-19
330809-92-2: 7-Day Preliminary Oral Toxicity Study in Rats (No. 36700EXT)	330809-92-2	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-8	12-Aug-19
220207-15-8: Acute Dermal Toxicity Study in the Rat (No. 8833-005)	220207-15-8	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-9	12-Aug-19
220207-15-8: Acute Dermal Irritation Study in the Rabbit (No. 8835-005)	220207-15-8	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-10	12-Aug-19
220207-15-8: Bacterial Mutation Assay (No. 8837-007)	220207-15-8	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-11	12-Aug-19
220207-15-8: Acute Oral Toxicity Study in Rats (Acute Toxic Class Method) (No. 9563- 002)	220207-15-8	Sol,ay Fiirthor Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-12	12-Aug-19
220207-15-8: Acute Oral Toxicity Study in Rats (Acute Toxic Class Method) (No. 15300- 002)	220207-15-8	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-13	12-Aug-19
69991-62-4: Acute Toxicity (Acute Oral Tox, Skin, Sensitization) (No. 234541)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-14	12-Aug-19
69991-62-4: Acute Toxicity Study in Brachydanio rerio (No. 4923/1)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-15	12-Aug-19
69991-62-4: Acute Toxicity Study in Daphnia magna (No. 4924/1)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-16	12-Aug-19
69991-62-4: Algal Growth Inhibition Test in Selenastrum capericornutum (No. 4925/1)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-17	12-Aug-19

69991-62-4: Acute Oral Toxicity Study in the Rat (No. 8832-001)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-18	12-Aug-19
69991-62-4: Acute Dermal Irritation Study in Rabbit (No. 8835-001)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-19	12-Aug-19
69991-62-4: Acute Eye Irritation Study in Rabbit (No. 8834-001)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-20	12-Aug-19
69991-62-4: Delayed Dermal Sensitization Study in Guinea Pig (8836-001)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-21	12-Aug-19
69991-62-4: Bacterial Mutation Assay (No. 8837-001)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-22	12-Aug-19
69991-62-4: Acute Dermal Toxicity Study in the Rat (No. 8833-1)	69991-62-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-23	12-Aug-19
220182-27-4: Acute Oral Toxicity in rats (No. 960288)	220182-27-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-24	12-Aug-19
220182-27-4: Acute Dermal Toxicity Study in Rats (No. 960289)	220182-27-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-25	12-Aug-19
220182-27-4: Acute Dermal Irritation Study in Rabbits (occlusive patch) (No. 970588)	220182-27-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-26	12-Aug-19
220182-27-4: Study to Induce Gene Mutations in Strains of Salmonella typhimurium and Eschcrichia coli (No. 970591)	220182-27-4	Solvay Further Submission of Toxicology Studies in Response to NJDEP's Request and Request for Blood Serum Information, Exhibit A-27	12-Aug-19

Index of Solvay's Further Response to Informational Requests to NJDEP's Statewide PFAS Directive Exhibit A, A1-A2		Solvay Further Response to NJDEP, Attachment A	15-Nov-19
4-week oral toxicity study in rats followed by 2-week recovery period (No. 27080)	69991-62-4*	Solvay Further Response to NJDEP, Attachment A-1	15-Nov-19
10-13 Week Oral Toxicity Study in Rats Followed by an 8 Week Recovery Period Part I and II (No. 41950)	69991-62-4*	Solvay Further Response to NJDEP, Attachment A-2	15-Nov-19

***As noted in Solvay's November 15, 2019 Letter to NJDEP, reports 27080 and 41950 are not studies conducted on the molecule identified by CAS # 69991-62-4, itself. These two reports were identified as relevant by analogy.**

Appendix 2: Tables of annual usage of PFAS "replacement" surfactants with four CAS #s used at Solvay facility in West Deptford, NJ, submitted to NJDEP by Solvay.

(Note: CAS # 69991-62-4 is not a ClPFPECA. It is the CAS # for another type of PFAS, dicarboxylic acid polyethers, used by Solvay in West Deptford, NJ.)

Exhibit G

West Deptford Replacement Surfactants Usage and Estimated Emissions: CAS 220207-15-8

Year	Amount Used[a]	Air[b]	Process Waste Water[c]
	(kg)	(kg)	(kg)
1996	15	4	10
1997	0	0	0
1998	22	6	14
1999	23	6	15
2000	48	13	32
2001	0	0	0
2002	677	116	382
2003	1,681	369	1,045
2004	2,270	451	1,353
2005	3,613	721	2,158
2006	3,987	774	2,356
2007	4,507	921	2,718
2008	4,370	858	2,594
2009	987	221	573
2010	4,641	1,187	3,082
2011	4,679	1,215	3,130
2012	4,091	1,060	2,732
2013	3,399	880	2,020
2014	3,076	778	1,071
2015	1,421	364	539
2016	4,547	1,182	2,353
2017	4,203	1,076	2,796
2018	2,130	554	1,018

West Deptford Replacement Surfactants Usage and Estimated Emissions: CAS 330809-92-2

Year	Amount Used[a]	Air[b]	Process Waste Water[c]
	(kg)	(kg)	(kg)
1996	0	0	0
1997	0	0	0
1998	0	0	0
1999	0	0	0
2000	0	0	0
2001	91	0	4
2002	0	0	0
2003	0	0	0
2004	1	0	1
2005	2	0	2
2006	0	0	0
2007	0	0	0
2008	55	9	30
2009	822	136	475
2010	9,208	1,697	6,572
2011	7,703	1,420	5,499
2012	9,072	1,661	6,397
2013	8,287	1,514	5,345
2014	8,992	1,663	3,595
2015	9,158	1,692	3,770
2016	8,368	1,544	4,622
2017	11,835	2,171	8,377
2018	12,549	2,318	6,407

[a] Usage data are estimated from production and accounting records

[b] Emissions data are estimated using engineering calculations

[c] Estimated from analysis of process samples and mass balance equations; process water is not directly discharged to "Waters of the State" as that phrase is defined in N.J.S.A. 58:10A-3t and the regulations thereunder at N.J.A.C. 7:14A-1.2

West Deptford Replacement Surfactants Usage and Estimated Emissions: CAS 220182-27-4

Year	Amount Used[a]	Air[b]	Process Waste Water[c]
	(kg)	(kg)	(kg)
1996	0	0	0
1997	0	0	0
1998	0	0	0
1999	0	0	0
2000	0	0	0
2001	0	0	0
2002	0	0	0
2003	0	0	0
2004	0	0	0
2005	691	133	534
2006	249	48	192
2007	193	37	149
2008	1,064	205	821
2009	624	120	437
2010	11	2	8
2011	0	0	0
2012	0	0	0
2013	0	0	0
2014	0	0	0
2015	0	0	0
2016	0	0	0
2017	0	0	0
2018	0	0	0

West Deptford Replacement Surfactants Usage and Emissions: CAS 69991-62

Year	Amount Used[a]	Air[b]	Process Waste Water[c]
	(kg)	(kg)	(kg)
1996	0	0	0
1997	0	0	0
1998	0	0	0
1999	0	0	0
2000	0	0	0
2001	0	0	0
2002	0	0	0
2003	0	0	0
2004	6	1	4
2005	89	22	58
2006	74	18	48
2007	294	71	190
2008	1,246	301	806
2009	711	172	409
2010	3,787	916	2,450
2011	3,832	927	2,479
2012	2,445	592	1,582
2013	1,290	312	744
2014	3,054	739	1,057
2015	2,833	686	1,053
2016	2,973	720	1,486
2017	2,728	660	1,765
2018	2,822	683	1,302

[a] Usage data are estimated from production and accounting records

[b] Emissions data are estimated using engineering calculations

[c] Estimated from analysis of process samples and mass balance equations; process water is not directly discharged to "Waters of the State" as that phrase is defined in N.J.S.A. 58:10A-3t and the regulations thereunder at N.J.A.C. 7:14A-1.2

Appendix 3. Toxicokinetic parameters for ClPFPECAs in male and female rats in RTC (2006)

Males

Dose level (mg/kg)	[redacted] – M3 (MW=578.5)				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	370.2	544	65550	299662
	[redacted] – M4 (MW=744.5)				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	124.3	385	22516	72388
	[redacted] – N2 (MW=462.5)				
2.0	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	4545.4	481	791984	3249932
	[redacted] – N3 (MW=628.5)				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	689.3	454	123729	464508
	[redacted] – N4 (MW=794.5)				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(5-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	6	196.9	201	30768	57915

* Calculated from t_{max}

Females

Dose level (mg/kg)	[redacted] – M3 FRACTION (MW=578.5)				
	t_{max} (h)	C_{max} (ng/ml)	°T ½ (h)	°$AUC_{(24-216)}$ (ng/ml·h)	°$AUC_{(inf)}$ (ng/ml·h)
	168	472.5	2185	77653	877949
	[redacted] – M4 FRACTION (MW=744.5)				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	160.7	346	26563	63751
	[redacted] – N2 FRACTION (MW=462.5)				
2.0	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(2-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	2	4581.3	39	167950	176042
	[redacted] – N3 FRACTION (MW=628.5)				
	t_{max} (h)	C_{max} (ng/ml)	°T ½ (h)	°$AUC_{(24-216)}$ (ng/ml·h)	°$AUC_{(inf)}$ (ng/ml·h)
	168	773.8	763	130770	584697
	[redacted] – N4 FRACTION (MW=794.5)				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	234.7	160	27116	44431

* Calculated from t_{max}
° Calculated from 24 hours

Appendix 4. Benchmark Dose modeling results for increased liver weight in male and female rats in 4-week and 13-week studies (RTC, 2006; RTC, 2016), and red blood cell parameters in male rats in 13-week study (RTC, 2016). Viable models are highlighted in gray (CV are Constant Variance models and NCV are Non-Constant Variance models).

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Females	-	Exponential 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.366	0.334	0.404	0.030	-12.17	-0.148	0.208	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.584	0.431	0.765	0.302	-16.08	0.063	0.050	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.297	0.258	0.346	0.000	-4.07	-0.192	0.261	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.594	0.451	0.799	NA	-14.49	0.047	0.043	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.789	0.782	0.798	NA	-14.82	0.007	-0.039	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.585	0.417	0.782	0.251	-15.83	0.072	0.053	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.585	0.424	0.782	0.251	-15.83	0.072	0.053	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Power (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.593	0.451	0.762	0.416	-16.49	0.047	0.043	Viable - Recommended	Lowest AIC Modeled control response std. dev. >|1.5| actual response std. dev.
Liver Weight	Females	4 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.355	0.326	0.390	0.108	-8.54	-0.804	1.486	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.573	0.385	0.809	0.427	-10.37	0.315	0.348	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Females	4 weeks	Exponential 4 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.277	0.237	0.320	0.002	-1.41	-0.893	1.791	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.000	0.000	0.000	<0.0001	77.73	4.278	4.278	Unusable	BMD computation failed
			Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.778	0.760	0.791	0.675	-10.82	0.000	-0.296	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.572	0.368	0.822	0.375	-10.21	0.372	0.372	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.572	0.380	0.817	0.375	-10.21	0.372	0.372	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.586	0.410	0.804	0.534	-10.61	0.226	0.296	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
Liver Weight	Females	4 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.374	0.336	0.447	0.011	-10.43	-1.413	1.722	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.589	0.456	0.739	0.195	-15.82	0.547	0.508	Viable - Alternate	
			Exponential 4 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.330	0.261	0.524	0.000	-2.39	-1.724	1.694	Questionable	Goodness of fit p-value < 0.1
			Exponential 5 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.598	0.474	0.796	NA	-14.41	0.408	0.444	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.778	0.764	0.790	0.481	-17.00	-0.031	-0.502	Viable - Recommended	Lowest AIC
			Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.593	0.448	0.756	0.155	-15.47	0.648	0.517	Viable - Alternate	
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.593	0.449	0.756	0.155	-15.47	0.647	0.517	Viable - Alternate	
			Power (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.598	0.474	0.737	0.297	-16.41	0.408	0.444	Viable - Alternate	

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Females	13 weeks	Exponential 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.104	0.088	0.128	0.032	-14.57	-0.285	0.271	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.203	0.134	0.287	0.803	-19.41	0.035	0.034	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.097	0.077	0.123	0.004	-10.95	-0.323	0.285	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.198	0.103	0.286	NA	-17.41	0.010	0.036	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.120	0.106	0.193	NA	-17.45	0.006	0.028	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.202	0.135	0.225	0.796	-19.41	0.035	0.034	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.174	0.132	0.192	0.822	-21.08	-0.055	0.082	Viable - Recommended	Lowest AIC Modeled control response std. dev. >|1.5| actual response std. dev.
			Power (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.200	0.132	0.219	0.809	-19.41	0.014	0.034	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
Liver Weight	Females	13 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.101	0.086	0.122	0.051	-11.26	-1.658	1.547	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1
			Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.205	0.128	0.287	0.875	-15.21	0.000	0.094	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
			Exponential 4 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.092	0.073	0.115	0.006	-7.73	-1.859	1.634	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1
			Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.205	0.127	0.286	NA	-13.21	-0.002	0.065	Questionable	Constant variance test failed (Test 2 p-value < 0.05) d.f.=0, saturated model (Goodness of fit test cannot be calculated)

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Females	13 weeks	Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.135	0.108	0.223	NA	-13.23	0.000	0.057	Questionable	Constant variance test failed (Test 2 p-value < 0.05) d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.204	0.129	0.224	0.870	-15.21	-0.001	0.090	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.173	0.125	0.190	0.842	-16.89	-0.411	0.411	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
			Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.202	0.127	0.299	0.879	-15.21	0.000	0.091	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
Liver Weight	Females	13 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.108	0.089	0.146	0.014	-12.31	-1.796	1.602	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.215	0.146	0.288	0.896	-18.81	-0.009	0.015	Viable - Alternate	
			Exponential 4 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.102	0.079	0.149	0.001	-8.66	-1.934	1.618	Questionable	Goodness of fit p-value < 0.1
			Exponential 5 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.225	0.105	0.279	NA	-16.79	-0.008	-0.093	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.118	0.109	0.119	0.881	-18.80	0.254	-0.051	Viable - Alternate	
			Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.210	0.147	0.229	0.989	-20.80	-0.008	0.025	Viable - Recommended	Lowest AIC
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.174	0.138	0.197	0.661	-20.00	-0.493	0.486	Viable - Alternate	
			Power (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.216	0.144	0.295	0.907	-18.81	-0.010	-0.022	Viable - Alternate	
Liver Weight	Males	4 weeks	Exponential 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.232	0.216	0.250	<0.0001	3.37	-0.029	-0.239	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.232	0.216	0.250	<0.0001	3.37	-0.029	-0.239	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.139	0.119	0.159	0.074	-11.82	0.063	0.063	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.194	0.140	0.252	NA	-13.02	0.004	0.007	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Males	4 weeks	Hill (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.195	0.142	0.253	NA	-13.02	0.004	0.007	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.150	0.140	0.168	0.141	-13.09	0.024	0.024	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.150	0.140	0.168	0.141	-13.09	0.024	0.024	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Power (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.150	0.140	0.182	0.141	-13.09	0.024	0.024	Viable - Recommended	Lowest AIC Modeled control response std. dev. >|1.5| actual response std. dev.
Liver Weight	Males	4 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.244	0.230	0.261	<0.0001	2.68	-0.672	-1.794	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.244	0.230	0.261	<0.0001	2.68	-0.673	-1.795	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.133	0.112	0.158	0.101	-13.63	0.654	0.654	Viable - Alternate	
			Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.195	0.129	0.271	NA	-14.31	0.000	0.000	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.196	0.130	0.271	NA	-14.31	0.000	0.000	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.153	0.143	0.170	0.102	-13.75	-1.027	-0.122	Viable - Alternate	
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.153	0.143	0.170	0.102	-13.75	-1.027	-0.122	Viable - Alternate	
			Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.153	0.143	0.182	0.102	-13.75	-1.027	-0.122	Viable - Recommended	Lowest AIC
Liver Weight	Males	4 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.250	0.221	0.271	<0.0001	4.31	-0.899	-1.823	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.250	0.221	0.271	<0.0001	4.31	-0.900	-1.822	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.134	0.111	0.158	0.088	-11.67	0.652	0.652	Questionable	Goodness of fit p-value < 0.1
			Exponential 5 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.195	0.132	0.267	NA	-12.57	0.007	0.001	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.197	0.134	0.268	NA	-12.57	0.009	0.000	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Males	4 weeks	Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.152	0.142	0.169	0.100	-11.96	-1.029	-0.038	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.152	0.142	0.169	0.100	-11.96	-1.029	-0.038	Questionable	Goodness of fit p-value < 0.1
			Power (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.152	0.142	0.162	0.100	-11.96	-1.029	-0.038	Questionable	Goodness of fit p-value < 0.1
Liver Weight	Males	13 weeks	Exponential 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.048	0.044	0.052	0.147	3.57	-0.230	0.236	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.066	0.046	0.094	0.186	3.48	-0.154	0.076	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.037	0.032	0.042	0.002	11.29	-0.316	0.356	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.067	0.048	0.100	NA	4.96	-0.123	0.072	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.076	0.054	0.096	NA	3.73	0.013	0.012	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.065	0.044	0.095	0.164	3.67	-0.165	0.085	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.065	0.045	0.095	0.164	3.67	-0.165	0.085	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
			Power (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.067	0.048	0.093	0.265	2.97	-0.123	0.072	Viable - Recommended	Lowest AIC Modeled control response std. dev. >|1.5| actual response std. dev.
Liver Weight	Males	13 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.047	0.043	0.051	0.354	11.41	-0.968	1.022	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.064	0.044	0.101	0.332	12.28	-0.767	0.293	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Males	13 weeks	Exponential 4 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.034	0.029	0.039	0.013	17.55	-1.180	1.702	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.076	0.045	0.100	NA	13.34	0.000	0.000	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.076	0.046	0.099	NA	13.34	0.000	0.000	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.063	0.039	0.102	0.306	12.38	-0.812	0.338	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.063	0.040	0.102	0.306	12.38	-0.812	0.338	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
			Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.066	0.042	0.099	0.424	11.98	-0.634	0.268	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
Liver Weight	Males	13 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.048	0.044	0.054	0.178	4.74	-1.424	1.289	Viable - Alternate	
			Exponential 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.066	0.047	0.091	0.306	4.34	-0.999	0.375	Viable - Alternate	

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Liver Weight	Males	13 weeks	Exponential 4 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.000	0.000	0.000	<0.0001	90.77	3.129	3.129	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.000	0.000	0.000	<0.0001	90.77	3.158	3.158	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
			Hill (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.074	0.052	0.094	NA	5.29	-0.215	0.099	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.065	0.046	0.092	0.272	4.50	-1.063	0.416	Viable - Alternate	
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.065	0.046	0.092	0.272	4.50	-1.063	0.416	Viable - Alternate	
			Power (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.067	0.049	0.091	0.424	3.93	-0.831	0.338	Viable - Recommended	Lowest AIC
HCT	Males	13 weeks	Exponential 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.262	0.156	0.624	0.003	179.73	0.346	3.392	Questionable	Goodness of fit p-value < 0.1 |Residual at control| > 2
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.262	0.156	0.624	0.003	179.73	0.346	3.392	Questionable	Goodness of fit p-value < 0.1 |Residual at control| > 2

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
HCT	Males	13 weeks	Exponential 4 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.006	0.002	Infinity	0.005	178.40	0.227	0.227	Questionable	Goodness of fit p-value < 0.1 BMD 3x lower than lowest non-zero dose
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.261	0.000	Infinity	0.001	181.71	0.347	3.368	Unusable	BMD computation failed
			Hill (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Power (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Hill (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Linear (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Power (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
HCT	Males	13 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.249	0.153	0.637	0.003	180.86	0.135	1.542	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.249	0.153	0.637	0.003	180.86	0.135	1.542	Questionable	Goodness of fit p-value < 0.1
			Exponential 4 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.248	0.000	Infinity	0.001	182.84	0.134	1.536	Unusable	BMD computation failed
			Exponential 5 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.249	0.153	0.637	0.001	182.86	0.135	1.542	Questionable	Goodness of fit p-value < 0.1
			Hill (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.000	0.000	Infinity	0.020	177.14	0.034	0.034	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.252	0.157	0.634	0.003	180.89	0.131	1.560	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.252	0.157	0.635	0.003	180.89	0.131	1.560	Questionable	Goodness of fit p-value < 0.1
			Power (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.252	0.157	0.634	0.003	180.89	0.131	1.560	Questionable	Goodness of fit p-value < 0.1
			Hill (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.020	0.000	Infinity	NA	180.64	0.015	0.015	Unusable	BMD computation failed
			Linear (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.252	0.157	0.634	0.003	180.89	0.131	1.560	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.017	0.011	0.113	NA	173.35	0.000	0.000	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 2 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.143	0.058	Infinity	0.001	182.13	1.535	1.023	Questionable	Goodness of fit p-value < 0.1
			Power (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.020	0.000	Infinity	0.007	178.58	0.019	0.019	Unusable	BMD computation failed

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
HCT	Males	13 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.289	0.169	0.643	0.002	181.57	0.061	1.443	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.289	0.169	0.643	0.002	181.57	0.062	1.442	Questionable	Goodness of fit p-value < 0.1
			Exponential 4 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.044	0.013	Infinity	0.002	180.19	-1.094	0.064	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose
			Exponential 5 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.287	0.000	Infinity	0.000	183.53	0.062	1.430	Unusable	BMD computation failed
			Hill (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.000	0.000	Infinity	0.003	179.66	0.023	0.023	Unusable	BMD computation failed
			Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.290	0.175	0.610	0.001	181.61	0.061	1.458	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.290	0.180	0.674	0.001	181.61	0.061	1.458	Questionable	Goodness of fit p-value < 0.1
			Power (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.290	0.174	0.674	0.001	181.61	0.061	1.458	Questionable	Goodness of fit p-value < 0.1
			Hill (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.000	0.000	Infinity	0.003	179.67	0.041	0.041	Unusable	BMD computation failed
			Linear (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.290	0.175	0.616	0.001	181.61	0.061	1.458	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 3 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.022	0.012	0.110	NA	172.61	-0.115	-0.115	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 2 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.213	0.070	Infinity	0.000	182.79	-0.162	1.004	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3
			Power (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.061	0.000	Infinity	0.003	179.29	-1.402	-0.010	Unusable	BMD computation failed
HGB	Males	13 weeks	Exponential 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.298	0.171	0.906	0.046	66.67	0.059	0.589	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.298	0.171	0.906	0.046	66.67	0.058	0.590	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 4 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.265	0.000	Infinity	0.016	68.36	0.013	0.448	Unusable	BMD computation failed
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.298	0.000	0.915	0.013	68.66	0.057	0.587	Unusable	BMD computation failed
			Hill (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Power (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
HGB	Males	13 weeks	Hill (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Linear (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Power (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
HGB	Males	13 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.290	0.169	0.944	0.043	67.24	0.063	1.108	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.290	0.169	0.944	0.043	67.24	0.063	1.108	Questionable	Goodness of fit p-value < 0.1
			Exponential 4 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.166	0.015	Infinity	0.017	68.66	1.573	0.413	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose
			Exponential 5 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.290	0.169	0.944	0.012	69.24	0.063	1.108	Questionable	Goodness of fit p-value < 0.1
			Hill (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.101	0.000	Infinity	0.025	67.94	1.763	0.025	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.291	0.172	0.936	0.042	67.25	0.062	1.117	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.291	0.172	0.936	0.042	67.25	0.062	1.117	Questionable	Goodness of fit p-value < 0.1
			Power (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.291	0.172	0.936	0.042	67.25	0.062	1.117	Questionable	Goodness of fit p-value < 0.1
			Hill (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.122	0.000	Infinity	NA	69.37	1.620	0.034	Unusable	BMD computation failed
			Linear (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.291	0.172	0.936	0.042	67.25	0.062	1.117	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.027	0.014	0.109	NA	64.93	0.000	0.000	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 2 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.231	0.070	Infinity	0.014	68.97	-0.078	0.788	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3
			Power (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.124	0.000	Infinity	0.036	67.31	1.603	0.031	Unusable	BMD computation failed
HGB	Males	13 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.297	0.164	0.940	0.043	69.21	0.054	1.095	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1
			Exponential 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.296	0.163	0.939	0.043	69.21	0.055	1.096	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
HGB	Males	13 weeks	Exponential 4 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	-9999.000	0.000	Infinity	0.038	69.22	-9999.000	0.038	Unusable	BMD computation failed
			Exponential 5 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.295	0.000	0.944	0.012	71.20	0.058	1.089	Unusable	BMD computation failed
			Hill (NCV - normal)	frequentist	Restricted	Std. Dev.	1	-9999.000	0.000	Infinity	0.046	68.87	-9999.000	-0.013	Unusable	BMD computation failed
			Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.297	0.180	0.927	0.042	69.22	0.055	1.105	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.297	0.169	0.927	0.042	69.22	0.055	1.105	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1
			Power (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.297	0.165	0.932	0.042	69.22	0.055	1.105	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1
			Hill (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	-9999.000	0.000	Infinity	NA	70.86	-9999.000	-0.006	Unusable	BMD computation failed
			Linear (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.297	0.168	0.932	0.042	69.22	0.055	1.105	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1
			Polynomial Degree 3 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.153	0.015	0.223	NA	65.74	0.216	-0.144	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 2 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.245	0.070	Infinity	0.015	70.87	-0.132	0.735	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3
			Power (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.263	0.000	Infinity	0.050	68.73	-0.854	-0.067	Unusable	BMD computation failed
RBC	Males	13 weeks	Exponential 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.154	0.107	0.239	0.032	35.09	0.500	0.261	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.154	0.107	0.295	0.032	35.09	0.500	0.261	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
RBC	Males	13 weeks	Exponential 4 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.154	0.107	0.239	0.032	35.09	0.500	0.261	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Exponential 5 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.151	0.065	0.294	0.009	37.11	0.509	0.253	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
			Hill (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Power (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Hill (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Linear (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
			Power (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
RBC	Males	13 weeks	Exponential 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.147	0.104	0.244	0.029	35.33	1.422	0.714	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.147	0.104	0.297	0.029	35.33	1.422	0.714	Questionable	Goodness of fit p-value < 0.1
			Exponential 4 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.147	0.104	0.244	0.029	35.33	1.422	0.714	Questionable	Goodness of fit p-value < 0.1
			Exponential 5 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.147	0.104	0.296	0.029	35.33	1.422	0.714	Questionable	Goodness of fit p-value < 0.1
			Hill (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.148	0.053	0.297	0.008	37.32	1.415	0.719	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.181	0.109	0.284	0.008	37.18	1.122	0.961	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.162	0.108	0.276	0.008	37.28	1.271	0.847	Questionable	Goodness of fit p-value < 0.1
			Power (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.150	0.108	0.295	0.029	35.31	1.388	0.742	Questionable	Goodness of fit p-value < 0.1
			Hill (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.120	0.028	0.297	NA	39.21	1.687	0.409	Questionable	BMD/BMDL ratio > 3 d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Linear (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.150	0.108	0.246	0.029	35.31	1.388	0.742	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.025	0.013	0.112	NA	32.21	0.001	0.001	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)

Parameter	Sex	Age	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	*P*	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
RBC	Males	13 weeks	Polynomial Degree 2 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.163	0.071	0.277	0.008	37.28	1.271	0.847	Questionable	Goodness of fit p-value < 0.1
			Power (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.116	0.026	0.295	0.008	37.14	1.714	0.362	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3
RBC	Males	13 weeks	Exponential 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.148	0.099	0.247	0.029	37.32	1.421	0.710	Questionable	Goodness of fit p-value < 0.1
			Exponential 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.148	0.099	0.272	0.029	37.32	1.421	0.709	Questionable	Goodness of fit p-value < 0.1
			Exponential 4 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.148	0.099	0.247	0.029	37.32	1.421	0.708	Questionable	Goodness of fit p-value < 0.1
			Exponential 5 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.148	0.099	0.266	0.029	37.32	1.421	0.709	Questionable	Goodness of fit p-value < 0.1
			Hill (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.251	0.040	0.300	NA	42.17	-0.006	1.665	Questionable	BMD/BMDL ratio > 3 d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.182	0.105	0.283	0.008	39.17	1.120	0.956	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.164	0.103	0.276	0.008	39.28	1.268	0.843	Questionable	Goodness of fit p-value < 0.1
			Power (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.151	0.103	0.296	0.029	37.30	1.387	0.737	Questionable	Goodness of fit p-value < 0.1
			Hill (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.120	0.025	0.281	NA	41.21	1.686	0.408	Questionable	BMD/BMDL ratio > 3 d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Linear (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.151	0.103	0.247	0.029	37.30	1.387	0.737	Questionable	Goodness of fit p-value < 0.1
			Polynomial Degree 3 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.025	0.013	0.109	NA	34.21	0.011	-0.007	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
			Polynomial Degree 2 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.164	0.068	0.277	0.008	39.28	1.268	0.842	Questionable	Goodness of fit p-value < 0.1
			Power (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.117	0.023	0.295	0.008	39.14	1.711	0.364	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3