Public Version – Confidential Business Information (CBI) is redacted

TECHNICAL SUPPORT DOCUMENT: INTERIM SPECIFIC GROUND WATER QUALITY CRITERION FOR PERFLUOROPOLYETHER DICARBOXYLATES (PFPE-DCAs)

(CAS Number 69991-62-4)

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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

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

CHO – Chinese hamster ovary

CI – confidence interval

ClPFPECA — chloroperfluoropolyether carboxylate

Cmax — maximum observed serum or plasma concentration

DAF – Dosimetric Adjustment Factor

DWQI — New Jersey Drinking Water Quality Institute

FCN – food contact notification

FDA – U.S. Food and Drug Administration

GAC — granular activated carbon

GCUA – Gloucester County Utilities Authority

GHS - Globally Harmonized System of Classification and Labelling of Chemicals

GWQS – Ground Water Quality Standards

HED — Human Equivalent Dose

HFPO-DA — hexafluoropropylene oxide-dimer acid; GenX

ISGWQC — Interim Specific Ground Water Quality Criterion

ISGWQS — Interim Specific Ground Water Quality Standard

LD_{50} — lethal dose to 50% of animals

LOAEL — Lowest Observed Adverse Effect Level

NADH — reduced nicotinamide adenine dinucleotide

NJDEP — New Jersey Department of Environmental Protection

NOAEL — No Observed Adverse Effect Level

NOEL – No Observed Effect Level

OEL – Occupational Exposure Limit

PCO – palmitoyl-CoA oxidation

PFAS — per- and polyfluoroalkyl substances

PFBA — perfluorobutanoic acid

PFBS — perfluorobutane sulfonate

PFHxA — perfluorohexanoic acid

PFHxS — perfluorohexane sulfonate

PFNA — perfluorononanoic acid

PFOA — perfluorooctanoic acid

PFOS — perfluorooctane sulfonate

PFPE-DCAs – perfluoropolyether dicarboxylic acids

PFUnDA — perfluoroundecanoic acid

POD — point of departure

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

STOT — specific target organ toxicity

$t_{1/2}$ – half-life

T_{max} — time to Cmax

UF — uncertainty factor

USEPA — United States Environmental Protection Agency

SUMMARY

An Interim Specific Ground Water Quality Criterion (ISGWQC) was developed for the perfluoropolyether dicarboxylic acids (PFPE-DCAs) used and discharged at the Solvay facility in West Deptford, NJ. PFPE-DCAs are long-chain PFAS that occur as mixtures of congeners with different carbon (n=9-12) and oxygen chain lengths. No information on toxicokinetics or health effects of PFPE-DCAs in humans was identified, while toxicokinetic and toxicology studies of PFPE-DCAs have been conducted in rats. Half-life data indicates that PFPE-DCAs are bioaccumulative in both male and female rats. The toxicological database for PFPE-DCAs in rats includes acute oral, dermal, and eye irritation studies and repeated dose oral studies of 4-week and 13-week durations. No information on developmental, reproductive, immune system, or carcinogenic effects of PFPE-DCAs is available.

Effects of PFPE-DCAs in rats in repeated dose studies included hepatic effects in both sexes, decreases in red blood cell (RBC) parameters in males, increased serum triglycerides in females, and histopathological changes indicative of lung toxicity in males and females. While other effects also occurred, these four endpoints were selected for dose-response evaluation because they were sensitive, occurred in a dose-related manner, are adverse or a precursor to an adverse effect, and are considered relevant to humans.

Dose-response evaluation for these endpoints in the 13-week study was performed, and the following points of departure (PODs) were considered for Reference Dose (RfD) development: increased liver weight in females - 0.095 mg/kg/day (lower confidence limit on the benchmark dose; BMDL); decreased RBC count in males 0.038 mg/kg/day (BMDL); increased serum triglycerides – 0.03 mg/kg/day (No Observed Adverse Effect Level; NOAEL); and increased incidence of aggregations of alveolar macrophages in females – 0.013 mg/kg/day (BMDL). To account for the much slower excretion of long-chain PFAS such as PFPE-DCAs in humans than rats, the PODs were converted to Human Equivalent Doses (HEDs) with a dosimetric adjustment factor (DAF) of 100. Since no human half-life data for PFPE-DCAs are available, this DAF is based on an assumed human:rat half-live ratio for PFPE-DCAs of 100, which is supported by a human:rat half-life ratios of 60-146 for other long-chain PFAS. A total uncertainty factor (UF) of 3000 was applied to the HEDs to derive candidate RfDs for each of the four endpoints. This total UF includes individual UFs of 10 to protect sensitive human subpopulations, 3 to account for toxicodynamic differences between humans and experimental animals, 10 to account for more sensitive effects from chronic exposure, and 10 to account for the incomplete toxicology database for the PFPE-DCAs (e.g., no data on developmental, reproductive, or immune system toxicity).

The RfD of 0.32 ng/kg/day for increased relative liver weight was selected as the basis for the ISGWQC because it is well-established as a sensitive effect of long-chain PFAS that is indicative of hepatic toxicity and relevant to humans, occurred in both males and females in both repeated dose studies, increased in magnitude with longer exposure to PFPE-DCAs, and persisted after exposure to PFPE-DCAs ended. The candidate RfDs for the other three endpoints (RBC count – 0.13 ng/kg/day; serum triglycerides – 0.1 ng/kg/day; aggregations of alveolar macrophages -

0.04) were below 0.32 ng/kg/day, supporting the conclusion that the RfD for increased liver weight is not overly conservative. Default assumptions for adult drinking water consumption and the default Relative Source Contribution (RSC) factor of 20% were applied to derive an ISGWQC of 2.1 ng/L. This ISGWQC applies to the total concentration of PFPE-DCA congeners detected in groundwater. The newly adopted Ground Water Quality Standards (GWQS) specify that ISGWQC "shall be rounded to two significant figures when all components of the equations are available in two or more significant figures," the ISGWQC was rounded to 2.1 ng/L (0.0021 µg/L).

INTRODUCTION

Establishment of Interim Specific Ground Water Quality Criterion (ISGWQC) and Interim Specific Ground Water Quality Standard (ISGWQS) for PFPE-DCAs

The New Jersey Ground Water Quality Standards (GWQS) 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) and an Interim Specific Ground Water Quality Standard (ISGWQS) 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 ISGWQS for perfluoropolyether dicarboxylates (PFPE-DCAs)[1]. PFPE-DCAs are per- and polyfluoroalkyl substances (PFAS) that have been used as processing aids and discharged to the environment by the Solvay Specialty Polymers USA[2] (Solvay) facility in West Deptford, NJ. Development of an ISGWQC for the PFPE-DCAs used by Solvay in West Deptford was requested of the NJDEP Division of Science and Research by the NJDEP Contaminated Site Remediation and Redevelopment (CSRR) 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 PFPE-DCAs generally follow United States Environmental Protection Agency (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 PFPE-DCAs indicate that they cause toxicity at low doses and are highly bioaccumulative in laboratory animals. NJDEP is not

[1] Throughout this document, unless otherwise stated, "perfluoropolyether dicarboxylates," abbreviated as "PFPE-DCAs" refers to the compounds designated by CAS # 69991-62-4.
[2] Referred to as "Solvay" throughout this document.

aware of any information on health effects or bioaccumulation of PFPE-DCAs in humans. PFPE-DCAs have been detected in onsite ground water at the Solvay facility in West Deptford at estimated concentrations substantially above 10 µg/L (10,000 ng/L) (Integral Consulting, 2021) and in groundwater offsite at estimated concentrations up to several hundred nanograms per liter (Integral Consulting, 2022a). Drinking water sources (private wells and public water systems) in this vicinity have not been tested for PFPE-DCAs and it is not known if they are impacted. NJDEP has determined that, based on this information, an ISGWQS for PFPE-DCAs 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 at https://www.nj.gov/dep/wms/bears/gwqs.htm. 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 at N.J.A.C. 7:9C-1.9(c), NJDEP is proceeding with the establishment of an ISGWQS for PFPE-DCAs even though a PQL for PFPE-DCAs has not been developed at this time. This document provides the basis for the ISGWQC (i.e., the health-based criterion) for PFPE-DCAs.

Sources of information on PFPE-DCAs[3]

In 2019, NJDEP (2019) issued a Directive that required Solvay and other companies that use PFAS to provide information on "replacement PFAS" used in New Jersey including their "toxic characteristics." In response to the Directive, Solvay provided a Safety Data Sheet (SDS (Solvay, 2020) for [redacted] with the Chemical Abstract Service Number (CAS #) 69991-62-4 that was used at their New Jersey facility. The chemical structures of the individual PFPE-DCA congeners in this mixture are provided [redacted] and in Integral Consulting (2021), as discussed in the section on *Nomenclature and Chemical/Physical Properties* below.

The SDS states that the PFPE-DCAs are classified "by analogy" as Category 1 for specific target organ toxicity (STOT) from repeated dose exposure according to Globally Harmonized System

[3] Publicly available versions of the Safety Data Sheets and toxicology studies for CAS # 69991-62-4 that were submitted to NJDEP by Solvay and are mentioned herein are posted at https://www.nj.gov/dep/dsr/pfas-alternative.htm

of Classification and Labelling of Chemicals (GHS) criteria.[4] 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."[4] (SCHC-OSHA Alliance, 2017). The *Toxicological Information* section of the SDS (Solvay, 2020) states that the liver is a target organ for repeated dose ingestion toxicity of the PFPE-DCAs, and that the No Observed Effect Levels (NOELs) for liver toxicity "by analogy" with "similar substances" in oral 28-day and 90-day rat studies are 0.5 mg/kg/day and 0.03 mg/kg/day, respectively. [redacted] Furthermore, the 4-week and 13-week study reports (RTC, 2005; RTC, 2006) that were later obtained by NJDEP (see below) state that the test material was >85% "dicarboxy chain ends perfluoropolyethers". This and other toxicity information from the SDS (Solvay, 2020) is discussed in the section on *Laboratory Animal Toxicology Studies*, below.

After learning from the SDS that data indicating repeated dose toxicity were available, NJDEP requested that Solvay provide all available toxicology studies on the PFPE-DCAs 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 confidential business information (CBI), but they were later made publicly available by Solvay with the trade names of the substances that were tested redacted. They include the studies of half-life, acute oral and dermal toxicity, and repeated dose (4-week and 13-week) toxicity in rats; dermal and eye irritation in rabbits; skin sensitization in guinea pigs; and genotoxicity in bacteria that are reviewed below, as well as ecological toxicity studies in *Danio rerio* (zebrafish), *Daphnia magna*, and *Scenedesmus subspicatus* that are not reviewed herein.

Additionally, Solvay Solexis S.p.A. (Solvay's Italian affiliate) submitted four additional toxicology studies conducted by an Italian contract laboratory to the U.S. Food and Drug Administration (FDA). Although these four studies were not submitted to NJDEP by Solvay, NJDEP has obtained the FDA files on this PFAS that include these studies. They are reviewed below and include an additional acute oral rat study, a Chinese hamster ovary cell (CHO) chromosome aberration study, a mouse bone marrow micronucleus study, and an additional bacterial mutagenicity study.

[4] "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)

Additional information on the PFPE-DCAs used by Solvay is limited. No publications were located in PubMed searches for the CAS number "69991-62-4" or for "PFAS," "perfluoropolyether," or "perfluoroether," and "dicarboxylic acid" or "dicarboxylate." A publication by Berends and Doornaert (2019) that develops a non-regulatory "corporate occupational exposure limit" (OEL) for CAS # 69991-62-4 in air (discussed in *Guidance, Standards, and Regulatory Actions* below) was identified in a Google search for this CAS #.

As discussed below, Solvay's PFPE-DCA products (CAS # 69991-62-4) are approved for use in food contact materials by the FDA (FDA, undated) and German authorities (OECD, 2020). Additional state and international regulatory authority documents and peer-reviewed publications that list CAS # 69991-62-4 as a PFAS that is approved for use in food contact materials were identified through internet searches. However, these documents and publications do not provide any additional information on the PFAS with this CAS #.

<u>Nomenclature</u>

The SDS (Solvay, 2020) for CAS # 69991-62-4 provides the trade name [redacted] and the chemical name "ethene, 1,1,2,2-tetrafluoro-, oxidized, polymd., reduced."

[redacted]

[redacted]

Solvay (Thomas, 2021) referred to CAS # 69991-62-4 as "bifunctional surfactant." Solvay also stated that this CAS # has the general chemical structure shown below and that a typical production lot of this CAS # contains "nine primary identified fractions."

HOOC-CF2-(OCF2CF2)B-(OCF2)A-OCF2-COOH

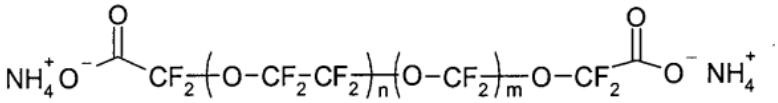
where: A = 0 to 4 and B = 1 to 4

Solvay (Thomas, 2021) also includes an analytical method for "Bi-functional Surfactant" (i.e., CAS # 69991-62-4). The nomenclature and chemical formulas for the nine congeners designated by this CAS # that are included in the analytical method are shown in Table 1. As shown in Table 1, these congeners contain between 9 and 12 carbons and several ether oxygens.

Table 1. Chemical structures of PFPE-DCA congeners designated by CAS # 69991-62-4

Analyte	Formula
BFS_AB2	$C_9H_2O_8F_{14}$
BFS_A3B	$C_9H_2O_9F_{14}$
BFS_B3	$C_{10}H_2O_8F_{16}$
BFS_A2B2	$C_{10}H_2O_9F_{16}$
BFS_A4B	$C_{10}H_2O_{10}F_{16}$
BFS_AB3	$C_{11}H_2O_9F_{18}$
BFS_A3B2	$C_{11}H_2O_{10}F_{18}$
BFS_B4	$C_{12}H_2O_9F_{20}$
BFS_A2B3	$C_{12}H_2O_{10}F_{20}$

Similarly, in information submitted to the FDA (FDA, 2004), Solvay Solexis S.p.A. (Solvay's Italian affiliate) provided the following structure for the ammonium salt of the PFAS whose acid form has CAS # 69991-62-4:



FDA (2004) states that the chemical name for this PFAS is "ammonium salt of ethene, tetrafluoro-, oxidized, polymerized, reduced" and the common name is "perfluoropolyether dicarboxylic acid ammonium salt."

Chemical and physical properties

The following information on chemical and physical properties is excerpted from the SDS for CAS # 69991-62-4 for Solvay in West Deptford (Solvay, 2020), which states: "Physical and Chemical properties here represent typical properties of this product. Contact the business area using the Product information phone number in Section 1 for its exact specifications."

Physical state: liquid

Color: white

Odor: odorless
Molecular weight: 600 - 900 Da
pH: ca. 0.0
Melting point/freezing point: No data available
Boiling point/boiling range: Not applicable
Flash point: The product is not flammable.
Evaporation rate (Butylacetate = 1): No data available
Flammability (liquids): The product is not flammable.
Flammability / Explosive limit: No data available
Autoignition temperature: No data available
Vapor pressure: < 0.00008 mmHg (< 0.0001 hPa) (68 °F [20 °C])
Vapor density: No data available
Density: 1.6 - 1.7 g/cm^3 (68 °F [20 °C])
Relative density: No data available
Water solubility: partly soluble
Solubility in other solvents: Fluorinated solvents - soluble
Partition coefficient: n-octanol/water - No data available
Decomposition temperature: > 266 °F (> 130 °C)
Viscosity: No data available
Explosive properties: Not explosive
Oxidizing properties: Not considered as oxidizing

Production and use

According to information provided to NJDEP by Solvay, products with the CAS # 69991-62-4 were used at the Solvay facility in West Deptford, NJ, as processing aids in the manufacture of fluoropolymers including polyvinylidene fluoride (PVDF). As discussed above, PFAS with this CAS # are also used in food contact materials.

No information on the annual amount of the PFAS with CAS # 69991-62-4 produced or used in the U.S. or worldwide was identified.

A table provided by Solvay of annual use and discharge to air and water (kg/year) for perfluoropolyether dicarboxylic acids with CAS # 69991-62-4 at the West Deptford, NJ facility from 1996-2018 is found in Appendix 2. The table shows that a small amount (6 kg) of substances with this CAS # was first used at the facility in 2004, and it was used in each subsequent year through 2018. Between 1,246 and 3,787 kg were used each year between 2008 and 2018, except for 2009 (711 kg), with the largest amount (3,787 kg) used in 2010.

Information for Fluorolink 7900, a product with CAS # 69991-62-4, at Solvay in West Deptford, NJ was provided to the NJDEP Community Right to Know Survey 2009 Chemical Inventory Report. In the NTC Laboratory-FEC Production area, average daily inventory and maximum daily inventory were stated to be 1,000 to 9,999 pounds. In the Polymer-1st Floor East Side area, average daily inventory and maximum daily inventory were stated to be 10,000 to 24,999 pounds.

GUIDANCE, STANDARDS, AND REGULATORY ACTIONS

Guidance values or standards for PFPE-DCAs in groundwater or other environmental media have not been developed by USEPA, other states, or internationally.

Solvay S.A. in Belgium developed a non-regulatory "corporate occupational exposure limit" (OEL), called a "Solvay Acceptable Exposure Limit," of 0.0035 mg/m^3 for Fluorolink 7900 (CAS # 69991-62-4) in air (Berends and Doornaert, 2019). This value is based on "effects on liver (and lungs at higher dose levels)" in rats, but the details of its derivation are not provided. The Solvay Acceptable Exposure Level for this CAS # is 14 to 6,200 times lower than the Solvay Acceptable Exposure Levels for seven other chemicals used by Solvay that are included in the paper. The authors state that no regulatory OEL has been developed for this substance. They further state that Solvay selected this substance for development of a Solvay Acceptable Exposure Limit through a prioritization process that considers toxicity (e.g., carcinogenicity, reproductive toxicity, mutagenicity, high acute toxicity, and/or specific target organ toxicity after repeated exposure), worker exposure potential (number of workers potentially exposed and/or manufacture of large amounts), and sometimes specific physiochemical properties (e.g., high volatility for liquids, high dust potential for solids). It is stated that Solvay Acceptable Exposure Limits are based "on the existing methods for national or community OELs and guidance from the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation."

PFPE-DCA products (CAS # 69991-62-4) manufactured and supplied by Solvay Specialty Polymers Italy S.p.A. are approved for use in food contact materials by the U.S. Food and Drug Administration (FDA, undated). There are two FDA food contact notifications (FCNs; Numbers 398 and 537) for this CAS #.

FCN 398[5], effective April 13, 2004, is for "perfluoropolyether dicarboxylic acid (CAS Reg. No. 69991-62-4), ammonium salt" manufactured or supplied by Solvay Specialty Polymers Italy S.p.A.. The intended use is "as an oil and water repellent in the manufacture of food-contact paper and paperboard," and it is "to be used in the manufacture of paper and paperboard prior to sheet formation at a level not to exceed 1 percent by weight of the finished dry paper and paperboard."

[5] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=fcn&id=398&sort=FCN_No&order=DESC&startrow=1&type=basic&search=398

FDA FCN 537[6], effective November 19, 2005, is also for "perfluoropolyether dicarboxylic acid (CAS Reg. No. 69991-62-4), ammonium salt" manufactured or supplied by Solvay Specialty Polymers Italy S.p.A. The intended use is "as an oil and water repellent in the manufacture of food-contact paper and paperboard," and "when applied prior to the sheet-forming operation [it] is to be used at a level not to exceed 1 percent by weight of the finished dry paper and paperboard to be used in contact with all food types. When applied at the size press the total use level … is not to exceed 0.5 percent by weight of the finished dry paper and paperboard to be used in contact with aqueous foods and 1 percent by weight of the finished dry paper and paperboard to be used in contact with all other food types."

NJDEP has obtained the FDA files related to the two FCNs for CAS # 69991-62-4. An FDA memorandum dated April 6, 2004 for FCN 398 (FDA, 2004) reviews the toxicology studies submitted by Solvay for this PFAS, and it appears that FDA did not conduct an updated toxicology review for FCN 537. The following four toxicology studies were submitted to FDA for FCN 398: acute oral toxicity in rat (RTC, 2001a); bacterial mutation assay (RTC, 2001b); chromosome aberrations in Chinese hamster ovary cells (RTC, 2003a); mouse bone marrow micronucleus test (RTC, 2003b). The three genotoxicity studies (reviewed in more detail in *Genotoxicity* section below) were negative, and no mortality occurred in the acute toxicity study in rats at the single dose used, 2000 mg/kg. Based on these studies which did not show toxicity, FDA stated that this PFAS "did not induce genetic damage under the conditions tested and no information was found indicating toxic or carcinogenic activity for this compound." However, FDA did not consider the 4-week oral rat study with a NOAEL of 0.5 mg/kg/day (RTC, 2005) and the 13-week oral rat study with a NOAEL of 0.13 mg/kg/day (RTC, 2006), since they were not available when FDA conducted its toxicology review in 2004. As discussed in more detail below, these two studies report that this PFAS causes toxicity to multiple organs at low doses.

Perfluoropolyether carboxylates with CAS # 69991-62-4 have been approved by a German authority (German Bundesinstitut für Risikobewertung, BfR) for use in "paper/board: Max 0.5 %, based on the dry fibres weight. The correspondingly treated papers may not come into contact with aqueous and alcoholic foodstuff" (RIVM, 2018; OECD, 2020). According to RIVM (2018), the evaluations by the German authority are not publicly available.

It is noted that OECD (2020) states that the PFAS currently used in food packaging (paper and paperboard) are short-chain (defined as perfluorocarboxylic acids with carbon chain lengths < 8; perfluoroalkane sulfonic acids with carbon chain lengths < C6). These short-chain PFAS and non-fluorinated alternatives have replaced long-chain (defined as perfluorocarboxylic acids with carbon chain length ≥ 8; perfluoroalkane sulfonic acids with carbon chain lengths ≥ 6; precursors of these PFAS) for use in food packaging. However, PFPE-DCAs with CAS # 69991-62-4 are not short-chain, since, as discussed above, they were stated by Solvay to include PFAS with 9 to 12 carbon atoms in their chains.

[6] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=fcn&id=538&sort=FCN_No&order=DESC&startrow=1&type=basic&search=538

CAS # 69991-62-4 is listed as an example of substances for which reporting to USEPA of uses, production volumes, disposal, exposures, and hazards would be required in the USEPA (2021) proposed rule, "TSCA Section 8(a)(7) Reporting and Recordkeeping Requirements for Perfluoroalkyl and Polyfluoroalkyl Substances[7]."

To the Department's knowledge, this document is the first review of information relevant to human health risks of PFPE-DCAs in the environment.

ENVIRONMENTAL SOURCES, FATE, AND OCCURRENCE

No information on the environmental occurrence of CAS # 69991-62-4 outside of New Jersey was identified.

The table of annual usage of CAS # 69991-62-4 at the Solvay facility in West Deptford, NJ (Appendix 2) mentioned above also provides the estimated amounts (kg/year) of the PFPE-DCAs designated by this CAS # that were discharged to air and water annually from 1996-2018. Discharge to air (1 kg) and water (4 kg) began in 2004. Larger amounts (up to 2,479 kg) were discharged to water in subsequent years, with >1,000 kg discharged to water every year between 2010 and 2018, with the exception of 2013. Smaller amounts (several 100 kg) were released to air each year between 2008 and 2018, with the highest amount (927 kg) released in 2011.

PFPE-DCAs have been detected in onsite ground water at the Solvay facility in West Deptford at estimated concentrations substantially above 10 µg/L (10,000 ng/L) (Integral Consulting, 2021) and in groundwater offsite at estimated concentrations up to several hundred nanograms per liter (ng/L; Integral Consulting, 2022a). Drinking water sources (private wells and public water systems) in this vicinity have not been tested for PFPE-DCAs and it is not known if they are impacted.

The following information is based on information about wastewater at the Solvay facility that was provided by the NJDEP Site Remediation (now CSRR) program and included in NJDEP (2021): 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 to the Delaware River from 1996-2017. In 2017, Solvay 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 likely to be contaminated with PFPE-DCAs.

PFPE-DCAs were detected in soil samples from the Solvay site in West Deptford, NJ (Integral Consulting, 2022b). The highest estimated concentration of an individual PFPE-DCA congener was 32 ng/g (ppb).

[7] https://www.federalregister.gov/documents/2021/06/28/2021-13180/tsca-section-8a7-reporting-and-recordkeeping-requirements-for-perfluoroalkyl-and-polyfluoroalkyl

SOURCES OF HUMAN EXPOSURE

Human exposure to PFPE-DCAs has not been fully characterized. As mentioned above, PFPE-DCAs were detected in groundwater on and near Solvay's West Deptford facility, and levels in some of the offsite wells are estimated to be several hundred ng/L. However, public water supply wells and private wells in this area have not been tested for PFPE-DCAs, and drinking water is a potential source of human exposure that requires further investigation.

PFAS used at Solvay in West Deptford, NJ, including PFNA, perfluoroundecanoic acid (PFUnDA) (MacGillivary, 2021) and ClPFPECAs (NJDEP, 2021), have been detected in recreationally caught fish from waterbodies near the Solvay site, but it is not known whether PFPE-DCAs are also present in these fish. The potential presence of PFPE-DCAs in fish and other wildlife species consumed by humans in this vicinity therefore requires further investigation.

PFPE-DCAs 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 PFPE-DCAs 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 above, PFPE-DCAs used by Solvay were approved by the U.S. FDA and German authorities for use in food contact materials. Migration to food of the residual PFPE-DCAs in food contact materials is a potential route of human exposure.

HUMAN BIOMONITORING

NJDEP is not aware of any human biomonitoring data for PFPE-DCAs.

TOXICOKINETICS

Summary

No data are available on the absorption, distribution, metabolism, or routes of excretion (e.g., urine, feces) of PFPE-DCAs in humans or laboratory animals. However, perfluorinated dicarboxylic acids such as PFPE-DCAs are generally well absorbed after oral administration, not metabolized, and excreted primarily in the urine (Kudo, 2018), and this is likely to also be the case for PFPE-DCAs.

While no information on the human half-life of PFPE-DCAs was identified, the half-lives in male and female rats for the test substance representative of CAS # 69991-62-4 is similar to or longer than the half-lives of the long-chain perfluoroalkyl carboxylates, PFOA and PFNA. In this regard, PFPE-DCAs differ from the short-chain replacement PFAS introduced by other companies (e.g., hexafluoropropylene oxide-dimer acid [HFPO-DA; GenX] and perfluorobutane sulfonate [PFBS]), which have much shorter half-lives, and thus are much less bioaccumulative, than the long-chain PFAS that they replace (ITRC, 2023).

Human

NJDEP is not aware of any human toxicokinetic data for PFPE-DCAs. However, as discussed below, the half-lives in male and female rats of the test compound used in RTC (2005) and RTC (2006) is similar to or longer than that of perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA), which have human half-lives of several years. These rat half-life data suggest that PFPE-DCAs are also likely to be highly bioaccumulative in humans.

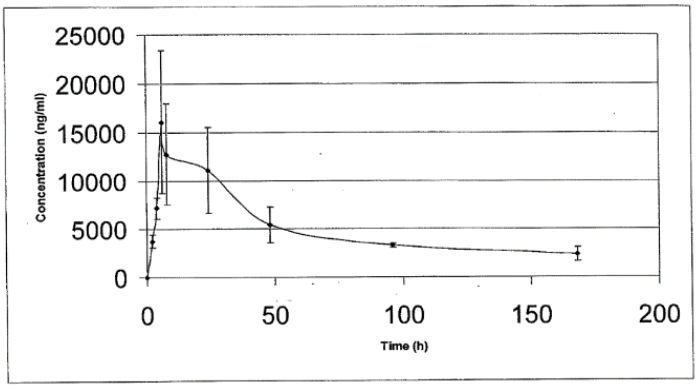
Laboratory animals

The half-life of [redacted] was estimated after single oral doses of 8 mg/kg in female rats (RTC, 2005) and 0.5 mg/kg in male rats (RTC, 2006). The half-life was also estimated in male and female rats after dosing with 0.5 mg/kg/day for 13 weeks (RTC, 2006). Additionally, plasma levels of the test substance were measured in male and female rats at the end of 11, 12, and 13 weeks of daily dosing with 0.03, 0.13, and 0.5 mg/kg/day (RTC, 2006). No information was provided on which congeners of PFPE-DCAs were present in the product that was used in these studies, and the results of these studies are reported as a single concentration, not as concentrations of individual congeners.

Half-life in female rats after single dose of 8 mg/kg (RTC, 2005)

Nine female rats were dosed by gavage with 8 mg/kg and were divided into three groups (n=3 per group). Blood samples were taken for analysis of the test compound in plasma from each group at three time points after dosing, as follows: Group 1 - 0, 4, 24 hours; Group 2 - 2, 8, 96 hours; Group 3 – 6, 48, 168 hours. Plasma concentrations at each time point are shown in Figure 1. The half-life of the test compound in female rats was estimated as approximately 58 hours (2.4 days) from plasma measurements at 0, 2, 4, 6, 24, 48, 96, and 168 hours after a single oral dose of 8 mg/kg (RTC, 2005). As shown in Figure 1, plasma concentrations of the test substance clearly declined over time after reaching a maximum concentration at 6 hours after dosing.

Figure 1. Plasma levels of test substance, [redacted], in female rats after single dose of 8 mg/kg (RTC, 2005)



[8] Solvay stated that the 4-week study (RTC, 2005) and the 13-week study (RTC, 2006) "are not studies conducted on the molecule identified by CAS # 69991-62-4, itself. These two reports were identified as relevant by analogy." [redacted]

The following toxicokinetic parameters were calculated from the plasma concentration data:

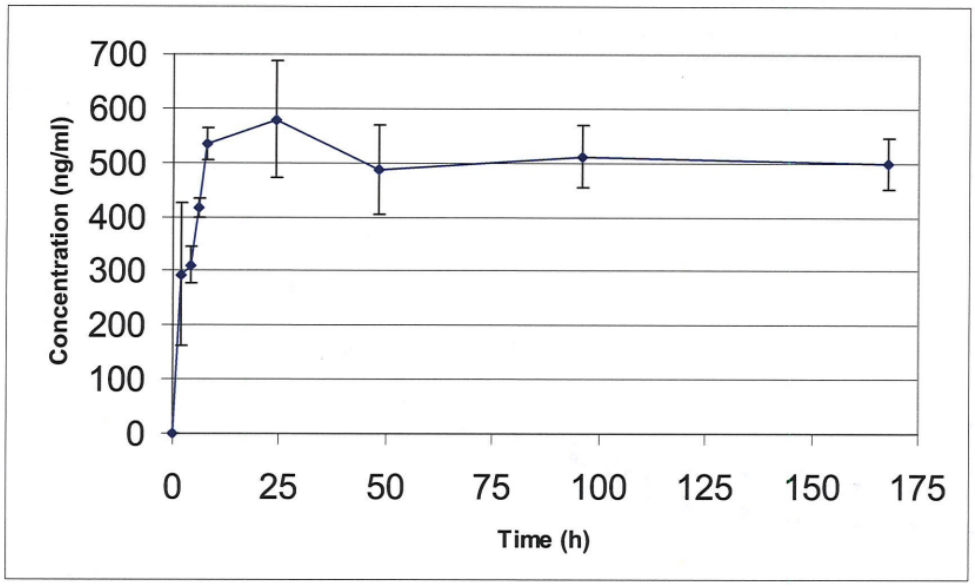
- Maximum observed plasma concentration (C_{max}) – 16,050 ng/ml
- Time to reach C_{max} (T_{max}) – 6 hours after dosing
- Half-life ($t_{1/2}$) – approximately 58 hours (2.4 days)
- Area under the concentration-time curve (AUC; calculated by the linear trapezoidal rule) – $AUC_{6\text{-}168\ hours}$ – 873,415 ng/ml/hr; $AUC_{infinity}$ - 1,069,642 ng/ml/hr

Half-life in male rats after single dose of 0.5 mg/kg (RTC, 2006)

Nine male rats were dosed with 0.5 mg/kg and were divided into three groups (n=3 per group). Blood samples were taken for analysis of the test compound in plasma from each group at three time points after dosing, as follows: Group 1 - 0, 4, 24 hours; Group 2 - 2, 8, 96 hours; Group 3 – 6, 48, 168 hours. Urine and feces were also collected during two 6-hour time periods from each of the three groups (Group 1: 6-12 and 42-48 hours; Group 2: 18-24 and 162-168 hours; Group 3: 0-6 and 90-96 hours), but these samples were not analyzed.

Plasma concentrations at each time point are shown in Figure 2. The half-life of the test compound in male rats was estimated to be approximately 1,037 hours (43.2 days) from plasma measurements at 0, 2, 4, 6, 24, 48, 96, and 168 hours after a single oral dose of 0.5 mg/kg (RTC, 2006). As shown in Figure 2, plasma concentrations of the test substance did not clearly decline over time between 48 hours and the last time point (168 hours).

Figure 2. Plasma levels of test substance, [redacted], in male rats after single dose of 0.5 mg/kg (RTC, 2006)



The following toxicokinetic parameters were calculated from the plasma concentration data:

- C_{max} – 580 ng/ml
- T_{max} – 24 hours after dosing
- $t_{1/2}$ – approximately 1037 hours (43.2 days)

- $AUC_{6\text{-}168\ hours}$ – 84,686 ng/ml/hr
- $AUC_{infinity}$ – 830,571 ng/ml/hr

Plasma levels in male and female rats at weeks 11, 12, and 13 of treatment period (RTC, 2006)
Plasma levels were measured in blood samples taken from the same 3 animals per sex per dose group (0.03, 0.13, and 0.5 mg/kg/day) approximately 2 hours after the last dose at the end of weeks 11, 12, and 13 of the treatment period. Since steady-state is reached after dosing for 4 to 5 half-lives (Ito, 2011), steady-state was reached prior to 11 weeks (77 days) of dosing based on the half-life estimates (males – 7.8 days; females – 11.4 days; Table 3, below) obtained after 13 weeks of dosing with 0.5 mg/kg/day. The data shown in Table 2 indicate that plasma concentrations were generally proportional to dose and were generally several fold lower in females than in males at the same dose. These data also demonstrate that measured plasma levels in the same animals varied during weeks 11, 12, and 13, suggesting that the mean of the plasma serum levels at these three time points provides an estimate of the steady-state level. The plasma level in males dosed repeatedly with 0.5 mg/kg/day (mean after 11, 12, and 13 weeks of dosing – 43,952 ng/ml) was generally consistent with the plasma level of 45,726 ng/ml measured 24 hours after the last dose in five other males dosed with 0.5 mg/kg/day for 13 weeks (Table 3), and it was 75-fold higher than the C_{max} of 580 ng/ml in males after a single 0.5 mg/kg dose (above).

Table 2. Plasma concentrations (ng/ml) of the test substance, [redacted], in male and female rats at the end of 11, 12, and 13 weeks of dosing (n=3 per data point; RTC, 2006)

Dose	***0.03 mg/kg/day***		***0.13 mg/kg/day***		***0.5 mg/kg/day***	
	Males	***Females***	***Males***	***Females***	***Males***	***Females***
Week 11	1536±257	574±55	7421±1140	2677±553	29,686±10,657	17,838±4130
Week 12	1774±899	274±171	11,854±7778	3645±420	68,425±17,405	13,197±13,571
Week 13	3010±915	1015±126	11,390±505	6916±1897	32,666±8992	32,867±9217

Half-life in male and female rats after 13 weeks of dosing with 0.5 mg/kg (RTC, 2006)[9]
Plasma levels were measured in blood samples taken from male and female animals (n=5 per sex) in the recovery group that had been dosed with 0.5 mg/kg/day for 13 weeks. Blood samples were taken approximately 24, 48, 96, 144, and 192 hours after administration of the last dose. Urine and feces were also collected at 0-6, 6-12, 12-24, 48, 72, 96, 120, 144, 168, and 192 hours after the last dose, but these samples were not analyzed.

Plasma concentrations in males and females at each time point up to 192 hours (7 days) after dosing ended are shown in Figures 3 and 4. As shown in these figures, plasma concentrations of the test substance clearly declined over time after dosing with 0.5 mg/kg/day ended. Half-lives were estimated as 187 hours (7.8 days) in males and 274 hours (11.4 days) in females.

[9] The data tables in Addendum IV (Volume II, p. 192-193) of RTC (2006) incorrectly indicate that the animals in the recovery group had been dosed with 2.0 mg/kg/day rather than 0.5 mg/kg/day.

Figure 3. Plasma levels of the test substance, [redacted], in male rats in recovery group after 13 weeks of dosing with 0.5 mg/kg/day (RTC, 2006)

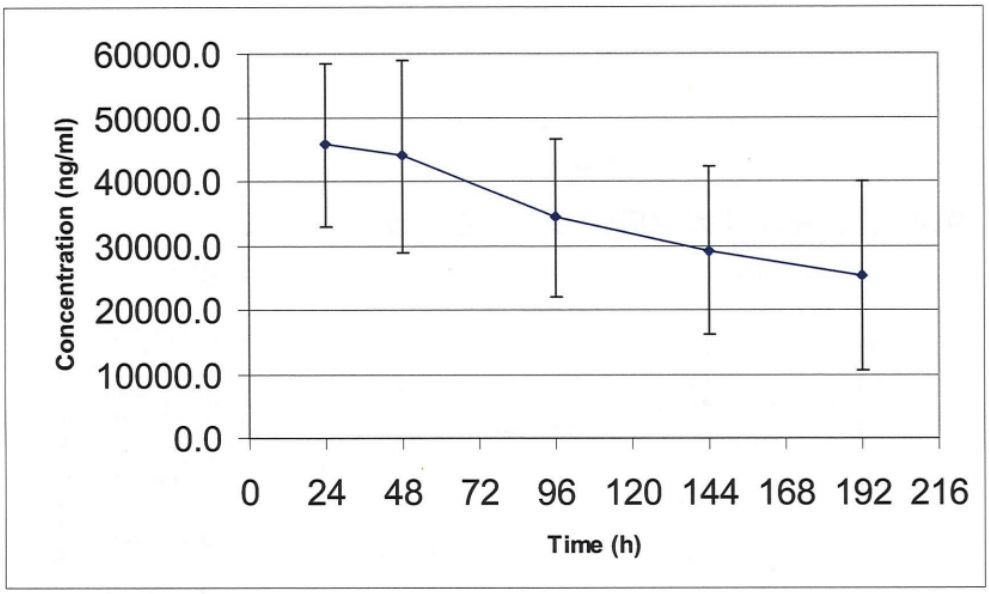
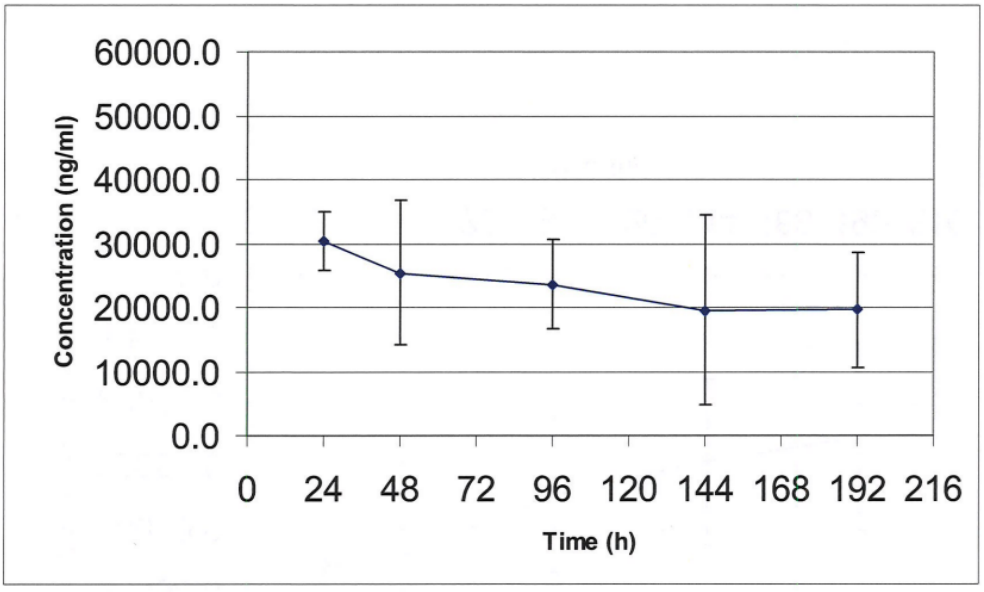


Figure 4. Plasma levels of the test substance, [redacted], in female rats in recovery group after 13 weeks of dosing with 0.5 mg/kg/day (RTC, 2006)



Summary of half-life estimates

Available half-life values for the test substance in RTC (2005) and RTC (2006) are summarized in Table 3. Comparison of the four half-life estimates is complicated by the fact that each is based on a different dosing regimen and/or sex. That being said, it is noted that the half-life in males after a single dose of 0.5 mg/kg/day (43.2 days), is much longer than the half-life in males

(7.8 days) or females (11.4 days) after repeated daily administration of this same dose (0.5 mg/kg/day) for 13 weeks. The half-life in males after a single dose of 0.5 mg/kg (43.2 days) is also much longer than the half-life in females after a single dose of 8 mg/kg (2.4 days).

A potential explanation for the much longer half-life in males given a single dose of 0.5 mg/kg is that the initial plasma concentration (580 ng/L) was much lower than for the other three half-life estimates (16,050 ng/L to 43,952 ng/L). For many PFAS, the excretion rate is controlled by renal reabsorption which may be saturated at high plasma concentrations (Kudo, 2018).

It is notable that the half-life estimates of 7.8 – 43.2 days in male rats and 2.4 – 11.4 days in female rats are similar to or longer than the half-lives in rats for PFOA (4-6 days in males; 2-4 hours [0.08-0.17 days] in females) and PFNA (30 days in males; 1.4-2.4 days in females) (reviewed in DWQI, 2015). After the same dosing regimen (0.5 mg/kg/day for 13 weeks), the half-life of the test substance was similar in male and female rats, in contrast to the much more rapid excretion of PFOA and PFNA in female rats than in males.

Table 3. Half-life estimates for the test substance, [redacted], in male and female rats

Dose (dosing regimen)	***Sex***	***Initial Plasma Concentration (ng/ml)***	***Half-life (days)***	***Citation***
8 mg/kg (one dose)	Female	16,050[a]	2.4	RTC (2005)
0.5 mg/kg (one dose)	Male	580[b]	43.2	RTC (2006)
0.5 mg/kg/day (13 weeks)	Female	30,346[c]	11.4	RTC (2006)
0.5 mg/kg/day (13 weeks)	Male	45,726[c]	7.8	RTC (2006)

[a] C_{max} (6 hours after single dose). [b] C_{max} (24 hours after single dose). [c] C_{max} (24 hours after last dose). .

HEALTH EFFECTS IN HUMANS

NJDEP is not aware of any information on human health effects of PFPE-DCAs.

LABORATORY ANIMAL TOXICOLOGY STUDIES

The following mammalian toxicology studies of PFPE-DCAs were provided to NJDEP by Solvay: two dermal irritation studies in rabbits (Inveresk Research International, 1986; RTC, 2001d); one acute dermal study in rats (RTC, 2001c); two dermal sensitization studies in guinea pigs (Inveresk Research International, 1986; RTC, 2001e); one acute eye irritation study in rabbits (RTC, 2001f); two acute oral rat studies (Inveresk Research International, 1986; RTC, 2002a); one 4-week oral study with a 2 week recovery period in rats (RTC, 2005) and one 13-week oral study with an 8 week recovery period in rats (RTC, 2006). No inhalation studies were

provided. Publicly available versions of all of these studies are posted at https://www.nj.gov/dep/dsr/pfas-alternative.htm. An additional acute oral rat study (RTC, 2001a) was submitted by Solvay Solexis S.p.A. (Solvay's Italian affiliate) to the FDA and obtained by NJDEP. No information was provided on the individual PFPE-DCA congener(s) present in the substances that were tested in these studies.

The names of the products tested in the toxicology studies are confidential business information. The dermal, eye irritation, and acute oral toxicology studies were conducted on substances ([redacted]) with the CAS # 69991-62-4, which refers to a mixture of multiple congeners of PFPE-DCAs. The percentages of individual congeners in the substances tested were not provided. As mentioned above, Solvay stated that the 4-week study (RTC, 2005) and the 13-week study (RTC, 2006) "are not studies conducted on the molecule identified by CAS # 69991-62-4, itself. These two reports were identified as relevant by analogy." [redacted].

All of the studies were sponsored by Italian chemical companies and conducted at contract toxicology laboratories, and there are no peer-reviewed journal publications for any of these studies. The dermal and acute oral studies were sponsored by Montefluos S.p.A. and Ausimont S.p.A., and the 4-week and 13-week studies were sponsored by Solvay Solexis S.p.A.

No data for PFPE-DCAs were identified for reproductive or developmental effects, chronic toxicity/carcinogenicity, or for specific toxicological effects known to be sensitive endpoints for other PFAS (e.g., immunotoxicity, mammary gland development). With the exception of the two acute dermal irritation studies and the eye irritation study that were conducted in rabbits and the skin sensitization test that was conducted in guinea pigs, all of the studies that have been identified were conducted in rats, and there are no data from mice or non-human primates (i.e., monkeys). Toxicological data for PFPE-DCAs from mice would be informative since mice are more sensitive than rats to several other PFAS (e.g., HPFO-DA [GenX], PFOA).

Dermal and eye irritation studies

Dermal irritation

Three dermal irritation studies of undiluted test substances containing PFCAs were identified, including one study in rats and two studies in rabbits. Effects indicative of dermal irritation including erythema, edema, hardening, necrosis, and/or scab formation were reported in all three studies. The dermal irritation studies are summarized below:

Inveresk Research International (1986): Dermal irritation was evaluated in two male and one female New Zealand White rabbits. The test substance was [redacted] (CAS # 6991-62-4), batch number L377, a clear colorless liquid with specific gravity 2.04 mg/L. Hair was clipped from the backs of the rabbit 24 hours before treatment. A volume of 0.5 ml undiluted test material was applied to the backs of the rabbits and covered with a 2.5 cm^2 gauze patch. The patch was

covered with micropore tape and the trunk of the rabbit was bound with an elastic bandage. After 4 hours, the patches were removed and excess test material was wiped off. Dermal reactions were assessed 1 hour after the 4-hour exposure ended and 24, 48, and 72 hours after the test material was applied. Moderate to severe erythema and edema occurred in all animals at all time points (1 hour after exposure ended – 72 hours after exposure began). The authors concluded that "severe irritant responses" occurred after 4 hours of occluded exposure to the test material and that the test material is "severely irritant to rabbit skin."

RTC (2001d): Dermal irritation was evaluated in three female New Zealand White rabbits. The test material was [redacted] (CAS # 6991-62-4), Lot # 90100/66, received from Ausimont S.p.A. Hair was clipped from the backs of each animal on the day before dosing. The next day, 0.5 ml of the test substance (undiluted) was spread over a 2.5 cm^2 gauze square. The gauze square was applied to the clipped skin, covered with aluminum foil, and held in place with an elastic bandage. The gauze patch was removed after 4 hours of exposure, and excess test material was removed by swabbing with water. The treated skin was evaluated approximately 1, 24, 48, and 72 hours and 7 and 14 days after dosing. No mortality, systemic effects, or notable changes in body weight occurred during the study. Erythema and edema were reported starting at the first observation time point, 1 hour after exposure ended. Signs of necrosis occurred in all three animals at 24 hours, and the edema and erythema were more severe than at the earlier time point. Erythema (ranging from "well defined" to moderate to severe) and edema (ranging from very slight to moderate) persisted in all three animals until the end of the study 14 days after treatment, and scabs were observed in all animals at this time point. The authors concluded that the test substance "has a severe irritant effect on the skin of the rabbit, this appearing not completely reversible."

RTC (2001c): Dermal irritation was evaluated in 5 male and 5 female Hsd: Sprague-Dawley SD rats. The test substance was [redacted] (CAS # 6991-62-4), Lot # 90199/66. On the day before dosing (Day 0), hair was clipped from the backs of the animals over an area estimated to be at least 10% of the total body surface. The next day (Day 1), a dose of 2000 mg/kg body weight was spread over a gauze patch the size of the treatment site (assumed, but not stated, to be the clipped area). The gauze patch was applied to the skin and covered with aluminum foil, and it was held in place by an elastic bandage around the trunk. After 24 hours of exposure, the gauze patch was removed and the skin was washed with warm water to remove remaining test substance. Animals were observed through Day 15, at which time they were sacrificed. No mortality, clinical signs, or unexpected changes in body weight occurred during the study. Hardening of the treated site and/or necrosis occurred on one or more days in all treated males and females, beginning on Day 6 and persisting in some animals until the end of the study on Day 15. Necropsy findings included abrasions or scabs at the treated site in 4 of 5 males and all females. The authors concluded that the test substance "has no systemic toxic effect in the rat following dermal exposure over a period of 24 hours at a level of 2000 mg/kg." Effects on the skin were not mentioned in the *Conclusion* section.

Dermal sensitization

Two skin sensitization studies in female Dunkin-Hartley guinea pigs were identified. Neither study demonstrated that PFPE-CAs are dermal sensitizers. These studies are summarized below:

Inveresk Research International (1986): Dermal sensitization was evaluated with the Buehler sensitization test in a study that included 20 control and 20 treated female Dunkin-Harley guinea pigs. The test substance was [redacted] (CAS # 6991-62-4), batch number L377, a clear colorless liquid with specific gravity 2.04 mg/L.

In the induction phase of the study, a Webril (cotton) patch coated with 0.4 ml of distilled water or test material was applied to a shaved 4 x 6 cm^2 area on the mid-backs of control and treated animals, respectively, for 6 hours on 3 consecutive days each week for 3 consecutive weeks. The treated area was evaluated for irritation 24 hours after each patch application. Slight to moderate erythema was reported at most time points in all treated animals, but it was not reported in controls.

In the challenge phase, which was performed 4-weeks after induction, a Webril patch coated with 0.4 ml test material was applied to a shaved 5 x 5 cm^2 area on the left flanks of control and treated animals for 6 hours. The treated area was assessed 24 and 48 hours after the test substance was applied. Erythema, considered to be positive response, occurred in all control and treated animals. The authors stated that these results indicated that the test material caused irritation, not sensitization, and it was not possible to repeat the test with diluted test material at concentration that did not cause irritation. The authors concluded that it was not possible to determine whether the test substance cause sensitization in addition to irritation.

RTC (2001e): Dermal sensitization was evaluated with the Magnusson and Kliman test in female Dunkin-Harley guinea pigs. The test substance was [redacted] (CAS # 6991-62-4), batch number 90100/66, an opaque liquid.

Dose-range study

An initial dose-range study was performed to determine the concentrations of the test substance to be used for intradermal injection and dermal application in the challenge phase of the study.

Two animals were each injected intradermally at six sites with 0.1 ml of 1%, 5%, 10%, 20%, 50%, or 100% of the test material dissolved in corn oil. Because both animals died on or before day 4, they could not be examined on day 7 as planned. Two animals were then each injected intradermally at six sites with 0.1 ml of 0.01%, 0.05%, 0.1%, 0.5%, 1%, or 5% of the test material dissolved in corn oil, and the injection site was examined 6 days later. Necrosis was reported in both animals at concentrations of >0.5%, and mild erythema was reported in all animals at concentrations ≥0.1%. The concentration selected for intradermal injection in the challenge phase of the study was 0.1%.

To determine the concentration of the test substance for dermal application in the challenge phase, two intradermal injections of Freund's complete adjuvant (FCA; 50% in sterile water)[10] were first administered to the scapula (from which hair had been clipped) of five animals. Seven days later, gauze patches (2 cm^2) soaked with 2 ml of test substance (5%, 10%, 20%, 50%, or 100%, diluted with corn oil) were applied to both flanks of each animal and covered with foil, and the trunk was wrapped with a bandage. Two different concentrations of test substance (one on each flank) were tested in each animal, and each concentration was tested in two animals. The gauze patches were removed after 24 hours, and the sites were evaluated 24 and 48 hours later. The test substance did not cause a dermal effect at a 5% concentration, a 10% concentration caused erythema in one of the two animals tested, and necrosis occurred after exposure to concentrations $\geq$ 20%. Based on these results, a concentration of 0.5% was selected for dermal application in the challenge phase.

Main study

The main study that evaluated dermal sensitization included 10 control and 20 treated animals. It included two induction phases (intradermal injection and dermal application), followed by the challenge phase.

In the first induction stage (injection), three intradermal injections (0.1 ml each) were administered to each animal in a 2 x 4 cm^2 area of the scapula which had been clipped to remove hair. Treated animals were injected with emulsified FCA, 0.1% test substance in corn oil (vehicle), and 0.1% test substance in FCA. Control animals were injected with emulsified FCA, corn oil, and corn oil in FCA. In both treated and control animals, the first two injections listed above were near each other and the third injection was further away. Skin reactions were evaluated 24 hours after the injections. Injection of corn oil caused no response; injection of FCA, FCA and corn oil, and test substance and corn oil caused well defined erythema, and injection of test substance and FCA caused moderate erythema with the beginning of necrosis. It was noted that two treated animals were found dead 2 and 4 days after dosing, and it was stated that necropsy did not reveal "abnormalities that could be clearly attributed" to treatment with the test substance.

The second induction stage (dermal application) began 7 days after the intradermal injections. A gauze patch covered with 0.4 ml of test substance at 5% concentration in corn oil (treated animals) or corn oil (controls) was applied to the area near the injections site, covered with foil, and the animal was wrapped with a bandage. The gauze patches were removed after 48 hours and the area was washed with water, and the dermal reaction was evaluated 24 hours later. Discrete erythema (lowest severity in scoring system used) occurred in 3 of 20 treated animals, while no dermal effects were observed in the 10 controls.

[10] FCA is a mixture of paraffin oil, an emulsifier, and killed mycobacteria which "enhances the potential of a substance to cause a delayed hypersensitivity reaction" (RTC, 2001e).

The challenge phase began 3 weeks after the first induction phase (intradermal injection). Gauze patches (2 x 2 cm^2) coated with 0.2 ml of the test substance (0.5%) were applied to a clipped 5 x 5 cm^2 area on the right flank of all animals (treated [induced] and controls), and a gauze patch coated with 0.2 ml corn oil was similarly applied to the left flank of all animals. The patches were covered with foil and the animals were bandaged. The patches were removed after 24 hours, and dermal reactions were evaluated 24 and 48 hours later. There was no response to either the vehicle or the test substance in any of the control or treated (induced) animals. Additionally, there were no notable changes in body weight during the study.

The authors concluded that the test substance "did not elicit a sensitization response in the guinea pig."

Eye irritation

An acute eye irritation study in three female New Zealand White rabbits (RTC, 2001f) was identified. The test substance was [redacted] (CAS # 6991-62-4), batch number 90199/66, an opaque liquid. A volume of 0.1 ml of the test substance was introduced into the right eye of each animal. The eye, including conjunctiva, iris, and cornea, was examined 1, 24, 48, and 72 hours, and 7, 14, and 21 days after dosing. At 1, 24, and 48 hours, "well defined to moderate" chemosis (swelling of the conjunctiva), redness, and discharge; slight inflammation of the iris; and "slight to well defined" corneal opacity occurred in all three animals. At 72 hours, effects were generally more severe than at the earlier time points. "Moderate to severe" chemosis, moderate redness, "well defined to moderate" ocular discharge, and "well defined" corneal opacity occurred in all three animals. Inflammation of the iris remained "slight" in two animals, and it was more severe in the third animal. Ocular effects persisted until the end of the study, 21 days after dosing.

Acute oral studies

Three acute oral rat studies of CAS # 69991-62-4 were identified (Inveresk Research International, 1986; RTC, 2001a; RTC, 2002a). These three studies provided differing estimates of the median oral lethal dose (LD_{50}) of >5000 mg/kg (Inveresk Research International, 1986; >2000 mg/kg (RTC, 2001a), and <2000 mg/kg (RTC, 2002a). The acute oral rat studies are summarized below:

Inveresk Research International (1986): An acute oral study was conducted in male and female Sprague-Dawley rats. The test substance was [redacted] (CAS # 6991-62-4), batch number L377, a clear colorless liquid with specific gravity 2.04 mg/L.

A pre-dose range study was performed in which one male and one female animal per dose level were administered 2.04, 4.08, 6.12, or 10.20 g/kg of the test substance by gavage. The test substance was not diluted with a vehicle, and the volume administered therefore differed depending on the dose. The animals were weighed before dosing, and they were observed for 5 days. Clinical signs included hypokinesia, piloerection, soiled coat, and ataxia; doses at which

these effects occurred were not stated. Mortality occurred in 0/2 animals at 2.04 mg/kg, 1/2 at 4.08 g/kg, and 2/2 at 6.12 and 10.20 g/kg. No body weight data were provided.

A dose ranging study in which one male and one female animal per dose level were administered 1, 2, 3, 4, 5, 6, or 7 g/kg of the test substance by gavage. The test substance was not diluted with a vehicle, and the volume administered therefore differed depending on the dose. The animals were weighed before dosing and at death or at the end of the 14-day observation period. Clinical signs included hypokinesia, sedation, piloerection, soiled coat, and ataxia; doses at which these effects occurred were not stated. There was no mortality at doses ≤5 g/kg, and there was mortality in 2/2 animals at ≥6 g/kg. No body weight data were provided.

In the main study, 5 male and 5 female animals per dose level were administered 4, 4.5, or 5 g/kg test substance by gavage. As in the range finding studies, the test substance was not diluted with a vehicle, and the volume administered differed depending on the dose. The animals were weighted before dosing and at 7 and 14 days after dosing, or at death. Clinical signs including hypokinesia, sedation, piloerection, soiled coat, and ataxia occurred in both sexes on days 1-4 at 4.5 g/kg animals and days 2-5 at 5 g/kg, while no clinical signs occurred at 4 mg/kg. No mortality occurred at 4 or 4.5 g/day, mortality occurred 2 days after dosing in 1/5 males and 2/5 females at 5 mg/kg. No changes were observed at necropsy in the rats that survived until sacrifice at 14 days. Red stained fluid was observed in the gut of the 3 animals that died 2 days after dosing. The body weight data were provided, but no statistical evaluation was performed and there were no control animals for comparison to the dosed animals. The authors concluded that the LD_{50} could not be calculated but that it was >5 g/kg (i.e., >5000 mg/kg).

RTC, 2001a [11]. An acute oral study was conducted in Hsd: Sprague-Dawley SD rats. The name of the test substance was redacted in the publicly available version of the study obtained from the FDA, and it was a clear liquid. Five male and 5 female animals were dosed with 2000 mg/kg of the test substance diluted in corn oil such that the dose volume was 10 ml/kg. Animals were observed for 14 days after dosing, and they were weighed on the day before dosing, at dosing, and 7 and 14 days after dosing. No mortality or unexpected changes in body weight occurred during the study. The only clinical signs reported were piloerection and hunched posture on the day of dosing in both sexes. At necropsy, abnormal mucoid material was found in the small intestine of several males, and no abnormalities were observed in females. The authors concluded that a single oral dose of 2000 mg/kg did not cause toxic effects in rats and that the LD_{50} was >2000 mg/kg.

RTC (2002a). An acute oral study was conducted in male and female Sprague-Dawley rats. The test substance was [redacted] (CAS # 6991-62-4), batch number 90111/66, an opaque liquid. In all three phases of the study (initial, dose-range, and main study), the test substance diluted in corn oil was administered by gavage such that that the volume administered was 10 ml/kg.

[11] As discussed above, RTC (2001a) was not submitted to NJDEP. It was submitted by Solvay-Solexis S.p.A. to the FDA as part of information submitted for Food Contact Notification 000398 (CAS # 69991-62-4).

An initial study was performed in which 5 males and 5 females were administered 2000 mg/kg of the test substance. Animals were observed for 14 days after dosing. Clinical signs included piloerection, liquid feces, lethargy, brown staining around muzzle and/or eyes, semi-closed eyes, and, in females, salivation and rales. Mortality occurred between Days 2 and 11 in 4/5 males and 5/5 females. Body weight "appeared slightly reduced" in the surviving male. Necropsy findings in the animals in which mortality occurred included "abnormal coloration (dark or pale) of the spleen, thymus, liver, lungs, adrenals, stomach, and cervical lymph nodes. "Abnormal content (white or yellow, mucoid material)" was found in the stomach and duodenum of two animals in which mortality occurred and the one surviving animal.

A dose-range study was then performed in which one male and one female animal per dose level were administered 100, 200, 400, 800, or 1600 mg/kg of the test material. Animals were observed for 7 days after dosing. No mortality occurred at any dose level. Clinical signs included piloerection after dosing, hunched posture, and liquid feces at 800 and 1600 mg/kg, as well as decreased activity after dosing at 1600 mg/kg.

In the main study, five males and five female animals per dose level were administered 1000, 1800, or 3240 mg/kg of the test material. Animals were observed for 14 days after dosing. Clinical signs included piloerection and liquid or soft feces in most animals, as well as lethargy, hunched posture, and rales in some animals. No mortality occurred at 1000 mg/kg. At 1800 mg/kg, mortality occurred in 7/10 animals (4/5 males; 3/5 females), and at 3240 mg/kg, mortality occurred in all (10/10) animals. Decreased body weight occurred over the course of the study in one surviving female dosed with 1800 mg/kg. It was also reported that body weight gain was "slightly reduced" in surviving animals, but no statistical evaluation is shown and there is no control group for comparison. Necropsy findings in some animals with mortality included abnormal contents in the stomach and small intestine and abnormal size and color of the spleen, prostate, seminal vesicles, stomach, and/or mesentery. In surviving animals, abnormal content in the jejunum and urinary bladder was observed in one surviving female, and some animals had stained fur and/or skin.

The LD_{50} was calculated from the data from the main study (1000, 1800, 3240 mg/kg) and the initial study (2000 mg/kg/) as 1610 mg/kg (95% confidence interval [CI]: 1359-1908 mg/kg) in males; 1781 mg/kg (95% CI: not calculable) in females; and 1676 mg/kg (95% CI: 1533-1832 mg/kg) overall. The authors concluded that a single oral dose of the test item has a "toxic effect" in rats, and that the LD_{50} in this study was <2000 mg/kg.

Repeated Dose Oral Studies

Note: Because only one 4-week study with 2-week recovery period (RTC, 2005), and one 13-week study with 8-week recovery period (RTC, 2006) are available, these studies are referred to as the "4-week study" and "13-week study" (without citations) below.

The oral repeated dose studies are summarized below:

4-week study with 2-week recovery period (RTC, 2006): The test substance was [redacted], Batch Number 90156/96-2, as white granules. The purity was stated to be >85% "referred to dicarboxy end perfluoropolyethers."

Study design
Hsd: Sprague Dawley (i.e., Harlan Sprague Dawley) rats, approximately 4 weeks old were dosed with 0, 0.5, 2.5, or 8 mg/kg/day of the test substance in distilled water (dosing volume = 10 ml/kg/day) for 28 days by oral gavage; the controls were dosed with distilled water. The control and each of the dose groups included 5 males and 5 females that were sacrificed at the end of the 4-week dosing period, and the control and 8 mg/kg/day groups also included 5 additional animals per sex (the recovery group) that were sacrificed 14 days after dosing ended. A toxicokinetic study was conducted in an additional group of 9 females given a single oral gavage dose of 8 mg/kg. The design and results of the toxicokinetic study are discussed above in the *Toxicokinetics* section of this document.

The animals were observed for reaction to treatment before, immediately after, and 1 hour after (and 2 hours after, for the first 7 days of dosing) each daily dose. Additionally, an assessment of clinical signs and a neurotoxicity evaluation were performed on each animal before treatment began and weekly during the study. Reactivity to sensory (auditory, visual, proprioceptive) 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 during week 4 of the treatment period and week 2 of the recovery period. Hematological, clinical chemistry, and coagulation parameters were measured in blood samples that were also taken during week 2 of treatment and week 2 of recovery.

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, kidneys, thymus, and seminal vesicles, and on any tissues with abnormalities, in all dose groups. Histopathological evaluation was performed on a longer list of tissues in the control and 8 mg/kg/day (high dose) groups, and on any animal that died during the treatment period. Histopathological examination was also performed on the liver, lungs, kidneys, thymus, and seminar vesicles of the control and high dose (8 mg/kg/day) recovery groups.

The portions of the livers remaining after removal of sections for histopathological evaluation (~4 g from left lateral lobe) were frozen in liquid nitrogen. The study protocol states that, if histopathological changes in the liver were observed, these frozen liver samples would be assessed for activity of two liver enzymes that are indicators of peroxisome proliferation, cyanide-insensitive palmitoyl-CoA oxidation (PCO) and catalase activity. However, assessment

of the activity of these enzymes was not performed even though treatment-related histopathological changes in the liver occurred, and it is stated that this was a "deviation from the protocol."

Results[12]

Mortality: One female in the high dose (8 mg/kg/day) group died after blood was drawn on day 28 of treatment. This animal exhibited clinical signs (hypoactivity, pale, cold to touch, slowed breathing, dark urine, semi-closed eyes) on the day of death. Based on histopathological evaluation (described below), the death was considered to be treatment related.

Clinical signs and neurotoxicity: No clinical signs were observed after daily dosing during the study with the exception of tremors on one day in one male in the high dose (8 mg/kg/day) group.

No effects related to treatment were found during the more detailed weekly evaluations of clinical signs, neurotoxicity parameters (with the exception of mobility impairment and slight ataxia on one occasion in one male in the high dose group), reaction to sensory stimuli, grip strength, or motor activity.

Body weight and food consumption: Body weight was significantly lower than in control animals at 8 mg/kg/day starting on day 15 (males – 7%; females – 6%) through the end of the treatment period on day 29 (males – 20%; females – 6%). In males in this dose group, body weight decreased by 14% between day 8 and day 29. Body weight at this dose level remained significantly lower than in controls at the end of the 2-week recovery period (males-24%; females-9%). Food consumption was not affected by treatment during the treatment or recovery periods.

Hematology: The following hematological changes were noted during week 4 of the treatment period: In males, white blood cells (WBC) were significantly decreased by 25% and the percentage of lymphocytes was significantly increased by 8% at 8 mg/kg/day. The percentage of eosinophils was decreased at 0.5, 2.5 and 8 mg/kg/day by 51%, 35%, and 70%, respectively; the decrease at 2.5 mg/kg/day (35%) was not significant. Hemoglobin and hematocrit were significantly decreased only in the low dose (0.5 mg/kg/day) group. In females, platelets were significantly decreased by 20%, and prothrombin time was significantly increased by 25% at 8 mg/kg/day.

At the end of the 2-week recovery period, parameters related to red blood cells (RBCs) were significantly decreased in the 8 mg/kg/day males as follows: RBC count: -11%; hemoglobin: -14%; hematocrit: -15%; mean RBC volume: -5%; mean corpuscular hemoglobin: -4%. In

[12] In this section and in the Results section for the 13-week study, "statistically significant" or "significant" refers to changes in treated groups that were significant at $p<0.05$ or $p<0.01$ compared to the control group. Unless stated otherwise, all changes mentioned were statistically significant.

females, there were significant decreases in WBC (33%) and percentage of neutrophils (41%) and an increase in percentage of lymphocytes (7%).

The hematological changes at the end of the treatment and recovery periods were discounted by the study authors as "incidental" and "of no toxicological importance." However, these effects should not necessarily be discounted. Specifically, in another section of the study report (RTC, 2005), it is stated that the decrease in WBCs may be related atrophy of the thymus caused by the test substances. Additionally, some of the effects on RBC parameters observed in this study, including decreases in RBC count, hemoglobin, and hematocrit, also occurred at much lower doses, only in males, at the end of the treatment period in 13-week study (RTC, 2006). Furthermore, ClPFPECAs (NJDEP, 2021) and numerous other PFAS (e.g., perfluorobutanoic acid [PFBA], perfluorohexanoic acid [PFHxA], PFOA, PFNA, PFBS, perfluorohexane sulfonate [PFHxS], perfluorooctane sulfonate [PFOS], 4,8-dioxa-3H-perfluorononanoate [ADONA], and HFPO-DA [GenX]) caused the same effects on RBC parameters in rats that were observed in males at the end of the recovery period in rats, as reviewed in ITRC (2023).

Clinical chemistry: Statistically significant changes in clinical chemistry parameters were reported at 0.5, 2.5, and/or 8 mg/kg/day at week 4 of treatment and 8 mg/kg/day (the only dose tested) at week 2 of recovery. RTC (2005) states that most of the changes showed a dose-related trend, and that most of the changes observed at 4 weeks of treatment were also present at week 2 of recovery. It was noted that most of the clinical chemistry data for the female rat in the high dose (8 mg/kg/day) group that died on Day 28 were not included in the analysis because they were "so high as to upset the means." However, it is not clear that omitting these data is justified, especially since, as mentioned above, the death of this animal was considered to be treatment related.

Statistically significant changes were as follows:

Enzymes:

- Alkaline phosphatase (ALP) was increased in males and females, respectively, by 76% and 36% at 2.5 mg/kg/day and 78% and 60% at 8 mg/kg/day at week 4 of treatment. It was increased by 80% in males and 46% in females at week 2 of recovery.

- Alanine aminotransferase (ALT) was increased in females by 58% at 8 mg/kg/day at week 4 of treatment and 32% at week 2 of recovery.

- Aspartate aminotransferase (AST) was increased in males by 50% and females by 42% at 8 mg/kg/day in week 4 of treatment. It was increased by 37% in males in week 2 of recovery.

Lipids:

- Triglycerides were increased by 35% at 2.5 mg/kg/day and 40% at 8 mg/kg/day in males and by 51% at 0.5 mg/kg/day, 75% at 2.5 mg/kg/day and 67% at 8 mg/kg/day in females at week 4 of treatment. They remained elevated by 23% in males at week 2 of recovery.

Protein:

- Total protein was decreased by 15% at 2.5 mg/kg/day and 27% at 8 mg/kg/day in males and 14% at 8 mg/kg/day in females at week 4 of treatment. It remained decreased by 22% in males at week 2 of recovery.

- Albumin was decreased by 16% at 8 mg/kg/day in males, while it was increased by 7% at 0.5 mg/kg/day and 11% at 2.5 mg/kg/day in females. It remained decreased by 16% in males at week 2 of recovery.

- Globulin was decreased in males and females, respectively, by 39% and 22% at 2.5 mg/kg/day and 43% and 33% at 8 mg/kg/day at 4 weeks of treatment. It remained decreased by 34% in males and 28% in females at week 2 of recovery.

- The changes in albumin and globulin mentioned above resulted in a significant increase in the albumin/globulin (A/G) ratio at all doses (16%, 70%, 48% in males and 18%, 43%, 45% in females at 0.5, 2.5, and 8 mg/kg/day, respectively) at 4 weeks of treatment. This ratio remained increased by 33% and 45% in males and females, respectively, at week 2 of recovery.

Other parameters:

- Urea was increased by 30% at 0.5 mg/kg/day, 22% at 2.5 mg/kg/day, and 46% at 8 mg/kg/day in males and by 21% at 2.5 mg/kg/day and 24% at 8 mg/kg/day in females at 4 weeks of treatment. It remained increased by 50% in males at week 2 of recovery.
- Creatinine was decreased in males by 26% at 2.5 mg/kg/day and 29% at 8 mg/kg/day at 4 weeks of treatment. It was decreased by 32% in males and 18% in females at week 2 of recovery.
- Changes in electrolytes (chloride and potassium, and/or calcium) occurred at some dose levels at week 4 and/or at week 2 of recovery.

Urinalysis: Urine volume was increased in females in a dose-related manner, with statistically significant increases at 2.5 mg/kg/day (35%) and 8 mg/kg/day (59%) after 4 weeks of treatment and 83% at the end of recovery. RTC (2005) states the protein in the urine was slightly reduced at 8 mg/kg/day at the end of treatment, but these data are not shown in the summary tables for urinalysis parameters.

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 many of these changes persisted until the end of the 2-week recovery period. RTC (2005) states

that these changes are "supported by findings observed at macroscopic and microscopic examination of these organs" that were "regarded as an effect of the treatment with the test item, which was not reversible over a 2-week period."

Effects on relative organ weights are summarized as follows: Relative liver weight was increased in a dose-related fashion with statistical significance at the end of treatment at all doses in males, at the mid- and high doses in females, and at the end of recovery in both sexes. At the end of treatment, it was increased by 21, 53, and 70% in males and 16, 39, and 62% in females at 0.5, 2.5, and 8 mg/kg/day, respectively. The magnitude of the increase in relative liver weight did not decrease during the 2-week recovery period. At the end of the recovery period, relative liver weight was increased by 89% in males and 60% in females compared to the controls in the recovery group.

Relative spleen weight at the end of treatment was decreased in males and females, respectively, by 11% (not statistically significant) and 21% at 2.5 mg/kg/day and by 27% and 32% at 8 mg/kg/day. In males, relative testes weight was increased by 27% at 8 mg/kg/day at the end of treatment and 21% at the end of recovery, relative thyroid weight was increased by 41% at 8 mg/kg/day at the end of treatment, and relative brain weight[13] was increased by 22% at 8 mg/kg/day at the end of treatment and 30% at the end of recovery. Additionally, relative kidney weight was increased in males by 11% at 2.5 mg/kg/day and 27% at 8 mg/kg/day at the end of treatment, and by 31% in males and 17% in females at the end of recovery. Relative thymus weight in males at 8 mg/kg/day was decreased by 57% at the end of treatment and 41% at the end of recovery. Increased relative weights of the adrenals (37%) and epididymis (9%) were also observed in males at the end of recovery.

Macroscopic pathology: A gross pathology examination was performed on a female rat that died on day 28, the last day of the dosing period and on the other animals at terminal sacrifice. The 8 mg/kg/day female that died on day 28 had incomplete collapse of the lungs, pale liver and pancreas, and a scab on the head, in addition to the other effects noted below.

Enlarged liver was observed in 4/5 males and 1/5 females at 2.5 mg/kg/day and 4/5 males and 1/5 females at 8 mg/kg/day. Thymus size was decreased in 4/5 males and 1/5 females (the female that was found dead) at 8 mg/kg/day. The size of seminal vesicles was also decreased in males at 8 mg/kg/day. At the end of recovery, the liver was enlarged in 5/5 males, thymus size was decreased in 4/5 males, and seminal vesicle size was decreased in 1/5 males. No macroscopic changes were reported in females at the end of the recovery period.

Microscopic pathology: Histopathological changes in the liver occurred in both males and females at the end of dosing and at the end of recovery. Hepatocellular hypertrophy was not observed in any control or low-dose (0.5 mg/kg/day) animals, while it occurred in all males and females at 2.5 and 8 mg/kg/day at the end of dosing and in 4/5 males and 3/5 females at the end

[13] Absolute brain weight, which was not affected by treatment with test substance, is generally considered more relevant than relative brain weight.

of recovery. Additional hepatic effects included hepatocytic necrosis in 2/5 males at 8 mg/kg/day at the end of dosing and 2/5 males at the end of recovery; single cell apoptosis/necrosis in 5/5 males and 3/5 females at 8 mg/kg/day at the end of dosing and 2/5 males and 1/5 females at the end of recovery; and hepatocellular vacuolation in 3/5 males at 2.5 mg/kg/day and 2/5 males and 1/5 females at 8 mg/kg/day at the end of dosing, and 5/5 males at the end of recovery. Bile duct proliferation occurred in the control, 0.5, 2.5, and 8 mg/kg/day groups in 2/5, 5/5, 4/5, and 5/5 males and 1/5, 4/5, 5/5, and 4/5 females, respectively.

In the lungs, aggregation of alveolar macrophages occurred in 1/5 males at 2.5 mg/kg/day, 4/5 males and 3/5 females at 8 mg/kg/day at the end of treatment, and 2/5 males at the end of recovery. This effect was stated to be "possibly suggestive of a phospholipidosis condition." This change was also seen in 1/5 control males but, in this case, it was considered to be part of a chronic inflammatory process that was not present in other control or treated animals.

Atrophy of the thymus, which was more severe in males, occurred in 1/5 males at 2.5 mg/kg/day and 5/5 males and 3/5 females at 8 mg/kg/day. This effect persisted in 5/5 males and 3/5 females at the end of recovery. Colloid depletion of the seminal vesicles was observed in 5/5 males at 8 mg/kg/day and in 2/5 males at the end of recovery. It also occurred in 1/5 control males at the end of dosing; this animal also exhibited unilateral testicular aplasia. Finally, foci of mineralization in the kidney occurred in 1/5 females at 2.5 mg/kg/day, 4/5 females at 8 mg/kg/day, and 2/5 females at the end of recovery.

Conclusions

The study authors concluded that the effects on body weight, hematological parameters, clinical chemistry, organ weight, and gross and microscopic pathology summarized above indicated an "evident toxic effect" of the test substance at the two higher dose levels (2.5 and 8 mg/kg/day), and that most effects persisted until the end of the 2-week recovery period at 8 mg/kg/day, the only dose level evaluated during recovery. Additionally, the study authors concluded that "males appeared to be more sensitive than females to the test substance," based on incidence and severity of the observed effects. It was further concluded that the less severe effects at the lowest dose (0.5 mg/kg/day), while not considered adverse, were "the first step of a dose-related effect which became adverse" at the higher dose levels. Based on these conclusions, a No Observed Effect Level (NOEL) was not identified by the study authors.

13-week study with 8-week recovery period (RTC, 2016): The test material was [redacted], batch Number 90156/96-2, as white granules. The purity was stated to be >85% "referred to dicarboxy end perfluoropolyethers."

Study design

Sprague Dawley rats (15 per sex/dose group for the control and high dose groups; 10 per sex/dose group for the low and mid dose groups), approximately 4 weeks old, were dosed daily with 0, 0.03, 0.13, or 0.5 mg/kg/day of the test substance in water for a minimum of 13 weeks by

oral gavage; the controls were dosed with water. The dosing volume was 10 ml/kg body weight. In each dose group, 10 males and 10 females were sacrificed at the end of the dosing period. In the control and high dose groups, 5 per sex per dose group (the recovery groups) were sacrificed 8 weeks later. An additional "satellite" group of 9 male rats was dosed with 0.5 mg/kg for a toxicokinetic study (see *Toxicokinetics* section, above).

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 were performed on each animal before treatment began and weekly during the study. 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.

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 0.5 mg/kg/day groups during week 13 of dosing.

Hematological, clinical chemistry, and coagulation parameters were measured in blood samples and urinalysis was performed on urine samples that were taken during week 13 of treatment period and week 8 of the 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 evaluation was performed on liver, lung, and spleen from all animals at the end of the 13-week dosing period and the 8 week recovery period, on a longer list of tissues on all animals in the control and 0.5 mg/kg/day (high dose) groups at the end of 13 weeks of treatment, and on all abnormalities from all dose groups.

Additionally, liver samples taken at sacrifice from 5 males and 5 females from the control, 0.03, 0.13, and 0.5 mg/kg/day dose groups and the control and 0.5 mg/kg/day recovery groups were shipped on dry ice to Huntingdon Life Sciences (Cambridgeshire, England) where they were stored at stored at approximately -75ºC. Cyanide-insensitive PCO (an indicator of peroxisome proliferation) and protein concentration were measured in 3000xg supernatant prepared from each sample of the liver tissue.

Results

(Note: The results of the evaluation of hepatic peroxisome proliferation, as indicated by cyanide-insensitive PCO activity, are discussed in the Mode of Action section below.)

Mortality: There was no mortality during the study.

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

No treatment related effects were reported in the more detailed evaluations of clinical signs and neurotoxicity that were performed weekly.

Motor activity was significantly decreased in males dosed with 0.13 and 0.5 mg/kg/day at the end of the 13-week treatment period, while no effects were seen in females at the end of treatment or in either sex at the end of the 8-week recovery period.

Body weight and food consumption: Relatively small decreases in body weight (≤10%), although not statistically significant at most time points, were consistently observed in the high dose (0.5 mg/kg/day) males and females starting at week 8 of treatment and throughout the recovery period. The decrease in body weight was statistically significant ($p<0.01$) in males during week 13 of treatment and in females during week 11 of treatment ($p<0.05$) and week 1 ($p<0.05$) and week 2 ($p<0.01$) of recovery. Although it is stated in the study report that the decreased body weight was attributed to overnight fasting prior to blood sampling during week 13 of treatment, the decrease began prior to week 13 of treatment and only occurred in the high dose male and female groups.

There were no statistically significant changes in food consumption during the treatment or recovery periods.

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 and at the end of the recovery period. At the end of the dosing period, there were dose-related decreased in RBC count, hemoglobin, and hematocrit in males that were statistically significant at the two higher doses (0.13 and 0.5 mg/kg/day). These decreases were relatively small in magnitude, with decreases of 10% for RBC count, and 6% for both hemoglobin and hematocrit in the high dose group (0.5 mg/kg/day). Additionally, mean RBC volume and mean corpuscular hemoglobin were both increased by 4% in the high dose males.

The authors of the study report stated that these changes were "insufficient in magnitude to be of toxicological significance." However, these effects are relevant and should not be discounted. As mentioned above, RBC count, hematocrit and hemoglobin were also decreased in males at the end of the 2-week recovery period in the 4-week study, and numerous other PFAS caused the same effects on these RBC parameters.

In females, the percentage of neutrophils wase significantly increased by 65% and the percentage of lymphocytes was significantly decreased by 9% in the low dose (0.03 mg/kg/day) dose group, but there were no statistically significant hematological changes in the other two dose groups.

There were no statistically significant hematological effects in males or females at the end of the recovery period.

Clinical chemistry: Statistically significant ($p<0.05$ or $p<0.01$) changes in clinical chemistry parameters during week 13 of the dosing period and week 8 of the recovery period are shown in Table 4, below. Some of the changes during week 13 are consistent with those reported at higher doses after 4 weeks of exposure (RTC, 2005; see above), including increased ALP in males and females, increased triglycerides in females, increased creatinine and urea in males, decreased protein in males, increased albumin in males and decreased albumin in females, decreased globulin in males, and increased A/G ratio in males and females.

Some changes persisted until the end of the 8-week recovery period including increased ALP in males and females, increased triglycerides in females, increased urea in males, and increased globulin and A/G ratio in females.

Serum triglycerides were increased in females at all three dose levels in a dose-related manner, with increases of 27% (not statistically significant), 40%, and 63% at 0.03, 0.13, and 0.5 mg/kg/day, respectively. An increase of 54% persisted until the end of recovery in females dosed with 0.5 mg/kg/day.

Table 4: Statistically significant ($p<0.05$) changes in clinical chemistry parameters compared to control group during week 13 of dosing period and week 8 of recovery period

	Males				**Females**			
	Treatment (Week 13)			**Recovery (Week 8)**	**Treatment (Week 13)**			**Recovery (Week 8)**
Dose (mg/kg/day)	**0.03**	**0.13**	**0.5**	**0.5**	**0.03**	**0.13**	**0.5**	**Recovery (0.5)**
Alkaline phosphatase (ALP)	-11%	+25%	+101%	+47%			+65%	+29%
Alanine aminotransferase (ALT)		+30%						-14%
Total bilirubin			-25%				-31%	
Cholesterol		-27%				-20%		
Triglycerides						+40%	+63%	+54%
Urea			+36%	+29%				
Creatinine		-13%	-23%					
Protein		-7%	-14%				+5%	
Albumin			-7%			+8%	+14%	+13%
Globulin			-23%					-19%
Albumin/globulin (A/G) ratio			+24%			+20%	+32%	+38%
Calcium	-3%	-4%	-8%					
Chloride			+2%					
Phosphate				+18%				
Sodium				-1%				+1%

Organ weights: At the end of the treatment period, absolute and relative liver weights were significantly ($p<0.05$ or $p<0.01$) increased in a dose-related manner in males and females at

0.13 and 0.5 mg/kg/day. Relative liver weights were increased by 14% and 15% at 0.13 mg/kg/day and 43% and 61% at 0.5 mg/kg/day in males and females, respectively. At the end of the 8 week recovery period, relative liver weights remained significantly elevated by 37% in males and 39% in females that had been dosed with 0.5 mg/kg/day.

Additionally, absolute and relative kidney weights were increased in high dose (0.5 mg/kg/day) males and females; relative kidney weights were increased by 18% in males and 14% in females. In males, absolute (but not relative) weights of adrenals, heart, spleen, and thymus were decreased at 0.5 mg/kg/day, and absolute weight of testes was decreased at both 0.13 and 0.5 mg/kg/day. Aside from the liver (discussed above), there were no significant changes in absolute or relative organ weights at the end of the recovery period in either sex.

Macroscopic pathology: No macroscopic changes related to treatment were observed in males or females sacrificed at the end of the treatment period or the recovery period.

Microscopic pathology: Histopathological changes associated with treatment were observed in the livers, lungs, spleen, stomach, and uterus, as described below.

At the end of the dosing period, hepatocytic hypertrophy occurred in 2/10 males and 2/10 females at 0.13 mg/kg/day and 9/10 males and 9/10 females at 0.5 mg/kg/day; it did not occur in control or low dose (0.03 mg/kg/day) males or females (n=10 per sex per dose group). Other hepatic changes included pigmentation in 1/10 males at 0.5 mg/kg/day and 1/10, 2/10, and 2/10 females at 0.03, 0.13, and 0.5 mg/kg/day, respectively; cholangitis in 1/10 males at 0.5 mg/kg/day; and chronic inflammation in 1/10 males at 0.13 mg/kg/day. At the end of the recovery period, hepatocytic hypertrophy persisted in all treated (0.5 mg/kg/day) males and females but was not observed in controls (n=5 per sex per dose group), and hepatic pigmentation occurred in 2/5 treated males but was not observed in controls or females.

In the lungs, aggregations of alveolar macrophages increased in a dose-related fashion in females at the end of the treatment period, occurring in 3/10, 3/10, 5/10, and 7/10 animals in the control, 0.03, 0.13, and 0.5 mg/kg/day groups, respectively. This effect was described in the study report as "phospholipidosis, represented by alveolar foamy macrophages, associated with interstitial inflammatory cell infiltrate." Aggregations of alveolar macrophages also occurred in males but did not increase in a dose-related manner (1/10, 3/10, 3/10, and 2/10 in the control, 0.03, 0.13, and 0.5 mg/kg/day groups, respectively). At the end of the recovery period, the incidence of aggregations of alveolar macrophages were increased in both males and females treated with 0.5 mg/kg/day (0/5 and 4/5 males and 1/5 and 3/5 females in control and treated groups, respectively), and the study report states that "alveolar foamy macrophages were clearly seen in treated males and females."

At the end of the dosing period, pigmentation of the spleen occurred in 1/10, 4/10, 4/10, and 4/10 females in the control, 0.03, 0.13, and 0.5 mg/kg/day groups, respectively. Additionally, chronic inflammation and edema of the stomach occurred in 2/10 males dosed with 0.5 mg/kg/day and

was accompanied by mucosal ulceration in one of these animals; these effects did not occur in controls or females, and the stomachs of animals in the two lower dose groups were not evaluated. Finally, hydrometra of the uterus occurred in 1/10, 1/1, 1/2, and 4/10 females that were evaluated in the control, 0.03, 0.13, and 0.5 mg/kg/day groups, respectively.

Conclusions
RTC (2006) concludes, in summary, that "signs of an evident adverse effect of the test item were seen at the 2 higher dose levels" (0.13 and 0.5 mg/kg/day), and that "most of the observed effects were not reversible over an 8-week recovery period in the high dose animals." The study report concludes that the liver was the main target organ based on increased liver weight and histopathological changes, and that the lungs were also a target organ based on histopathological effects. Effects in both the liver and the lung occurred in a dose-related manner and persisted until the end of the 8-week recovery period. Since no statistically significant effects in the liver or the lungs occurred at 0.03 mg/kg/day, the authors concluded that this dose was the NOEL in this study.

Additionally, serum triglycerides in females were increased in a dose-related manner, although the increase was not statistically significant at the lowest dose, 0.03 mg/kg/day, and this effect persisted until the end of the recovery period. The increase in serum triglycerides caused by PFPE-DCAs is noteworthy because several other PFAS (e.g., PFOA, PFNA, PFOS, ClPFPECAs are associated with increased serum lipids in humans (DWQI, 2015; DWQI, 2017; DWQI, 2018; NJDEP, 2021). However, in contrast to PFPE-DCAs in this study, these other PFAS cause decreased levels of serum lipids including triglycerides in rodents (DWQI, 2015; DWQI, 2017; DWQI, 2018; NJDEP, 2021).

MODE OF ACTION

Genotoxicity
As is generally the case for other PFAS (DWQI, 2015; DWQI, 2017; DWQI, 2018; NJDEP, 2021; ITRC, 2023), negative results were reported in the genotoxicity studies of CAS # 6991-62-4 (PFPE-DCAs) that were identified for review.

Solvay provided one study on bacterial mutagenicity of CAS # 6991-62-4 (PFPE-DCAs; [redacted]) to NJDEP (RTC, 2001g). Three additional genotoxicity studies of CAS # 6991-62-4 were submitted by Solvay's Italian affiliate to the FDA. These include another bacterial mutagenicity study (RTC, 2001b), a chromosome aberration study in Chinese hamster ovary (CHO) cells (RTC, 2003a), and a micronucleus test in mice (RTC, 2003b). All of these studies were conducted at contract toxicology laboratories in Italy and were sponsored by Ausimont. The studies are summarized below:

Bacterial mutagenicity
Both bacterial mutagenicity studies (RTC, 2001b; RTC, 2001g) used the same protocol to test PFPE-DCAs (dissolved in dimethylsulfoxide), with and without metabolic activation with liver

S9[14] 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 RTC (2001g), the test substance was [redacted], lot number 90199/66, a colorless liquid. In RTC (2001b), the trade name of the test substance was not available in the redacted study provided by the FDA; the lot number was 90215/18, and it was a colorless liquid. In these studies, two independent mutagenicity studies (one using the plate incorporation method and the second using a 30-minute pre-incubation step) were performed in triplicate at concentrations of PFPE-DCAs of up to 5000 µg/ plate. This upper concentration was selected after preliminary studies in RTC (2001g), which were completed before RTC (2001b). The studies reported in RTC (2001g) determined that 5000 µg/plate, but not concentrations ≤1580 µg/plate, caused toxicity in all five strains in the absence of metabolic activation and slight toxicity in TA 1537 with metabolic activation. Toxicity tests were also conducted in RTC (2001b), and no toxicity was observed in any of the five strains of bacteria. The test substances were negative for mutagenicity at all concentrations and test conditions in these studies.

Chromosome aberrations

PFPE-DCAs (CAS # 6991-62-4) were evaluated for their potential to cause chromosomal damage in Chinese hamster ovary (CHO) cells *in vitro* in the presence and absence of liver S9 from rats induced with phenobarbital and beta-naphthoflavone (RTC, 2003a). The trade name of the test substance was not available in the redacted study provided by the FDA; the batch number was 00003/61, and it was a colorless liquid. Two assays for chromosomal damage were conducted.

In the first assay, CHO cells were exposed to 0, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, or 5000 µg/L of the test substance dissolved in distilled water for 3 hours, with or without metabolic activation, and cells were harvested at 20 hours (approximately 1 cell cycle). Toxicity of varying degrees, as indicated by reduced cell count, occurred at 2500 and 5000 ug/L (marked degree) and 1250 ug/L (mild degree) in the absence of metabolic activation. In the presence of metabolic activation, toxicity occurred at 5000 ug/L (severe degree), 2500 ug/L (marked degree), and 313, 625, and 1250 ug/L (moderate to mild degree). Based on guidelines stating that the highest dose-level scored for chromosome aberrations should cause moderate toxicity, the dose levels selected for scoring were 1250, 2500, and 5000 µg/L without metabolic activation and 313, 625, and 1250 µg/L with metabolic activation. The number of cells with chromosome aberrations, excluding gaps[15], was not increased at any dose level with or without metabolic activation. The number of cells with aberrations including gaps was increased at 1250 and 2500 µg/L without activation and 313 and 653 µg/L with activation.

[14] S9 is the 9000g supernatant of liver homogenate. It contains the microsomal and cytosolic fractions in which enzymes that metabolize xenobiotics are present.

[15] A gap is "an achromatic lesion smaller than the width of one chromatid, and with minimum misalignment of the chromatids" (OECD, 2013). It is noted that OECD (2013) guidance for the *in vitro* mammalian chromosome aberration test states: "Gaps are recorded and reported separately but not included in the total aberration frequency."

In the second assay, CHO cells were exposed to 0, 39.1, 78.1, 156, 313, 625, 1250, 2500, or 5000 µg/L of the test substance dissolved in distilled water without metabolic activation until evaluation after 20 hours of exposure. Moderate toxicity occurred at 2500 and 5000 µg/L, with no significant toxicity at lower doses. The doses selected for scoring of chromosome aberrations were 625, 1250, and 2500 µg/L. No increases in the frequency of chromosome aberrations (including or excluding gaps) were observed at any dose level. The authors concluded that the test substance did not "induce chromosomal aberrations in Chinese hamster ovary cells after in vitro treatment in the absence or presence of S9 metabolic activation, under the reported experimental conditions."

Micronucleus test

PFPE-DCAs (CAS # 6991-62-4) were evaluated for their potential to cause micronuclei in male and female CD-1 mice (RTC, 2003b). The trade name of the test substance was Fomblin Z Diac A, batch number 00003/61, a colorless liquid, and it was administered by gavage in corn oil.

In a preliminary toxicity study, male and female mice (2 per sex per dose level) were administered 1000 or 2000 mg/kg of the test substance and sacrificed 48 hours later for examination of bone marrow from the femur. No clinical signs were observed, and there were no effects on the proliferation of erythropoietic cells in the bone marrow.

In the main study, mice (5 per sex per dose level) were administered 0, 500, 1000, or 2000 mg/kg test substance, and bone marrow from the femur was examined after sacrifice 24 hours after dosing. In the control and high dose (2000 mg/kg) groups, 5 additional animals per sex were dosed, and their bone marrow was examined after sacrifice 48 hours after dosing. Mortality occurred in 2 male and 2 female animals given 2000 mg/kg which was attributed to dosing error in one of the males and one of the females; additional animals were substituted for the animals that died. Smears of bone marrow cells were examined for depression of polychromatic (immature) erythrocytes, micronuclei in polychromatic erythrocytes, and the number of normal and micronucleated normochromatic (mature) erythrocytes. Based on group means for the number of micronucleated cells per 1000 mature or polychromatic erythrocytes in males, females, and males and females combined, there was no increase in the number of micronucleated cells at any dose at either time point (24 or 48 hours). Additionally, there was no effect on the ratio of immature to mature erythrocytes or the percentage of immature erythrocytes out of total erythrocytes, indicating that the test substance did not inhibit erythropoietic cell division. An additional statistical analysis of the polychromatic cell data based on the original observations (data from individual animals, rather than micronucleus frequency per 1000 cells in entire dose group) was performed. This analysis considered the degree of heterogeneity in each group when making comparisons between the treated and control groups. In this analysis, a slight but statistically significant increase in the incidence of micronucleated polychromatic erythrocytes compared to controls was observed at 500 mg/kg in males ($p<0.5$), females ($p<0.05$), and males and females combined ($p<0.01$) after 24 hours; no increase was seen at the higher dose levels. It was stated that these results were likely due to a very low incidence of micronucleated polychromatic erythrocytes in the control group, and that the incidence in the

treated groups, except for one value, was within the historical control range. Based on this information, these increases were not considered to be biologically significant. Additionally, the incidence of micronucleated polychromatic erythrocytes was significantly decreased ($p<0.05$) at 2000 mg/kg compared to controls after 48 hours of exposure. The authors concluded that, based on the results of this study, the test substance "administered by oral gavage, does not induce micronuclei in the polychromatic erythrocytes of treated mice, under the reported experimental conditions."

Mode(s) of action for systemic effects

In general, effects of PFAS occur through multiple modes of action including activation of receptors that control the expression of genes involved in many biological pathways. As reviewed in DWQI (2017): "Much attention has been focused on the potential human relevance of effects [of PFAS in rodents] that occur through activation of the nuclear receptor, peroxisome proliferator-activated receptor-alpha (PPAR-alpha). This question arises because many PPAR-alpha activating compounds cause rodent liver tumors; the human relevance of these tumors is subject to debate due to lower levels and/or differences in intrinsic activity of PPAR-alpha in human liver."

DWQI (2017) further states: "However, the uncertainty about human relevance does not necessarily apply to PPAR-alpha mediated [hepatic] effects other than liver tumors [or to PPAR-alpha mediated effects in other organs]." Additionally, it is well established that hepatic, developmental, and other effects of PFAS occur through both PPAR-alpha dependent and PPAR-alpha independent modes of action (reviewed in DWQI, 2015; DWQI, 2017; DWQI, 2018).

In the 13-week study (RTC, 2006), cyanide insensitive PCO activity, an indicator of peroxisome proliferation induction and PPAR-alpha activation in rodents (Corton et al., 2018), was measured in 3000 x g supernatant from livers of male and female rats in all dose groups at the end of the treatment and recovery periods. As shown in Table 5, PCO activity (nmol/min/mg protein) was increased at 0.13 and 0.5 mg/kg/day in a dose-related manner, with increases of approximately 11-fold in males and 9-fold in females at the end of treatment in the high dose (0.5 mg/kg/day) group; PCO activity was increased by approximately 13-fold in males and 11-fold in females at this dose on a nmol/min/g liver basis. An increase in PCO activity of approximately 5-fold persisted at the end of the 8 week recovery period in both males and females that had been dosed with 0.5 mg/kg/day. These results indicate that the PFPE-DCA test substance activated PPAR-alpha in both male and female rats.

Table 5: Hepatic cyanide insensitive palmitoyl CoA oxidase (PCO) activity* compared to controls at the end of treatment and recovery period (RTC, 2006)

	Males				Females			
	Treatment (Week 13)			Recovery (Week 8)	Treatment (Week 13)			Recovery (Week 8)
Dose (mg/kg/day)	**0.03**	**0.13**	**0.5**	**0.5**	**0.03**	**0.13**	**0.5**	**0.5**
PCO activity (nmol/min/mg protein)	110%	309%**	1097%**	512%**	92%	188%**	911%**	537%**
PCO activity (nmol/min/g liver)	103%	292%**	1285%**	539%**	73%	164%**	1121%**	614%**

* PCO activity was assayed as nanomoles of reduced nicotinamide adenine dinucleotide (NADH) formed per minute per mg of 3000 x g supernatant protein (nmol/min/mg/protein) and nanomoles of NADH formed per minute per g of liver (nmol/min/g liver).
** $p<0.01$

As discussed above, the modes of action of other PFAS involve activation of other receptors, which may include PPAR-beta, PPAR-gamma, constitutive activated receptor, pregnane X receptor, hepatocyte nuclear factor 4-α, and estrogen receptor-alpha (DWQI, 2015: DWQI, 2017: DWQI, 2018). However, activation of these other receptors by PFPE-DCAs has not been evaluated. Relevant to this point, activation of PPAR-alpha causes decreased serum lipids including triglyceride in both humans and experimental animals; this is the basis for the use of fibrates as cholesterol-reducing agents in humans (DWQI, 2017). However, as discussed above, PFPE-DCAs caused increases in serum triglyceride levels in male and female rats in the 4-week study and in females in the 13-week study (RTC, 2006). This increase in serum triglycerides indicates that PFPE-DCAs act through PPAR-alpha independent effects as well as activating PPAR-alpha, as shown by induction of PCO activity.

DEVELOPMENT OF ISGWQC

Consideration of potential for human health effects

No information on toxicokinetics or health effects of PFPE-DCAs in humans was identified. However, other long-chain carboxylic acid PFAS, including PFOA, PFNA, and ClPFPECAs, are bioaccumulative in humans with half-lives of several years, and exposure to these PFAS is associated with multiple human health effects (DWQI, 2015; DWQI, 2017; NJDEP, 2021). This information suggests a need for caution about human exposures to PFPE-DCAs and supports 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 (10^{-6}) lifetime cancer risk level for carcinogens and no adverse effects from lifetime ingestion for non-carcinogens. No information is available regarding the carcinogenic potential of PFPE-DCAs 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. Toxicological effects of PFPE-DCAs in rats in the 13-week study (RTC, 2006) were considered for dose-response evaluation and potential use in RfD since this study was of subchronic duration and used lower doses than the 4-week study (RTC, 2005). The effects that were selected for consideration as the basis for the RfD were increased relative liver weight in males and females, increased serum triglycerides in females, decreased RBC parameters (RBC count, hemoglobin, and hematocrit) in males, and increased incidence of aggregations of alveolar macrophages in females (Table 6). Other statistically significant effects in the 13-week study were not considered as the basis for RfD development because they occurred only at the highest dose (e.g., increased relative kidney weight) or their toxicological significance is less clear (e.g., changes in A/G ratio).

Table 6. Summary of dose-response data for toxicological effects considered for RfD development (RTC, 2006)

		Dose (mg/kg/day)				
Effect	*Sex*	*0*	*0.03*	*0.13*	*0.5*	*Recovery (0.5)*
Relative liver weight (liver weight/body weight relative to control value)	M	1	0.98	1.14**	1.43**	1.37**
	F	1	1.04	1.15**	1.61**	1.39**
RBC count (% change compared to control)	M	0	-2%	-5%*	-10%**	No effect
Hemoglobin (% change compared to control)	M	0	-2%	-4%*	-6%**	
Hematocrit (% change compared to control)	M	0	-2%	-5%*	-6%**	
Serum triglycerides (% change compared to control)	F	0	+26%	+40%**	+63%**	+54%*
Aggregations of alveolar macrophages (incidence)	F	3/10	3/10	5/10	7/10	Control – 0/5 Treated – 4/5

*p<0.05 **p<0.01

Relative liver weight. Increased relative liver weight was one of the four endpoints selected for dose-response evaluation. This effect is a well-established and sensitive endpoint for PFAS in general (Bil et al., 2021; ITRC, 2023). Relative liver weight was increased in a dose-related fashion in the two studies of PFPE-DCAs in which organ weights were measured (4-week study,

RTC, 2005; 13-week study, RTC, 2006), and this effect persisted until the end of the recovery period in both studies. The increase in relative liver weight was greater in the 13-week study than in the 4-week study at the same dose level, 0.5 mg/kg/day, indicating that the magnitude of this effect increased with longer exposure duration (Table 7). As discussed above, the increased liver weight caused by PFPE-DCAs was accompanied by increased serum levels of liver enzymes, hepatocellular hypertrophy, and other histopathological changes indicative of liver injury (necrosis, vacuolation, bile duct proliferation) in the 4-week and/or 13-week studies. The authors of the 13-week study concluded that the liver was "a main target organ" for PFPE-DCAs based on effects on organ weight and histopathological changes (RTC, 2006). Detailed mode of action evaluations of other PFAS, including PFOA (DWQI, 2017), PFOS (DWQI, 2018), PFNA (DWQI, 2015), HFPO-DA (GenX; USEPA, 2018), and ClPFPECAs (NJDEP, 2021) have concluded that increased relative liver weight caused by these PFAS in rodents is indicative of liver toxicity that is relevant to humans, and there is no information to indicate that this is not also true for PFPE-DCAs.

In the 13-week study (RTC, 2006), relative liver weight was increased in males and females in a dose-related fashion, with statistically significant increases at the two higher doses (0.13 and 0.5 mg/kg/day), while it was not increased at the lowest dose, 0.03 mg/kg/day. Therefore, the NOAEL and LOAEL for increased relative liver weight in both males and females were identified as 0.03 mg/kg/day and 0.13 mg/kg/day, respectively.

Table 7: Relative liver weights compared to control groups in 4-week (RTC, 2005) and 13-week (RTC, 2006) repeated dose studies

Dose (mg/kg/day)	4-week study (RTC, 2005)				13-week study (RTC, 2006)			
	End of dosing		After 2 week recovery		End of dosing		After 8 week recovery	
	M (5)	F (5)	M (5)	F (5)	M (10)	F (10)	M (5)	F (5)
0.03					0.98	1.04		
0.13					1.14**	1.15**		
0.5	1.21*	1.16			1.43**	1.61**	1.37**	1.39**
2.5	1.53**	1.39**						
8	1.70**	1.62**	1.89**	1.60**				

*p<0.05 **p<0.01

RBC parameters. Decreases in RBC parameters (RBC count, hemoglobin, and hematocrit) in male rats in the 13-week study (RTC, 2006) were also selected for dose-response evaluation. These effects were relatively small in magnitude, did not occur in females, and were not observed in males in the 4-week study or at the end of recovery in the 13-week study. 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, HFPO-DA[GenX], ITRC, 2023; ClPFPECAs, NJDEP, 2021) also cause decreases in these three parameters. There is no information to suggest that decreases in RBC parameters caused by PFPE-DCAs 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 hematological effects (decreased RBC count, hemoglobin, and hematocrit) 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 the draft USEPA (2005) PFOA risk assessment.

In the 13-week study of PFPE-DCAs (RTC, 2006), statistically significant decreases in RBC parameters (RBC count, hemoglobin, hematocrit) occurred in males at 0.13 and 0.5 mg/kg/day, but not at 0.03 mg/kg/day, the lowest dose tested. Therefore, the NOAEL and LOAEL for decreased RBC parameters in male rats were identified as 0.03 and 0.13 mg/kg/day, respectively.

Serum triglycerides. Increased serum triglycerides in female rats was another endpoint selected for dose-response evaluation. Serum triglycerides were increased at all doses in a dose-related fashion in female rats in the 13-week study (RTC, 2006) although the increase at the low dose (0.03 mg/kg/day) was not statistically significant, and this effect persisted until the end of the recovery period. However, serum triglycerides were not elevated in male rats or in the 4-week study (RTC, 2005). As discussed above, the increase in serum triglycerides caused by PFPE-DCAs is notable because other long-chain PFAS are associated with increased serum lipids in humans, while, in contrast, these other PFAS generally cause decreases in serum lipids including triglycerides in rodents. The increase in serum triglycerides caused by PFPE-DCAs in female rats is considered relevant to humans, and it is considered adverse since increased serum triglycerides increase the risk of cardiovascular disease (Miller et al., 2011). Since the increase in serum triglycerides of 26% at the low dose (0.03 mg/kg/day) was not statistically significant, this dose was identified as the NOAEL, and the mid-dose of 0.13 mg/kg/day, at which the increase was significant, was identified as the LOAEL.

Aggregations of alveolar macrophages. An increase in incidence of aggregations of alveolar macrophages in female rats was the final endpoint selected for dose-response evaluation. In the 13-week study (RTC, 2006), the incidence of aggregations of alveolar macrophages was increased in females in the middle and high dose groups (0.13 and 0.5 mg/kg/day) in a dose-related fashion in females, although the increases were not statistically significant (potentially due to the small number of animals [10] per dose group). This effect also occurred in males in the 13-week study, but the incidence did not increase with dose. Additionally, the incidence in both males and females was increased at the end of the recovery period, although the increases were not statistically significant (while noting that there were only 5 animals per sex in the control and treated groups). From a qualitative perspective, this effect was described in the 13-week study report (RTC, 2006) as "phospholipidosis, represented by alveolar foamy macrophages, associated with interstitial inflammatory cell infiltrate." The report also states that alveolar foamy macrophages and phospholipidosis were present in males and females at the end of recovery and that the lungs were a target organ based on histopathological effects. These effects were also reported in treated animals in the 4-week study (RTC, 2005) at the end of the treatment and recovery periods. There is no information to suggest that these histopathological changes in the lungs are not relevant to humans, and these effects are considered to be adverse.

Because the increased incidence of aggregations of alveolar macrophages was not statistically significant at any dose level, a NOAEL and LOAEL were 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 if relative liver weight and red blood cell parameters was performed using USEPA BMDS (Version 3.3), and the BMD modeling for triglycerides and aggregations of alveolar macrophages was performed using USEPA BMDS Online (Release ID 2023.03.1). There are no differences in the models that are included or the results obtained in these two versions of USEPA BMD modeling software. The complete output from the BMD modeling is found in Appendix 3.

Relative liver weight: BMD modeling of the datasets from male and female rats in the 13-week study (RTC, 3006) was performed using a 10% change in relative liver weight as the Benchmark Response (BMR), consistent with previous New Jersey PFAS risk assessments (DWQI, 2015; DWQI, 2017: NJDEP, 2021; Toxics in Biota Risk Subcommittee, 2022). For comparison purposes, BMD modeling was also performed for the datasets for this endpoint from males and females in the 4-week study (RTC, 2005).

Because a restricted model fit the dataset for females from the 13-week study, BMD modeling with unrestricted models was not performed, in accordance with USEPA BMD guidance (USEPA, 2012). For the other three datasets (males and females from the 4-week study; males from the 13-week study), modeling with unrestricted models was also performed because none of the restricted model fit the dataset. 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 8.

In the 13-week study, the BMDL for females was 0.095 mg/kg/day, and the graphical results for the recommended model, Exponential 3 (normal, constant), are shown in Figure 5. In males, none of the models fit the dataset, and the LOAEL and NOAEL for increased liver weight were 0.13 mg/kg/day and 0.03 mg/kg/day, respectively. Therefore, the POD for females was identified as the BMDL, 0.095 mg/kg/day, and the POD for males was identified as the NOAEL, 0.03 mg/kg/day. The BMDLs for the datasets from the 4-week study, developed for comparison purposes, were higher (0.14-0.16 mg/kg/day for males; 0.27 mg/kg/day for females).

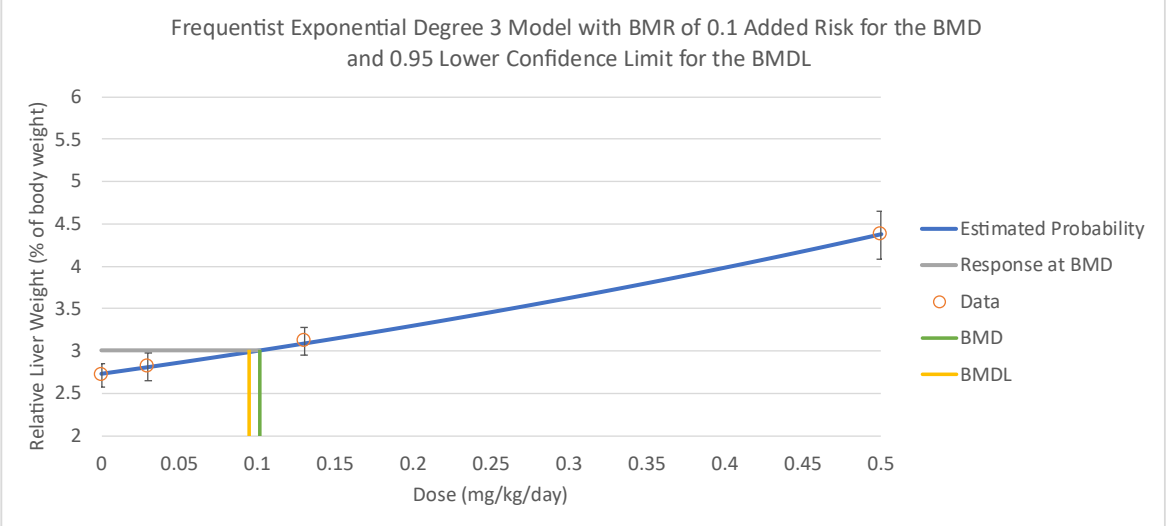
Since a BMDL is preferable to a NOAEL as a POD, the BMDL of 0.095 mg/kg/day for female rats from the 13-week study was selected as the POD for increased relative liver weight.

Table 8: Data and results of BMD modeling for increased relative liver weight in male and female rats exposed to PFPE-DCAs for 4 weeks (RTC, 2005) and 13 weeks (RTC, 2006)
(Data and BMDL results for the 4-week study are presented for comparison purposes only.)

Dose (mg/kg/day)	*n*	*Relative liver weight (% of body weight)*		*Recommended models and BMDLs (mg/kg/day) for 10% change*
		Mean	*Standard Deviation*	
4-week study (RTC, 2005) - Males				
0	5	4.336	0.298	Hill model (normal, non-constant): BMDL = 0.14 Exponential 5 (lognormal): BMDL = 0.16 Note: Both BMDLs are 3-fold lower than the lowest non-zero dose. (Presented for comparison purposes only)
0.5	5	5.267	0.163	
2.5	5	6.623*	0.317	
8	5	7.372*	0.743	
4-week study (RTC, 2005) - Females				
0	5	4.093	0.386	Exponential 5 (normal, constant): BMDL = 0.27 (Presented for comparison purposes only)
0.5	5	4.737	0.237	
2.5	5	5.6928*	0.382	
8	5	6.617*	0.723	
13-week study (RTC, 2006) - Males				
0	10	2.846	0.198	None of the models fit.
0.03	10	2.793	0.144	
0.13	10	3.254*	0.214	
0.5	10	4.056*	0.258	
13-week study (RTC, 2006) - Females				
0	10	2.716	0.136	Exponential 3 (normal, constant): BMDL = 0.095
0.03	10	2.815	0.161	
0.13	10	3.113*	0.166	
0.5	10	4.37*	0.283	

* $p < 0.01$

Figure 5. Graphical results for recommended BMD model for increased relative liver weight in female rats in 13-week study (RTC, 2006)



Hematological effects: RBC parameters (RBC count, hemoglobin, hematocrit) were decreased in males in the 13-week study. As shown in Table 9, these changes were statistically significant at the mid dose (0.13 mg/kg/day, $p<0.05$) and the high dose (0.5 mg/kg/day, $p<0.01$). BMD modeling with a BMR of 1 standard deviation, as recommended in USEPA (2012) BMD guidance, was performed for all three endpoints. Because a restricted model fit the dataset for RBC count, BMD modeling with unrestricted models was not performed, in accordance with USEPA BMD guidance (USEPA, 2012). For RBC count, the BMDL was 0.038 mg/kg/day, and the graphical results for the recommended model, Hill (normal, constant variance), are shown in Figure 6. For hemoglobin and hematocrit, modeling was performed with both restricted and unrestricted models, and none of the models fit the data. As discussed above, the LOAEL and NOAEL for these two effects were 0.13 mg/kg/day and 0.03 mg/kg/day, respectively. Therefore, the POD for decreased RBC count was identified as the BMDL, 0.038 mg/kg/day, and the POD for hemoglobin and hematocrit were identified as the NOAEL, 0.03 mg/kg/day.

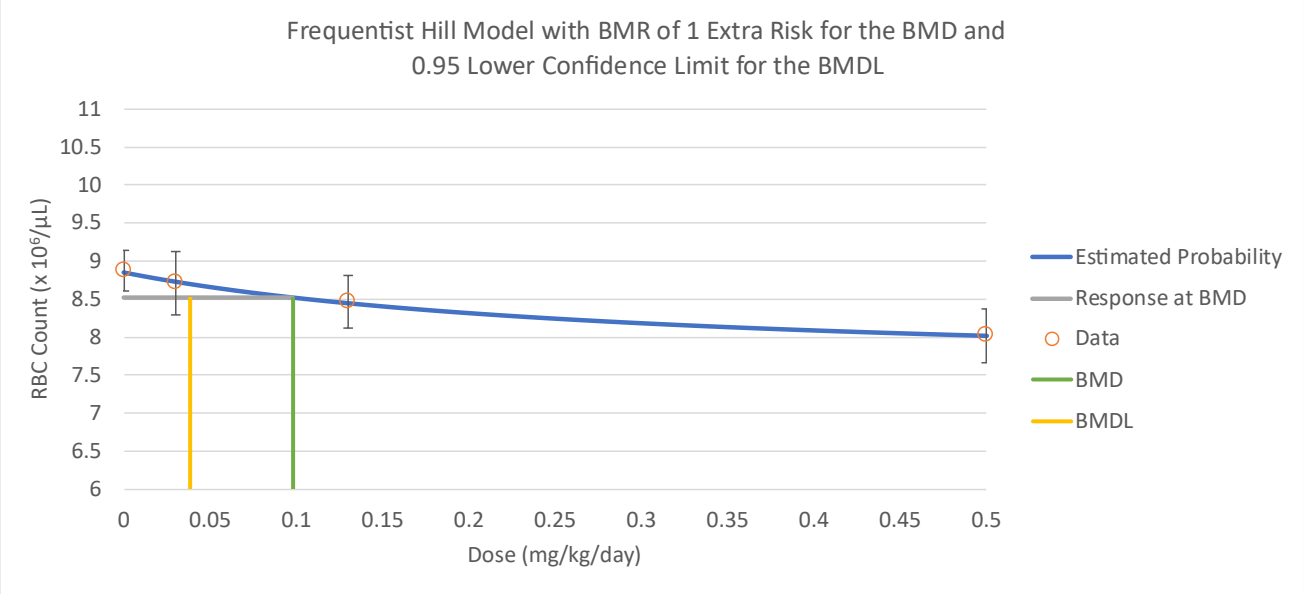
Since a BMDL, when available, is preferable to a NOAEL as a POD, the BMDL of 0.038 mg/kg/day for decreased RBC count was selected as the POD for hematological effects to be used in RfD derivation.

Table 9: Red blood cell parameters in male rats in 13-week study (RTC, 2006)

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	8.871	0.27	16.16	0.27	46.53	0.7
0.03	10	8.71	0.41	15.88	0.37	45.7	1.11
0.13	10	8.463*	0.342	15.44*	0.72	44.41*	2.03
0.5	10	8.019**	0.354	15.26**	0.63	43.63**	1.79

*p<0.05; **p<0.01.

Figure 6. Graphical results for recommended BMD model for decreased red blood cells in male rats in 13-week study (RTC, 2006)



Serum triglycerides: As shown in Table 10, serum triglycerides were increased in a dose-related manner at all doses in females in the 13-week study, and this effect was statistically significant ($p<0.01$) at the two higher doses (0.13 and 0.5 mg/kg/day). Serum triglycerides were also considerably increased (26%) at the NOAEL of 0.03 mg/kg/day, but this increase was not statistically significant at $p<0.05$. BMD modeling with a BMR of 1 standard deviation was performed for this endpoint, as recommended in USEPA (2012a) BMD guidance, and none of the restricted or unrestricted models fit the dataset. Therefore, the POD for increased serum triglycerides was identified as the NOAEL, 0.03 mg/kg/day.

Table 10: Serum triglycerides in female rats in 13-week study (RTC, 2006)

Dose (mg/kg/day)	*n*	*Mean*	*Standard Deviation*
0	10	24.45	2.44
0.03	10	30.74	9.77
0.13	10	34.28*	7.2
0.5	10	39.89*	8.63

*p<0.01

Aggregations of alveolar macrophages: As shown in Table 11, the incidence of aggregations of alveolar macrophages was increased in a dose-related manner in females at the two higher doses (0.13 and 0.5 mg/kg/day) in the 13-week study. While the increase was not statistically significant (possibly due to the small n [10 per dose group]), USEPA BMD modeling guidance (USEPA, 2012) states that BMD modeling is appropriate when there is "a statistically or biologically significant dose-related trend." The increased incidence of aggregations of alveolar macrophages in females in the 13-week study is considered to be biologically significant for the following reasons: It also occurred in males, and it persisted in both sexes until the end of the

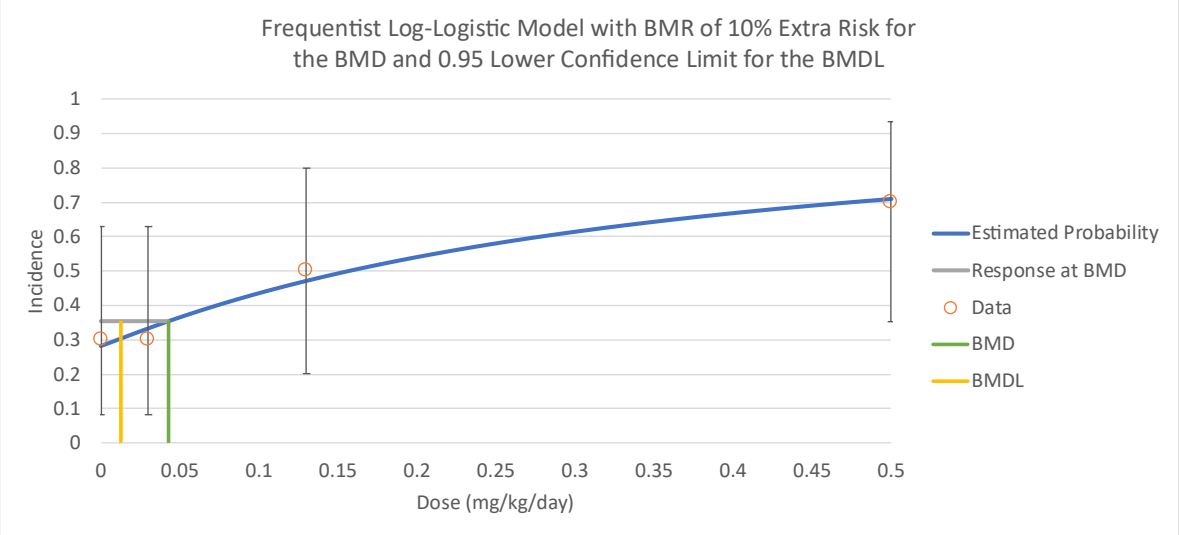
recovery period in the 13-week study. Additionally, it occurred in high dose males and females in the 4-week study, and it persisted in males until the end of the recovery period. Furthermore, in the 4-week study report (RTC, 2005), the histopathological changes associated with this effect were described as differing qualitatively ("possibly suggestive of a phospholipidosis condition") in the treated animals from those in the single control animal identified as exhibiting this effect ("part of a chronic inflammatory process that was not present in other control or treated animals"). In the 13-week study (RTC, 2006), these changes were described as "phospholipidosis, represented by alveolar foamy macrophages, associated with interstitial inflammatory cell infiltrate," and the study authors concluded that the lung was a target organ for toxicity based on these histopathological changes.

BMD modeling with a BMR of 10% increased incidence, as recommended in USEPA (2012) BMD guidance was performed for this endpoint. Several models fit the data, and the lowest BMDL (0.013 mg/kg/day) from the log logistic model was recommended and selected as the POD. The graphical results for the log logistic model are shown in Figure 7. It is noted that this BMDL is below the lowest dose used (0.03 mg/kg/day) and that the incidence of this effect was not increased at 0.03 mg/kg/day.

Table 11: Incidence of aggregations of alveolar macrophages in female rats in 13-week study (RTC, 2006)

Dose (mg/kg/day)	*n*	*Incidence*
0	10	3
0.03	10	3
0.13	10	5
0.5	10	7

Figure 7. Graphical results for recommended BMD model for increased incidence of aggregations of alveolar macrophages in male rats in 13-week study



The PODs identified above for the four toxicological endpoints for which dose-response evaluation was performed are shown in Table 12.

Table 12. Points of Departure (PODs) for toxicological endpoints from the 13-week rat study (RTC, 2006)

Endpoint	*Sex*	*POD (mg/kg/day)*	*Basis*
Relative liver weight	F	0.095	BMDL, 10% change
RBC count	M	0.038	BMDL, 1 SD change
Serum triglycerides	F	0.03	NOAEL
Aggregations of alveolar macrophages	F	0.013	BMDL, 10% increased incidence

Interspecies dosimetric adjustment

In general, PFAS are excreted much more rapidly in rats than in humans. For this reason, the same administered dose results in a much higher internal dose (i.e., body burden) in humans than in rats, and this interspecies difference in internal dose must be accounted for in developing toxicity factors for PFAS that are based on rat data. When human and rat half-lives are available, the much higher internal dose from a given administered dose in humans than in rats can be accounted for by adjusting the POD based on rat data by the ratio of human:rat half-lives, also referred to as the dosimetric adjustment factor (DAF), to determine the human equivalent dose (HED). This approach has been used in the development of toxicity factors (RfDs and cancer slope factors) for other PFAS including short-term Reference Doses for PFOA and PFOS (USEPA, 2009), cancer slope factor for PFOA (DWQI, 2017), chronic and subchronic Reference Doses for PFBS (MDH, 2020; USEPA, 2021), and chronic Reference Doses for ClPFPECAs (NJDEP, 2021) and perfluoroundecanoic acid (PFUnDA; Toxics in Biota Risk Subcommittee, 2022).

As discussed in the *Toxicokinetics* section above, the half-life of PFPE-DCAs was determined to be 7.8 – 43.2 days in male rats and 2.4 – 11.4 days in female rats, with the two values for each sex based on studies using different doses (0.5 mg/kg/day versus 8 mg/kg/day) and/or dosing regimens (single dose versus 13-week daily dosing). These half-life values indicate that PFPE-DCAs are equally or more bioaccumulative in rats than PFOA, which has rat half-lives of 4-6 days in males and 2-4 hours (0.08-0.17 days) in females and PFNA, which has rat half-lives of 30 days in males and 1.4-2.4 days in females (reviewed in DWQI, 2015). It was also noted that the half-life of PFPE-DCAs was similar in male and female rats, in contrast to the much more rapid excretion of PFOA and PFNA in female rats.

No information on the human half-life of PFPE-DCAs is available. However, their half-lives in rats and their chemical structure (perfluorinated compounds with congeners containing 9-12 carbons) suggest that they are likely to have long half-lives (several years) in humans, as is the case for other long-chain PFAS such as PFOA, PFNA, PFUnDA, and ClPFPECAs.

DAFs based on human:rat half-life ratios were determined during the development of New Jersey's toxicity factors for several other long-chain carboxylic acid PFAS including PFOA (8 carbons), PFUnDA (11 carbons; estimated value), and ClPFPECAs (8-17 carbons). Additionally, the human:rat half-life ratio for perfluorodecanoic acid (PFDA; 10 carbons) is available from information presented in USEPA (2023a). Half-lives of some of these PFAS are much longer in male rats than in female rats, but this sex difference has not been established for PFPE-DCAs. When this sex difference in excretion rate exists, the DAF is lower when it is based on the half-life of male rats, resulting in a higher Reference Dose, all other parameters being equal. The human:rat half-life ratios of 60 - 146 for the four PFAS shown below are based on half-lives from male rats:

- PFOA: Human:rat half-life ratio = 840 days (2.3 years): 7 days = 120 (DWQI, 2017).
- PFUnDA: Human:rat half-life ratio (estimated) = 4380 days (12 years): 30 days = 146 (Toxics in Biota Risk Subcommittee, 2022).
- ClPFPECAs: Human:rat half-life ratio = 1095 days (3 years): 18.3 days = 60 (NJDEP, 2021).
- PFDA: Human:rat half-life ratio = 7662 days (men; 21.9 years): 72 days = 111 (USEPA, 2023a).

A human:rat half-life ratio could not be developed for PFPE-DCAs because no human half-life information is available for PFPE-DCAs. As such, a human:rat half-life ratio of 100 was selected for use as the DAF in RfD derivation. Since the available half-life data for PFPE-DCAs in rats does not clearly identify a shorter half-life in females than males, this DAF is assumed to apply to PODs from both male and female rats. The assumption of a human:rat half-life ratio of 100 is considered reasonable and not overly conservative, based on the ratios of 60, 111, 120, and 146 for the other four long-chain PFAS. HEDs derived by application of the DAF of 100 to the PODs for each endpoint are shown in Table 13.

Table 13. Human equivalent doses (HEDs) derived by application of dosimetric adjustment factor (DAF) to points of departure (PODs)

Endpoint	*Sex*	*POD (mg/kg/day)*	*DAF*	*HED*	
				mg/kg/day	*ng/kg/day*
Relative liver weight	F	0.095	100	0.00095	950
RBC count	M	0.038	100	0.00038	380
Serum triglycerides	F	0.03	100	0.0003	300
Aggregations of alveolar macrophages	F	0.013	100	0.00013	130

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 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:

- $UF_{intraspecies}$ – 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.

  The default UF of 10 was applied to the HEDs for all endpoints to account for potentially more sensitive human subpopulations.

- $UF_{subchronic}$ – Applied when a subchronic study is used to account for potential effects at lower doses with chronic exposure. The PODs for all endpoints considered for RfD derivation are from the 13-week (subchronic) study (RTC, 2006), and no chronic studies are available.

  The default UF of 10 was applied to the HEDs for all endpoints to account for potential effects at lower doses with chronic exposure.

- $UF_{interspecies}$ – Applied when the RfD is based on animal data 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 PFPE-DCAs, the interspecies toxicokinetic difference is accounted for with the DAF based on 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.

  A UF of 3 was applied to the HEDs for all endpoints to account for potential interspecies toxicodynamic differences.

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

  Since the PODs for all endpoints was a NOAEL or a BMDL, a UF of 1 (no adjustment) was applied to all HEDs.

- $UF_{database}$ – 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, and lack of

sufficient data for other specific effects that have been identified for the contaminant being evaluated or related contaminants.

Because there are no data on reproductive, developmental, or immune system effects of PFPE-DCAs, a UF of 10 was applied to the HEDs for all endpoints to account for potentially more sensitive toxicological effects.

As shown above, the same UFs (intraspecies – 10; interspecies – 3; LOAEL-to-NOAEL – 1; subchronic-to-chronic – 10; database – 10) were applied to the HEDs for all endpoints for a total UF of 3000 for all endpoints. The candidate RfDs derived by application of this total UF to the HEDs are shown in Table 14. 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.

Table 14. Candidate Reference Doses (RfDs) developed by application of total uncertainty factor (UF) of 3000 to human equivalent doses (HEDs)

Endpoint	*Sex*	*HED (ng/kg/day)*	*Total UF*	*RfD (ng/kg/day)*
Relative liver weight	F	950	3000	0.32
RBC count	M	380	3000	0.13
Serum triglycerides	F	300	3000	0.1
Aggregations of alveolar macrophages	F	130	3000	0.04

Selection of RfD for use in ISGWQC development

The RfD of 0.32 ng/kg/day for increased relative liver weight in female rats is selected for use in derivation of the ISGWQC. While this RfD is the highest of the four candidate RfDs (Table 14), it is based on a BMDL for a sensitive and well-established effect of PFPE-DCAs and other PFAS that has been determined to be indicative of adversity and is relevant to humans (DWQI, 2015; DWQI, 2017). This effect occurred in both the 4-week (RTC, 2005) and 13-week (RTC, 2006) studies and persisted until the end of recovery in both studies. Additionally, comparison of data from the 4-week and 13-week studies indicates that the magnitude of this effect increases with longer exposure duration. In addition to increased relative liver weight, other indicators of hepatic toxicity (increased serum levels of liver enzymes; histopathological changes indicative of liver damage) were reported in the 4-week and/or 13-week study. As discussed below, the lower candidate RfDs for the three other endpoints support the conclusion that the RfD of 0.32 ng/kg/day for increased liver weight is not overly conservative.

A decrease in RBC count is considered adverse or a precursor to an adverse effect. However, an RfD based on this endpoint was not judged to be as scientifically supportable as the RfD based on increased relative liver weight for the following reasons: The decreases in RBC caused by PFPE-DCA are relatively small in magnitude (10% decrease at highest dose), and they occurred

only in males. Additionally, decreased RBCs did not persist until the end of recovery in the 13-week study, and they did not occur in the 4-week study that used higher doses but was of shorter duration than the 13-week study. While not selected as the final RfD, the candidate RfD of 0.13 ng/kg/day for decreased RBC count supports the conclusion that the higher RfD for increased relative liver weight of 0.32 ng/kg/day is not overly conservative.

The dose-related increase in serum triglycerides in female rats in the 13-week study is considered to be an adverse effect, and it persisted until the end of the recovery period. The increase in serum triglycerides is notable because (as discussed above) other long-chain PFAS are associated with increased serum lipids in humans, while, in contrast, these other PFAS generally cause decreases in serum lipids including triglycerides in rodents While this effect did not occur in male rats in the 13-week study, it did occur in both sexes or in the 4-week study (RTC, 2005). , However, it is preferable that an RfD be based on a BMDL, while the candidate RfD for increased serum triglycerides is based on a NOAEL. While not selected as the final RfD, the candidate RfD of 0.1 ng/kg/day for increased serum triglycerides supports the conclusion that the higher RfD for increased relative liver weight of 0.32 ng/kg/day is not overly conservative.

The dose-related increase in the incidence of aggregations of alveolar macrophage in female rats in the 13-week study is considered to be an adverse effect indicating that the lung is a target organ for PFPE-DCAs. This effect also occurred in males and persisted in both sexes until the end of the recovery period in the 13-week study. Additionally, it occurred in high dose males and females in the 4-week study and persisted in males until the end of the recovery period. While the increased incidence in female rats in the 13-week study was not statistically significant, it was appropriate to develop a BMDL for these data because the increase was considered to be biologically significant. The candidate RfD based on the increased incidence of alveolar macrophages was the lowest of the four candidate RfDs. However, the BMDL for this effects, 0.013 ng/kg/day, appears to be uncertain because it is approximately 2-fold lower than the lowest dose, 0.03 ng/kg/day, at which the incidence of this change was not increased compared to the control group. While not selected as the final RfD, the candidate RfD of 0.04 ng/kg/day for increased incidence of aggregations of alveolar macrophages provides support for the conclusion that the higher RfD for increased relative liver weight of 0.32 ng/kg/day is not overly conservative.

The RfD applies to the total of the nine PFPE-DCA congeners shown in Table 1.

Application of exposure factors

An ISGWQC of 2.1 ng/L is derived from the RfD of 0.32 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. This ISGWQC applies to the total concentration of PFPE-DCA congeners detected in groundwater. The rationale for the choice of the exposure factors is provided below.

$$\frac{0.32 \text{ ng/kg/day} \times 80.0 \text{ kg} \times 0.2}{2.4 \text{ L/day}} = 2.1 \text{ ng/L } (0.0021 \text{ µg/L})$$

Where:

0.32 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 GWQS at N.J.A.C. 7:9C-1.7c(4)iii specify that ISGWQC "shall be rounded to two significant figures when all components of the equations are available in two or more significant figures. Otherwise, the final criteria shall be rounded to one significant figure." As such, the ISGWQC is rounded to 2.1 ng/L (0.0021 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 PFPE-DCAs are the current USEPA (2015) default assumptions for chronic (lifetime) drinking water exposure, and they are also used as the default assumptions for New Jersey Health-based Maximum Contaminant Levels and GWQS. It must be emphasized that, while default adult exposure assumptions were used, the potential for higher-than-adult exposure to PFPE-DCAs 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 PFPE-DCAs, developmental toxicity is generally a sensitive endpoint for long-chain PFAS with long human half-lives such as PFPE-DCAs, and it is therefore likely to also be a sensitive endpoint for PFPE-DCAs.

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, and these PFAS have also been detected in human umbilical cord blood and placenta (Fromme et al., 2010; Post et al., 2012; DWQI, 2017; Post et al., 2017; Goeden et al., 2019). 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 (Post et al., 2012; DWQI, 2017). 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 PFPE-DCAs to the fetus or through breast milk, the information discussed above indicates a high likelihood of developmental exposure to PFPE-DCAs via contaminated drinking water that is similar to 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, 2021). 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 (2021), 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 developed a toxicokinetic model to predict early life drinking water exposures to bioaccumulative PFAS which was published in a peer-reviewed journal (Goeden et al., 2019). 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 drinking water guidelines for bioaccumulative PFAS (e.g., PFOA, PFOS, PFNA, PFHxS) by several states including Minnesota, Michigan and New Hampshire (reviewed in Post, 20211). Use of this model to develop the ISGWQC for PFPE-DCAs would be a scientifically supportable and public health protective approach if the required PFAS-specific factors (e.g., human half-life, placental transfer ratio, breastmilk transfer ratio) needed for the model were available for PFPE-DCAs.

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). As discussed in the Source of Human Exposure section above, PFPE-DCAs have been detected in groundwater and soil near the Solvay facility in West Deptford, NJ, but their potential occurrence in other environmental media has not been sufficiently

investigated. As such, there are insufficient data to develop a chemical-specific RSC for PFPECAs, and the default value of 0.2 is therefore used in the ISGWQC.

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 will potentially occur when drinking water is contaminated with PFPE-DCAs. 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, 2021).

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 PFPE-DCAs, 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 PFPE-DCAs are discussed below.

- Solvay stated that the 4-week study (RTC, 2005) and the 13-week study (RTC, 2006) "are not studies conducted on the molecule identified by CAS # 69991-62-4, itself," and that "these two reports were identified as relevant by analogy." [redacted]. In the absence of additional information, it is assumed that the toxicity and toxicokinetics of the substance tested in these studies represents those of the PFPE-DCA congeners identified by CAS # 69991-62-4 that are present in New Jersey groundwater.

- Without additional toxicological data on endpoints for which there are data gaps, it is not possible to definitively determine whether the ISGWQC for PFPE-DCAs is sufficiently protective. A major uncertainty regarding human health risks of PFPE-DCAs 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 PFPE-DCAs is sufficiently protective. 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 PFPE-DCAs. The interspecies uncertainty factor is intended to account for this uncertainty.

- No data are available on toxicokinetics and health effects in humans. Bioaccumulative PFAS (e.g., PFOA, PFOS) such as PFPE-DCAs are associated with human health effects at very low exposure levels (DWQI, 2017; DWQI, 2018; DWQI, 2023), and toxicity factors and/or drinking water guidelines for long-chain PFAS based on human data are much lower than those based on animal data (USEPA, 2023a; USEPA, 2023b; DWQI, 2023; USEPA, 2023c). For this reason, it cannot be definitively concluded that an ISGWQC based on animal toxicology data is sufficiently protective of human health effects, including sensitive subpopulations.

- Without information on maternal transfer of PFPE-DCAs to breast milk, it is not possible to definitively determine whether the ISGWQC for PFPE-DCAs 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 PFPE-DCAs 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 PFPE-DCAs (e.g., liver) are also target organs for other PFAS including PFOA, PFNA, and ClPFPECAs. Therefore, toxicological interactions may occur when there is co-exposure to PFPE-DCAs and other PFAS. Although PFOA, PFNA, ClPFPECAs, and PFPE-DCAs are known to co-occur in groundwater in the area of New Jersey impacted by PFPE-DCA contamination, the potential for additive toxicity of PFPE-DCAs and other PFAS was not considered in development of the ISGWQC.

ISGWQC RECOMMENDATION

The recommended ISGWQC for PFPE-DCAs is 2.1 ng/L, (0.0021 µg/L). This ISGWQC applies to the total concentration of PFPE-DCAs detected in groundwater.

CITATIONS

Berends, A. and Doornaert, B. (2019). Corporate occupational exposure limits: An example of a strategy. Environ, Qual, Manage 28:27–31.

Bil,, W., Zeilmaker, M., Fragki, S., Lijzen, J., Verbruggen, E., Bokkers, B. (2021). Risk assessment of per- and polyfluoroalkyl substance mixtures: a relative potency factor approach. Environ. Toxicol. Chem. 40:859-870.

[redacted]

[redacted]

Corton J.C., Peters, J.M., Klaunig, J.E. (2018). The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Arch Toxicol. 92:83-119.

DWQI (2015). New Jersey Drinking Water Quality Institute. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). New Jersey Drinking Water Quality Institute Health Effects Subcommittee. June 22, 2015.

DWQI (2017). New Jersey Drinking Water Quality Institute. Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). New Jersey Drinking Water Quality Institute Health Effects Subcommittee. February 15, 2017.

DWQI (2018). New Jersey Drinking Water Quality Institute. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). New Jersey Drinking Water Quality Institute Health Effects Subcommittee. June 5, 2018.

DWQI (2020). New Jersey Drinking Water Quality Institute. Health-Based Maximum Contaminant Level Support Document:1,4-Dioxane – Public Review Draft. New Jersey Drinking Water Quality Institute Health Effects Subcommittee. July 2020.

DWQI (2023). New Jersey Drinking Water Quality Institute. Health Effects Subcommittee Review of Interim USEPA Health Advisories for PFOA and PFOS and Other Relevant Information. December 2, 2022; updated June 12, 2023.

FDA (undated). U.S. Food and Drug Administration. Inventory of Effective Food Contact Substance (FCS) Notifications. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=fcn Accessed on September 14, 2023.

FDA (2004). U.S. Food and Drug Administration. Memorandum from Division of Food Contact Notifications, Chemistry Group I, HFS-275 to Division of Food Contact Notifications, Regulatory Group II, HFS-275. Attn: P. Honigfort. FCN-398: Solvay-Solexis S.p.A., through Keller & Heckman; submissions of 12/11/03 and 1/26/04. Perfluoropolyether dicarboxylic acid, ammonium salt, as a grease-proofing agent for paper/paperboard. March 23, 2004.

Fromme, H., Tittlemier, S.A., Völkel, W., Wilhelm, M., Twardella, D. (2009). Perfluorinated compounds exposure assessment for the general population in Western countries. Int. J. Hyg. Environ. Health. 212: 239-270.

Goeden, H. M., Greene, C. W., & Jacobus, J. A. (2019). A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. Journal of exposure science & environmental epidemiology, 29(2), 183–195.

Integral Consulting (2021). Technical Memorandum from Erin Palko and Scott Drew to Erica Bergman, NJDEP. November 12, 2021.

Integral Consulting (2022a). Technical Memorandum from Erin Palko and Scott Drew to Kristine Iazzetta, NJDEP. April 28, 2022.

Integral Consulting (2022b). Conceptual Site Model. July 2022.

Inveresk Research International (1986). Acute toxicity tests. Report Number 3531. May 1986. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/acute-oral-dermal-eye-irritation-toxicity-studies-69991-62-4.pdf

Ito S. (2011). Pharmacokinetics 101. Paediatrics & child health, 16(9), 535–536.

ITRC (2023). Interstate Technology and Regulatory Council (ITRC) PFAS Technical and Regulatory Guidance Document. Section 17.2. Additional Information for Human Health Effects. https://pfas-1.itrcweb.org/17-additional-information/#17_2. Accessed September 14, 2023.

Kudo, N. (2018). Chapter 6 - Metabolism and Pharmacokinetics. In: DeWitt, J.C. (editor). Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances. Humana Press.

MacGillivray, A.R. (2021). Temporal trends of per- and polyfluoroalkyl substances in Delaware River fish, USA. Integr. Environ. Assess. Manag. 17:411-421.

MDH (2023). Minnesota Department of Health. Toxicological Summary for: Perfluorobutane sulfonate. https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf. Accessed July 12, 2024.

Miller, M., Stone, N.J., Ballantyne, C., Bittner, V., Criqui, M.H., Ginsberg, H.N., Goldberg, A.C., Howard, W.J., Jacobson, M.S., Kris-Etherton, P.M., Lennie, .TA., Levi, M., Mazzone, T., Pennathur, S. (2011). Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 123:2292-333.

NJDEP (2019). New Jersey Department of Environmental Protection. Statewide PFAS directive, information request, and notice to insurers. March 25, 2019. https://www.nj.gov/dep/docs/statewide-pfas-directive-20190325.pdf

NJDEP (2021). New Jersey Department of Environmental Protection. Technical Support Document: Interim Specific Ground Water Quality Criterion for Chloroperfluoropolyether Carboxylates. Division of Science and Research. October 20, 2021. https://dep.nj.gov/wp-content/uploads/dsr/clpfpecas-tsd.pdf

OECD (2013). Organisation for Economic Co-operation and Development. OECD Guideline for the Testing of Chemicals. Proposal for Updating Test Guideline 473. *In Vitro* Mammalian Chromosomal Aberration Test. September 29, 2013. https://www.oecd.org/env/ehs/testing/TG473_sept2013_WNT%20CR%20Sept.pdf

OECD (2020). Organisation for Economic Co-operation and Development. PFASs and Alternatives in Food Packaging (Paper and Paperboard) Report on the Commercial Availability and Current Uses. Series on Risk Management No. 58. https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/PFASs-and-alternatives-in-food-packaging-paper-and-paperboard.pdf

Post, G.B., Louis, J.B., Cooper, K.R., Boros-Russo, B.J., Lippincott, R.L. (2009). Occurrence and potential significance of perfluorooctanoic acid (PFOA) detected in New Jersey public drinking water systems. Environ. Sci. Technol. 43: 4547–4554.

Post, G.B., Cohn, P.D., Cooper, K.R. (2012). Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. Env. Res. 116: 93-117.

Post, G. B., Gleason, J. A., & Cooper, K. R. (2017). Key scientific issues in developing drinking water guidelines for perfluoroalkyl acids: Contaminants of emerging concern. PLoS biology, 15(12), e2002855.

Post G. B. (2021). Recent US state and federal drinking water guidelines for per- and polyfluoroalkyl substances. Environ. Toxicol. Chem. 40: 550–563.

RIVM (2018). Per- and polyfluoroalkyl substances (PFASs) in food contact material. Netherlands Institute for Public Health and the Environment. RIVM Letter report 2018-0181. https://www.rivm.nl/bibliotheek/rapporten/2018-0181.pdf

RTC (2001a). Acute oral toxicity study in the rat. RTC Report Number 8832-002/T/202/2001. November 14, 2001. Submitted to U.S. Food and Drug Administration, November 21, 2003.

RTC (2001b). Bacterial mutation assay (S. typhimurium and E. coli). RTC Report Number 8837-002-M-06101. Submitted to U.S. Food and Drug Administration, November 21, 2003.

RTC (2001c). Acute dermal toxicity study in the rat. RTC Report Number 8833-1/T/317/2001. Publicly available version without CBI. https://dep.nj.gov/wp-content/uploads/dsr/acute-oral-dermal-eye-irritation-toxicity-studies-69991-62-4.pdf

RTC (2001d). Acute dermal irritation study in the rabbit. RTC Report Number 8835-001/T/308/2001. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/acute-oral-dermal-eye-irritation-toxicity-studies-69991-62-4.pdf

RTC (2001e). Delayed dermal sensitisation study in the guinea pig (Magnusson and Kligman test). RTC Report Number 8836-001/T/380/2001/ Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/acute-oral-dermal-eye-irritation-toxicity-studies-69991-62-4.pdf

RTC (2001f). Acute eye irritation study in the rabbit. RTC Report Number 8834-001/T/407/2001. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/acute-oral-dermal-eye-irritation-toxicity-studies-69991-62-4.pdf

RTC (2001g). Bacterial mutation assay (*S. typhimurium* and *E. coli*). RTC Report Number 8837-001-M-06001. November 7, 2001. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/bacterial-mutation-assay-69991-62-4.pdf

RTC (2002a). Acute oral toxicity study in the rat. RTC Report Number 8832-001/T/051/2002. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/acute-oral-dermal-eye-irritation-toxicity-studies-69991-62-4.pdf

RTC (2003a). Chromosome aberrations in Chinese hamster ovary cells *in vitro*. RTC Study Number 9764. Submitted to U.S. Food and Drug Administration, November 21, 2003.

RTC (2003b). Micronucleus test. RTC Study Number 9763. January 24, 2003. Submitted to U.S. Food and Drug Administration, November 21, 2003.

RTC (2005). 4 week oral toxicity study in rats followed by a 2 week recovery period (Two volumes). RTC Study No. 27080. October 21, 2005. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/4-week-oral-toxicity-study-in-rats-2005.pdf.

RTC (2006). 13 week oral toxicity study in rats followed by an 8 week recovery period. RTC Study No. 41950. July 12, 2006. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/13-week-oral-toxicity-study-in-rats-2006.pdf.

SCHC-OSHA Alliance (2017). Hazard Communication Information Sheet reflecting the US OSHA Implementation of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). March 2017. https://www.schc.org/assets/docs/ghs_info_sheets/specific_target_organ_toxicity-single_exposure.pdf. Accessed April 17, 2021.

Sibinski, L.J. (1987). Final report of a two year oral (diet) toxicity and carcinogenicity study of fluorochemical FC-143 (perfluorooctanoate ammonium carboxylate) in rats. Vol. 1-4, 3M Company/RIKER. No.0281CR0012; 8EHQ-1087-0394, October 16, 1987.

Solvay (2020). Safety Data Sheet CAS # 69991-62-4. Concentration (%) ≥99 - <100. Revision 11/4/2020. Publicly available version without CBI information. https://dep.nj.gov/wp-content/uploads/dsr/sds-69991-62-4.pdf.

Thomas, D. (2021). Letter from D. Thomas, Solvay Specialty Polymers, to M. Strynar, USEPA Office of Research and Development, Re: Solvay Specialty Polymers USA, LLC Monofunctional and Bifunctional Surfactant Reference Standards. October 28, 2021.

Toxics in Biota Risk Subcommittee (2022). Technical Support Document: Reference Dose and Fish Consumption Triggers for Perfluoroundecanoic Acid (PFUnDA). October 26, 2022. https://dep.nj.gov/wp-content/uploads/dsr/pfunda-fish-consumption-trigger.pdf

USEPA (2000). United States Environmental Protection Agency. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. Office of Science and Technology. Office of Water. Washington, DC. EPA 822-B-00-004. October 2000.

USEPA (2002). United States Environmental Protection Agency. A review of the Reference Dose and Reference Concentration processes. Prepared for the Risk Assessment Forum. EPA/630/P-02/002F. December 2002. Final Report.

USEPA (2005). United States Environmental Protection Agency. Draft risk assessment of the potential human health effects associated with exposure to perfluorooctanoic acid and its salts. Office of Pollution Prevention and Toxics, January 4, 2005.

USEPA (2009). United States Environmental Protection Agency. Provisional Health Advisories for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). USEPA Office of Water, January 8, 2009.

USEPA (2012a). United States Environmental Protection Agency. Benchmark Dose technical guidance. Risk Assessment Forum. Washington DC. EPA/100/R-12/001. June 2012.

USEPA (2012b). United States Environmental Protection Agency. Preamble to IRIS Toxicological Review of Ammonia, Noncancer Inhalation. EPA/635/R-16/163Fa. September 2016.

USEPA (2015). United States Environmental Protection Agency. Human Health Ambient Water Quality Criteria: 2015 Update. Office of Water. EPA 820-F-15-00. June 2015.

USEPA (2018). United States Environmental Protection Agency. Human health toxicity values for hexafluoropropylene oxide (HFPO) dimer acid and its ammonium salt (CASRN 13252-13-6 and CASRN 62037-80-3) also known as "GenX Chemicals." EPA-823-P-18-001. Public Comment Draft. Office of Water. Health and Ecological Criteria Division. Washington, DC. November 2018.

USEPA (2021). United States Environmental Protection Agency. Human health toxicity values for perfluorobutane sulfonic acid (CASRN 375-73-5) and related compound potassium perfluorobutane sulfonate (CASRN 29420-49-3). Office of Research and Development Center for Public Health and Environmental Assessment. EPA/600/R-20/345F. April 2021.

USEPA (2023a). United States Environmental Protection Agency. IRIS Toxicological Review of Perfluorodecanoic Acid [PFDA, CASRN 335-76-2] and Related Salts. External Review Draft. Integrated Risk Information System, Office of Research and Development. EPA/635/R-23/056a. April 2023.

USEPA (2023b). United States Environmental Protection Agency. Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water. Public Comment Draft. Office of Water, Health and Ecological Criteria Division. EPA 822P23005. March 2023.

USEPA (2023c). United States Environmental Protection Agency. Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS)in Drinking Water. Public Comment Draft. Office of Water, Health and Ecological Criteria Division. EPA 822P23007. March 2023.

Appendix 1: List of documents submitted to NJDEP by Solvay on for PFPE-DCAs (CAS # 69991-62-4) and other alternative PFAS (chloroperfluoroether carboxylates, ClPFPECAs) at Solvay facility 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: Table of annual usage and discharge of PFAS "replacement" surfactants with CAS # 69991-62-4 used at Solvay facility in West Deptford, NJ, submitted to NJDEP by Solvay.

Exhibit G

West Deptford Replacement Surfactants Usage and Emissions: CAS 69991-62-4

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	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. Benchmark Dose modeling results toxicological endpoints from 4-week study (RTC, 2005) and 13-week study (RTC, 2006)
(CV – constant variance; NCV – non-constant variance)

Relative liver weight, 13-week study (RTC, 2006), males

Model	Analysis Type	Restriction	Risk Type	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Exponential 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.12862	0.116	0.163919	0.017363	-4.9569787	-	6.804412982	0.943410654	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2
Exponential 5 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	0.12531	0.0772	0.130258	NA	-8.6260197	-	0.368438642	1.679416587	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Hill (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Hill (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Linear (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models

Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.132279	0.119224	0.1686173	0.0279961	-3.340454916	-	1.922577499	0.031610739	Questionable	Goodness of fit p-value < 0.1
Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.125276	0.071987	0.1306238	NA	-6.131180641	-	-8.6121E-08	0.423695769	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.124924	0.121443	0.1272643	NA	-6.13118065	-	2.47432E-07	0.42369544	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.112675	0.099468	0.1472807	0.0624852	-4.946185673	-	1.565427626	0.333521306	Questionable	Goodness of fit p-value < 0.1
Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.112769	0.099533	0.1472841	0.0624813	-4.946060567	-	1.564470466	0.329011424	Questionable	Goodness of fit p-value < 0.1
Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.112673	0.099468	0.1512503	0.0624852	-4.946185778	-	1.565418	0.333605388	Questionable	Goodness of fit p-value < 0.1
Hill (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.125181	0.121945	0.1273769	NA	-6.131180651	-	1.31832E-07	0.423695974	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.112673	0.099468	0.1292492	0.0624852	-4.946185778	-	1.565418048	0.333605428	Questionable	Goodness of fit p-value < 0.1
Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.108445	0.076125	0.1106897	NA	-6.240752556	-	0.090939046	0.302901752	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Polynomial Degree 2 (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.077598	0.054271	0.1235865	0.0582598	-4.905594727	-	-1.462013751	1.057264676	Questionable	Goodness of fit p-value < 0.1
Power (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.085907	0.047562	0.141475	0.0296438	-3.762008479	-	0.979548392	0.842975114	Questionable	Goodness of fit p-value < 0.1
Exponential 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
Exponential 5 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.124548	0.094949	0.130248	NA	-6.234804933	-	-0.014523615	0.502631738	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Hill (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.125663	0.12278	0.1289053	NA	-6.234805158	-	-0.014523605	0.502631639	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.111142	0.096638	0.1429901	0.0334456	-4.072331425	-	1.621197397	0.454866894	Questionable	Goodness of fit p-value < 0.1
Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.111733	0.096322	0.1140461	0.031209	-3.933902633	-	1.618032913	0.419127853	Questionable	Goodness of fit p-value < 0.1
Power (NCV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.111142	0.096639	0.147254	0.0334456	-4.072330853	-	1.621256389	0.454830145	Questionable	Goodness of fit p-value < 0.1
Hill (NCV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.124562	0.122521	0.1284105	NA	-6.234805147	-	-0.014523609	0.502631679	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (NCV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.111142	0.096638	0.1286117	0.0334456	-4.072331441	-	1.621203237	0.454880661	Questionable	Goodness of fit p-value < 0.1
Polynomial Degree 3 (NCV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.076306	0.051323	0.0778852	NA	-2.206277473	-	-1.431504253	1.432508961	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Polynomial Degree 2 (NCV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.088707	0.086711	0.0905229	0.0206488	-3.511808007	-	0.901469608	0.84875388	Questionable	Goodness of fit p-value < 0.1
Power (NCV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.088564	0.051608	0.0903968	0.0132598	-2.733891539	-	1.074312554	0.889442218	Questionable	Goodness of fit p-value < 0.1

Relative liver weight, 13-week study (RTC, 2006), females

Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Exponential 3 (CV - normal)	**frequentist**	**Restricted**	**Rel. Dev.**	**0.1**	**0.101542**	**0.094636**	**0.1402801**	**0.8768785**	**-15.22701665**	**-**	**0.379082467**	**-0.335953895**	**Viable - Recommended**	**Lowest AIC**
Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.091409	0.063126	0.1377487	NA	-11.44778204	-	-0.071953289	-0.100409828	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.091254	0.074874	0.1374273	NA	-11.4723493	-	0.000271069	-0.093196426	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.09127	0.074876	0.1373635	0.89458	-13.47223108	-	-0.000338024	-0.094044704	Viable - Alternate	
Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.091396	0.074868	0.1377468	0.8378981	-13.44793615	-	-0.07198976	-0.100007753	Viable - Alternate	

Relative liver weight, 4-week study (RTC, 2005), males

Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Exponential 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	0.1	1.72482	1.363908	2.4215436	<0.0001	48.57820006	-	17.19923846	-11.34425146	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2
Exponential 5 (CV - lognormal)	**frequentist**	**Restricted**	**Rel. Dev.**	**0.1**	**0.24532**	**0.164889**	**0.390484**	**0.3484688**	**23.24794482**	**-**	**-0.86352914**	**-0.86352914**	**Viable - Recommended**	**Lowest AIC** **BMDL 3x lower than lowest non-zero dose**
Hill (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Hill (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Linear (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Unrestricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models

Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	1.899781	1.519752	2.6896337	<0.0001	48.53987581	-	2.77571958	-2.357263874	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
Exponential 5 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.269702	0.169188	0.5027311	0.4106309	27.96412761	-	0.591599407	-0.348489466	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	0.197579	0.113288	0.4559356	NA	29.28715432	-	1.58191E-08	1.58191E-08	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	1.51392	1.15775	2.1634875	<0.0001	46.49637345	-	2.705885199	-2.204460835	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	1.514625	1.157748	2.1634209	<0.0001	46.49637748	-	2.705998167	-2.205856621	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	1.514074	1.157752	2.1793891	<0.0001	46.49637279	-	2.706075912	-2.204927477	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
Hill (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.197579	0.034076	0.4559992	NA	29.28715432	-	-8.85126E-08	-8.85126E-08	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	1.514074	1.157752	2.0931635	<0.0001	46.49637279	-	2.706075834	-2.204927484	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.373964	0.116239	0.6236083	NA	31.18647478	-	1.035432551	-0.821863104	Questionable	Constant variance test failed (Test 2 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 (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.423372	0.329894	0.5702344	0.1045151	29.92241261	-	1.220257522	-0.914840003	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
Power (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.033465	0.003902	0.1609078	0.0725033	30.51257286	-	0.175806824	0.175806824	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3 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

Relative liver weight, 4-week study (RTC, 2005), females

Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Exponential 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	1.926571	1.560741	2.7346565	0.0024602	36.68927667	-	2.179511268	-1.934462306	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2
Exponential 5 (CV - normal)	**frequentist**	**Restricted**	**Rel. Dev.**	**0.1**	**0.460967**	**0.269735**	**0.9778541**	**0.3908112**	**27.4106786**	**-**	**0.657090893**	**-0.42441831**	**Viable - Recommended**	**Lowest AIC**
Hill (CV - normal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Rel. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed
Power (CV - normal)	frequentist	Restricted	Rel. Dev.	0.1	1.561641	1.213444	2.2612609	0.0059517	34.92241506	-	2.028012362	-1.763762022	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2
Hill (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.252219	0.039361	0.8322225	NA	28.67426215	-	1.02548E-06	-3.28561E-07	Questionable	BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	1.561641	1.213444	2.1191707	0.0059517	34.92241506	-	2.028012342	-1.763762032	Questionable	Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2
Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.372126	0.154602	0.3798289	NA	28.8870298	-	0.322706326	-0.253600857	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	Rel. Dev.	0.1	0.588584	0.422378	0.6007674	0.2466932	28.01619605	-	0.902605222	-0.676868875	Viable - Alternate	
Power (CV - normal)	frequentist	Unrestricted	Rel. Dev.	0.1	0.13287	0.019134	0.5333623	0.4842063	27.163637	-	0.104730687	0.104730687	Questionable	BMD/BMDL ratio > 3 BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose

RBC count, 13-week study (RTC, 2006), males

BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
1	0.207907	0.153625	0.3312972	0.3993034	32.59859197	-	-0.966499627	0.865559353	Viable - Alternate	
1	0.101413	0.04774	0.264686	0.7255475	32.88576352	-	0.110337074	0.182904244	Viable - Alternate	
1	**0.097747**	**0.038017**	**0.26032**	**0.7678479**	**32.84966204**	**-**	**0.116833794**	**0.137966136**	**Viable - Recommended**	**Lowest BMDL**
1	0.217181	0.160993	0.3648691	0.3719855	32.74032503	-	-1.003065764	0.920757419	Viable - Alternate	
1	0.240388	0.157802	0.2453642	0.120398	35.17465953	-	-1.112617501	1.034976428	Viable - Alternate	
1	0.215346	0.160933	0.3379159	0.1598701	34.73797831	-	-1.007494737	0.900702773	Viable - Alternate	

Hemoglobin, 13-week study (RTC, 2006), males

Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Exponential 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.372491	0.238241	0.7077877	0.0669143	70.97320561	-	8.001237835	21.45733986	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2
Exponential 5 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.070545	0.022501	0.2679791	NA	69.56451904	-	0.418267343	0.218482697	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Hill (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Hill (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Linear (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models

Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.353286	0.232455	0.7134385	0.0697328	69.88993428	-	0.471672916	1.319992603	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	Std. Dev.	1	0.066183	0.022107	0.2693655	0.9950674	66.56380263	-	-0.004325116	0.002288687	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Modeled control response std. dev. >|1.5| actual response std. dev.
Hill (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.061528	0.017715	0.8286743	NA	68.56376441	-	-1.29543E-06	-1.93365E-06	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 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	Std. Dev.	1	0.35981	0.238479	0.7202423	0.0672376	69.96280855	-	0.447356433	1.340476553	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.
Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.363932	0.238404	0.7205103	0.0671546	69.96528015	-	0.414247489	1.35670038	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.
Power (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.358617	0.238506	0.720197	0.0672422	69.96267223	-	0.457166454	1.335636289	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.
Linear (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.358617	0.238503	0.7202483	0.0672422	69.96267223	-	0.457166627	1.335636213	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.
Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.101168	0.020336	0.1032621	NA	69.06616206	-	0.147563421	0.408726989	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 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 2 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.085024	0.05233	0.0867843	0.650569	66.76894787	-	0.097419336	0.240325725	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	Unrestricted	Std. Dev.	1	0.072344	0.002945	0.4028161	0.3373486	67.48424585	-	0.560371199	-0.077730138	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 20 BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev.

Exponential 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.35727	0.232282	0.7186794	0.0011689	69.9064593	-	0.491844604	1.31653975	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Exponential 5 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.066183	0.022064	0.2694505	0.0050087	66.56380266	-	-0.004325139	0.002288581	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Hill (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.330055	0.326673	0.3334342	NA	76.89316395	-	0.982831655	1.388215558	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 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.358617	0.238503	0.7202501	0.0011383	69.96267223	-	0.457166197	1.335636382	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.359345	0.238241	0.3667835	0.000334	71.9791803	-	0.453953971	1.336329914	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Power (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.358617	0.238506	0.720197	0.0011383	69.96267223	-	0.457166567	1.335636293	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Hill (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.040983	0.003327	0.0418311	NA	68.13725066	-	0.431091491	-0.268644604	Questionable	BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.358617	0.238506	0.7202242	0.0011383	69.96267223	-	0.457166645	1.335636148	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 3 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.095966	0.021167	0.0979522	0.0009824	68.83115551	-	0.009336737	0.350707186	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 2 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.083496	0.052397	0.0852242	0.0045635	66.74996195	-	0.148525837	0.140081717	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Power (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.07235	0.002944	0.4028199	0.0031612	67.48424585	-	0.56033598	-0.077683545	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 20 BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev.

Hematocrit, 13-week study (RTC, 2006), males

Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation	BMDS Recommendation Notes
Exponential 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.319258	0.213617	0.5343814	0.0715397	154.3085825	-	23.03932619	61.55584978	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2
Exponential 5 (CV - lognormal)	frequentist	Restricted	Std. Dev.	1	0.070656	0.02514	0.2157405	0.9177397	151.0442452	-	-2.198011733	2.55602156	Questionable	Constant variance test failed (Test 2 p-value < 0.05) |Residual for Dose Group Near BMD| > 2 |Residual at control| > 2
Hill (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Restricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Hill (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Linear (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 3 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Polynomial Degree 2 (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Power (CV - lognormal)	frequentist	Unrestricted	Std. Dev.	-	-	-	-	-	-	-	-	-	Unusable	BMD computation failed; lower limit includes zero Model was not run. Lognormal distribution is only compatible with exponential models
Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.302697	0.207563	0.5336589	0.0735642	153.1658509	-	-1.70798304	1.322887487	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	Std. Dev.	1	0.302697	0.207563	0.5360408	0.0223389	155.1658509	-	-1.707983047	1.322887487	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.
Hill (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.060904	0.018984	0.2219944	NA	151.9466582	-	-8.16067E-07	6.23819E-08	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 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	Std. Dev.	1	0.308384	0.213662	0.5525808	0.0701165	153.2618524	-	-1.722466988	1.341215595	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.

Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.308634	0.21366	0.5525786	0.0701166	153.2618493	-	-1.722272564	1.342558595	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.
Power (CV - normal)	frequentist	Restricted	Std. Dev.	1	0.311918	0.21355	0.5538827	0.0695826	153.2771393	-	-1.700297913	1.318162537	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.
Hill (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.060904	0.009338	0.2322704	NA	151.9466582	-	1.02708E-07	-1.36736E-07	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.308543	0.213661	0.5525883	0.0701167	153.2618477	-	-1.722342919	1.342067632	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.
Polynomial Degree 3 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.072168	0.020982	0.2337572	NA	151.9953518	-	-0.092867863	0.179449796	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 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 2 (CV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.083587	0.051285	0.2124516	0.6550918	150.1461989	-	0.10324094	0.254630043	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	Unrestricted	Std. Dev.	1	0.062935	0.004639	0.2841663	0.3937715	150.6739221	-	0.516213137	-0.084085607	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev.

Exponential 3 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.302697	0.207563	0.5361262	0.0011236	153.1658509	-	-1.707983035	1.322887541	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Exponential 5 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.06654	0.024612	0.2147783	0.0044804	149.9624093	-	-0.0933775	0.052441643	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Hill (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.047876	0.020248	0.0495078	NA	151.4283678	-	-0.079188448	-0.143832122	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 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.310543	0.212812	0.3169711	0.0003047	155.338953	-	-1.719311818	1.343135067	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 2 (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.3086	0.213637	0.5527264	0.0003163	155.2636695	-	-1.722257798	1.342114393	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Power (NCV - normal)	frequentist	Restricted	Std. Dev.	1	0.317974	0.205479	0.324556	0.000218	156.008736	-	0.39892012	1.84108245	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Hill (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.047773	0.018109	0.0494013	NA	151.4285703	-	-0.070712199	-0.146963483	Questionable	Modeled control response std. dev. >|1.5| actual response std. dev. d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Linear (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.308544	0.213661	0.5525869	0.0010738	153.2618477	-	-1.722342833	1.342067779	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 3 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.15003	0.146942	0.1531022	NA	157.1368747	-	-0.13628469	1.60925522	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 2 (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.086899	0.051158	0.0886982	0.0040123	150.1830794	-	0.125840666	0.405514146	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Power (NCV - normal)	frequentist	Unrestricted	Std. Dev.	1	0.063997	0.004639	0.2841757	0.0031386	150.6742719	-	0.505873133	-0.074756862	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev.

Triglycerides, 13-week study (RTC, 2006), females

Input Settings

Setting	Value
BMR	1.0 Standard Deviation
Distribution	Lognormal + Constant variance
Modeling Direction	Up (↑)
Maximum Polynomial Degree	3
Confidence Level	0.95
Tail Probability	0.01

Frequentist Summary

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	Recommendation and Notes
ExponentialM3	0.206	0.294	0.512	0.054	275.209	55.988	-41.692	**Questionable** Residual at control greater than 2.0 Goodness of fit p-value less than 0.1 Constant variance test failed (Test 2 p-value < 0.05) Abs(Residual of interest) greater than 2.0
ExponentialM5	0.018	0.059	0.204	0.422	272.02	38.024	-5.897	**Questionable** Residual at control greater than 2.0 Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio greater than 3.0 Abs(Residual of interest) greater than 2.0
0.5		10		39.89		8.63		

Input Settings

Setting	Value
BMR	1.0 Standard Deviation
Distribution	Normal + Constant variance
Modeling Direction	Up (↑)
Maximum Polynomial Degree	3
Confidence Level	0.95
Tail Probability	0.01

Frequentist Summary

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	Recommendation and Notes
ExponentialM3	0.248	0.336	0.559	0.072	282.227	-0.281	-1.672	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
ExponentialM5	0.02	0.078	0.283	0.292	280.086	0.797	-0.462	**Questionable** Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio greater than 3.0
Hill	0.014	0.059	0.253	0.442	279.566	0.511	-0.207	**Questionable** Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL

								ratio greater than 3.0
Polynomial 2°	0.211	0.303	0.537	0.092	281.739	1.172	-1.565	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
Polynomial 3°	0.211	0.303	0.537	0.092	281.739	1.172	-1.565	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
Power	0.21	0.293	0.3	0.088	281.826	1.212	-1.614	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
Linear	0.211	0.303	0.537	0.092	281.739	1.172	-1.564	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
Hill	0.003	0.048	0.246	-	281.005	0.1	-0.015	**Questionable** lowest dose/BMDL ratio greater than 3.0 lowest dose/BMDL ratio greater than 10.0 Zero degrees of

								freedom; saturated model Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio greater than 3.0
Polynomial 2°	0.058	0.104	0.31	0.207	280.57	-0.286	-0.709	**Questionable** Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
Polynomial 3°	0.186	0.276	0.282	-	281.007	-0.001	-0.004	**Questionable** Zero degrees of freedom; saturated model Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)
Power	0.028	0.047	0.255	0.942	278.979	0.042	-0.006	**Questionable** Control stdev. fit greater than 1.5 Constant variance test failed (Test 2 p-value < 0.05)

Input Settings

Setting	Value
BMR	1.0 Standard Deviation
Distribution	Normal + Nonconstant variance
Modeling Direction	Up (↑)
Maximum Polynomial Degree	3
Confidence Level	0.95
Tail Probability	0.01

Frequentist Summary

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	Recommendation and Notes
ExponentialM3	0.211	0.315	0.321	<0.001	284.041	1.175	-1.792	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5
ExponentialM5	<0.001	0.004	0.029	0.309	270.148	0.266	0.266	**Questionable** lowest dose/BMDL ratio greater than 3.0 lowest dose/BMDL ratio greater than 10.0 lowest dose/BMD ratio greater than 3.0 BMD/BMDL ratio greater than 3.0
Hill	<0.001	0.003	0.023	0.168	271.702	0.262	0.262	**Questionable** lowest dose/BMDL ratio greater than 3.0 lowest dose/BMDL ratio greater than 10.0 lowest dose/BMD ratio greater than 3.0 lowest dose/BMD ratio greater than 10.0 BMD/BMDL ratio greater than 3.0 BMD/BMDL ratio greater than 20.0
Polynomial 2°	0.166	0.297	0.303	<0.001	283.624	1.18	-1.567	**Questionable** Goodness of fit p-

								value less than 0.1 Control stdev. fit greater than 1.5
Polynomial 3°	0.169	0.277	0.514	<0.001	283.421	1.198	-1.606	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5
Power	0.16	0.336	0.343	<0.001	284.077	-0.193	-1.971	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5
Linear	0.169	0.277	0.514	<0.001	283.421	1.198	-1.606	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5
Hill	0	<0.001	-	-	272.982	0.264	0.264	**Unusable** lowest dose/BMD ratio greater than 3.0 lowest dose/BMD ratio greater than 10.0 Zero degrees of freedom; saturated model BMDL does not exist
Polynomial 2°	0.023	0.186	0.19	<0.001	283.501	0.703	-1.45	**Questionable** Goodness of fit p-value less than 0.1 Control stdev. fit greater than 1.5 BMD/BMDL ratio greater than 3.0
Polynomial 3°	0.103	0.105	0.107	-	284.098	-0.034	-0.98	**Questionable** Zero degrees of freedom; saturated

								model Control stdev. fit greater than 1.5
Power	0	<0.001	-	0.289	270.922	0.263	0.263	**Unusable** lowest dose/BMD ratio greater than 3.0 lowest dose/BMD ratio greater than 10.0 BMDL does not exist

Incidence of aggregations of alveolar macrophages, 13-week study (RTC, 2006), females

Input Settings

Setting	Value
BMR	10% Extra Risk
Confidence Level	0.95
Maximum Multistage Degree	3

Frequentist Summary

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	Recommendation and Notes
Hill	<0.001	0.104	0.48	-	58.515	<0.001	<0.001	**Questionable** lowest dose/BMDL ratio greater than 3.0 lowest dose/BMDL ratio greater than 10.0 Zero degrees of freedom; saturated model BMD/BMDL ratio greater than 3.0 BMD/BMDL ratio greater than 20.0

Gamma	0.027	0.058	0.462	0.91	54.704	-0.234	0.017	**Viable**
LogLogistic[ab]	0.013	0.043	0.482	0.748	56.618	-0.232	0.116	**Recommended - Lowest BMDL** BMD/BMDL ratio greater than 3.0
Multistage 1°	0.027	0.058	0.315	0.91	54.704	-0.234	0.017	**Viable**
Multistage 2°	0.027	0.058	0.389	0.91	54.704	-0.234	0.017	**Viable**
Multistage 3°	0.027	0.058	0.42	0.91	54.704	-0.234	0.017	**Viable**
Weibull	0.027	0.058	0.485	0.91	54.704	-0.234	0.017	**Viable**
LogProbit	0.047	0.104	0.493	0.824	54.898	0.518	-0.142	**Viable**

[a] Recommended best-fitting model
[b] Lowest BMDL.