UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

August 15, 2023

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Order under Section 4 of the Toxic Substances Control Act (TSCA)

Chemical Substance Subject to this Order:

Chemical Name: 2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy)propanoyl fluoride

Chemical Name Synonyms: Perfluoro(2-methyl-3-oxahexanoyl) fluoride; Hexafluoropropylene oxide-derived acyl fluoride

Chemical Name Acronym: HFPO-DAF

Chemical Abstracts Service Registry Number (CASRN): 2062-98-8

Docket Identification (ID) Number: EPA-HQ-OPPT-2021-0903

(To access the docket, go to https://www.regulations.gov)

Testing Required by this Order:

Testing is listed by physical-chemical and health effect study types: health effect testing is further listed by exposure route. All tests listed under Tier 1.1 are required as part of the initial response to the Order. Testing under Tiers 1.2 and 1.3 will be performed in accordance with the decision logic shown in **Figure 1** of **Section V.A**.

1. Physical-Chemical Properties

Tier 1.1- test required

a. Melting Point/Melting Range (**OECD 102 (1995)**) (OECD, 1995b)

b. Boiling Point (**OECD 103 (1995)**) (OECD, 1995c)

c. Vapor Pressure (**OECD 104 (2006)**) (OECD, 2006)

d. Water Solubility (**OECD 105 (1995)**) (OECD, 1995a)

e. Determination of pH, Acidity and Alkalinity (**OECD 122 (2013)**) (OECD, 2013)

f. Hydrolysis as a Function of pH (**OECD 111 (2004)**) (OECD, 2004b)

2. Health Effects: Dermal Route

Tier 1.2 – test required – specific protocol may depend on results of the Tier 1.1 Vapor Pressure test

a. In Vitro Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method (**OECD 431 (2019)**) (OECD, 2019)

b. In Vitro Membrane Barrier Test Method for Skin Corrosion (**OECD 435 (2015)**) (OECD, 2015b)

Tier 1.3 – test required dependent on results of Tier 1.1 Hydrolysis as a Function of pH as well as Tier 1.2 Skin Corrosion tests

a. Skin Absorption: In Vitro Method (**OECD 428 (2004)**) (OECD, 2004c)

b. Defined Approaches on Skin Sensitization (**OECD 497 (2021)**) (OECD, 2021a)

c. In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (**OECD 439 (2021)**) (OECD, 2021b)

3. Health Effects: Ocular Route

Tier 1.1 - test required

a. Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (**OECD 437 (2020)**) (OECD, 2020a)

Tier 1.2 - test required dependent on results of Tier 1.1 Bovine Corneal Opacity Test as well as Tier 1.1 Hydrolysis as a Function of pH; specific protocol may depend on results of the Tier 1.1 Vapor Pressure test

a. Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification (**OECD 492B (2022)**) (OECD, 2022)

4. Health Effects: Mechanistic

Tier 1.2 – test required dependent on results of Tier 1.1 Hydrolysis as a Function of pH; specific protocol may depend on results of the Tier 1.1 Vapor Pressure test

a. Bacterial Reverse Mutation Test (**OECD 471 (2020)**) (OECD, 2020b)

b. One of the following **(dependent upon hydrolysis half-life)**:

i. In Vitro Mammalian Chromosomal Aberration Test (**OECD 473 (2016)**) (OECD, 2016a)

ii. In Vitro Mammalian Cell Micronucleus Test (**OECD 487 (2016)**) (OECD, 2016b)

iii. In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene (**OECD 490 (2016)**) (OECD, 2016c)

Recipients of this Order:

Company Name: 3M Company

Company Name: The Chemours Company FC LLC

Company Name: E I Du Pont de Nemours and Company

Dear Recipient:

This Order requires you and the other named manufacturer(s) and/or processor(s) of HFPO-DAF (CASRN 2062-98-8) to develop and submit certain information for HFPO-DAF, or otherwise respond to the U.S. Environmental Protection Agency (referred to herein as "EPA" or "the Agency"). Failure to respond to this Order, or failure to otherwise comply with its requirements, is a violation of section 15 of the Toxic Substances Control Act (TSCA), 15 U.S.C. § 2614. Any person who violates TSCA shall be liable to the United States for penalties in accordance with TSCA Section 16, 15 U.S.C. § 2615.

This Order is **effective 5 calendar days after its date of signature by the EPA.** The timeframes and options for responding are described in **Unit IV** (Responding to this Order). Please note that the email transmitting this Order to you will provide the calendar date for the response deadlines as defined in **Unit III** (Deadlines for Responding to this Order), but the official deadlines are provided in this Order. A subsequent email will provide a company-specific Order number for you to use in responses and communications about this Order.

This Order is organized as follows:

I. PURPOSE AND AUTHORITY

A. OVERVIEW

This Order is being issued under the authority of the Toxic Substances Control Act (TSCA), 15 U.S.C. § 2601 *et seq*. TSCA Section 4 authorizes the EPA to require the development of necessary information related to chemical substances and mixtures.

This Order requires the identified recipients to develop and submit information on 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoyl fluoride (perfluoro(2-methyl-3-oxahexanoyl) fluoride; HFPO-DAF). See **Unit II** for a discussion of the scope of this Order.

Information on testing requirements is provided in **Appendix E**. The EPA encourages the formation of industry consortia to jointly conduct testing between the recipients of this Order. See **Unit VIII** for more information on this topic.

The Order requires each identified recipient to identify as a Manufacturer or Processor via an "Identification Response." A recipient who (1) does not currently manufacture or process the chemical substance(s) identified in this Order, (2) does not intend to manufacture or process the chemical substance(s) within the period of testing provided by the Order, ***and*** (3) has not manufactured or processed the chemical substance(s) during the five years preceding the date of this Order may claim to not be subject to the Order. Note that the most immediate deadline is to identify as a Manufacturer, Processor, or both—or to Claim Not Subject to the Order—within 30 calendar days after the effective date of this Order. See **Unit IV.A** for more information on this topic.

Recipients who identify as a Manufacturer or Processor of the chemical substance(s) (via the submitted "Identification Response") must respond using one of the three "Initial Response" options provided: Develop the Information, Submit Existing Information, or Request an Exemption. General information on these response options is provided below. Detailed information on each of these options, including their requirements (as applicable), is provided in **Unit IV.B**.

Option 1: Develop the Information

Use this option when you intend to develop information in response to all of the requirements of this Order that apply to you or use this option in conjunction with other response options identified in this section as appropriate. This option is available if you are conducting the testing on your own or as part of a consortium.

Manufacturers who are required to test a chemical substance or mixture pursuant to a TSCA Section 4 order are also required to pay a fee (see **Unit VII**).

Option 2: Submit Existing Information

Use this option to submit an existing study and/or other scientifically relevant information that you believe the EPA may not have considered, along with supporting rationale that explains how the submittal(s) meets part or all of the information described as necessary in **Unit II**. If the EPA determines that the submitted information satisfies one or more data requirements identified by this Order, the Agency will extinguish any associated test requirement(s).

Option 3: Request an Exemption

Any person required by this Order to conduct tests and submit information on a chemical may apply for an exemption from a requirement of the Order to conduct testing. An exemption is not a removal of all responsibility from this Order. Rather, the exemption is a means by which an entity may conditionally forgo conducting the required testing if another person has submitted or will submit such testing under Section 4 of TSCA. A person who is granted an exemption may be required to reimburse the person(s) who submit(s) the required testing or another exemption holder who reimbursed a data submitter.

B. TERMINOLOGY USED IN THIS ORDER

The term "manufacture" means to import into the customs territory of the United States, to produce, or to manufacture. 15 U.S.C. § 2602(9). Manufacture and import of the chemical as a byproduct, impurity, and as a component of an article are also included.

The term "process" means the preparation of a chemical substance or mixture, after its manufacture, for distribution in commerce—(A) in the same form or physical state as, or in a different form or physical state from, that in which it was received by the person so preparing such substance or mixture, or (B) as part of an article containing the chemical substance or mixture. 15 U.S.C. § 2602(13).

There is no *de minimis* volume or concentration that would be excluded from this definition of "process." Additionally, if a chemical substance or mixture containing impurities is processed for commercial purposes, the impurities also are processed for commercial purposes, and all components of a mixture are processed for commercial purposes.

The term "distribution in commerce" means to sell, or the sale of, the substance, mixture, or article in commerce; to introduce or deliver for introduction into commerce, or the introduction or delivery for introduction into commerce of, the substance, mixture, or article; or to hold, or the holding of, the substance, mixture, or article after its introduction into commerce. 15 U.S.C. § 2602(5). As examples, this term includes selling to other entities that may further process the subject chemical substance as well as distribution to sites owned and/or operated by the processing company where a commercial advantage is obtained by such distribution.

The term "chemical" or "substance" means a chemical substance or a chemical substance in a mixture.

The term "Order recipient" refers to a company listed on the Order. In regard to the testing requirements, any consortium representing Order recipients will be considered the Order recipient.

C. PERSONS SUBJECT TO THIS ORDER

1. Persons Identified

An order issued under Section 4(a) of TSCA may require the development of information by any person who manufactures or processes, or intends to manufacture or process, a chemical substance or mixture subject to the Order. The recipients of this Order are listed at the top of the Order.

For purposes of this Order, a recipient is subject if it has manufactured or processed the chemical at any time during the five years preceding the date of this Order. If a recipient of this Order has not manufactured or processed the chemical during the prior five years, the recipient is nevertheless subject to the Order if they intend to manufacture or process the chemical within the period of testing provided by this Order.

A person who contracts with a producing manufacturer to manufacture or produce a chemical substance is also a manufacturer if (1) the producing manufacturer manufactures or produces the substance exclusively for that person, and (2) that person specifies the identity of the substance and controls the total amount produced and the basic technology for the plant process.

A producing manufacturer is one who physically manufactures the chemical substance and generally provides the site, staff, and equipment necessary to manufacture the chemical substance.

A recipient who is an importer of record of a chemical substance identified by this Order is responsible for the testing requirements of this Order, even if the recipient does not store, handle, use, or otherwise directly deal with the chemical.

The means by which the EPA identified each recipient subject to this Order does not govern whether a recipient is subject to this Order. Ultimately, any recipient that meets the criteria discussed in this section is subject to this Order, regardless of the basis on which the EPA identified the recipient.

2. Corporate Structure of Recipients; Changes of Ownership

The EPA has attempted to identify the highest-level U.S. corporate entity for purposes of issuing this Order. The highest-level U.S. corporate entity is ultimately responsible for satisfying the obligations of this Order, although the highest-level U.S. corporate entity may delegate its responsibilities under this Order to a U.S. subsidiary. Where the corporate entity named in this Order is not the highest-level U.S. corporate entity, the EPA nonetheless considers notification of the company named in this Order to constitute notification of the highest-level U.S. corporate entity and holds both the identified company and the highest-level U.S. corporate entity ultimately responsible for satisfying the obligations of this Order.

In the event of mergers, acquisitions, or other transactions that create a corporate successor in interest (subsequent to the manufacturing or processing that triggered the reporting obligation, and either before or after receipt of this Order), that successor in interest is responsible for satisfying the obligations of this Order. The successor in interest must notify the EPA of its identity within 14 days following the transaction.

II. SCOPE OF TSCA SECTION 4 TEST ORDER

A. STATUTORY STANDARD

Under section 4(a)(1)(A)(i) of TSCA, the EPA shall require testing of a chemical substance or mixture to develop appropriate test data if the Administrator finds that:

(I) The manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment,

(II) There is insufficient information and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(III) Testing of such substance or mixture with respect to such effects is necessary to develop such information.

In making section 4(a)(1)(A)(i) findings, the EPA considers, among other things, physical-chemical properties, fate and transport, exposure, and toxicity information to make the finding that the chemical substance or mixture may present an unreasonable risk. For finding (II) above, the EPA examines whether existing information is adequate to reasonably determine or predict the effects on health or the environment from the chemical substance or mixture. In making the third finding that testing is necessary, the EPA considers whether testing which the Agency might require is necessary to develop the needed information.

B. BASIS FOR THIS ORDER

The EPA is issuing this Order on the authority of section 4(a)(1)(A)(i) of TSCA. As explained above, in **Unit II.A**, to issue an Order under section 4(a)(1)(A)(i) on a chemical substance or mixture, the EPA must make three findings, as provided below.

1. TSCA Section 4(a)(1)(A)(i)(I): The manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.

The EPA finds that the manufacture, distribution in commerce, processing, use, or disposal of HFPO-DAF may present an unreasonable risk of injury to human health or the environment.

HFPO-DAF is a member of the group of chemicals known as per- and polyfluoroalkyl substances (PFAS). For the purposes of this Order, the EPA's Office of Pollution Prevention and Toxics (OPPT) is using a structural definition for identifying PFAS. Specifically, this definition includes substances that meet any of the following criteria:

(i) R-(CF_2)-CF(R′)R″, where both the CF_2 and CF moieties are saturated carbons

(ii) R-CF_2OCF_2-R′, where R and R′ can either be F, O, or saturated carbons

(iii) $CF_3C(CF_3)R'R''$, where R′ and R″ can either be F or saturated carbons

Note that agencies as well as programs within a given agency may define PFAS differently as applicable to the statute and regulatory needs. HFPO-DAF fits the definition of PFAS provided above as well as other definitions of PFAS (e.g., OECD's definition). The definition being used for this Order is not meant to represent an agency-wide definition but is consistent with the recent definition provided in a Significant New Use Rule on PFAS designated as inactive on the TSCA inventory (Federal Register: Per- and Poly-Fluoroalkyl Chemical Substances Designated as Inactive on the TSCA Inventory; Significant New Use Rule). The definition could be revised for future cycles as more information is gathered on PFAS.

Hazard and Exposure for PFAS

PFAS have been used in industry and consumer products since the 1940s because of their useful properties. There are thousands of different PFAS, some of which have been more widely used and studied than others. Studies show that some PFAS may break down very slowly or break down into other PFAS that break down very slowly, and can build up in people, animals, and the environment over time (ATSDR, 2021); (USEPA, 2022b).

Studies in laboratory animals indicate some PFAS can cause reproductive, developmental, liver, kidney, and immunological toxicity. In addition, exposure to some PFAS produces tumors in laboratory animals. In humans, the most consistent findings from epidemiology studies are increased cholesterol levels among exposed populations, with more limited findings related to infant birth weights, effects on the immune system, cancer (e.g., Health Effects Support Document for Perfluorooctanoic Acid (PFOA) (USEPA, 2016b)), and thyroid hormone disruption (e.g., Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) (USEPA, 2016a). In humans and animals, some PFAS can cause adverse effects on the respiratory system following acute inhalation exposures (e.g., corrosion, chemical pneumonitis) (Nlm, 2022). In some cases, cardiac sensitization may be a concern, where the heart is damaged in a way that it becomes sensitive to epinephrine (aka adrenaline) which can lead to potentially fatal arrhythmias (ECETOC, 2009). Visit these EPA webpages for more information on general concerns associated with PFAS: PFAS Explained (USEPA, 2022c) and Our Current Understanding of the Human Health and Environmental Risks of PFAS (USEPA, 2022b).

Current research has shown that people can be exposed to PFAS by working in occupations that deal with PFAS and products containing PFAS, drinking water contaminated with PFAS, eating certain foods that may contain or be packaged in PFAS-containing materials, swallowing contaminated soil or dust, breathing air containing PFAS, and using products made with PFAS or that are packaged in materials containing PFAS (ATSDR, 2021). These exposures are compounded when populations are exposed via more than one exposure route.

Hazard for 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoyl fluoride (HFPO-DAF)

HFPO-DAF is part of the larger group of chemicals described above as PFAS.

The relevant routes of exposure for HFPO-DAF include oral, dermal, inhalation, and ocular. The EPA examined whether existing information is adequate to reasonably determine or predict the effects on health from HFPO-DAF. The EPA considered all reasonably available human health-related toxicity studies for:

- Acute Toxicity
- Subchronic Toxicity
- Chronic Toxicity including Cancer Bioassays
- Developmental Toxicity
- Reproductive Toxicity
- Immunotoxicity
- Neurotoxicity
- Toxicokinetics
- Mutagenicity
- Sensitization/Irritation

The EPA queried for toxicity data from three sources – the EPA Toxicity Value Database (ToxValDB) (Judson, 2018), the EPA Chemical Information System (CIS), and the EPA Category Assessment Portal (CAP). The EPA ToxValDB is a compilation of publicly-derived experimental toxicity data on ~34,000 chemicals from 43 distinct sources including U.S. EPA, U.S. Food and Drug Administration (FDA), California Office of Environmental Health Hazard Assessment (OEHHA), Agency for Toxic Substances and Disease Registry (ATSDR), Department of Energy (DOE), California Department of Public Health (DPH), the World Health Organization (WHO), Health Canada, the European Chemicals Agency (ECHA), European Food Standards Agency (EFSA), and the European Commission's Cluster of Systems of Metadata for Official Statistics (COSMOS) database. These sources include toxicity data from the scientific literature, reports, regulatory toxicology study submissions, or government-sponsored studies (e.g., U.S. National Toxicology Program). The EPA CIS and CAP are internal platforms for managing data submissions under TSCA, including toxicity studies. Most of the data within these platforms have been provided by industry in conjunction with TSCA submissions and are not currently publicly available. The EPA also considered additional toxicity data provided by the Test Order recipients before issuance of the Test Order. The data provided by Test Order Recipients which EPA considered for the data needs specified in this Order are publicly available at the Regulations.gov docket specific for this Order.

Five studies were identified and considered prior to the issuance of this HFPO-DAF Test Order pursuant to the requirements specified at TSCA sections 4(h)(1)(A), 26(k) to consider reasonably available information. Each study underwent Data Quality Evaluation per the draft TSCA Systematic Review Protocol (USEPA, 2021a) (**Appendix F**). Submitted test reports/studies on the chemical substance reported hazards for acute inhalation and acute oral toxicity, short-term (sub-acute) inhalation toxicity, and dermal irritation/corrosion. In particular, available data from a dermal irritation/corrosion study in rabbits indicated that HFPO-DAF is corrosive to rabbit skin. Furthermore, the acute and sub-acute inhalation studies found both portal-of-entry (lung) and systemic (liver) effects. In the absence directly measured HFPO-DAF hydrolysis products, the observed systemic effects were potentially due to a

GenX compound (*i.e.,* HFPO-DA, aka HFPO dimer acid, CASRN 13252-13-6), the predicted hydrolysis product of HFPO-DAF, which has been shown to cause liver and other effects (USEPA, 2021b).

In addition to being a PFAS and having specific studies indicating health concerns, HFPO-DAF contains an acyl fluoride functional group (*i.e.,* a carbonyl group bonded on one side to an alkyl chain and on the other side to a fluorine atom: R-C(=O)-F). Acyl fluorides are highly reactive, and have electrophilic functional groups that can react with cellular nucleophiles, including DNA, proteins, and glutathione (Klaassen, 2019; Klaunig and Wang, 2019). Reaction of acyl halides with DNA and/or proteins can lead to the formation of adducts. DNA adducts can eventually lead to mutations and, in some circumstances, cancer or increase susceptibility for cancer as an indirect genotoxic carcinogen (Klaassen, 2019; Klaunig and Wang, 2019). Most indirect genotoxic carcinogens require metabolic activation in a target organ/cell to produce the DNA-damaging event (Klaunig and Wang, 2019). The acyl fluoride moiety is expected to be rapidly hydrolyzed and has been observed to potentially be more stable than other acyl halides, e.g., acyl chlorides (Liang et al., 2021). Measuring experimental physical chemical properties is critical to understanding HFPO-DAF stability and reactivity, as a distinct acyl fluoride and for subsequent hazard testing.

Increased risk of certain types of cancer are associated with exposure to PFAS generally (USEPA, 2022b), and supports potential genotoxicity concerns for HFPO-DAF. Further, the structure of HFPO-DAF was analyzed using two computational toxicology tools: OncoLogic™ version 9.0 and the OECD QSAR Toolbox version 4.5. OncoLogic™ predicts that HFPO-DAF may be a direct-acting genotoxic agent (due to the acyl fluoride moiety) and has moderate concern for cancer via inhalation exposure. The OECD QSAR Toolbox predicts that HFPO-DAF is a skin sensitizer but not a respiratory sensitizer. It should be noted that generally PFAS are known to have unique properties which may impact the applicability of certain models. For HFPO-DAF, this chemical is within the applicability domain of these two models; the EPA interprets the model outputs with caution. Additional information on the results of analyses using the two computational toxicology tools can be found in **Appendix G**.

In summary, for HFPO-DAF, the EPA identified potential hazards for acute toxicity, skin corrosion, serious eye damage, skin sensitization, genetic toxicity, carcinogenicity, and specific target organ toxicity.

Exposure for 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoyl fluoride (HFPO-DAF)

Based on available boiling point experimental data and modeled estimates of physical-chemical property values for HFPO-DAF using EPA's model, Open (Quantitative) Structure-activity/property Relationship App (OPERA v 2.9), the EPA predicts it to be a soluble, volatile liquid at standard temperature and pressure:

- Vapor pressure: 251 mmHg
- Water solubility: 0.60 mg/L
- Melting point: -90 °C
- Boiling point: 81 °C

- Boiling point (experimental): 40-56 °C (see footnote 1)

Following review of the available boiling point data, the EPA has determined none of the available studies meet the minimum study quality criteria for boiling point studies. The experiments were not performed in duplicate; the pressure at which the boiling points were measured was not reported; the experimental apparatus was insufficiently described; and there were impurities present that could affect the measurement. See reporting requirements in OECD 103 (OECD, 1995c) for more information. Based on the physical-chemical properties indicating it is a soluble, volatile liquid, exposures via oral, dermal, inhalation, and ocular routes are of concern for this substance. Manufacturing, processing, use, disposal, and/or distribution in commerce of liquid substances may lead to dermal, inhalation, and ocular exposures to workers. Further, manufacturing and processing activities may occur at elevated temperatures, increasing exposure via inhalation. Environmental emissions monitoring, specifically regional-scale chemical transport modeling together with deposition measurements found HFPO-DAF primarily in the gas phase (D'Ambro et al., 2021), support potential for inhalation exposures.

In evaluating exposure to HFPO-DAF, among other sources, the Agency considered: (a) its status on the TSCA Inventory, (b) reporting on the substance under the Chemical Data Reporting Rule, and (c) North Carolina Department of Environmental Quality (NCDEQ) emission reports.

Section 8(b)(4)(A) of TSCA required the EPA to designate as "active" in commerce any chemical substance manufactured or processed within a specified ten-year period, based on information provided by manufacturers and processors of such chemical substances. HFPO-DAF is listed as "active" on the TSCA Inventory, as a result of this reporting, indicating a potential for exposure.

Data submitted to the EPA under the Chemical Data Reporting (CDR) rule at 40 CFR part 711 indicates that HFPO-DAF is manufactured (defined to include importing) in quantities of more than 1,000,000 pounds in a given year and used as a reactant in other basic organic chemical manufacturing. CDR also indicates that workers may have been exposed to the chemical (see "Type of Process or Use" and "Number of Workers Reasonably Likely to be Exposed" data elements).

This reporting supports that there may be worker exposure to HFPO-DAF. Furthermore, the North Carolina Department of Environmental Quality (NCDEQ) has issued Air Quality Permits for certain activities involving HFPO-DAF—including "HFPO Process" and "HFPO product container decontamination process"—which indicates possible exposure concerns (Erm, 2020). Such concerns are further supported by air emissions reports provided to NCDEQ that document empirically that HFPO-DAF was released into the air after scrubbing from the reporting facility (Ws, 2020, 2018). Given the hazard and exposure concerns identified for HFPO-DAF, as discussed above, the EPA finds that HFPO-DAF may present an unreasonable risk of injury to health or the environment. The general hazard and exposure concerns for PFAS further support this conclusion.

[1] Paleta et al. (1996): 40-48 °C (Paleta et al., 1996); Kawa et al. (1982): 52-54 °C (Kawa et al., 1982); Pasenok et al. (1996): 52-55 °C. (Pasenok et al., 1996); Ishikawa and Sasabe (1984): 52-56 °C (Ishikawa and Sasabe, 1984); SOLVAY (2015): 55 °C (2013); Chengxue et al. (1982) (Zhao et al., 1982).

2. TSCA Section 4(a)(1)(A)(i)(II): There are insufficient information and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted.

This Order addresses only those data needs discussed in the Order and does not address whether there are additional unmet data needs for HFPO-DAF. The EPA may, in the future, make statutory findings to support additional testing requirements.

The EPA estimated the human health hazard of HFPO-DAF based on its estimated and measured physical/chemical properties on the chemical substance by comparing it to structurally analogous chemical substances for which there is information on human health hazard, and other structural information. Absorption of the chemical substance is expected to be poor via the lungs and good via the skin and GI tract based on predicted physical/chemical properties.

Data from five toxicity studies were reviewed (**Appendix F**) and found to support the identification of the following health outcomes as a result of HFPO-DAF exposure: mortality, nutritional/metabolic, lung/respiratory, skin, skin irritation, and other (clinical signs of toxicity and muscle pathology). Due to study design limitations, specifically the number of exposure levels and the duration of exposures, the available data are insufficient to determine a potential Point of Departure (POD) for any health outcome.

HFPO-DAF is expected and reported to hydrolyze in water to give 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid (aka HFPO-DA, a GenX chemical, CASRN 13252-13-6) and hydrogen fluoride (HF, CASRN 7664-39-3). The rate of this hydrolysis and HFPO-DAF phase partitioning potential is expected to be pH-dependent. Released as a gas, the rate of hydrolysis is further expected to be dependent upon atmospherically relevant conditions (D'Ambro et al., 2021). Given that the acyl fluoride moiety is expected to underlie some of the toxic effects of HFPO-DAF, the rates of hydrolysis at physiologically-relevant pH in the lung and stomach are necessary to interpret the toxicity and predict adverse effects following exposure to HFPO-DAF.

The EPA is requiring *in vitro* toxicity studies to examine portal-of-entry effects in animal tissue. Available rodent studies conducted via the inhalation route have indicated lung/ respiratory effects (Table F1) and inhalation is a route of exposure of concern for HFPO-DAF. However, portal of entry effects in human-based tissues related to the airway are not being required at this time because the relevant *in vitro* assays (Mallek et al., 2022) are difficult to perform using liquid exposures and are considered too technically challenging at this time. Together, the required studies will build upon the available data and predicted hazards to support the data needs identified by the Agency.

3. TSCA Section 4(a)(1)(A)(i)(III): Testing of such substance or mixture with respect to such effects is necessary to develop such information.

The EPA finds that testing of HFPO-DAF—as described in **Appendix E** and listed at the beginning of this Order—is necessary to ascertain physical-chemical properties and develop human health-related toxicity data that the EPA requires to determine or predict the effects discussed in this Order. Further details as to the purpose of each required test of this Order are discussed in **Unit V.**

C. OTHER USES OF THIS DATA: PFAS TERMINAL CATEGORIES

The EPA developed the National PFAS Testing Strategy: Identification of Candidate Per- and Polyfluoroalkyl Substances (PFAS) for Testing (Testing Strategy; USEPA, 2021b) (USEPA, 2021c)to deepen the understanding of the impacts of PFAS, including potential hazards to human health and the environment, to address variation among effects seen for various endpoints for different PFAS (e.g., Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research; Fenton et al., 2021 (Fenton et al., 2021)), and to aid the EPA in identifying and selecting PFAS for which the Agency will require testing,.

The Testing Strategy provides categories of PFAS based on information about similarities in structure and certain physical-chemical properties. As described in the Testing Strategy (USEPA, 2021c), the EPA used computer software developed by Su and Rajan (Su and Rajan, 2021) to systematically analyze the chemical structures of a starting list of 6,504 PFAS into nine primary categories based on their structure. Substances that did not meet the conditions of membership for one of the primary categories based on the structural rules were placed into an additional category denoted as "Others." This was further refined by the presence/absence of a ring substructure (cyclic/acyclic), with additional subcategorization based on carbon chain length and similarity of chemical fingerprinting, resulting in "terminal categories" of PFAS.

Using this approach, the EPA categorized HFPO-DAF as belonging to the "Others, lt8, sub-cluster 1, sub-sub-cluster 2" terminal category. An additional factor in the initial categorization approach is substance volatility, as predicted by OPERA (Mansouri, 2022). For HFPO-DAF, it is notable that OPERA version 2.8 and the more recent version (2.9) both predict HFPO-DAF to be a liquid at standard temperature and pressure, but the models predict different vapor pressures (40.7 mmHg and 251mmHg, respectively). This uncertainty in the volatility of HFPO-DAF underscores the need for the required physical-chemical tests.

This Order pertains to 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoyl fluoride (HFPO-DAF; CASRN 2062-98-8), but the EPA's concerns related to this PFAS, and its decision to issue this Order pursuant to TSCA Section 4(a)(1)(A)(i), may also exist for other PFAS in its terminal category. As the EPA continues to improve its understanding of PFAS, categorization of these chemical substances will evolve. The EPA may determine that testing is required on other PFAS in the same terminal category as HFPO-DAF.

D. ADDITIONAL TSCA SECTION 4 CONSIDERATIONS

1. The EPA is reducing testing on vertebrates via grouping approaches

Section 4(h)(1)(B)(ii) states that the EPA will encourage and facilitate "the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category." The EPA's application of a category approach described in **Unit II.C** reduces the use of vertebrate animals by testing representatives of categories rather than many more individual PFAS.

2. The EPA is using a tiered testing strategy

This Order includes a tiered testing approach, consistent with Section 4(a)(4) of TSCA. Tiers denote different types of testing, with vertebrate tests confined to Tiers 2 and 3. Generally the cost- and time-

intensiveness of testing increases with higher tiers. In this order, Tier 1 has been broken into sub-tiers (Tiers 1.1, 1.2, and 1.3) because the results of earlier Tier 1 tests need to be known before study plans can be developed for later Tier 1 tests. Each sub-tier is a checkpoint where the Agency and the companies subject to this Order will confer regarding the design or relevance of later studies. Tier 1 testing includes physical-chemical properties and in vitro testing to inform and guide whether additional short-term in vivo toxicity and/or toxicokinetic tests and associated testing parameters should be considered. Depending on the results of Tier 1 tests and the type of toxicities identified for the PFAS categories based on existing available data, Tier 2 tests may include in vitro skin absorption testing, in vivo genotoxicity testing, acute in vivo inhalation toxicity testing, and in vivo toxicokinetic testing in rats and/or mice with evaluation of metabolites. Tier 2 tests are used to inform which species and doses to use in Tier 3 testing. Tier 3 consists of testing to identify dose levels (i.e., points of departure) for risk evaluation. No Tier 2 (whole animal) toxicity or Tier 3 tests are included in this Order.

An initial set (Tier 1.1) of physical-chemical property tests (*i.e.*, water solubility, melting point, boiling point, vapor pressure, and pH) is developed to affirm the HFPO-DAF physical state, predicted routes of exposure, and applicable testing. The results of the vapor pressure test will determine how the Tier 1.2 skin corrosivity tests should be run (e.g., in a closed system and/or analytical measurements of test article concentration). The rate of hydrolysis (Tier 1.1) is needed to determine if the Tier 1.2 genotoxicity tests and reconstructed human cornea-like epithelium test (RHCE) tests are relevant. If these tests are relevant, then the vapor pressure test results may also inform the protocols for these tests. The result of the hydrolysis test is critical for many of the subsequent Tier 1.2 and 1.3 tests because if HFPO-DAF rapidly hydrolyzes to HFPO-DA (CASRN 13252-13-6), these tests may reflect the toxicity of the hydrolysis product and not the parent. Furthermore, HFPO-DA has relatively more toxicity information, suggesting additional tests assessing systemic toxicity (Tier 2 type tests) may not be needed for HFPO-DAF and could instead be read-across from HFPO-DA and hydrofluoric acid (HF).

Portal of entry effects (eye and skin corrosion) are of concern for HFPO-DAF and testing for these effects is required as Tier 1.1 (Bovine Corneal Opacity) and Tier 1.2 (skin corrosivity) tests, independent of the hydrolysis test result. The Tier 1.1 eye and Tier 1.2 skin corrosivity test results will inform the applicability of subsequent, related Tier 1 tests (Tier 1.2 RHCE for eye hazard and Tier 1.3 skin absorption, sensitization and irritation tests, respectively).

The results of the skin corrosion testing at Tier 1.2 will inform whether skin absorption, sensitization and irritation tests are feasible at Tier 1.3, since corrosive chemicals will destroy the artificial skin and lead to an invalid result. Similarly, the results of the Tier 1.1 ocular corrosivity test will inform if the Tier 1.2 RHCE test will be feasible. If the EPA determines higher tier testing is infeasible based on results of the lower tier testing, higher tier testing will be deemed unnecessary and no longer required per TSCA section 4(a)(4).

3. The EPA is using non-vertebrate testing

As part of the consideration of non-vertebrate approaches, consistent with section 4(h)(1) of TSCA, the EPA reviewed OCSPP test methods and data evaluation reports, OECD test guidelines and guidance, and other peer-reviewed and/or publicly available methodology/protocol repositories. None of the testing included in this order requires the use of vertebrates. The EPA took steps to harmonize its testing requirements with the approaches taken by other parts of the Agency, including the New Chemicals Program and the Office of Pesticide Programs. The need for further testing (including the potential for

both vertebrate and non-vertebrate testing) will be re-evaluated once the data from this Order are received and reviewed by the EPA.

III. DEADLINES FOR RESPONDING TO THIS ORDER

This section describes the deadlines for this Order and possible modifications to such deadlines.

A. DEADLINES FOR RESPONSES TO THIS ORDER

The table below provides the response deadlines for this Order. Deadlines that fall on a weekend or holiday will remain and will not be extended to the next weekday. Descriptions of these response options and the required process associated with each option is provided in **Unit IV.**

Deadlines for Responses, Study Plans, and Test Reports

Identification Response and Initial Response Deadlines

Order Requirement	**Recipient's Deadline (Days after the effective date of the Order)**	**The EPA Response Deadline* (Days after the effective date of the Order)**
Identification Response		
Identify as a Manufacturer, Processor or Both	30	n/a
Claim that You Are Not Subject to this Order	30	45
Initial Response		
Submit Existing Data (Option 2)	30	45
Notify the EPA of the Intention to Develop the Information - On Own or as Part of a Consortium (Option 1)	65	n/a
Request an Exemption (Option 3)	65	80

Tier 1.1 Study Plans and Test Report Deadlines

Tier 1.1 tests: • **Melting Point/Melting Range (OECD 102)** • **Boiling Point (OECD 103)** • **Vapor Pressure (OECD 104)** • **Water Solubility (OECD 105)** • **Determination of pH, Acidity and Alkalinity (OECD 122)** • **Hydrolysis as a Function of pH (OECD 111)** • **Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (OECD 437)**	**Recipient's Deadline (Days after the effective date of the Order)**	**The EPA Response Deadline* (Days after the effective date of the Order)**
Submit Pre-Draft Study Plan Check-in (via email)**	95	110
Submit Draft Study Plan	125	140
Submit Final Study Plan	170	185
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

*See **Unit III.B** for potential automatic extensions associated with the EPA responses.
See **Unit VI.B for details.

The EPA will notify Test Order recipients in writing of their Tier 1.2 testing obligations after the evaluation of specific Tier 1.1 test results. Tier 1.2 deadlines will use the same structure as the Tier 1.1 tests. However, Tier 1.2 submission deadlines will be calculated based on the date of the EPA's notification to proceed with Tier 1.2 tests rather than the effective date of the HFPO-DAF Test Order.

Multiple Tier 1.2 notifications may be presented to Test Order recipients, based on the timing of the EPA's approval of the Tier 1.1 submissions.

Tier 1.2 Study Plans and Test Report Deadlines

Tier 1.2 tests: • **Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification (OECD 492B)** • **In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method (OECD 431)** • **In Vitro Membrane Barrier Test Method for Skin Corrosion (OECD 435)** • **Bacterial Reverse Mutation Test (OECD 471)** • **One of the following (dependent upon hydrolysis half-life):** o **In Vitro Mammalian Chromosomal Aberration Test (OECD 473)** o **In Vitro Mammalian Cell Micronucleus Test (OECD 487)** o **In Vitro Mammalian Cell Gene Mutation Tests Using Thymidine Kinase Gene (OECD 490)**	**Recipient's Deadline (Days after the EPA notification to proceed with the Tier 1.2 Testing)**	**The EPA Response Deadline* (Days after the EPA notification to proceed with the Tier 1.2 Testing)**
Submit Pre-Draft Study Plan Check-in (via email)**	30	45
Submit Draft Study Plan	60	75
Submit Final Study Plan	105	120
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

*See **Unit III.B** for potential automatic extensions associated with the EPA responses.
See **Unit VI.B for details.

The EPA will notify Test Order recipients in writing of their Tier 1.3 testing obligations after the evaluation of specific Tier 1.2 test results. Tier 1.3 deadlines will use the same structure as the Tier 1.1 and 1.2 tests. However, Tier 1.3 submission deadlines will be calculated based on the date of the EPA's notification to proceed with Tier 1.3 tests. Multiple Tier 1.3 notifications may be presented to Test Order recipients, based on the timing of the EPA's approval of the Tier 1.2 submissions.

Tier 1.3 Study Plans and Test Report Deadlines

Tier 1.3 tests: • **Skin Absorption: In Vitro Method (OECD 428)** • **Defined Approaches on Skin Sensitization (OECD 497)** • **In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (OECD 439)**	**Recipient's Deadline (Days after the EPA notification to proceed with the Tier 1.3 Testing)**	**The EPA Response Deadline* (Days after the EPA notification to proceed with the Tier 1.3 Testing)**
Submit Pre-Draft Study Plan Check-in (via email)**	30	45
Submit Draft Study Plan	60	75
Submit Final Study Plan	105	120
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

*See **Unit III.B** for potential automatic extensions associated with the EPA responses.
See **Unit VI.B for details.

B. Automatic Extensions to Deadlines

Where a deadline exists for an EPA response, the recipient's deadline is automatically extended should the Agency fail to meet any EPA response deadline set forth in **Unit III.A**. Specifically, deadlines will be automatically extended should the EPA fail to respond within 15 calendar days of the deadline for a response option if the response was submitted in the CDX application prior to the deadline provided. For each day exceeding the 15-day period following the associated deadline, the deadline is extended by one day.

If a recipient amends their response after the deadline for the selected response option has passed, any associated or subsequent deadlines are not extended. Therefore, the EPA recommends that recipients submit their amendments or extension requests as early as practicable to ensure adequate time to perform any required testing given that the Agency will not automatically extend deadlines for any such amendments to responses.

Deadlines will not be extended for submissions received after the deadline for the given submission. For example, a recipient may submit existing data after the 30-day deadline, but the deadline to submit a Draft Study Plan will not be extended due to the submission of the existing data. Further, the EPA is not obligated to respond within 15 days to a submission that arrives after the deadline for the given type of submission.

Other than potential automatic extensions to deadlines described here, **Unit III.C** provides the process for requesting an extension to a deadline.

C. Requesting an Extension to a Deadline for Responding to this Order

If you believe you cannot submit the required identification as a manufacturer, processor, or both; Order response; draft study plan; final study plan; or final test report to the Agency by the deadline(s) specified in this Order and intend to seek additional time to meet the requirement(s), you must submit a request to the Agency through the EPA's CDX portal as soon as you know you may need an extension. Your request must include: (1) a detailed description of the expected difficulty, including—as applicable—technical and laboratory difficulties, and (2) a proposed schedule including alternative dates for meeting such requirement(s) on a step-by-step basis (including, but not limited to, the contact information for the laboratory/laboratories, when you first consulted with the laboratory/laboratories, and details related to the delay(s) you are experiencing).

Generally, the EPA expects that an Extension Request for submitting an Initial Response, Pre-Draft Study Plan Check-in, Draft Study Plan, Final Study Plan, or Final Test Report will be submitted 15 days or more prior to the deadline. An extension request submitted within 15 days of the deadline, outside of compelling circumstances, is less likely to be granted.

For extension requests related to the Final Test Report, in the event deviation(s) arise that are expected to prevent submission of the final test report by the applicable deadline, an extension request must be submitted immediately. Please note in **Unit VI.C.1.**, the description of the required inclusion of a master schedule and status updates at adequate intervals in the study plan which will assist in obviating the need for substantial extensions. If the test sponsor fails to promptly submit an extension request, the Agency may require more frequent status updates/check-ins for the duration of the study.

The EPA will grant or deny deadline extension requests in at its discretion. Additionally, a grant of an extension request for one milestone does not impact the deadline for a subsequent milestone.

IV. RESPONDING TO THIS ORDER

You are required to respond to this Order, even if you believe your company is not subject to this Order. Failure to provide a response is a violation of section 15 of TSCA.

A. STEP 1: SUBMIT AN IDENTIFICATION RESPONSE

Identify as a Manufacturer or Processor

You will receive an e-mail from the EPA within five days of the Order being signed (i.e., by the effective date of the Order) that provides a CDX Order number for purposes of complying with this Order. Then, within 30 calendar days of the effective date of this Order, you, as a recipient of this Order, are required to respond to this Order through the EPA's Central Data Exchange (CDX) portal, informing the Agency whether you will be responding to this Order as manufacturer, processor, or both if you manufacture and process the chemical.

Claim that You Are Not Subject to the Order

Alternatively, you may claim that you are not subject to this Order if you do not manufacture or process the chemical(s) identified by this Order; do not intend to manufacture or process the chemical(s) within the period of testing required by this Order (see **Unit V.B**); and have not manufactured or processed the chemical(s) at any time during the five years preceding the effective date of this Order. An explanation of the basis for your claim, along with appropriate supporting information to substantiate that claim, must accompany your response in the CDX portal so that the EPA can evaluate the claim. Your claim must include (1) a statement explaining why your company is not subject to this Order, and (2) the certifying statement "I certify that the statements made in this letter are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine, imprisonment or both under applicable law."

The statement explaining why your company is not subject to this Order must, aside from unique case-specific scenarios as described below, indicate that your company has not imported, manufactured, or processed the subject chemical substance (intentionally or unintentionally) within the five years prior to the effective date of this Order and does not intend to manufacture (including import) or process the chemical within the period of testing required by this Order (see **Unit V.B**). However, certain companies may have unique case-specific situations that present a compelling case that they are not "manufacturers" of the chemical substance that is subject to the action and may submit such information for the EPA's consideration. For example, a company may have gone into bankruptcy and be in the hands of receivers who do not seek to continue the company's manufacturing activities involving the chemical substance subject to the testing requirements. Such situations are anticipated to be uncommon and will be highly fact-determinant; decisions for such situations will be made on a case-by-case basis.

To assert a claim using this option, you must do so within 30 days of the effective date of this Order.

If based on the evidence you provide and other evidence available to the EPA, the Agency deems your claim to be inadequately substantiated, the EPA will deny your claim, and the original requirements in

this Order will remain. You must use the EPA's CDX portal to choose one of the other identification options either (1) within 20 calendar days of being notified by the EPA of the denial of which subsequent deadlines will also be tolled by 20 calendar days, or (2) by the deadline for the response as provided by the order in **Unit III.A**, the deadline being whichever of these two dates is later.

If your claim is approved, the EPA will notify you that you are not subject to this Order. The EPA expects to provide such notification within 45 days of the effective date of this Order.

B. Step 2: Submit an Initial Response

A recipient must develop information in response to the Order consistent with Option 1, unless they meet the requirements to respond using Option 2 or 3. See **Unit III** to review the deadlines for this Order. You must respond to the Order by selecting the response option(s) in the CDX application.

Option 1: Develop the Information

Use this option if you are conducting the testing on your own or as part of a consortium for any or all of the testing required of your company as provided in **Unit V.**

Manufacturers who are required to test a chemical substance or mixture pursuant to a TSCA section 4 order are also required to pay a fee (see **Unit VII**).

For details on the steps of this response option, see **Unit VI.** If you're a member of a consortium, see **Unit VIII**.

As applicable, it is imperative that you consult with consultants, laboratories, and any other entities necessary for conducting the testing required by this Order as soon as possible. Untimely extension requests will not be granted, and the EPA requires supporting documentation to demonstrate that consultations with laboratories was timely (e.g., correspondence with the laboratory).

Note that the EPA requires a Pre-Draft Study Plan Check-in where you must identify the laboratory selected. See **Unit VI.B.** for more details about this requirement.

Outside of extenuating circumstances, extension requests must be made 15 days before a draft or final study plan is due. More information is available in **Unit III.C**.

For more information on this Order's required tests, required protocols/methodologies, and deadlines for submission of test reports see **Unit V and Appendix E**.

Option 2: Submit Existing Information

Use this option to submit an existing study and/or other scientifically relevant information that you believe the EPA has not considered, along with supporting rationale that explains how the submittal(s) meets part or all of the information described as necessary in **Unit II**. If the EPA determines that the submitted information satisfies one or more data requirements identified by this Order, the Agency will extinguish any associated test requirement(s).

The EPA's determination regarding whether the study and/or other relevant information satisfies part or all of the testing requirements or obviates the need for the information described as necessary in **Unit II** will be based on the weight of the scientific evidence from all relevant information reasonably available to the Agency. The Agency will notify you of its determination through CDX. If the Agency determines that the study and/or other scientifically relevant information satisfies the need in lieu of the testing required in this Order, and the original testing requirement is no longer needed, the EPA will extinguish those testing obligations from this Order that are no longer necessary, with respect to the appropriate recipients of this Order. If the study was your only testing obligation under the Order, all your obligations under this Order will be extinguished upon notification by the Agency.

If the EPA determines that the study and/or other scientifically relevant information does not satisfy that need, you must modify your response in the EPA's CDX portal to choose one of the other response options in Unit **IV** (1) within 20 calendar days of being notified by the EPA, or (2) by the deadline for the response as provided by the order in **Unit III.A**, whichever of these two dates is later.

This option is intended only for information you believe the Agency may not have considered that would directly satisfy the EPA's data need. This option does not apply to alternative interpretations of information already discussed in this Order, or other arguments why the EPA does not need new information unless such arguments are supported by data that you believe the Agency may not have considered. Any submission that does not depend upon new information does not extend the deadlines in the Order, regardless of whether the EPA informs the submitter that it does not satisfy the data need. If the EPA believes that existing information presented in the submission was included only for the purpose of qualifying for this option and could not reasonably be expected to obviate the need for the applicable testing requirement, the Agency will determine that the submission does not qualify for the option. Regardless of when the Agency informs the Order recipient that the submission does not qualify under the option, the applicable deadlines are not extended.

Note that the submission of existing information will not extend the deadline for the draft study plan submission for that testing requirement unless the existing information is submitted within 30 days of the effective date of the Order and the EPA does not respond within 45 days of the effective date of the Order. Thus, failure to submit existing information prior to the 30-day deadline will result in a need to submit a draft study plan by the 125-day deadline. See Unit **III.B** for information on the potential automatic extension of deadlines.

Option 3: Request an Exemption

Any person required by this Order to conduct tests and submit information on a chemical may apply for an exemption from a requirement of the Order to conduct testing (see TSCA section 4(c) (1)). An exemption is not a removal of all responsibility from this Order. Rather, the exemption is a means by which an entity may forgo conducting the required testing if another person has submitted or will submit such testing under Section 4 of TSCA. If an entity believes that they should not be subject to the Order, it should have provided such a response during the Identification Response (see **Unit IV.A**).

A person who is granted an exemption may be required to reimburse the person(s) who submit(s) the required testing or another exemption holder who reimbursed a data submitter. See **Appendix B** for further details regarding cost sharing.

The EPA will grant a request for exemption from the requirement to conduct tests and submit information on a chemical substance if:

1. Information on the subject chemical or an equivalent chemical has been submitted in accordance with a rule, order, or consent agreement under TSCA section 4(a), or is being developed in accordance with such a rule, order (including this Order), or consent agreement, and

2. Submission of information by the exemption applicant would be duplicative of this information.

An exemption request must be submitted through the CDX portal and contain the following:

1. This Order number, the chemical identity, and the CAS Registry No. of the test substance subject to this Order on which the application is based.

2. The specific testing requirement(s) from which an exemption is sought.

3. The basis for the exemption request when another company(ies) has/have submitted the information or is/are developing information for the subject chemical or an equivalent chemical pursuant to a TSCA section 4(a) rule, order, or consent agreement. Your request must identify the company(ies) that submitted or is/are developing the information. Note that you may have an obligation to reimburse any companies that complied with the requirement to submit information to the EPA.

4. The chemical identity of the equivalent chemical (the test substance in the information submitted or being developed) on which the application is based.

5. The equivalence data (chemical data or biological test data intended to show that two substances or mixtures are equivalent (see Appendix A)) if data on an equivalent chemical is being submitted.

6. The name, mailing address, telephone number, and e-mail address of applicant.

7. The name, mailing address, telephone number, and e-mail address of appropriate individual to contact for further information.

8. A Statement of Financial Responsibility: The following sworn and signed statement (additionally, this statement must be notarized if the signatory is not the person submitting the response in CDX) must accompany each request for an exemption:

   > "I understand that if this application is granted, I must pay fair and equitable reimbursement to the person or persons who incurred or shared in the costs of complying with the requirement to submit information that obviates the need for the exemption holder to develop new, duplicative, information."

The EPA's grant of an exemption is conditional upon the completion of the required tests according to the specifications of this Order (or other applicable rule, order, or consent agreement), including any

modifications approved by the EPA. If the Agency subsequently determines that equivalent data has not been submitted in accordance with the applicable rule, order, or consent agreement, the Agency will provide notice through CDX of its preliminary decision to terminate the exemption. Within 30 days after receipt of such notice, the exemption holder may submit information in the CDX portal to either rebut the EPA's preliminary decision to terminate the exemption or notify the EPA of its intent to develop the required information pursuant to the specifications established in this Order and any modifications approved by the EPA. If the exemption holder submits information to rebut the EPA's preliminary decision to terminate the exemption, then the EPA will provide the exemption holder an opportunity to request a hearing prior to issuing a final decision to terminate the exemption. Following the receipt of information to rebut the EPA's preliminary decision and any subsequent hearing, the EPA will render a final decision on whether to terminate the exemption, taking into account information submitted to rebut the EPA's preliminary decision and information presented at any hearing, as applicable. The Agency may, at its discretion, make use of procedures and standards applicable to exemptions regarding TSCA Section 4 rules, contained in 40 CFR part 790, subpart E.

If an exemption holder receives the Agency's preliminary decision to terminate the exemption and does not submit information to rebut that preliminary decision or request a hearing, or if an exemption holder receives the Agency's final decision to terminate the exemption following the submission of information to rebut that preliminary decision or a hearing, the exemption holder must resubmit a response in accordance with one of the options described in **Unit IV.B** of this Order within 30 calendar days of receipt of the Agency's decision to terminate the exemption, including as applicable the information required under **Unit V** of this Order. Failure to timely resubmit the response will constitute a violation of this Order and of TSCA section 15(1). Should the EPA terminate the exemption, a draft study plan will be due 30 days from the termination, with the final study plan being due 60 days from the termination.

If the EPA extinguishes a testing obligation pursuant to **Unit IV.B.2** of this Order (submission of existing information), the corresponding exemption will be extinguished, as the exemption will no longer be necessary. In such a situation, companies who requested an exemption from that specific testing obligation are not required to reimburse the company that submitted existing information.

As explained in **Appendix B** on Cost Sharing, persons who receive exemptions from testing have an obligation to reimburse the person(s) who perform the required testing and submit the required information for a portion of the costs incurred in complying with the requirement to submit such information, and any other person required to contribute to a portion of such costs. Normally, this is worked out by the parties involved following the EPA's notification that the testing requirement has been satisfied, without the involvement of the EPA. However, if agreement cannot be reached on the amount or method of reimbursement, and the company who is entitled to reimbursement requests in accordance with the procedures in **Appendix B** that the EPA order reimbursement, the Administrator shall order the person granted the exemption to provide fair and equitable reimbursement. See TSCA section 4(c).

V. OVERVIEW OF TESTING REQUIRED BY THIS ORDER

This unit applies to Option 1: Develop the Information and Option 2: Submit Existing Information (**Units IV.B.1** and **IV.B.2**).

Where the required protocol is an EPA guideline, the guideline is available on the EPA OCSPP Test Guideline website (USEPA, 2015) or from the National Technical Information Service (NTIS), Attn: Order Desk, 5285 Port Royal Road, Springfield, VA 22161 (tel: 703-605-6000). This Test Guideline website also provides information on OECD guidelines, alternatively available via OECD Guidelines for the Testing of Chemicals (OECD, 2018a). **Appendix E** provides additional sources for guidelines associated with specific testing.

The EPA reserves the right to extinguish specific testing obligations where existing information subsequently comes to the Agency's attention that in the EPA's scientific judgment obviates the need for specific test data required under this Order. Additionally, the EPA may extinguish testing requirements due to other reasons (e.g., testing becomes infeasible due to previously unforeseen technical considerations), in the discretion of the Agency.

See **Appendix E** for details on the required test protocols.

A. Overview of Test Requirements

HFPO-DAF is a soluble, volatile liquid. Therefore, oral, dermal, inhalation, and ocular routes of exposure are relevant. This chemical has existing inhalation, oral, and dermal toxicity data (Table F1). These available studies were used to inform the testing requirements in this order. Physical-Chemical Properties

Physical-chemical property testing

Physical-Chemical property testing includes the following:

- Melting Point/Melting Range (**OECD 102 (1995)**) (OECD, 1995b)
- Boiling Point (**OECD 103 (1995)**) (OECD, 1995c)
- Vapor Pressure (**OECD 104 (2006)**) (OECD, 2006)
- Water Solubility (**OECD 105 (1995)**) (OECD, 1995a)
- Determination of pH, Acidity and Alkalinity (**OECD 122 (2013)**) (OECD, 2013)
- Hydrolysis as a Function of pH (**OECD 111 (2004)**) (OECD, 2004b)

***In vitro* health effects testing**

In vitro health effects testing includes the following (see explanation in **Unit II.D.2** and **Figure 1**, below on which tests may be required):

- In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method (**OECD 431 (2019)**) (OECD, 2019)
- In Vitro Membrane Barrier Test Method for Skin Corrosion (**OECD 435 (2015)**) (OECD, 2015b)

- In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (**OECD 439 (2021)**) (OECD, 2021b)
- Defined Approaches on Skin Sensitization (**OECD 497 (2021)**) (OECD, 2021a) (OECD, 2021a)
- Skin Absorption: In Vitro Method (**OECD 428 (2004)**) (OECD, 2004c)
- Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (**OECD 437 (2020)**) (OECD, 2020a)
- Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification (**OECD 492B (2022)**) (OECD, 2022)
- Bacterial Reverse Mutation Test (**OECD 471 (2020)**) (OECD, 2020b)
- In Vitro Mammalian Chromosomal Aberration Test (**OECD 473 (2016)**) (OECD, 2016a)
- In Vitro Mammalian Cell Micronucleus Test (**OECD 487 (2016)**) (OECD, 2016b)
- In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene (**OECD 490 (2016)**) (OECD, 2016c)

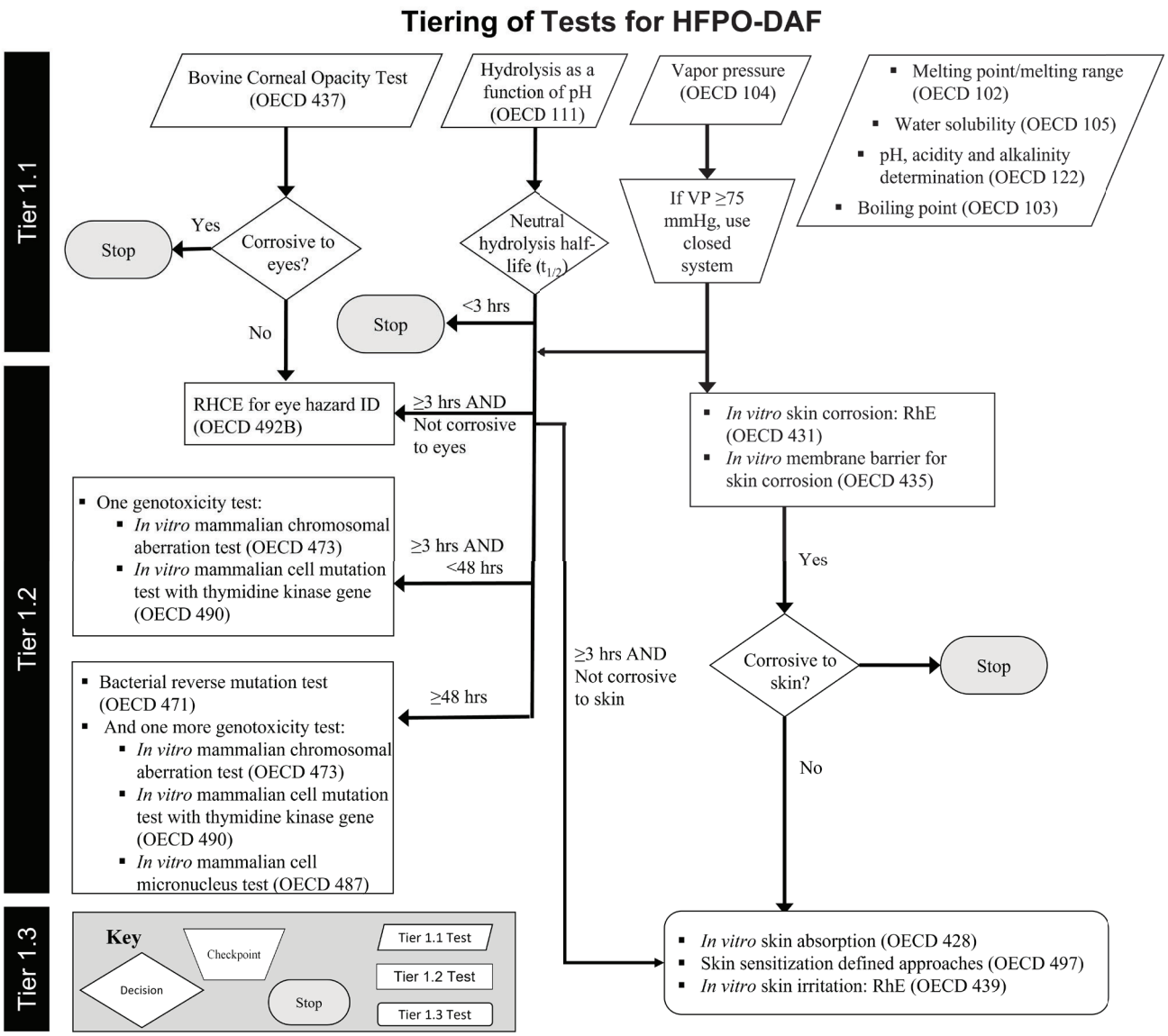

Figure 1. Tiering of tests in the Order. In this order, Tier 1 (non-vertebrate testing) has been broken into sub-tiers (Tiers 1.1, 1.2, and 1.3) because the results of earlier Tier 1 tests need to be known before study plans can be developed for later tests. Each sub-tier is a checkpoint where the Agency and the companies subject to this Order will confer regarding the design of later studies. Tier 1.1 tests are shown in parallelograms, Tier 1.2 tests in rectangles, and Tier 1.3 tests in rounded-corner rectangles. Decision points are in diamonds. Note: If the experimental vapor pressure (VP) ≥ 75 mmHg, then Tier 1.2 tests may need to be run in a closed system to prevent loss of test article from the system and/or analytical measurements of test article concentration should be taken at the beginning and end of the experiment (including a cell-free control where applicable) to account for evaporative losses; losses should be kept to <50% during the course of testing otherwise the results will be considered invalid.

The hydrolysis as a function of pH is important for several reasons, including but not limited to: 1) it is a key parameter when assessing route-specific exposure pathways (i.e., inhalation, oral, dermal) and extrapolating between routes; 2) it is a measure of stability in environmental media (e.g., drinking water, air); 3) it is relevant to the design of later *in vitro* tests carried out in aqueous media (e.g., eye irritation,

genotoxicity); 4) rapid hydrolysis to HFPO-DA (a GenX substance) may determine whether subsequent testing is needed or if read-across to HFPO-DA effects is appropriate. The tiered testing rules are constructed in a way to avoid loss of more than 50% of the parent compound HFPO-DAF due to hydrolysis during the course of *in vitro* testing in aqueous media, which may cause a false negative result due to deactivation of the test chemical.

Skin corrosion tests are required to be run before the skin sensitization, absorption, and irritation tests. If a chemical causes physical breakdown of the skin, there is no reason to run the latter tests as they will give an invalid result. Likewise, the Bovine Corneal Opacity test is run before the Reconstructed Human Cornea-like Epithelium (RHCE) test. If HFPO-DAF is corrosive to eyes, as determined in the Tier 1.1 test, the RHCE test will not be required.

B. DEADLINES FOR REQUIRED TESTING PROTOCOL(S)/METHODOLOGY(IES)

For Tier 1.1 testing, as discussed in the table in **Unit III.A**, draft study plans and final study plans are due 125 and 170 days after the effective date of the Order, respectively. The final test reports for Tier 1.1 tests and all testing milestones for Tier 1.2 are provided in the table below. Following receipt of the Tier 1.1 test reports, the EPA will provide notification as to how certain parameters of Tier 1.2 testing should be conducted. Similarly, deadlines associated with draft study plans, final study plans and test reports for Tier 1.2 testing will commence upon the EPA's confirmation that the review of the Tier 1.1 test reports is completed. See the table below for more information.

Deadlines that fall on a weekend or holiday will remain and will not be extended to the next weekday.

Final Test Report Deadline

Test Names	Protocols/Methodologies	Deadlines to Submit Tier 1.1 Final Test Reports and Tier 1.2 Study Plans and Final Test Reports
Required Physical/Chemical Properties		
Tier 1.1: Melting Point/Melting Range	OECD 102 (1995)	365 days after effective date of the Order
Tier 1.1: Boiling Point	OECD 103 (1995)	365 days after effective date of the Order
Tier 1.1: Vapor Pressure	OECD 104 (2006)	365 days after effective date of the Order
Tier 1.1: Water Solubility	OECD 105 (1995)	365 days after effective date of the Order
Tier 1.1: Determination of pH, Acidity and Alkalinity	OECD 122 (2013)	365 days after effective date of the Order
Tier 1.1: Hydrolysis as a Function of pH	OECD 111 (2014)	390 days after effective date of the Order
To pursue discussions with the EPA to combine aspects of the Tier 1.2 or Tier 1.3 tests, Order recipients must initiate discussion with EPA within 30 days of submitting the final test report for the Tier 1.1 or Tier 1.2 tests, respectively.		
Required Health Effects Dermal Route		
Tier 1.2: In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method	OECD 431 (2019)	446 days after EPA notification to proceed with the Tier 1.2 Testing
Tier 1.2: In Vitro Membrane Barrier Test Method for Skin Corrosion	OECD 435 (2015)	418 days after EPA notification to proceed with the Tier 1.2 Testing

Tier 1.3: In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method	OECD 439 (2021)	266 days after EPA notification to proceed with the Tier 1.3 Testing
Tier 1.3: Defined Approaches on Skin Sensitisation	OECD 497 (2021)	227 days after EPA notification to proceed with the Tier 1.3 Testing
Tier 1.3: Skin Absorption: In Vitro Method	OECD 428 (2004)	255 days after EPA notification to proceed with the Tier 1.3 Testing
Health Effects Ocular Route		
Tier 1.1 Bovine Corneal Opacity Test	OECD 437	238 days after the effective date of the Order
Tier 1.2: Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification	OECD 492B (2022)	199 days after EPA notification to proceed with the Tier 1.2 Testing
Health Effects Mechanistic		
Tier 1.2: Bacterial Reverse Mutation Test	OECD 471 (2020)	233 days after EPA notification to proceed with the Tier 1.2 Testing
One of the following (dependent upon hydrolysis half-life):		
Tier 1.2: In Vitro Mammalian Chromosomal Aberration Test	OECD 473 (2016)	323 days after EPA notification to proceed with the Tier 1.2 Testing
Tier 1.2: In Vitro Mammalian Cell Micronucleus Test	OECD 487 (2016))	294 days after EPA notification to proceed with the Tier 1.2 Testing
Tier 1.2: In Vitro Mammalian Cell Gene Mutation Tests Using Thymidine Kinase Gene	OECD 490 (2016))	323 days after EPA notification to proceed with the Tier 1.2 Testing

VI. REQUIREMENTS OF RESPONSE OPTION 1: DEVELOP THE INFORMATION REQUIRED BY THIS ORDER

A. OVERVIEW

The draft study plan for Tier 1.1 testing is due to the EPA **125 days** after the effective date of this Order. The EPA will then review the draft study plan and provide input to ensure adequacy of the final study plan. For the final study plans and the final test reports, see the Deadlines for Responses, Study Plans, and Test Reports table in **Unit III.A**.

All testing described in **Unit V** must be conducted in accordance with the Good Laboratory Practice (GLP) standards in 40 Code of Federal Regulations (CFR) part 792, as specified in the CFR on the Effective Date of this Order. You must provide a statement of compliance with these GLP standards when submitting information to the EPA pursuant to this Order.

Deviations from the test guideline or specific GLP standards are allowed if the EPA ultimately approves them in the final study plan. Deviations must be submitted prior to or be included in the draft study plan. A justification is required for each deviation. Justifications should demonstrate that, despite the deviation from the given test guideline or GLP standard, that data integrity, control of bias, and study quality will be maintained with similar effectiveness. Any requested deviations and corresponding justifications must be included in the draft study plan for the EPA's consideration and, if approved, described in the test report.

Once the EPA has completed its review of the submitted test reports and accepts the information as fully complying with your testing obligations under this Order, the Agency will notify you.

B. Pre-Draft Study Plan Check-in Requirements

If you choose to develop the required information to comply with this Order, you must provide a Pre-Draft Study Plan Check-in to the EPA by email, in which you must identify the laboratory selected for each testing requirement. The test sponsor must submit a documented contract or agreement between test sponsor and laboratory to develop the study plan and/or conduct the testing, e.g., quote, proposal, or statement of work. If such a document contains CBI, please do not submit the document via email and instead request alternate instructions to submit the CBI document to the EPA.

If the Test Sponsor believes an alternative method or deviation to the protocol(s)/methodology listed in the Order is necessary, the Pre-Draft Study Plan Check-in may also serve as an opportunity for the Test Sponsor to provide the proposed alternative for the EPA to comment on prior to the Draft Study Plan deliverable.

The EPA will provide by email confirmation that the Pre-Draft Study Plan Check-in is acceptable or not.

C. Draft and Final Study Plan Requirements

1. Study Plan Requirements for All Categories of Tests

If you choose to develop the required information to comply with this Order, you must obtain and review the required protocols/methodologies. **Unit V and Appendix E** provide the protocols/methodologies that must be followed to perform each required test.

If questions and/or issues arise during Study Plan development, the EPA encourages questions/comments be submitted along with the Study Plan submission in accordance with the draft study plan deadline. If the EPA's review of the draft study plan that includes questions/comments is delayed, the procedure outlined in **Unit III.B** will be followed for automatic extensions of the study plan.

In addition to requirements provided in **Appendix E** for a given test required by this Order, the Study Plans must contain the following information:

1. This Order number, excluding the unique 6-digit company number using X's in place of the unique company number so as to protect each company's private access to the reporting module via Central Data Exchange (CDX). For example, if your Order number is TO-2020-0000-438435-00-0 then provide this number in the Study Plan: TO-2020-0000-XXXXXX-00-0.

2. Name of test to be covered by the test protocol/methodology.

3. The name/number of the protocol/methodology identified in this Order which you intend to follow, a copy of the identified protocol/methodology with your proposed modifications, or a copy of the alternate protocol/methodology you propose to use. Justification(s) must be provided for any deviation from the protocol/methodology identified in this Order.

4. The identity of and supporting data on the chemical substance to be tested including physical constants, spectral and chromatographic data, chemical analysis, and stability under test and storage, and test conditions required by the protocol. A Certificate of Analysis of the test substance must be provided.

5. The sampling and analytical method that will be used. Submitted study plans without the sampling and analytical method will not be reviewed by the EPA and will not be in compliance with the study plan submission requirement.

6. A description of the preparation and processing of samples that will be done before sampling and during sampling, including equilibration, weighing, calibration, test conditions (temperature, humidity), number and type of samples, and identification of equipment and accessories used (make, model, size/capacity, and operating conditions), including the specific sampling media and sampling instruments that will be used.

7. A description of all quality assurance and quality control protocols used.

8. The name(s) and address(es) of the company(ies) sponsoring the test and whether they comprise a testing consortium.

9. The name(s), mailing address(es), phone number(s), and e-mail address(es) of the appropriate individual(s) for the EPA to contact concerning the planned test.

10. The name of the testing facility and the names, mailing addresses, telephone numbers, and email addresses of the testing facility's administrative officials, study director/project managers and quality control officer responsible for ensuring the testing protocol follows appropriate quality assurance and quality control procedures.

11. Include a master schedule, which includes the start and completion dates for the study, as well as "intervals adequate to ensure the integrity of the study" at which to inspect each study. 40 CFR 792 describes what constitutes an "adequate interval". The test sponsor must provide updates to the EPA on the status of the study pursuant to such intervals. The EPA may require shorter intervals/more frequent "check-ins" if the Agency believes the study completion date could be compromised.

12. If pilot/preliminary testing is necessary, start and end dates for the pilot/preliminary testing as well as for the full study.

13. Specifically for final study plans, written confirmation that, the laboratory is able to allocate resources necessary to conduct the testing, along with any constraints regarding the availability of such resources.

2. Modifying a Required Protocol/Methodology in a Draft Study Plan

The draft study plan must include the required protocols/methodologies outlined in **Unit V.A** and **Appendix E**. If you believe modifications of these required protocols/methodologies are necessary, you should propose the modification in the draft study plan and submit to the Agency with request for the

Agency to consider the modifications. Any consultation regarding modifications to the required protocols/methodologies will not extend the deadline for submission of the draft study plan.

Any submitted requests for modifications of the required protocols/methodologies must include a detailed description of the proposed modification as well as a detailed description of the justification and reasoning for such modifications. Requests for modifications of protocol/methodology or the use of an alternate protocol/methodology must discuss why such changes are appropriate and whether they could alter the validity of the study. The rationales do not have to be listed in a separate document in the study plan if they are included and clearly identified in the relevant section of the study plan describing the protocols/methodologies.

If the EPA has concerns about the requested protocol/methodology or your requested modifications of the required protocol/methodology, the Agency will inform you of concerns that must be addressed before the EPA will approve your study plan. The EPA has 15 days from the deadline for the study plan to respond. For each day following this period that the EPA does not respond, the EPA will extend the deadline for the final study plan by one day (see **Unit III.B**).

3. The EPA Review of Study Plans and Final Test Reports

The EPA will not conduct a substantive review of any draft study plan that does not meet the requirements as provided in **Unit VI.C** and **Appendix E**. Such a submission does not constitute meeting the deadline for the draft study plan submission. **Unit III** provides information on deadlines and the EPA response timelines.

Submitting a draft study plan, final study plan, and final test report which do not fully comply with the terms of this Order and by the deadlines provided in **Unit III** may result in a violation of TSCA section 15.

a. Study Plans

Following review of a draft study plan submission, the EPA will indicate what modifications, if any, are required and must be incorporated into the final study plan. Accompanying a proposed final study plan submission, the submitter must provide a clean and red-lined version. The red-lined version will indicate the changes incorporated into the final study plan as compared with the prior study plan submission.

If the EPA requires modifications to a submitted draft study plan, the Agency may elect to provide a line-by-line list of comments that must be addressed and corrected before the final study plan will be approved. If the submitter receives a line-by-line list of comments, the submitter must address each individual comment and include this in their response to the Agency along with the proposed final study plan.

Prior to initiating any test, the Company/Consortium must first address the EPA's input on the study plan and receive the EPA's acceptance of the final study plan.

The EPA's acceptance of a final study plan does not constitute pre-acceptance of any future test results. If testing conducted according to a requested protocol/methodology or requested modifications of the required protocol/methodology is initiated prior to the EPA approval, that testing will not satisfy the requirements of the Company under this Order.

If, after the final study plan has been approved or after testing is underway, you wish to make a modification to an identified protocol/methodology or use a different protocol/methodology, you must submit a request to the EPA to make these changes in your study and you must still meet the deadlines set out in **Unit V** and **Appendix E** for the relevant test or request an extension (see **Unit III.C**), if needed.

Following the approval of a final study plan, the EPA requires that the company/consortium provide email updates on the status of the associated testing pursuant to check-in intervals as provided in the study plan. These updates must be provided to both the EPA Order manager as well as tscatestorders@epa.gov. Further, should any deviation(s) arise that may prevent submission of the final test report by the applicable deadline, the company/consortium must notify the EPA immediately. See **Unit VI.B** for check-in requirements.

Note that submitting questions to the EPA regarding study plan requirements will not extend the deadline for a study plan submission.

b. Final Test Reports

Once the EPA has completed its initial review and accepted data for all test reports subject to this Order for a given testing requirement, the EPA will notify the designated contact for the company subject to this Order and any designated consortium that this testing requirement has been satisfied, which in turn will close out the testing requirement of this Order for the companies and participants in any consortium subject to this Order. Failure to file a final test report meeting all the requirements in this Order by the deadline in **Unit V** is a violation of TSCA. Your final test report must be submitted along with the data in the associated OECD harmonized template format, if available. OECD harmonized templates can be located at the OECD Harmonized Templates webpage(OECD, 2018b):

a. Melting Point/Melting Range OECD 102 (1995)

- *Harmonized Template Identifier:* OHT 2 (Melting point/freezing point)

b. Boiling Point OECD 103 (1995)

- *Harmonized Template Identifier:* OHT 3 (Boiling point)

c. Vapor Pressure OECD 104 (2006)

- *Harmonized Template Identifier:* OHT 7 (Vapor pressure)

d. Water Solubility OECD 105 (1995)

- *Harmonized Template Identifier:* OHT 8 (Water solubility)

e. Determination of pH, Acidity and Alkalinity OECD 122 (2013)

- *Harmonized Template Identifier:* OHT 20 (pH)

f. Hydrolysis as a Function of pH OECD 111 (2004)

- *Harmonized Template Identifier:* OHT 25 (Hydrolysis)

g. *Skin Irritation/Corrosion Tests:*

- *In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method OECD 431 (2019)*
- *In Vitro Membrane Barrier Test Method for Skin Corrosion OECD 435 (2015)*
- *In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method OECD 439 (2021)*
    - *Harmonized Template Identifier:* OHT 64 (Skin irritation/corrosion)

h. *Defined Approaches on Skin Sensitization OECD 497 (2021)*

- *Harmonized Template Identifier:* OHT 66-1 (Skin sensitization)

i. *Skin Absorption: In Vitro Method OECD 428 (2004)*

- *Harmonized Template Identifier:* OHT 59 (Dermal absorption)

j. *Eye Irritation/Corrosion Tests:*

- *Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage OECD 437 (2020)*
- *Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification OECD 492B (2022)*
    - *Harmonized Template Identifier:* OHT 65 (Eye irritation)

k. *Genotoxicity tests*

- *Bacterial Reverse Mutation Test OECD 471 (2020), and one of the following (dependent on hydrolysis half-life):*
    - *In Vitro Mammalian Chromosomal Aberration Test OECD 473 (2016)*
    - *In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene OECD 490 (2016)*
    - *In Vitro Mammalian Cell Micronucleus Test OECD 487 (2016)*
    - *Harmonized Template Identifier: OHT 70 (Genetic toxicity in vitro)*

VII. FEES FOR SUBMITTING INFORMATION

Per 40 CFR § 700.45, and taking into account the inflation adjustment that went into effect on January 1, 2022, the Test Order fee is $11,650 to be split evenly among the manufacturers who are required to conduct any of the test(s) subject to the Test Order (accounting for small business considerations). Processors are not subject to this fee. Manufacturers who submit existing information or receive an

exemption in compliance with this Order and are not required to conduct any of the test(s) subject to the Test Order are also not subject to this fee.

Small businesses may be subject to no more than 20% of the amount of the applicable fee. A company may qualify for a "small business concern" discount if their total number of employees is at or below the maximum allowed in the final rule for that company's North American Industry Classification System (NAICS) code (see 40 CFR 700.43). In order for an entity to qualify as a "small business concern," its number of employees shall not exceed the size standard for the applicable industry. When calculating the number of employees, the company must include the employees of all parent and subsidiary companies within the corporate chain. Please note that small business fees are only applicable to qualifying small businesses who are either not associated with a consortium or associated with an all-small business consortium. See the TSCA User Fees webpage (USEPA, 2021e) for more information.

A company can identify itself as a small business when responding to this Order via the CDX application. The "small business concern" discount will be included in the determination of company-specific invoices for the distribution of the $11,650 fee across all manufacturers conducting testing for the given Test Order. Where a consortium is responsible for the fee for its members for purposes of this Order, and at least one of the members is not a small business, the EPA does not apply a "small business concern" discount to the portion of the $11,650 distributed to the consortium.

Fees for Test Orders under TSCA section 4 will be invoiced electronically by the EPA. Invoice notices will be populated into the specific user's "Copy of Record" screen in CDX and will contain a button that will initiate the payment process. When an invoice is generated, notification e-mails will be sent to the user's CDX inbox and the e-mail address associated with the relevant CDX account. Payment information will be collected in CDX and then submitted to Pay.gov for processing.

Note that there are many fees associated with TSCA-related activities. See the TSCA Fees table webpage (USEPA, 2021f) for more information. The TSCA section 4 Test Order fee is separate from these fees. A company's inclusion in or exclusion from other TSCA fees is unrelated to that company's status with regards to TSCA section 4 Test Order fees.

Pursuant to 40 CFR § 700.45, the applicable fee shall be paid in full no later than 120 days after the effective date of the Order. Should the EPA invoice the fee more than 90 days after the effective date of the Order, payment will be due within 30 days of such invoicing.

VIII. INSTRUCTIONS IF YOU CHOOSE TO PARTICIPATE IN A CONSORTIUM

If you choose to form or join a consortium to share in the cost of developing the required information, you (as well as the other Order recipients who are participants in the consortium) must, individually in the CDX portal, state your intention to participate in a testing consortium for each specific chemical and specific test. Consortium participants must individually respond in the CDX portal with their intent to participate before consortium leads are able to add them to the consortium. See the CDX instructions in the section titled "Join a Consortium Response to Order" in the CDX Section 4(a)(2) of the Toxic Substances Control Act User Guide (USEPA, 2022a).

In addition, the designated lead for the consortium must submit a consortium response to the EPA in the CDX portal. The response must confirm the formation of the consortium, identify its member companies, and list the testing obligations that the consortium plans to fulfill on behalf of each company

by indicating each specific test. The response must also include contact information for the designated lead of the consortium, who must be domiciled in the United States. The designated lead for the consortium must submit the response and required information on behalf of the consortium and its member companies by the deadlines listed in **Unit III.A**. Submissions made on behalf of the consortium must be in accordance with instructions in **Appendix C**. Note that a consortium lead need not be a recipient of an Order; other entities (such as trade organizations) may act as a lead and submit the information required under this Order. After the results of the last required test of this Order are submitted and the EPA accepts the information as complying with this Order, or the EPA accepts existing information submitted by the Consortium, the EPA will provide notification of compliance with this Order to this Order's recipients and the designated lead of the consortium.

Even if you agree to jointly submit the information as part of a consortium, each Order Recipient is still required to comply with this Order (with the study plan and results being submitted by the consortium) and is individually liable in the event of any failure to comply with this Order. If the consortium fails to submit the information or meet any of the requirements of this Order on the recipient's behalf, the recipient will be in violation of this Order unless the recipient submits the required information or meets the requirement individually.

The Agency has provided a list of the manufacturers and processors that have received this Order at the top of this Order in the Summary Information section. This list of manufacturers and processors can be used to help Order Recipients form a consortium to jointly develop information, consolidate testing and share the cost of testing. Information on cost sharing is provided in **Appendix B**.

IX. CONFIDENTIALITY

Under TSCA section 14(b)(2), health and safety studies submitted under TSCA and data reported to or otherwise obtained by the Administrator from health and safety studies are not protected from disclosure if the studies and data concern a chemical that is offered for commercial distribution, or for which testing is required under TSCA section 4 or notification is required under TSCA section 5. However, TSCA section 14(b)(2) does not apply to information that discloses processes used in the manufacturing or processing of a chemical substance or mixture or, in the case of a mixture, the portion of the mixture comprised of the chemical subject to this Order. Therefore, some or all of the information in the studies required to be submitted under this Order might not be eligible for TSCA confidential business information (CBI) protections.

The EPA has recently promulgated a rule governing assertion and treatment of confidentiality claims regarding submissions under TSCA, contained in a new section 703 of Title 40 of the Code of Federal Regulations. This rule is effective on July 31, 2023. Assertion of CBI claims in submissions made on or after this date is governed by this rule. Assertion of claims before this date, while not subject to this rule, will in most cases be similarly handled by the EPA. The information below addresses some of the topics contained in the rule.

Information submitted under TSCA that you wish to have the EPA protect as confidential business information (CBI) must be clearly identified as such when submitted. For sections of the report that are claimed as CBI, the report must be accompanied by a sanitized version of the report only removing the specific information claimed as CBI. A sanitized test report that redacts all or most of the study may be rejected by the EPA as not satisfying the requirements of this Order.

When claiming information as CBI, you must certify to the following:

> "I hereby certify to the best of my knowledge and belief that all information entered on this form is complete and accurate.
>
> I further certify that, pursuant to 15 U.S.C. § 2613(c), for all claims for confidentiality made with this submission, all information submitted to substantiate such claims is true and correct, and that it is true and correct that
>
> (i) My company has taken reasonable measures to protect the confidentiality of the information;
>
> (ii) I have determined that the information is not required to be disclosed or otherwise made available to the public under any other Federal law;
>
> (iii) I have a reasonable basis to conclude that disclosure of the information is likely to cause substantial harm to the competitive position of my company; and
>
> (iv) I have a reasonable basis to believe that the information is not readily discoverable through reverse engineering.
>
> Any knowing and willful misrepresentation is subject to criminal penalty pursuant to 18 U.S.C. § 1001."

In addition, information claimed as CBI must be substantiated upon submission, with the exception of information described in TSCA Section 14(c)(2). See guidance for substantiating CBI claims (USEPA, 2021g).

Failure to follow the statutory requirements for asserting and substantiating a CBI claim may result in the information being made available to the public without further notice to the submitter.

When a claim of CBI is asserted for certain information under TSCA section 14, the Administrator will generally protect that information from disclosure for 10 years (*e.g.*, unless the protection from disclosure is withdrawn by the person that asserted the claim), whereupon the claim must be reasserted and re-substantiated if the submitter wishes to maintain the CBI claim. In certain cases, the EPA may review claims prior to the expiration of the 10-year period.

Under circumstances stated in TSCA section 14(d), the EPA may disclose information claimed as CBI to other persons including, for example, Federal and State authorities, health and environmental professionals, poison control centers, and emergency responders.

X. CONSEQUENCES OF FAILURE TO COMPLY WITH THIS ORDER

Failure to comply with any of the requirements in this Order is a violation of TSCA section 15 and could subject you to civil and/or criminal penalties under TSCA section 16, 15 U.S.C. § 2615 as modified by the Federal Civil Penalties Inflation Adjustment Act. Each day that failure to meet the requirements continues constitutes a separate violation.

XI. REFERENCES

The following is a listing of the documents that are generally applicable to this Order. Please note that references, guidance, and information from additional sources could be considered, with the EPA approval, during the development of study plans.

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XII. PAPERWORK REDUCTION ACT NOTICE

This collection of information is approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. § 3501 et seq. (OMB Control No. 2070-0033). Responses to this collection of information are mandatory under the Toxic Substances Control Act (TSCA), 15 U.S.C. § 2601 et seq. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The public reporting and recordkeeping burden for this collection of information is estimated to be 137 hours for the average response on a per-chemical basis. Under the PRA, burden is defined at 5 CFR 1320.3(b). Send comments on the Agency's need for this information, the accuracy of the provided burden estimates and any suggested methods for minimizing respondent burden to the Regulatory Support Division Director, U.S. Environmental Protection Agency (2821T), 1200 Pennsylvania Ave., NW, Washington, D.C. 20460. Include the OMB control number in any correspondence. Do not send the completed form to this address.

XIII. FOR FURTHER INFORMATION CONTACT

For technical information contact: TSCATestOrders@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: TSCA-Hotline@epa.gov.

XIV. SIGNATURE

Under the authority in TSCA Section 4(a)(1), the United States Environmental Protection Agency hereby issues this Order to take effect five days after the date of my signature.

MICHAL FREEDHOFF

Digitally signed by MICHAL FREEDHOFF
Date: 2023.08.15 10:32:43 -04'00'

Michal Freedhoff,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

APPENDIX A - EQUIVALENCE DATA

For purposes of this Order, "equivalence data" means "chemical data or biological test data intended to show that two substances or mixtures are equivalent." 40 CFR § 790.3. Also, when a chemical substance is "equivalent," it means "that a chemical substance is able to represent or substitute for another in a test or series of tests, and that the data from one substance can be used to make scientific and regulatory decisions concerning the other substance," as defined in 40 CFR § 790.3.

If testing under TSCA section 4(a) is required of an equivalent chemical substance, the EPA may grant an exemption from testing to the manufacturer or processor of one substance if the information required under TSCA section 4(a) is submitted or is being developed on the other, and the manufacturer or processor submits the following information to support equivalence with its exemption application:

1. The chemical identity of each chemical substance or mixture manufactured or processed by the applicant for which the exemption is sought. The exact type of identifying data required may be specified in this Order and may include all characteristics and properties of the applicant's substance or mixture, such as boiling point, melting point, chemical analysis (including identification and amount of impurities), additives, spectral data, and other physical or chemical information that may be relevant in determining whether the applicant's substance or mixture is equivalent to the specific test substance.

2. The basis for the applicant's belief that the substance or mixture for which the exemption is sought is equivalent to the test substance or mixture.

3. Any other data which exemption applicants are directed to submit in this Order which may have bearing on a determination of equivalence. This may include a description of the process by which each chemical substance or mixture for which an exemption is sought is manufactured or processed prior to use or distribution in commerce by the applicant.

APPENDIX B – COST SHARING

The EPA encourages Order recipients that are responsible for developing the same information on the same chemical(s) to avoid duplicative testing and share the cost of information development. If a test is conducted according to a final, approved protocol, it is sufficient that the test is conducted once. Two ways to avoid duplicative testing are discussed in this Order. They are forming or joining a consortium, discussed in **Unit VIII**, or requesting an exemption, discussed in **Unit IV.B.3**.

Consortia

Persons that form or join a consortium typically execute an agreement with the other members of the consortium concerning how costs will be shared and how the consortium will operate.

Exemptions

Persons that receive exemptions from testing have an obligation to reimburse the person(s) who perform the testing and submit the required information that is the basis for the exemption for a portion of the costs incurred in complying with the requirement to submit such information, and any other person required to contribute to a portion of such costs. Apportionment of costs is often (and ideally) negotiated between the companies involved, without the EPA participation. The EPA has promulgated regulations that explain how the EPA views fair and equitable reimbursement in the context of TSCA Section 4(a) test rules. In general, those regulations (40 CFR § 791.40 through § 791.52) make a presumption that a person's fair share of the test costs is in proportion to their share of the total production volume of the test chemical over a specified period of time that begins one calendar year before the effective date of the rule and continues up to the latest data available upon resolution of a dispute. While those regulations do not bind the EPA action regarding reimbursement with respect to TSCA Section 4 orders, recipients may wish to consider them as they decide how to share the costs.

If an order recipient has been granted an exemption, and agreement cannot be reached on the amount and method of sharing the cost of developing the information, the person whose information is the basis for the exemption may request that the Administrator order the person(s) granted the exemption to provide fair and equitable reimbursement after considering all relevant factors, including the share of the market and the effect on the competitive position of the person required to provide reimbursement in relation to the person to be reimbursed. See TSCA Section 4(c)(3)(A). Upon receipt of such a request, the EPA will determine fair and equitable reimbursement and issue an order accordingly. The Agency may, at its discretion, make use of procedures and standards applicable to data reimbursement regarding TSCA Section 4 rules, contained in 40 CFR part 791.

APPENDIX C - How to Access the CDX Application and Recordkeeping Requirements

How to Access the CDX Application

The initial response, draft and final study plans, final test reports with underlying data, existing studies, any testing related requests, and all related correspondence must be submitted electronically to the EPA as follows:

1. Submit to the EPA's CDX system. CDX is the point of entry on the Environmental Information Exchange Network (Exchange Network) for submissions to the Agency.

2. The URL for the CDX website is *https://cdx.epa.gov/* which takes you to the CDX homepage.

3. On the homepage you may select "Log in" or, if you haven't already registered, select "Register with CDX."

4. Once you have logged on to CDX, follow the instructions for submitting TSCA Section 4 Order information. To access the instructions, select "Report electronically" on the EPA Assessing and Managing Chemicals under TSCA webpage.

5. The CDX Help Desk is available for data submission technical support between the hours of 8:00 am and 6:00 pm (EST) at 1-888-890-1995 or helpdesk@epacdx.net. The CDX Help Desk can also be reached at 970-494-5500 for international callers. Additionally, CDX Test Order guidance materials are available for users to follow.

The EPA may revise these submission instructions with advance notice, including providing direction to submit certain documents and/or requests via email rather than the CDX application (except for situations where CBI may be involved).

Recordkeeping

You must retain copies of all information documenting your compliance with this Order for ten years. This includes your response and other documents and correspondence submitted to comply with this Order, such as test protocols, testing related requests, final test reports with their underlying data, and any penalties remitted.

APPENDIX D - Order Recipient Selection

This Appendix describes the process by which the EPA identified recipients of this Order. This information is for your use and does not govern the obligations under this Order or the identities of the companies subject to this Order. A recipient of this Order that manufactures or processes the chemical as per the definitions provided in **Unit I.B** is subject to this Order, regardless of the basis on which the EPA identified the recipient.

The EPA queried for companies with known associations with HFPO-DAF from the EPA Chemical Information System (CIS) within the past 15 years that could lead the EPA to the manufacturers and/or processors of HFPO-DAF during the five years preceding the effective date of this Order. The EPA CIS is an internal platform for managing data and reporting submissions under TSCA. Some submission types that are housed in CIS include Chemical Data Reporting (CDR), Pre-manufacture Notifications, and Notice of Activity forms. Based on these such submissions, the EPA has included entities associated with this chemical substance.

APPENDIX E - Specific Requirements and Guidance for This Order

This appendix provides requirements of study plans and test reports for specific testing requirements of this Order.

For information on how the EPA determined the need for testing in this Order, refer to **Unit II.B**.

1. **Physical-Chemical Properties**

Tier 1.1

a. Melting Point/Melting Range OECD 102 (1995); OCSPP 830-7200/OPPT 796.1300/OPP 63-5 (1998)

i. Study Plans

See **Unit VI.C** of the Order for overall requirements for study plans.

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. Harmonized Template OHT 2 (Melting point/Freezing Point)
2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%202%20-%20ENDPOINT_STUDY_RECORD.Melting_v5.2%20-Dec%202018.doc

b. Boiling Point OECD 103 (1995) or OCSPP 830.7220/OPPT 796.1220/OPP 63-6 (1996)

i. Study Plans

See **Unit VI.C** of the Order for overall requirements for study plans.

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. Harmonized Template OHT 3 (Boiling Point)
2. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT-3-endpoint-study-record-BoilingPoint-v6.3-Sept-2020.doc

c. Vapor pressure OECD 104 (2006)

i. Study Plans

See **Unit VI.C** of the Order for overall requirements for study plans.

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

3. Harmonized Template OHT 6 (Vapour Pressure)

4. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%206%20-%20ENDPOINT_STUDY_RECORD.Vapour_v4.2%20-Dec%202018.doc

d. Water Solubility OECD 105 (1995)

i. Study Plans

See **Unit VI.C** of the Order for overall requirements for study plans.

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. Harmonized Template OHT 8 (Water Solubility)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%208%20-%20ENDPOINT_STUDY_RECORD.WaterSolubility_v4.2%20-Dec%202018.doc

e. Determination of pH, Acidity and Alkalinity (OECD 122 (2013))

i. Study Plans

See **Unit VI.C** of the Order for overall requirements for study plans.

1. The test must be performed on the hydrolyzed chemical. HFPO-DAF should be dissolved in water and allowed to hydrolyze before running the test. One potential approach would be to track the change in pH with time and to perform the test once the pH has stabilized.

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. Harmonized Template OHT 20 (Hydrolysis)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2020%20-%20ENDPOINT_STUDY_RECORD.Ph_v8.1%20-Nov%202021.docx

f. Hydrolysis as a Function of pH; (OECD 111, 2004b**)**

i. Study Plans

See **Unit VI.C** of the Order for overall requirements for study plans.

1. Follow the test performance criteria in OECD 111, including 'optional' testing at pH 1.2 for physiological conditions and reporting relevant hydrolysis products including and may not be limited to, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid (aka HFPO-DA, a GenX chemical, CASRN 13252-13-6) and hydrogen fluoride (HF, CASRN 7664-39-3).

2. Applicability and performance dependent on results of vapor pressure and water solubility, as noted in OECD 111.

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. Harmonized Template OHT 25 (Hydrolysis)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2025%20-%20ENDPOINT_STUDY_RECORD.Hydrolysis_v4.3%20-Dec%202018.doc

2. Health Effects: Dermal Route

Tier 1.2

a. In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method (OECD 431 (2019))

This testing identifies the potential corrosivity of a test substance when applied to skin, using a human relevant *in vitro* model. This test has capability, though limited, to sub-categorize corrosive test substances in accordance with United Nations (UN)

Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Subsequent testing addresses skin irritation and other localized skin effects.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. While it is conceivable that gases and aerosols can be tested using the TER test method, the current test guideline does not support testing of these phases (OECD 431(2019), Initial considerations).

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #64 (Skin irritation/corrosion). Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2064%20-%20ENDPOINT_STUDY_RECORD.SkinIrritationCorrosion_v9.1%20-Nov%202021.docx

b. In Vitro Membrane Barrier Test Method for Skin Corrosion (OECD 435 (2015))

This testing addresses potential skin corrosion *in vitro* and identifies corrosive test substances impact on skin membrane barrier integrity. This testing can enable sub-categorization of corrosive chemicals into the three UN GHS sub-categories of corrosivity and the three UN Transport Packing Groups for corrosivity hazard. Subsequent testing addresses skin irritation and other localized skin effects.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Consistent with the test guideline, a compatibility test should be performed prior to full testing to ensure detection by the chemical

detection system (CDS), via a detectable color change (OECD 435(2015), Principle of the test).

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance. See item #7 in the TG regarding pH range applicability of this test.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #64 (Skin irritation/corrosion). Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2064%20-%20ENDPOINT_STUDY_RECORD.SkinIrritationCorrosion_v9.1%20-Nov%202021.docx

Tier 1.3

a. Defined Approaches on Skin Sensitization (OECD 497 (2021))

This testing addresses the potential of an allergic response following repeated skin contact, and in accordance with UN GHS.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation and stability.

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan requirements, consistent with the test guideline must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan requirements and test guideline for handling chemical substance stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #66-1 (Skin sensitization). Harmonized Template URL: https://www.oecd.org/ehs/templates/harmonised-template-66-1-skin-sensitisation.docx

b. Skin Absorption: In Vitro Method (OECD 428 (2004) and OECD GD 28 for Conduct of Skin Absorption Studies (2004))

This testing addresses the fractional absorption of HFPO-DAF through the skin following application to excised skin. Data from this study will support route-to-route extrapolation from available oral data on the test substance.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation and stability. This may include whether a radio-labelled form of the test substance is feasible (OECD GD 28(2004)) (OECD, 2004a). The TG indicates radiolabeling is preferred to enable mass-balance tracking of the test substance, see item #13 and Figure 1 in the TG.

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance. For volatile substances, a charcoal filter should be used to capture any volatilized test substance, as applicable based on *tier 1.1,* see Figure 1 in the TG.

3. Must consider factors that influence skin permeation and mass balance of the applied test substance to excised skin (OECD GD 28 (2004) (OECD, 2004a); OECD GN 156 (2011) (OECD, 2011); (Hopf et al., 2020)) including the stability of the test substance. Other study requirements include determining, as experimentally feasible and applicable, the permeability coefficient (K_p), lag time (t_L) for the test substance to approach and/or reach steady state absorption rate, flux (J), and whether measurements are/are not taken at steady state. These measurements will impact the sampling frequency required for the test

substance, e.g., the faster the permeation of the test substance, the less time between sampling points (Hopf et al., 2020).

4. Must provide rationale for testing materials selected, including and may not be limited to, the diffusion cell, and the biochemical composition, e.g., physiological relevance, of the receptor fluid (Hopf et al., 2020).

5. Prior to performing testing, skin excisions must be characterized including and may not limited to, skin procurement and preparation, skin thickness and integrity to address spatial distribution and barrier function, respectively, and viability (Hopf et al., 2020).

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance preparation and stability and characterizing excised skin must be provided in the final test report.

3. Harmonized Template Identifier: OHT #59 (Dermal absorption). Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2059%20-%20ENDPOINT_STUDY_RECORD.DermalAbsorption_v8.1%20-Nov%202021.docx

c. In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (OECD 439 (2021))

This testing addresses the potential of reversible damage to skin *in vitro* and identifies irritant test substances using the RhE test system.

iii. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. While it is conceivable that gases and aerosols can be tested using the RhE test method, the current test guideline does not support testing of these phases (OECD 439 (2021), Initial considerations and limitations).

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance.

iv. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #64 (Skin irritation/corrosion). Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2064%20-%20ENDPOINT_STUDY_RECORD.SkinIrritationCorrosion_v9.1%20-Nov%202021.docx

3. Health Effects: Ocular Route

Tier 1.1

a. Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (OECD 437 (2020))

This testing comprises an in vitro procedure allowing the identification on its own of chemicals (substances and mixtures) not requiring classification (No Cat) or requiring classification for serious eye damage (Cat 1) according to the UN GHS ocular hazard categories.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation, stability, volatility, and applicability for this test protocol.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance preparation and stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #65 (Eye irritation) including reporting of corrosion. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2065%20-%20ENDPOINT_STUDY_RECORD.EyeIrritation_v9.1%20-Nov%202021.docx

Tier 1.2

b. Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification (OECD 492B (2022))

This testing comprises an in vitro procedure allowing the identification on its own of chemicals (substances and mixtures) not requiring classification (No Cat), requiring classification for eye irritation (Cat 2) and requiring classification for serious eye damage (Cat 1) according to the UN GHS ocular hazard categories.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation, stability, volatility, and applicability for this test protocol.

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance. See considerations in the TG for pH range applicability of this test.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

4. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

5. The study plan and test guideline requirements for handling chemical substance preparation and stability must be provided in the final test report.

6. Harmonized Template Identifier: OHT #65 (Eye irritation) including reporting of corrosion. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2065%20-%20ENDPOINT_STUDY_RECORD.EyeIrritation_v9.1%20-Nov%202021.docx

4. Health Effects: Mechanistic

Tier 1.2

a. Bacterial Reverse Mutation Test (OECD 471 (2020))

This testing screens for genotoxic activity and specifically, point mutation-induing activity, which involves substitution, addition, or deletion of one or more DNA base pairs. While required as part of a suite of testing for genotoxicity, this testing alone whether positive or negative is not sufficient to provide direct information on the mutagenic and/or carcinogenic potency of the test substance.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation and stability.

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance. See TG considerations for test substance solubility and propensity to precipitate.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance preparation and stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #70 (Genetic toxicity in vitro). Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2070%20-%20ENDPOINT_STUDY_RECORD.GeneticToxicityVitro_v10.1%20-Nov%202021.docx

b. One of the following (dependent upon hydrolysis half-life):

a. In Vitro Mammalian Chromosomal Aberration Test (OECD 473 (2016))

This testing uses cultured mammalian cells *in vitro* to identify test substances that cause structural chromosomal aberrations of two types: chromosome or chromatid.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation and stability.

2. Must consider the influence of selected cell lines characteristics on the detection of aberrations, *e.g., p53* status, genetic stability.

3. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *tier 1.1* which may impact testing applicability and performance. See TG considerations for test substance solubility and propensity to precipitate

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance preparation and stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #70 (Genetic toxicity in vitro). Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2070%20-

%20ENDPOINT_STUDY_RECORD.GeneticToxicityVitro_v10.1%20-Nov%202021.docx

b. In Vitro Mammalian Cell Micronucleus Test (OECD 487 (2016))

This *in vitro* test evaluates the potential of a test substance to cause genotoxicity via detection of micronuclei in the cytoplasm of interphase cells, of either human or mammalian origin.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation and stability.

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *Tier 1.1* which may impact testing applicability and performance. See TG considerations for test substance solubility and propensity to precipitate

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance preparation and stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #70 (Genetic toxicity in vitro). Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2070%20-%20ENDPOINT_STUDY_RECORD.GeneticToxicityVitro_v10.1%20-Nov%202021.docx

c. In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene (OECD 490 (2016))

This test evaluates potential genotoxicity via detection gene mutations induced by the test substance.

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans.

1. Must include considerations for test substance preparation and stability.

2. Deviations from the standard procedure needs to be scientifically justified and based on physical chemical properties results from *Tier 1.1* which may impact testing applicability and performance. See TG considerations for test substance solubility and propensity to precipitate

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test a are due by the deadline specified in the table in **Unit V.B.** and must include the following, as applicable:

1. The study plan and test guideline requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol.

2. The study plan and test guideline requirements for handling chemical substance preparation and stability must be provided in the final test report.

3. Harmonized Template Identifier: OHT #70 (Genetic toxicity in vitro). Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2070%20-%20ENDPOINT_STUDY_RECORD.GeneticToxicityVitro_v10.1%20-Nov%202021.docx

APPENDIX F – SUMMARY OF AVAILABLE DATA

Available toxicity studies on HFPO-DAF were reviewed in accordance with the draft TSCA Systematic Review Protocol (USEPA, 2021a). Data quality is evaluated based on overall health outcome, *e.g.,* nutritional/metabolic, not on an individual endpoint per health outcome, *e.g.,* body weight, nor overall study basis. All data were considered for the determination of additional toxicity testing needs in this Order.

Five studies were available. Two were acute inhalation studies in rats, one was an acute lethal dose oral study in rats, one was a short term (sub-acute) inhalation study in rats, and one was a dermal irritation/corrosion study in rabbits. See Table F2 for full reference IDs.

Existing studies sourced from the EPA internal databases had a range of study quality, and thus acceptability and sufficiency to fulfill the data needs identified for HFPO-DAF. 4/ Of the five existing studies, four studies were performed in male animals. One study (4 see Table F2, short term inhalation study in rats) did not specify sex (NS, in Table F1). Table F2 describes the limitations of each study considered, that contributed to the overall rating (H = High Confidence, M = Medium Confidence, L = Low Confidence, U = Uninformative) for the health outcome.

Testing feasibility and appropriateness depend on the experimental and biological stability and fate of HFPO-DAF.

Of the three available inhalation studies, one (reference ID 1, Table F2) was rated as Acceptable (Medium confidence). All three inhalation studies (1, 2 and 4 see Table F2; acute and short term) reported liver effects that implied systemic toxicity, including enlargement of the liver and/or liver cells, or increased liver weight. However, the quality of these gross liver pathology findings was unacceptable, based on uncertainty/lack of comparator/control, and/or lack of assessment/severity details. It was suggested (reference ID 2) without direct evidence, that HFPO-DAF caused pulmonary congestion and edema, and increased liver weight. None of these studies identified, nor tracked relevant metabolites or component forms of HFPO-DAF, e.g., GenX-related chemicals, and so it is unclear if these effects are directly attributable to HFPO-DAF. These inhalation studies were similar to OECD TGs 403(2009) (OECD, 2009) and 412(2018) (OECD, 2018c). The conduct of these studies pre-dated the 1981 adoption of these TGs.

The acute dermal study (reference ID 5.1 and 5.2) only tested a single male rabbit per exposure tested, using two different methods, e.g., uncovered (5.1) and covered (5.2). Only 5.2 was Acceptable (Medium confidence). Gross pathology findings for liver enlargement followed the dermal exposure. This study was similar to OECD TG 404(2015) (OECD, 2015a), which was performed in albino rabbits. The conduct of this study in 1965 pre-dated the 1981 adoption of these TGs.

The oral, gastric intubation study (reference ID 3), to determine a lethal dose was Acceptable (High confidence). The dose range of this study appeared to be appropriate, since the lowest dose resulting in animal death was in the middle of the dose range, 670mg/kg. The rat at this dose exhibited several clinical signs of toxicity before dying 2 days after dosing, compared to the top

dose, 2300 mg/kg resulting in death 1 hour after dosing. This study was similar to OECD TG 401 (1987) (OECD, 1987), which was deleted from OECD health effects testing in 2002.

Table F1. Health Outcome Endpoint Quality Review Results on available in vivo studies (H = High Confidence, M = Medium Confidence, L = Low Confidence, U = Uninformative)

	Reference ID	1	2	3	4	5.1[a]	5.2[a]
Study Info	Duration (A= acute, ST = Short Term)	A	A	A	ST	A	A
	Species (R= rat, Rb= rabbit)	R	R	R	R	Rb	Rb
	Sex (F= female, M= male, NS= not specified)	M	M	M	NS	M	M
	Route (I= inhalation, O=oral, D= dermal)	I	I	O – gastric intubation	I	D	D
Health Outcomes and Quality Review Results	Cardiovascular						
	Gastrointestinal		U				
	Immunological/hematological						
	Kidney						
	Liver	U			U		
	Mortality	M	L	H	L	M	M
	Neurological						
	Nutritional/Metabolic	M	L	H	U		
	Reproductive/Developmental						
	Lung/Respiratory	M	U		U		
	Skin					L	M
	Skin Irritation						M
	Thyroid						
	Other – Clinical Signs of Toxicity[b]	M	L	H	U		M
	Other – Pathology of trachea, bronchi, liver[c]		U				
	Other – Pathology of bone marrow, thyroid, GI tract, pancreas, spleen, skin, eye, testis, epididymis, heart, kidney, aorta, thymus, brain, adrenal gland[c]		U		U		
	Other – Pathology of muscle[c]						M

[a]The reference had two procedures for each animal tested (n= 1): study 5.1 was a single application of the test article, uncovered; and study 5.2 was a single 2-hour application of the test article, covered then washed off

[b]For individual endpoints that span more than one health outcome, and that can be grouped together for the same study quality rating

[c]Blinding is not required for clinical signs to enable detectable differences between controls and treatment that are attributable to the test substance exposure; clinical signs can be ambiguous if the outcome assessment methodology is not described, and may be attributable to other health outcomes, or may be secondary health outcomes

Table F2. Reference ID key and individual study quality limitations

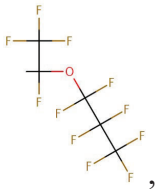
Reference ID number	Reference (multiple reference IDs reflect duplicate or related documents)	Description *Sponsor* *Contract Lab (if applicable)* *Project ID/Report Number (if any)* *Study title (include rat/mouse strain if available, may need to check methods section) (OECD # [if applicable])* *Year*	EPA Document ID
1 & 4	5890817	E. I. Dupont de Nemours & Co Haskell Laboratory 17-74 Initial Submission: Acute and subchronic[sic] inhalation toxicity study of propionic acid, tetrafluoro-2-(heptafluoropropoxy), acid fluoride with cover letter dated 10/15/92 Similar to OECD 403 and 412 in ChR-CD male rats December 5, 1973	8EHQ-1092-11765 88-920010035 OTS0555510
2 & 5	11147671	E. I. Dupont de Nemours & Co Haskell Laboratory 16-65 Acute inhalation and acute skin absorption toxicity, PMN substance analog #2, [Perfluoro (2-propoxy propionyl) fluoride], MR-604-1 Similar to OECD 403 in ChR-CD rats and OECD 404 in albino rabbits February 19, 1965	COMMS-23-0237
3	11194954	E. I. Dupont de Nemours & Co Haskell Laboratory 771-95 Approximate Lethal Dose (ALD) of H-21036 in Rats Similar to OECD 401 in Crl:CDBR rats February 8, 1996	COMMS-23-0247

Studies are available in the docket EPA-HQ-OPPT-2021-0903.

APPENDIX G – ADDITIONAL UNDERLYING INFORMATION

PREDICTIVE MODELING

Note that PFAS are known to have unique properties which may impact model applicability. HFPO-DAF was analyzed using the EPA's expert system OncoLogic™ 9 (USEPA, 2021d). The overall level of cancer concern was Low to Moderate, with the concern being highest for the inhalation route of exposure. The Oncologic Justification Report reads:

> Acyl or Benzoyl halides are reactive chemicals which may acylate critical macromolecules to exert carcinogenic action. Very few acylating agents have been adequately tested for carcinogenic activity. The most notable carcinogenic acylating agent is *N*,*N*-dimethylcarbamyl chloride. In view of the high tendency of acylating agents to be hydrolyzed, their potential activity is expected to be limited to the immediate vicinity of the point of contact. In general, low molecular weight, volatile acylating agents are of higher concern, particularly if the expected route of exposure is by inhalation.
>
> The acyl fluoride, where R1 is ethyl, has a baseline level of concern of LOW-MODERATE. [Note: OncoLogic™ looks at functional groups and the remainder of the molecule is considered an "R" group. In this case, OncoLogic™ assigned HFPO-DAF a general formula of R1-C(=O)-F
>
> 
> where R1 is , which OncoLogic™ is calling "ethyl" since OncoLogic™ does not recognize the ether linkage or anything past it.]
>
> In general, exposure by inhalation or injection provides the best chance of delivering the largest possible amount of direct-acting reactive chemical to target tissues because of a lesser absorption barrier and better chance of avoiding detoxification by protective nucleophiles such as glutathione. When the exposure to this compound is by inhalation or injection, the level of concern is expected to increase to moderate.
>
> Since the compound is unstable, the oral route of exposure provides significant opportunity for the compound to be inactivated by reacting with water and, after absorption, by subsequent reaction with protective nucleophiles such as glutathione. Based on this mechanism, the level of concern for oral exposure is expected to decrease to marginal.
>
> The dermal route of exposure provides a significant absorption barrier and opportunity for an unstable compound to be inactivated by reacting with water and subsequent reaction with protective nucleophiles. Based on this mechanism, the level of concern for dermal exposure is expected to decrease to LOW.

HFPO-DAF was analyzed using the "Protein binding alerts for skin sensitisation according to United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS)" and the "Respiratory sensitisation" profilers in the OECD QSAR Toolbox version 4.5. The skin sensitization profiler predicted that HFPO-DAF was a GHS Category 1A sensitizer based on its membership in the "(Thio)Acyl and (thio)carbamoyl halides, cyanides, azides, etc." chemical class. The respiratory sensitization profiler did not show any alerts for respiratory sensitization potential. Commercially available safety data sheets (SDS) for HFPO-DAF (CASRN 2062-98-8) further corroborate skin and respiratory sensitization with GHS hazard statements for causing severe skin burns and eye damage, severe eye damage and may cause respiratory irritation (SDS acyl fluoride) (Thermo, 2020).