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

January 4, 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: Trifluoro(trifluoromethyl)oxirane

Chemical Name Synonym: Hexafluoropropylene oxide

Chemical Name Acronym: HFPO

Chemical Abstracts Service Registry Number (CASRN): 428-59-1

Docket Identification (ID) Number: EPA-HQ-OPPT-2021-0910

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

Testing Required by this Order:

1. Physical-Chemical Properties

Tier 1

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

2. Health Effects: Inhalation Route

Tier 1

a. *In vitro* Respiratory Tract Epithelial Toxicity in Primary Human Cell Culture (**Appendix E**)

b. Partition Coefficient and ADME Inhalation Study (**Gargas, et al. (1986)**)

Tier 2

c. Two-Generation Reproduction Toxicity **(OECD 416 (2001))**

d. Developmental Neurotoxicity Study (**OECD 426 (2007)**)

e. Subchronic Neurotoxicity Study in Rodents (**OECD 424 (1997)**)

f. Combined Chronic Toxicity/Carcinogenicity Studies (**OECD 453 (2018)**)

Recipients of this Order:

Company Name: 3M Company

Company Name: The Chemours Company FC LLC

Company Name: Dupont de Nemours Inc

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 (CASRN 428-59-1) to develop and submit certain information for HFPO, 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 trifluoro(trifluoromethyl)oxirane (hexafluoropropylene oxide; HFPO). 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 ten 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 identified as a Manufacturer or Processor of the chemical substance(s) (via the submitted "Identification Response") identified in this Order 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 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).

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 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). Import also includes importing the chemical as an impurity in an article.

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.

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 ten years preceding the date of this Order. If a recipient of this Order has not manufactured or processed the chemical during the prior ten 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

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 may present an unreasonable risk of injury to human health or the environment.

HFPO 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 working structural definition for identifying PFAS. Specifically, this definition includes substances that structurally contain the unit R-(CF_2)-C(F)(R′)R″. Both the CF_2 and CF moieties are saturated carbons and none of the R groups (R, R′ or R″) can be hydrogen.

Note that agencies as well as programs within a given agency may define PFAS differently. HFPO fits the PFAS National Testing Strategy definition of PFAS as well as other definitions of PFAS (e.g., OECD's definition). The definition as described in the PFAS National Testing Strategy is not meant to represent an agency-wide definition. 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 (USEPA, 2022a; ATSDR, 2021).

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) (PubChem, 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, 2022b) and Our Current Understanding of the Human Health and Environmental Risks of PFAS (USEPA, 2022a).

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 trifluoro(trifluoromethyl)oxirane (HFPO)

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

Inhalation is the relevant route of exposure for HFPO. EPA examined whether existing information is adequate to reasonably determine or predict the effects on health from HFPO. 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 two sources – the EPA Toxicity Value Database (ToxValDB) (Judson, 2018) and the EPA Chemical Information System (CIS). 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 is an internal platform for managing data submissions under TSCA, including toxicity studies. Most of the data within CIS have been provided by industry in conjunction with TSCA submissions and are not currently publicly available. 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.

Seventeen toxicity studies were identified and considered prior to the issuance of this HFPO 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 toxicity, reproductive and developmental toxicity, specific target organ toxicity, and neurotoxicity. In particular, available data from an OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats showed severe neurotoxicity, including vacuolization and/or necrosis of brain neuronal cells. Further, acute toxicity and respiratory tract irritation, or portal of entry effects, were evident.

In addition to falling within the definition of PFAS and having specific studies indicating health concerns, HFPO contains an epoxide functional group (*i.e.,* a three-membered ring with two carbons and an oxygen). The TSCA New Chemicals Program Chemical Categories document states that "concerns for epoxides are for cancer and reproductive effects based on data for several analogous chemicals" (USEPA/OPPT, 2010). Epoxides are highly reactive, electrophilic functional groups that can react with cellular nucleophiles, including DNA, proteins, and glutathione (Klaassen, 2019; Klaunig and Wang,

2019). Reaction of epoxides with DNA and/or proteins can lead to the formation of adducts. DNA adducts can eventually lead to mutations and, in some circumstances, cancer (Klaassen, 2019; Klaunig and Wang, 2019). Other epoxides known to cause cancer include ethylene oxide (CASRN 75-21-8); along with epoxides formed from benzene (CASRN 71-43-2), benzo[*a*]pyrene (CASRN 50-32-8), and 1,3-butadiene (CASRN 106-99-0) which form epoxides following metabolism in the body (IARC, 2022).

In summary, for HFPO, EPA identified hazards for acute toxicity, carcinogenicity, reproductive and developmental toxicity, specific target organ toxicity, and neurotoxicity.

Exposure for trifluoro(trifluoromethyl)oxirane (HFPO)

Based on experimental data submitted to the Agency, supplemented by modeled estimates of physical-chemical property values for HFPO using EPA's model, Open (Quantitative) Structure-activity/property Relationship App (OPERA v 2.8), EPA concludes it is a highly volatile gas:

- Vapor pressure: 5,106.8 mmHg
- Water solubility: 0.016 mg/L
- Melting point: -121 °C (estimated by OPERA)
- Boiling point: -28.45 °C

Based on the physical-chemical properties indicating it is a highly volatile gas, exposure via inhalation is of concern for this substance. Additional information informing the Henry's Law Constant derived from the experimental water solubility test indicates that the value is >0.1 atm·m^3/mol but due to reactivity of HFPO in the aqueous phase (which makes the measurement of the Henry's Law Constant more difficult), EPA is considering this information qualitatively rather than quantitatively. Manufacturing, processing, use, disposal, and/or distribution in commerce of gaseous substances may lead to inhalation exposures to workers. Because of the potential for adverse effects and exposure via inhalation, there is a potential for risk. In evaluating potential exposures to HFPO, the Agency considered: (a) its status on the TSCA Inventory and (b) reporting on the substance under the Chemical Data Reporting Rule.

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 is listed as "active" on the TSCA Inventory, as a result of this reporting, indicating a potential for exposure.

Additionally, Chemical Data Reporting (CDR) indicates that HFPO is manufactured (defined to include importing) in quantities of more than 1,000,000 pounds in a given year and used as a reactant for plastics material and resin manufacturing and 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. Furthermore, the North Carolina Department of Environmental Quality (NCDEQ) has issued Air Quality Permits for certain activities involving HFPO—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 was released into the air after scrubbing from the reporting facility (WS, 2020, 2018).

Currently, there is a significant new use rule (SNUR) (40 CFR 721.4160) requiring that manufacturers notify EPA before "any use [of HFPO] other than as an intermediate in the manufacture of fluorinated substances in an enclosed process." This SNUR requires persons who intend to manufacture, import, or process HFPO for any use other than as an intermediate in the manufacture of fluorinated substances in an enclosed process to submit a Significant New Use Notice to EPA prior to the commencement of such manufacture, import, or processing. However, this SNUR does not restrict the manufacturing, importing, or processing of HFPO provided such activities are for the use of the chemical substance as an intermediate in the manufacture of fluorinated substances in an enclosed process (e.g., the SNUR does not require an enclosed process for the manufacturing of HFPO, repackaging (a processing activity) of HFPO, and other activities provided such activities are intended for HFPO being used as an intermediate in the manufacture of fluorinated substances in an enclosed process). Further, the SNUR does not provide restrictions on the disposal of HFPO. Although EPA anticipated there would be low levels of exposure to HFPO at the time EPA finalized this SNUR in 1987, EPA now believes there are exposure concerns for the reasons discussed above that support the issuance of this Order (e.g., given the production volumes reported to CDR and releases of the chemical that have been reported). *See* 52 FR 41296, 41298 (Oct. 27, 1987).

Given the hazard and exposure concerns identified for HFPO, as discussed above, the EPA finds that HFPO may present an unreasonable risk of injury to health or the environment. The hazard, generally, and exposure concerns for PFAS further support this conclusion.

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 the insufficient data that has been identified for purposes of the Order. The EPA may in the future determine the availability of data 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 is insufficient for other hazard endpoints and exposure scenarios.

EPA estimated the human health hazard of HFPO based on its estimated physical/chemical properties and available data 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 good via lungs and nil via the skin and GI tract based on physical/chemical properties.

Data from seventeen toxicity studies were reviewed (**Appendix F**) and determined to provide evidence of health concerns, but these studies were insufficient to predict the specific health effects of concern EPA has identified for PFAS, epoxides, and for HFPO in particular (**Unit II.B.1**).

HFPO is expected and reported to hydrolyze in water to give 1,1,2,3,3,3-hexafluoropropane-1,2-diol (CASRN 77358-12-4), 3,3,3- trifluoro-2,2-dihydroxypropanoic acid (CASRN 10321-14-9) and hydrogen fluoride (HF, CASRN 7664-39-3). The rate of this hydrolysis is expected to be pH-dependent.

Given that the epoxide moiety is expected to underlie some of the toxic effects of HFPO, the rate of hydrolysis at physiologically-relevant pH in the lung is necessary to interpret the toxicity and predict adverse effects following exposure to HFPO. The rate of absorption of HFPO via inhalation is also unknown and is expected to be a critical parameter. Portal-of-entry effects in the lung have been demonstrated in animal models but their relevance for use in human health assessment is uncertain. EPA is requiring an *in vitro* toxicity study using cells of human origin to examine portal-of-entry effects in human tissue. Reproductive and developmental effects were observed in the OECD 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test). As stated in the OECD 422 Guideline, the study "is designed to generate limited information concerning the effects of a test chemical on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition. It is not an alternative to, nor does it replace the existing Test Guidelines 414, 415, 416 or 443" (OECD, 2016). EPA is requiring a 2-generation reproduction study (OECD 416) that will provide definitive information as it includes longer exposure periods and additional reproductive toxicity endpoints, which better characterize dose response relationships.

While the existing studies also support concerns for neurotoxicity in adults, there is nevertheless insufficient information to determine effects to earlier life stages which is the basis for EPA requiring a developmental neurotoxicity study (OECD 426). The subchronic neurotoxicity study in adult animals will examine how these effects and/or the exposure levels at which they occur change with a longer duration of exposure (i.e., 90-day as opposed to 28-day). EPA acknowledges that it may be possible to combine the measurements made in some guideline studies to potentially reduce the number of studies conducted and is amenable to such proposals.

Finally, EPA does not have sufficient information to predict HFPO's potential for causing cancer. EPA is aware of several available genotoxicity-related studies: a Mouse Blood Micronucleus test (OECD 474), a bacterial reverse mutation assay, an *in vitro* mammalian cell gene mutation test, and an *in vitro* Mammalian Chromosome Aberration test. While several of these tests had negative results (Mammalian Chromosome Aberration test was positive without metabolic activation), PFAS are thought to act via a non-mutagenic mode of action to cause cancer and therefore negative genotoxicity tests do not rule out carcinogenic potential by other mechanisms (USEPA, 2016b). Therefore, a combined chronic toxicity/carcinogenicity study is being required to examine how these effects and/or the exposure levels at which they occur change with a lifetime (as opposed to 28- or 90-day) duration of exposure, and to determine whether chronic exposure to HFPO results in tumors in rodents. 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 —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 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

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)), and to aid EPA in identifying and selecting PFAS for which the Agency will require testing, EPA developed the National PFAS Testing Strategy: Identification of Candidate Per- and Polyfluoroalkyl Substances (PFAS) for Testing (Testing Strategy) (USEPA, 2021b).

The Testing Strategy provides categories of PFAS based on information about similarities in structure and certain physical-chemical properties. The Testing Strategy identifies such categories as "terminal categories."

This Order pertains to trifluoro(trifluoromethyl)oxirane (HFPO; CASRN 428-59-1), which the EPA determined to be representative for the "Others, cyclic, volatile, sub-cluster 1" terminal category. As described in the Testing Strategy (USEPA, 2021b), the EPA used computer software developed by Su and Rajan (Su and Rajan, 2021) to systematically analyze the chemical structures from 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) and volatility (based on vapor pressure and Henry's Law Constant). The use of volatility to break down the primary structural categories was important when considering the route of exposure for testing. The secondary categories were further subdivided using chemical fingerprinting and similarity techniques (see Testing Strategy for details (USEPA, 2021b)). Of the 6,504 PFAS in the starting list, 48 PFAS are members of the "Others, cyclic, volatile, sub-cluster 1" terminal category, for which HFPO was identified as a representative.

EPA's concerns related to HFPO, and its decision to issue this Order pursuant to TSCA Section 4(a)(1)(A)(i), may also exist for other PFAS in this "Others, cyclic, volatile, sub-cluster 1" terminal category.

This order is the EPA's initial action to collect toxicity information for HFPO. The EPA anticipates that data provided on this chemical substance via this Order will also serve to inform understanding of other PFAS within the "Others, cyclic, volatile, sub-cluster 1" terminal category. Furthermore, the results of the required testing in this Order, taken together with existing information, may enable integrated approaches to testing and assessment (IATA) of other substances within the terminal category and potentially PFAS at large (OECD; https://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm). As EPA continues to improve its understanding of PFAS within this terminal category, EPA's understanding of how to categorize these chemical substances may evolve. Similarly, EPA may determine that testing is required on other PFAS categorized in the "Others, cyclic, volatile, sub-cluster 1" terminal category as it is currently defined.

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 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." 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. Certain information (*i.e.*, water solubility, boiling point, hydrolysis, vapor pressure, and Henry's Law Constant) is developed initially to ensure that *in vivo* inhalation toxicity tests on vertebrate animals are appropriate. The results of the partition coefficient and ADME inhalation study combined with results from the acute inhalation study (OECD 403) already available will be used to inform the study plan and test report requirements for subsequent *in vivo* tests. Specifically, the results will be used to select the most relevant species (rats or mice) for later testing and therefore reduce vertebrate use by half versus performing all toxicity tests in two species.

Section 4(a)(4) states that tiered testing regimes can be truncated when "information available to the Administrator justifies more advanced testing of potential health or environmental effects or potential exposure without first conducting screening-level testing." Available data on HFPO from an OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats showed severe neurotoxicity, including vacuolization and/or necrosis of brain neuronal cells. These findings support the need for the Subchronic Neurotoxicity Study (OECD 424) to better characterize the neurotoxic potential (i.e., longer exposure period, specialized study design [functional observational battery, motor activity measurements, additional histochemical characterization of nervous system tissue], more animals per exposure group increasing statistical power, analysis of time-to-peak-effect) in male and female adults and the Developmental Neurotoxicity Study (OECD 426) to better characterize the neurotoxic potential in maternal adults and offspring and establish the dose-response relationship. The request for these studies is consistent with the weight of evidence approach outlined in 40 CFR 158.34 ("Flagging of studies for potential adverse effects") and 40 CFR 158.500(e) ("Toxicology data requirements table") (footnote 28)(CFR, 2022). EPA acknowledges that it may be possible to combine the measurements made in these guideline studies to potentially reduce the number of studies conducted (and therefore reduce the number of laboratory animals used) (See **Unit V.A.4-7** for details).

3. The EPA is using non-vertebrate testing

As part of this consideration of non-vertebrate approaches, consistent with section 4(h)(1) of TSCA, 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. EPA is including in this Order a test utilizing human epithelial tissues that can be used to inform portal-of-entry effects on the respiratory tract epithelium. This test uses air-liquid interface cultures that have been successfully used with gaseous test articles (Bowers et al., 2021; Upadhyay and Palmberg, 2018) and will examine respiratory tract remodeling effects.

The EPA has determined that vertebrate testing is necessary for assessing the effects discussed in this Order (see below for details). Existing information and replacement methods (e.g., *in vivo* and *in vitro* toxicity information, computational toxicology and bioinformatics, high-throughput screening methods) are unavailable or cannot be used to address testing required by the Order, as discussed in greater detail below. Further information on the EPA review process that led to the inclusion of such testing requirements can be found in **Unit II.B**.

The partition coefficient and ADME testing requires the use of vertebrates. No scientifically valid non-vertebrate test method of equivalent or better scientific quality and relevance currently exists to determine/measure internal dosimetry from the inhalation route of exposure and toxicity for test substances in this terminal category. Existing information on other PFAS (which are not the subject of this Order, but which inform the testing required by this Order) has not demonstrated a clear pattern of rodent species' relevance to human health hazard (ATSDR, 2021). In the absence of evidence that either rats or mice are more human-relevant for PFAS inhalation exposure, experimental data are needed from both species to understand interspecies differences in accumulation, metabolism, and re-uptake and/or clearance of these substances. Testing both rats and mice is required in the ADME test within this Order to select the most appropriate rodent species (*i.e.*, rat or mouse) for higher tier inhalation toxicity testing.

A subsequent phase of testing (post-ADME study) includes a 2-Generation Reproduction Toxicity (OECD 416) and a Developmental Neurotoxicity Study (OECD 426). No scientifically valid non-vertebrate test method of equivalent or better scientific quality and relevance currently exists to determine/measure the effects on the developing fetus or on neonates. The last phase of testing also includes a Subchronic Neurotoxicity Study in Rodents (OECD 424). While *in vitro* tests exist for examining neuronal toxicity, these methods are not suitable for use with gaseous test articles (*i.e.,* neuronal cells cannot be grown at an air-liquid interface).

In addition, this Order includes the Combined Chronic Toxicity / Carcinogenicity Study (OECD 453) in one species. The neurotoxicity and other target organ toxicity seen in the existing OECD 422 may occur at lower dose levels with longer (*i.e.,* chronic) exposure regimes. Therefore, it is necessary to have chronic dosing data that allows for dose-response assessment for chronic endpoints. No cell-based assays are currently available for chronic exposure study designs. Additionally, no scientifically valid non-vertebrate test method of equivalent or better scientific quality and relevance currently exists to determine/measure an Inhalation Unit Risk (IUR) for test substances in this terminal category.

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 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		
Choose to Submit Existing Data (Option 2)	30	45

Choose 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 Study Plans and Test Report Deadlines

Tier 1 tests: • **Hydrolysis as a Function of pH** • **In vitro Respiratory Tract Epithelial Toxicity in Primary Human Cell Culture** • **Partition Coefficient and ADME Inhalation Study**	**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**)	

Tier 2 deadlines will have the same deadline structure as above in the Tier 1 Study Plans and Test Report Deadlines Table following confirmation from the EPA as to how to proceed to Tier 2 testing according to EPA's review of the Partition Coefficient and ADME Inhalation Study.

Tier 2 Study Plans and Test Report Deadlines

Tier 2 tests: • **2-Generation Reproduction Toxicity** • **Developmental Neurotoxicity Study** • **Subchronic Neurotoxicity Study in Rodents** • **Combined Chronic Toxicity/Carcinogenicity Studies**	**Recipient's Deadline (Days after EPA notification to proceed with the Tier 2 Testing)**	**The EPA Response Deadline* (Days after EPA notification to proceed with the Tier 2 Testing)**
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.

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.

Should a recipient amend their response, at any time, 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 to the EPA. Status updates/check-ins are described in **Unit VI.B**. 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 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 ten 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 ten 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 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 and deadlines in this Order will remain. If your claim is approved, the EPA will notify you that you are not subject to this Order through CDX correspondence. 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 EPA requires supporting documentation to demonstrate that consultations with laboratories was timely (e.g., correspondence with the laboratory).

Note that EPA requires a Pre-Draft Study Plan Check-in, during which you must identify the laboratory selected (e.g., quote, proposal, or statement of work that documents contract or agreement between test sponsor and laboratory to develop the study plan and/or conduct the testing).

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 EPA's CDX portal to choose one of the other response options in **Unit IV** within 10 calendar days of being notified by the EPA.

This option is intended only for information you believe the Agency may not have considered that would directly satisfy EPA's data need. This option does not apply to alternative interpretations of information already discussed in this Order, or other arguments why 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 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 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 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 EPA website also provides information on OECD guidelines, alternatively available via OECD Guidelines for the Testing of Chemicals (OECD, 2018c). **Appendix E** provides additional sources for guidelines associated with specific testing.

The EPA reserves the right to revise this Order 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.

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

A. Overview of Test Requirements

HFPO has been determined to be an insoluble and/or highly volatile gas; as such, inhalation is the most relevant route of exposure of concern. This chemical has existing inhalation toxicity data (Table 1). Two *in vivo* studies (OECD 422 and OECD 403 in rats), in particular, were used to inform additional testing requirements in this order.

1. Physical-Chemical Properties

Data/studies received from test order recipients before issuance of the test order provided information on HFPO water solubility (OECD 105), boiling point (OECD 103), vapor pressure (OECD 104), and Henry's Law Constant (Ji and Evans (2007), which confirmed the designation of HFPO as an insoluble and highly volatile gas. Outstanding testing includes hydrolysis as a function of pH (OECD 111). Hydrolysis as a function of pH influences stability in the respiratory tract and environmental media, as well as other parameters important for determining inhalation dosimetry and toxicity.

Physical-Chemical property testing includes the following:

- Hydrolysis as a Function of pH (OECD 111 (2004)); OECD (2004)

EPA lists Melting Point (OECD 102 (1995)) —which, if conducted, could replace the EPA-estimated *in silico* values (*i.e.*, modeled values) — as optional testing in Appendix E.

2. *In vitro* Respiratory Tract Epithelial Toxicity in Primary Human Cell Culture

Portal-of-entry effects are those effects that occur at the initial site of contact between a substance and the body. For the inhalation route of exposure (which is applicable for gases), the portal-of-entry is the respiratory tract. Recently, a number of academic and commercial entities have developed and characterized primary human cell culture models that replicate various regions of the respiratory tract epithelium and can be used for testing the toxicity of chemical substances (Mallek et al., 2022). These cell culture models are suitable for examining portal-of-entry effects from single (acute) exposures as well as short-term repeated exposures. Repeated exposure to toxic substances can cause airway remodeling, which can be measured in these models by looking for markers of dedifferentiation. The results of these experiments will be used as part of a weight of scientific evidence (WoSE) approach for evaluating toxicity from insoluble and/or highly volatile gases. The endpoints evaluated and measured in this *in vitro* test are physiologically relevant and will be compared to the apical endpoints measured in the *in vivo* respiratory tract for the adverse inhalation and portal-of-entry outcomes. Results from *in vitro* Respiratory Tract Epithelial Toxicity assays are also anticipated to inform PFAS category refinement.

3. Partition Coefficient and Absorption, Distribution, Metabolism, and Elimination (ADME) Inhalation Study (Gargas, et al. (1986))

An ADME study for investigating the biokinetics of the test substance must be conducted prior to the other *in vivo* tests below. This short-term study in two species (rats and mice) will determine pharmacokinetic parameters such as bioavailability, maximum blood concentration and the time to reach this maximum (C_{max} and T_{max}), and biomarkers of metabolism (particularly free fluoride). C_{max} and T_{max} will be used to guide the design of additional testing required by the Order. The ADME study based on Gargas et al. (1986) provides a detailed description of the toxicokinetics (TK) in two rodent species. The

acute inhalation toxicity (OECD 403) study provides more context and scaling (available in the docket at regulations.gov). The OECD 403 results, taken together with the ADME study results, will be used to select the more relevant species (rat or mouse; the species with slower chemical elimination) for the subsequent *in vivo* tests.

4. Two-Generation Reproduction Toxicity (OECD 416 (2001))

The two-generation reproduction testing is designed to provide general information concerning the effects of a test substance on the integrity and performance of the male and female reproductive systems, and on the growth and development of the offspring. The test substance is administered daily to several groups of males and females. At least three dose groups and a control group must be used. Dose levels will be selected by taking into account any previously observed toxicity and kinetic data available for the test compound or related materials. This study must be conducted via the inhalation route of exposure. Males and females of the Parent generation (5-9 weeks old) must be dosed during growth, during their mating, during the resulting pregnancies, and through the weaning of their first-generation offspring. The administration of the substance is continued to first generation offspring during their growth into adulthood, mating and production of a second generation (until the weaning). The species identified in the ADME study will be used in the two-generation reproduction study. The two-generation reproductive toxicity test will provide a no-effect level and data relevant for benchmark dose analysis.

The Agency is amenable to discussions that combine aspects of the two-generation reproduction study, the developmental neurotoxicity, combined chronic toxicity/carcinogenicity, and/or the subchronic neurotoxicity into fewer protocols to limit the number of laboratory animals used and make more efficient use of other resources. Such discussions must be initiated within 30 days of submitting the test report for the ADME study.

5. Developmental Neurotoxicity Study (OECD 426 (2007))

A developmental neurotoxicity study provides information on the effects of repeated exposure to a substance during *in utero* and early postnatal development and consists of observations to detect gross neurologic and behavioral abnormalities, and the evaluation of brain weights and neuropathology during postnatal development and adulthood. The test substance is administered daily to mated females from the time of implantation (GD 6) throughout lactation (PND 21). At least three dose groups and a control group must be used. Dose levels should be selected by taking into account any previously observed toxicity and kinetic data available for the test compound or related materials. This study must be conducted via the inhalation route of exposure. The species identified in the ADME study will be used in the developmental neurotoxicity study. Dams are tested to assess effects in pregnant and lactating females and may also provide comparative information. Offspring are randomly selected from within litters for neurotoxicity evaluation. The developmental neurotoxicity study will provide a no-effect level and data relevant for benchmark dose analysis of offspring and maternal endpoints.

The Agency is amenable to discussions that combine aspects of the two-generation reproduction study, the developmental neurotoxicity, combined chronic toxicity/carcinogenicity, and/or the subchronic neurotoxicity into a single protocol to limit the number of laboratory animals used and make more efficient use of other resources. Such discussions must be initiated within 30 days of submitting the test report for the ADME study.

6. Subchronic Neurotoxicity Study in Rodents (OECD 424 (1997))

The subchronic neurotoxicity study provides information on the potential neurotoxicity of chemicals in adult animals. At least three dose groups and a control group must be used. Dose levels will be selected by taking into account any previously observed toxicity and kinetic data available for the test compound or related materials. This study must be conducted via the inhalation route of exposure. The species identified in the ADME study will be used in the subchronic neurotoxicity study. Ninety days of inhalation dosing must be conducted unless the study is terminated early for animal welfare reasons in accordance with OECD guidance. The findings of the study will be evaluated in terms of the incidence, severity and correlation of neurobehavioral and neuropathological effects (neurochemical or electrophysiological effects as well if supplementary examinations are included), and any other adverse effects observed.

The Agency is amenable to discussions that combine aspects of the two-generation reproduction study, the developmental neurotoxicity, combined chronic toxicity/carcinogenicity, and/or the subchronic neurotoxicity into fewer protocols to limit the number of laboratory animals used and make more efficient use of other resources. Such discussions must be initiated within 30 days of submitting the test report for the ADME study.

7. Test No. 453: Combined Chronic Toxicity/Carcinogenicity Studies (OECD TG 453, 2018)

The combined chronic toxicity/carcinogenicity study provides information on the potential for carcinogenicity and the majority of chronic effects, and to determine dose-response relationships following prolonged and repeated exposure. At least three dose groups and a control group must be used. Dose levels will be selected by taking into account any previously observed toxicity and kinetic data available for the test compound or related materials. This study must be conducted via the inhalation route of exposure. The species identified in the ADME study will be used in the Combined chronic Toxicity/Carcinogenicity study. The study report must include measurements (weighing) and regular detailed observations (hematological examination, urinalysis, clinical chemistry), as well as necropsy procedures and histopathology. All these observations permit the detection of neoplastic effects and a determination of carcinogenic potential as well as the general toxicity.

The Agency is amenable to discussions that combine aspects of the two-generation reproduction study, the developmental neurotoxicity, combined chronic toxicity/carcinogenicity, and/or the subchronic neurotoxicity into fewer protocols to limit the number of laboratory animals used and make more efficient use of other resources. Such discussions must be initiated within 30 days of submitting the test report for the ADME study.

B. Deadlines for Required Testing Protocol(s)/Methodology(ies)

For Tier 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 tests and all testing milestones for Tier 2 are provided in the table below. Following receipt of the Partition Coefficient and ADME Inhalation Study test reports, the EPA will provide notification as to how certain parameters of Tier 2 testing should be conducted. Similarly, deadlines associated with draft study plans, final study plans and test reports for Tier 2 testing will commence upon EPA's confirmation that the review of the ADME test report is completed and EPA's selection of rodent species has been determined. 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.

Test Names	Protocols/Methodologies	Deadlines to Submit Tier 1 Final Test Reports and Tier 2 Study Plans and Final Test Reports
Required Physical/Chemical Properties		
Tier 1: Hydrolysis as a Function of pH	OECD 111 (2004)	415 days after effective date of the Order
Required Health Effects		
Tier 1: *In vitro* Respiratory Tract Epithelial Toxicity in Primary Human Cell Culture	Mallek, et al (2022)	365 days after effective date of the Order
Tier 1: Partition Coefficient and ADME Inhalation Study	Gargas, et al. (1986)	365 days after efective date of the Order
To pursue discussions with EPA to combine aspects of the Tier 2 tests, Order recipients must initiate discussion with EPA within 30 days of submitting the test report for the ADME study.		
Tier 2: 2-Generation Reproduction Toxicity	OECD 416 (2001)	Once the EPA confirms with the Order recipient that EPA's review of the *Partition Coefficient and ADME Inhalation Study* has concluded: the draft study plan is due within 125 days, the final study plan is due within 170 days, and the final test report is due within 1265 days
Tier 2: Developmental Neurotoxicity Study	OECD 426 (2007)	Once the EPA confirms with the Order recipient that EPA's review of the *Partition Coefficient and ADME Inhalation Study* has concluded: the draft study plan is due within 125 days, the final study plan is due within 170 days, and the final test report is due within 425 days
Tier 2: Subchronic Neurotoxicity Study in Rodents	OECD 424 (1997)	Once the EPA confirms with the Order recipient that EPA's review of the *Partition Coefficient and ADME Inhalation Study* has concluded: the draft study plan is due within 125 days, the final study plan is due within 170 days, and the final test report is due within 425 days
Tier 2: Combined Chronic Toxicity/Carcinogenicity Studies	OECD 453 (2018)	Once the EPA confirms with the Order recipient that EPA's review of the *Partition Coefficient and ADME Inhalation Study* has concluded: the draft study plan is due within 125 days, the final study plan is due within 170 days, and the final test report is due within 1495 days

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

A. OVERVIEW

The draft study plan for Tier 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 EPA by email, in which you must identify the laboratory selected and the specific test required (e.g., quote, proposal, or statement of work that documents contract or agreement between test sponsor and laboratory to develop the study plan and/or conduct the testing). 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 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 (note that to pursue discussions with EPA to combine aspects of the Tier 2 tests, you must initiate discussion with EPA within 30 days of submitting the test report for the ADME study). 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**).

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.

Submiting 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, 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 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, 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 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 III** 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, 2018d):

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

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

d. In vitro Respiratory Tract Epithelial Toxicity in Primary Human Cell Culture

- *Harmonized Template Identifier: OHT 86 (Additional Toxicological Information)*

e. Partition Coefficient and ADME inhalation study (Gargas et al. (1986))

f. 2-Generation Reproduction Toxicity OECD 416 (2001)

- *Harmonized Template Identifier:* OHT 73 (Toxicity to Reproduction)

g. *Developmental Neurotoxicity OECD 426 (2007)*

- *Harmonized Template Identifier:* OHT 76 (Neurotoxicity)

h. *Subchronic Neurotoxicity Study in Rodents OECD 424 (1997)*

- *Harmonized Template Identifiers:* OHT 76 (Neurotoxicity) and OHT 68 (Repeated dose toxicity: inhalation)

i. *Combined Chronic Toxicity/Carcinogenicity Studies OECD 453 (2018)*

- *Harmonized Template Identifier:* OHT 72 (Carcinogenicity)

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 test a chemical substance or mixture subject to the Test Order (accounting for small business considerations). Processors are not subject to this fee, nor are manufacturers who submit existing information or receive an exemption in compliance with this Order.

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, 2021c) 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, 2021d) 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 designated leads are able to add them to the consortium.

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.

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, 2021e).

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 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: 2023.01.04 12:41:01 -05'00'

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 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 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.

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 from the EPA Chemical Information System (CIS) within the past 15 years. 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. The Agency is amenable to discussions that combine aspects of the two-generation reproduction study, the developmental neurotoxicity, combined chronic toxicity/carcinogenicity, and/or the subchronic neurotoxicity into fewer protocols to limit the number of laboratory animals used and make more efficient use of other resources. Such discussions must be initiated within 30 days of submitting the test report for the ADME study.

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

I. Physical-Chemical Properties

a. Hydrolysis as a Function of pH; USEPA (2008); OECD (2004)

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 purposes and reporting products of hydrolysis.

iii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due 415 days after the effective date of the Order 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

II. Health Effects

a. *In vitro* Respiratory Tract Epithelial Toxicity in Primary Human Cell Culture; Mallek et al. (2022)

i. Study Plans

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

The study must involve primary respiratory tract epithelial cell culture from at least 5 human donors. A donor quality control experimental component must be performed prior to the full study. Cultures must have undergone mucociliary differentiation under air-liquid interface (ALI) conditions prior to use to

maximize representation of the respective region of the human respiratory tract *in vivo*. Non-human donors and/or cell lines may be considered with approval from the Agency based on an appropriate scientific rationale regarding the quality and relevance of the experimental data given the purposes described below. First, a quality control experiment must be performed to both demonstrate current proficiency at performing these methods and to characterize the donor epithelial cultures. The experiment must include at least 3 biological replicates per donor. There will be an acute study with a single exposure at six different test concentrations followed up by a short-term repeated dose study. Additional wells must be included for each donor for initial testing covering all of the endpoints for each study. The "age" of each cell culture as measured by the number of population doublings following isolation from the donor must be reported and matched as closely as possible (cultures with fewer doublings may need to be propagated *in vitro* so they match the ones with more doublings to control for the changes that take place over time in culture).

Test article exposures should be conducted while maintaining ALI conditions.

Transepithelial/transendothelial electrical resistance (TEER) measurements must be taken within 6 hours of the ending of the exposure, while LDH release and cytokine levels must be measured in conditioned media (either at sacrifice or when media is changed during the repeated exposure experiments) and apical washings collected at the same time as the conditioned medium. The amount of time between the ending of exposure and the TEER measurement should be as consistent as experimentally feasible and included in the report.

Donor tissue quality control and characterization:

- No exposure
- 3 inserts (wells) of tissues from each donor performed in triplicate
- Measurements:
    - Barrier integrity (TEER)
    - Hematoxylin and eosin stain (H&E) to characterize and identify cells by shape, structure and organization within the epithelial culture
    - Immunohistochemistry (IHC) for tumor protein 63 (p63), Mucin 5AC, Oligomeric Mucus/Gel-Forming (MUC5AC) for extracellular matrix composition and organization, and Forkhead Box J1 (FOXJ1) for ciliary expression
    - Cell viability (tetrazolium salt, 2-[2-methoxy-4-nitrophenyl]-3-[4-nitrophenyl]-5-[2,4-disulfophenyl]-2H-tetrazolium (or WST-8), viability assay and lactate dehydrogenase, or LDH, release)
    - Pro-inflammation (Cytokine/chemokine levels)

Acute:

- Single exposure (4 hr)
- 6 test concentrations
- 2 controls (mock-treatment [air-only] control and incubator control)
- Measurements:
    - Barrier integrity (TEER)
    - H&E
    - IHC for p63, MUC5AC, and FOXJ1
    - Cell viability (WST-8 viability assay and LDH release)

- Pro-inflammation (Cytokine/chemokine levels)
- Morphology (light microscopy observations)

- The purpose of this study is two-fold: to observe the effects of a single acute exposure on respiratory tract epithelial cells for integration with acute animal inhalation toxicity experiments in an IATA, and to select concentrations that do not cause excessive cytotoxicity for a subsequent repeated-exposure experiment.

Short-Term:

- Repeated exposures (6 hrs/day for 14 days)
- 2 test concentrations
- 2 controls (mock-treatment [air-only] control and incubator control)
- Measurements:
  - Barrier integrity (TEER)
  - H&E
  - Cell viability (WST-8 viability assay and LDH release)
  - Pro-inflammation (Cytokine/chemokine levels)
  - Morphology (light microscopy observations)
  - IHC for p63, MUC5AC, and FOXJ1 and of expected cell types to evaluate treatment-related de-differentiation/airway remodeling
  - Note: TEER, LDH release, cytokine levels, and light microscopy observations are non-destructive and must be performed on all wells.

The purpose of this study is to examine airway remodeling effects following treatment and to correlate these measurements with changes in inflammatory markers and loss of barrier integrity. These data will be informative of local and portal-of-entry effects on respiratory tract epithelial cells.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due 350 days after the effective date of the Order and must include the following, as applicable:

1. Report demonstration of lab competence and performance of this test.

2. Follow OECD Guidance Document (GD) no. 211 for describing non-guideline *in vitro* test methods (OECD, 2014).

b. Partition Coefficient and ADME Inhalation Study; Gargas et al. (1986)

i. Study Plans

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

1. Must include the following: Loss rate curves, first-order rate constant for rate of uptake, and substrate: air partition coefficients for saline, olive oil, blood, liver, muscle, and fat. Must be performed in both sexes of rats and mice.

2. Must include the following: pulmonary function testing, measured rates of respiration, analysis of bronchoalveolar lavage fluid, lactate dehydrogenase release, blood oxygen content, clinical biochemistry including blood fluoride levels, and gross necropsy including absolute and relative organ weights (OECD, 2018b).

3. Clinical signs should be evaluated to build the weight of evidence (WoE) for specific neurotoxicity hazards or other related effects in later testing. Clinical observations may not be limited to changes in skin, fur, eyes, mucous membranes, occurrence of secretions and secretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern and/or mouth breathing, and any unusual signs of urination or defecation). Further, any unusual responses with respect to body position, activity level (e.g., decreased or increased exploration of the standard area) and co-ordination of movement should also be noted. Changes in gait, (e.g., waddling, ataxia), posture (e.g., hunched-back) and reactivity to handling, placing or other environmental stimuli, as well as the presence of clonic or tonic movements, convulsions, or tremors, stereotypies (e.g., excessive grooming, unusual head movements, repetitive circling) or bizarre behavior (e.g., biting or excessive licking, self-mutilation, walking backwards, vocalization) or aggression should all be recorded for potential reporting.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test are due 365 days after the effective date of the Order 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. Report any portal-of-entry effects and clinical signs.

c. Two-Generation Reproduction Toxicity; OECD (2001)

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans. Additional requirements specific to OECD (2001) include:

1. Must be performed in the more sensitive species given the results of the Partition Coefficient and ADME Inhalation study.

2. With respect to thyroid measurements, T3, T4, and TSH must be measured for both male and female F0 animals.

3. Must preserve tissues for histopathological analysis of nasal and respiratory tract for portal of entry effects and to follow potential epithelial remodeling and other effects *in vivo* that were found in the *in vitro* respiratory tract epithelial toxicity testing. EPA will determine whether these tissues must undergo analysis based on study results. Sections of the nasal tissues and upper and lower respiratory tracts for histopathological examination must generally include at least 3 sections from the lungs, at least 4 sections from the nasal cavity/nose/turbinates, and sections from the larynx, tracheobronchial, bronchiolar, terminal/respiratory bronchiolar, and pulmonary regions of the respiratory tract, from each test animal. Examinations must clearly define and examine severity scores, and descriptions of potential legions for the microscopic analyses of these tissues (Corps et al., 2010; Renne et al., 2009; Harkema et al., 1987). The different regions (sections) of these tissues will ensure coverage of a variety of cell types, morphologies and their function/dysfunction following exposure, and information for dosimetry.

   Informative criteria must clearly define what morphologic features the pathologist observed to categorize a given change as minimal, mild, moderate, or severe, e.g., number of cell layers, approximate % area affected. There is concern that there might be difficulty interpreting severity if only vague statements are provided for each grade, which would hinder the ability to differentiate between adverse and non-adverse lesions and identify hazard. The consensus reached by Kaufmann et al. (2009) for an example of using descriptive terms and more detail in histopathology interpretive statements.

   Any revised scoring criteria with explicit rationale, must be provided for review prior to initiation of subsequent testing (Kaufmann et al., 2009).

4. Instead of the brain histological analysis typically performed under OECD 416, this test order requires that this histological analysis comprise 7 brain levels (sections) including the olfactory bulb, optic chiasm, infundibulum, cerebral peduncle, cranial nerve, and more that encompass approximately 50 neuroanatomic sites (NTP, 2015; Rao et al., 2014; Bolon et al., 2013; Rao et al., 2011).

   Informative criteria must clearly define what morphologic features the pathologist observed to categorize a given change as minimal, mild, moderate, or severe, e.g., number of cell layers, approximate % area affected.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, all study plan requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol. Test reports submitted to EPA for this test are due 1265 days after

EPA confirms with the Order recipient which species will be used based on EPA's conclusion of the review of the results from the ADME test.

1. Harmonized Template OHT 73 (Toxicity to Reproduction)

2. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2073%20-%20ENDPOINT_STUDY_RECORD.ToxicityReproduction_v9.1%20-Nov%202021.docx

d. Developmental Neurotoxicity Study via Inhalation; OECD (2007)

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans. Additional requirements specific to OECD 426 (2007) include:

1. Must be performed in the more sensitive species given the results of the Partition Coefficient and ADME Inhalation study.

2. Instead of the brain histological analysis typically performed under OECD 416, this test order requires that this histological analysis comprise 7 brain levels (sections) including the olfactory bulb, optic chiasm, infundibulum, cerebral peduncle, cranial nerve, and more that encompass approximately 50 neuroanatomic sites (NTP, 2015; Rao et al., 2014; Bolon et al., 2013; Rao et al., 2011).

3. Informative criteria must clearly define what morphologic features the pathologist observed to categorize a given change as minimal, mild, moderate, or severe, e.g., number of cell layers, approximate % area affected.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, all study plan requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol. Test reports submitted to EPA for this test are due 425 days after EPA confirms with the Order recipient which species will be used based on EPA's conclusion of the review of the results from the ADME test.

1. Harmonized Template OHT 76 (Neurotoxicity)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2076%20-%20ENDPOINT_STUDY_RECORD.Neurotoxicity_v10.1%20-Nov%202021.docx

e. Subchronic Neurotoxicity Study in Rodents via Inhalation; OECD (1997)

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans. Additional requirements specific to OECD 424 (1997) include:

1. Must be performed in the more sensitive test species given the results of the Partition Coefficient and ADME Inhalation study.

2. Must include the following: pulmonary function testing, measured rates of respiration, analysis of bronchoalveolar lavage fluid, lactate dehydrogenase release, blood oxygen content, body weight and food/water consumption, clinical observations, brain weight, neuropathology, motor activity, motor and sensory function, learning and memory.

3. Require histological analysis of 7 brain levels (sections) including the olfactory bulb, optic chiasm, infundibulum, cerebral peduncle, cranial nerve, and more that encompass approximately 50 neuroanatomic sites (NTP, 2015; Rao et al., 2014; Bolon et al., 2013; Rao et al., 2011).

   Informative criteria must clearly define what morphologic features the pathologist observed to categorize a given change as minimal, mild, moderate, or severe, e.g., number of cell layers, approximate % area affected.

4. Must be performed in both female and male sexes.

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, all study plan requirements must be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol. Test reports submitted to EPA for this test are due 425 days after EPA confirms with the Order recipient which species will be used based on EPA's conclusion of the review of the results from the ADME test.

1. Harmonized Templates OHT 76 (Neurotoxicity) and OHT 68 (Repeated dose toxicity: inhalation)

2. Harmonized Template URLs:
   https://www.oecd.org/env/ehs/testing/OHT%2076%20-%20ENDPOINT_STUDY_RECORD.Neurotoxicity_v10.1%20-Nov%202021.docx

   https://www.oecd.org/env/ehs/testing/OHT%2068%20-%20ENDPOINT_STUDY_RECORD.RepeatedDoseToxicityInhalation_v9.2%20-Nov%202021.docx

f. Combined Chronic Toxicity/Carcinogenicity Studies; OECD (2018a)

i. Study Plans

Please see **Unit VI.C** of the Order for overall requirements for study plans. Additional requirements specific to OECD 453 (2018) include:

1. Must include the following: morbidity, mortality, ophthalmological examination, body weight and food/water consumption, food efficiency, hematology and clinical biochemistry including blood fluoride levels, gross necropsy including absolute and relative organ weights, histopathology.

2. With respect to thyroid measurements, T3, T4, and TSH must be measured for both male and female F0 animals.

3. Require histopathological analysis of nasal and respiratory tract for portal of entry effects and to follow potential epithelial remodeling and other effects *in vivo* that were found in the *in vitro* respiratory tract epithelial toxicity testing. This histopathological analysis applies to tissues collected at the end of the study period, plus any animals sacrificed early due to excess toxicity/distress. Sections of the nasal tissues and upper and lower respiratory tracts for histopathological examination must generally include at least 3 sections from the lungs, at least 4 sections from the nasal cavity/nose/turbinates, and sections from the larynx, tracheobronchial, bronchiolar, terminal/respiratory bronchiolar, and pulmonary regions of the respiratory tract, from each test animal. Examinations must clearly define and examine severity scores, and descriptions of potential legions for the microscopic analyses of these tissues (Corps et al., 2010; Renne et al., 2009; Harkema et al., 1987). The different regions (sections) of these tissues will ensure coverage of a variety of cell types, morphologies and their function/dysfunction following exposure, and information for dosimetry.

   Informative criteria must clearly define what morphologic features the pathologist observed to categorize a given change as minimal, mild, moderate, or severe, e.g., number of cell layers, approximate % area affected.

   Any revisions or limitations of the scoring criteria with explicit rationale, must be provided for review and consideration for the overall WoSE (Kaufmann et al., 2009).

4. Require histological analysis of 7 brain levels (sections) including the olfactory bulb, optic chiasm, infundibulum, cerebral peduncle, cranial nerve, and more that encompass approximately 50 neuroanatomic sites (NTP, 2015; Rao et al., 2014; Bolon et al., 2013; Rao et al., 2011).

5. Informative criteria must clearly define what morphologic features the pathologist observed to categorize a given change as minimal, mild,

moderate, or severe, e.g., number of cell layers, approximate % area affected. Must be performed in either rats or mice, as directed by EPA and based on results of the Partition Coefficient and ADME Inhalation study and/or other prior testing.

ii. Test Reports

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

In addition to the requirements provided by **Unit VI.C**, all study plan requirements should be reflected in the final test report including all non-significant and negative results and/or deviations from the protocol. Test reports submitted to EPA for this test are due 1495 days after EPA confirms with the Order recipient which species will be used based on EPA's conclusion of the review of the results from the ADME test.

1. Harmonized Template OHT 72 (Carcinogenicity)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%2072%20-%20ENDPOINT_STUDY_RECORD.Carcinogenicity_v8.1%20-Nov%202021.docx

III. Optional Physical-Chemical Properties

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

i. Study Plans

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

No additional requirements

ii. Test Reports

In addition to the requirements provided by **Unit VI.C**, test reports submitted to the EPA for this test must include the following, as applicable:

1. Harmonized Template Identifier: OHT 2 (Melting point/freezing point)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%202%20-%20ENDPOINT_STUDY_RECORD.Melting_v8.1%20-Nov%202021.docx

APPENDIX F – SUMMARY OF AVAILABLE DATA

Available toxicity studies on HFPO were reviewed in accordance with the draft TSCA Systematic Review Protocol (USEPA, 2021a). Data quality is evaluated on an outcome-by-outcome basis (e.g., Health Outcome), not on a study-wide basis. All data were considered for the determination of additional toxicity testing needs in this Order.

Of the acute studies, one OECD 403 rat study and one guideline-equivalent rat study received Acceptable (High Confidence) on all Health Outcomes that were inventoried, including mortality (which is the primary Health Outcome for an acute toxicity study). There was an OECD 422 Combined Repeated-Dose and Reproduction/Developmental Toxicity Screening Test in rats that received Acceptable (High) on all Health Outcomes that were inventoried. There were three subchronic studies (one in rat, one in dog, and one in rabbit) that received Acceptable (Medium Confidence) on all Health Outcomes that were inventoried; these studies looked at a variety of organs and organ systems. Finally, of the three occupational studies in humans, only one received Acceptable (Medium Confidence) on all Health Outcomes that were inventoried. However, due to the cross-sectional study design (*i.e.,* data were analyzed from a population at a specific point in time), EPA was not able to draw any causal inferences from this study. The acute (OECD 403) and OECD 422 studies were conducted in accordance with OECD guidelines and Good Laboratory Practice (GLP). The OECD 474 mouse blood micronucleus test was Acceptable (High Confidence) on all Health Outcomes that were inventoried. The remaining ten studies received Low Confidence, Uninformative, or Not Applicable ratings.

Table 1. Health Outcome Endpoint Quality Review Results on available in vivo studies (H = High Confidence, M = Medium Confidence, L = Low Confidence, U = Uninformative, NA = Not Applicable)

	Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study Info	Duration (A= acute, SC = Subchronic, ST = Short Term) *assumed	A	A	A	A	A	A	A	A*	OECD 422	SC	SC	SC	ST *	SC	SC	SC	OECD 474
	Species (D=dog, R= rat, Rb= rabbit M=mouse, H= human)	D	R	D	R	R	R	Rb	M	R	R	D	Rb	R	H	H	H	M
	Route (I= inhalation, D= dermal, O=occupational)	I	I	I	I	I	I	D	I*	I	I	I	I	I	O	O	O	I
	Epi Study Type														Medical Records Review	Cross-Sectional	Cross-Sectional	
Health Outcomes	Cardiovascular			U						H				U		M	L	
	Gastrointestinal			U						H				U				
	Immunological/hematological					H				H	M	M	M			M	L	
	Kidney			U	U	H				H	M	M	M			M	L	
	Liver									H	M	M	M	U	U	M	L	
	Mortality		H	U	U	H	U	U	U	H	M	M	M	U				H
	Neurological			U		H	U	U	U	H	M	M	M	U				

	Nutritional/Metabolic		H			H	U		U	H	M	M	M	U				H
	Reproductive/Developmental									H	M	M	M	U				
	Respiratory			U	U	H				H	M	M	M			M	L	
	Skin							U		H								
	Thyroid									H	M	M	M					
	Other - Adrenal weights										M	M	M					
	Other - Clinical Signs of Toxicity	M	H		U	H				H								
	Other - Unspecified Gross Necropsy	M						NA						U				
	Other - Genotoxicity																	H

Reference ID key

Studies are available in the docket at regulations.gov.

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	OTS0215034_19450 HLO-256-66	E. I. du Pont de Nemours and Co. Hazleton Laboratories, Incorporated Acute Inhalation Exposure – dog Interim Report 1966	878220384
2	ECHA35_428591 DuPont-5408	E. I. du Pont de Nemours and Co. Haskell Laboratory for Toxicology and Industrial Medicine Laboratory Project ID: DuPont-5408 Inhalation Median Lethal Concentration (LC_{50}) in Crl:CD(SD)IGS BR Rats 2001	
3	OTS0215034_19449 HLO-255-66	E. I. du Pont de Nemours and Co. Hazleton Laboratories, Incorporated Report Number MRO-917-1 Acute inhalation exposure, six hours – dog Preliminary Report 1966	878220383
4	OTS0215034_19447	E. I. du Pont de Nemours and Co.	878220381

	HL-55-59	Haskell Laboratory for Toxicology and Industrial Medicine Haskell Laboratory Report No. 55-59 Medical Research Project MR-125 Acute inhalation study in ChR-CD Male Albino Rats 1959	
5	FYI-11-01681.pdf	Daikin Industries, Ltd Kashima Laboratory of Mistubishi Chemical Safety Institute Ltd Study No B030119 An Acute Toxicity Study of Hexafluoropropylene Oxide 2003	84110000006
6	OTS0215034_19448	E. I. du Pont de Nemours and Co. Haskell Laboratory for Toxicology and Industrial Medicine Haskell Laboratory Report No. 35-60, 42-60, 73-65 Acute Inhalation Toxicity -rats 1987	878220382
7	OTS0215034_19448	E. I. du Pont de Nemours and Co. Haskell Laboratory for Toxicology and Industrial Medicine Haskell Laboratory Report No. 35-60, 42-60, 73-65 Acute Skin Absorption Toxicity 1987	
8	OTS0215034_19457	E. I. du Pont de Nemours and Co. Haskell Laboratory for Toxicology and Industrial Medicine Haskell Laboratory Report No. 44-59 Haskell No. 2628 Screening Test for Anesthetic Properties 1982	878220391
9	C4_8EHQ-1107-17005A.pdf DuPont-20964	E. I. du Pont de Nemours and Co. DuPont Haskell Global Centers for Health and Environmental Sciences Laboratory Project ID: DuPont-20964 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in Crl:CD(SD) rats (OECD 422) 2007	
10	OTS0215034_19446 HLO-261-67 HLO-320-68	E. I. du Pont de Nemours and Co. Hazleton Laboratories, Incorporated Report Number MRO-0917-001 90-Day Exposure –Dogs, Rats, and Rabbits Final report 1968	
11	OTS0215034_19446 HLO-261-67 HLO-320-68	E. I. du Pont de Nemours and Co. Hazleton Laboratories, Incorporated Report Number MRO-0917-001 90-Day Exposure –Dogs, Rats, and Rabbits Final report 1968	

12	OTS0215034_19446 HLO-261-67 HLO-320-68	E. I. du Pont de Nemours and Co. Hazleton Laboratories, Incorporated Report Number MRO-0917-001 90-Day Exposure –Dogs, Rats, and Rabbits Final report 1968	
13	OTS0215034_19452 HL-17-65	E. I. du Pont de Nemours and Co. Haskell Laboratory for Toxicology and Industrial Medicine Haskell Laboratory Report No. 17-65 Medical Research Project MR-604 Subacute inhalation study in ChR-CD Male Albino Rats (1965)	
14	OTS0215034_19459	E. I. du Pont de Nemours and Co. Medical Record Review of HFPO Workers 1982	878220393
15	OTS0206316_20150	E. I. du Pont de Nemours and Co. Cross-Sectional Survey of Health Indices in Experimental Station Employees with Past History of Working in HFPO or Other Nafion® Areas 1983	878213770
16	OTS0206316_20149	E. I. du Pont de Nemours and Co. Health Indices in Fayetteville Plant Employees with Past History of Exposure to HFPO 1983	878213769
17	DuPont-17871-575	E. I. du Pont de Nemours and Co. DuPont Haskell Global Centers for Health & Environmental Sciences Laboratory Project ID: DuPont-17871-575 Crl:CD1(ICR) Mouse Blood Micronucleus Test by Inhalation (OECD 474) 2008	