ASSISTANT ADMINISTRATOR FOR CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

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

Chemical Substance Subject to this Order:

Chemical Name: 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide

Chemical Name Synonym(s): *N*-Methyl-*N*-(2-hydroxyethyl) perfluorooctanesulfonamide; 2-(*N*-Methylperfluoro-1-octanesulfonamido)ethanol

Chemical Name Acronym: NMeFOSE

Chemical Abstracts Service Registry Number (CASRN): 24448-09-7

Docket Identification (ID) Number: EPA-HQ-OPPT-2023-0544

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

Testing Required by this Order:

Testing is listed by physical-chemical properties, environmental fate and behavior, and health effects study types: health effects testing is further listed by exposure route. All tests listed under Tier 1.1 are required as part of the initial response to the Order. Further testing under Tiers 1 and 2 will be performed in accordance with the decision logic shown in **Figures 1** and **2** of **Section V.B**.

1. Physical-Chemical Properties

Tier 1.1- required testing

a. Melting point/ melting range **(OECD 102 (1995))**

b. Boiling point **(OECD 103 (1995))**

c. Vapor pressure **(OECD 104 (2006))** as applicable to liquids

d. Water solubility **(OECD 105 (1995))**

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

f. Determination of pH, Acidity and Alkalinity **(OECD 122 (2013))**, as applicable

g. Dissociation constants in water **(OECD 112 (1981))**

h. Surface Tension of Aqueous Solutions **(OECD 115 (1995))**

Tier 1.2 - required testing dependent on results of Tier 1.1 surface tension test

a. Assembly of Micelles or the Critical Micelle Concentration (CMC) **(ISO 4311)**

Tier 1.3 - required testing dependent on results of Tier 1.1 surface tension test and Tier 1.2 critical micelle concentration test

a. *n*-octanol/water Partition Coefficient HPLC Method, or K_{ow} **(OECD 117 (2022))**

2. Health Effects: *In Vitro* Dermal Route

Tier 1.2 – required testing dependent on results of Tier 1.1 Hydrolysis as a Function of pH test

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

3. Environmental Fate

Tier 1.3 - required testing dependent on results of Tier 1.1 surface tension test and Tier 1.2 critical micelle concentration test

a. Estimation of the Adsorption Coefficient, or K_{oc}, on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) **(OECD 121 (2001))**

Tier 2.1 - required testing

a. Bioaccumulation in Fish: Aqueous and Dietary Exposure **(OECD 305 (2012))**

4. Health Effects: Oral and Inhalation Routes

Tier 2.1 – required testing

a. Toxicokinetics, oral exposure **(OECD 417 (2010))**

Tier 2.2 – required testing in a single rodent species dependent on TK oral study results

a. Toxicokinetics, inhalation exposure **(OECD 417 (2010))**

b. Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test **(OECD 422 (2016)),** TK half-life dependent.

Recipients of this Order:

Company Name: 3M Company

Company Name: Wacker Chemical Corporation

Dear Recipient:

This Order requires you and the other named manufacturer(s) and/or processor(s) of NMeFOSE (CASRN 24448-09-7) to develop and submit certain information for NMeFOSE, or otherwise respond to the U.S. Environmental Protection Agency (referred to herein as "the 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.

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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 N-Methyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide (NMeFOSE, CASRN 24448-09-7). 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 5 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.

Section 4(b)(3) authorizes EPA to require testing from companies that manufacture or process a chemical substance subject to a Section 4(a) Order. A company does not have to be manufacturing or processing the substance at the time the Order is issued to be considered a company that manufactures or processes the substance (see Policies Regarding Manufacturers and Processors Subject to TSCA Section 4(a) Testing, https://www.epa.gov/system/files/documents/2022-08/Policy_Manufacturing_Processing_August_2022.pdf). Generally, the EPA typically includes companies has manufactured or processed a chemical substance during the five years prior to the effective date of the issued Order, though the Agency may apply a longer or shorter period of time when appropriate in specific cases.

For purposes of this Order, a recipient is subject if it has manufactured or processed the chemical at any time during the 5 years preceding the date of this Order. If a recipient of this Order has not manufactured or processed the chemical during the prior 5 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 NMeFOSE may present an unreasonable risk of injury to human health or the environment.

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

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

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

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

Note that agencies, as well as programs within a given agency, may define PFAS differently as applicable to the statute and regulatory needs. NMeFOSE fits the definition of PFAS provided above as well as other definitions of PFAS (e.g., OECD's definition). Though definitions of PFAS may differ, PFAS based on the definition used for purposes of this Order share common toxicity concerns. As discussed below, toxicity information on other PFAS meeting the above definition contribute to the may present finding made by this Order, along with information specific to NMeFOSE.

The definition being used for this Order is not meant to represent an agency-wide definition but is consistent with the recent definition proposed in a Significant New Use Rule on PFAS designated as inactive on the TSCA inventory (88 FR 4937, January 26, 2023 (FRL 9655-01-OCSPP)) and the Toxic Substances Control Act Reporting and Recordkeeping Requirements for Perfluoroalkyl and Polyfluoroalkyl Substances rule (88 FR 70516, October 11, 2023 (FRL-7902-02-OCSPP)). The definition could be revised for future cycles of Test Orders 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, 2022b; 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, there are consistent findings from epidemiology studies for increased cholesterol levels among exposed populations, with other limited findings related to infant birth weights, effects on the immune system, cancer (e.g., Health Effects Support Document for Perfluorooctanoic Acid (PFOA) (USEPA, 2016b)), and thyroid hormone disruption (e.g., Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) (USEPA, 2016a)). In humans and animals, some PFAS can cause adverse effects on the respiratory system following acute inhalation exposures (e.g., corrosion, chemical pneumonitis) (NLM, 2022). In some cases, cardiac sensitization may be a concern, where the heart is damaged in a way that it becomes sensitive to epinephrine (aka adrenaline) which can lead to potentially fatal arrhythmias (ECETOC, 2009). Visit these EPA webpages for more information on general concerns associated with PFAS: PFAS Explained (USEPA, 2022c) and Our Current Understanding of the Human Health and Environmental Risks of PFAS (USEPA, 2022b).

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

Hazard for 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide (NMeFOSE)

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

Based on predicted physical and chemical properties, all routes of exposure, including oral, dermal, and inhalation may be relevant for 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide. The EPA examined whether existing information is adequate to reasonably determine or predict the effects on health from 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide. The EPA considered all reasonably available human health-related toxicity studies identified in the following hazard domains:

- 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. The EPA also considered additional toxicity data provided by the Test Order recipients before issuance of the Test Order. The data provided by Test Order Recipients which the EPA considered for the data needs specified in this Order are publicly available at the Regulations.gov docket specific for this Order.

Seventeen studies were identified and considered prior to the issuance of this NMeFOSE Test Order pursuant to the requirements specified at TSCA sections 4(h)(1)(A) and 26(k), to consider reasonably available information. Each study underwent Data Quality Evaluation per the draft TSCA Systematic Review Protocol (USEPA, 2021a) (**Appendix F**). The seventeen studies included physical-chemical (**Table F1**), rat and rabbit toxicity (**Table F2**), environmental fate (**Table F3**), and ecotoxicity (**Table F4**) studies. Of the seventeen studies, eleven directly examined health effects *in vivo* that are relevant to human health hazard characterization. Nine of the eleven were single exposure (acute) studies and two were repeated-dose studies. One of the eleven, an acute inhalation study in rats, was uninformative due to deficiencies in the design and reporting of the study; four out of eleven were high confidence across all Health Outcomes (a cell proliferation assay in rat liver cells, an *in vivo* micronucleus assay in rats, a short-term oral toxicity study in rats, and a subchronic oral toxicity study in rats); four of the eleven were medium confidence across all Health Outcomes; and the remaining three of the eleven were a mix of medium and high confidence depending on the Health Outcome. NMeFOSE was found to be non-irritating to skin and eyes and to be toxic to the liver.

Increased risk of certain types of cancer are associated with exposure to PFAS, generally (USEPA, 2022b). Available *in vitro* and *in vivo* genotoxicity data on NMeFOSE reduce concerns for this mode of action for cancer, though non-genotoxic modes of action may still be possible. The structure of NMeFOSE was not within the applicability domain of OncoLogic version 9.3. NMeFOSE did not have any alerts for skin or respiratory sensitization in the OECD QSAR Toolbox version 4.5. It should be noted that, generally, PFAS are known to have unique properties which may impact the applicability of certain models (Dawson et al., 2023; Sosnowska et al., 2023).

NMeFOSE is a di-*N*-substituted sulfonamide. Expected biotransformations include *N*-dealkylation of the *N*-methyl group; oxidation of the *N*-hydroxyethyl group to the corresponding aldehyde and then carboxylic acid along with *N*-dealkylation of any of these groups; and hydrolysis of the sulfonamide to give the sulfonic acid (PFOS) and hydroxylamine (Mejia Avendaño and Liu, 2015; Benskin et al., 2013). PFOS is a known toxicant, causing a wide range of health effects including cholesterol increase, thyroid effects and infertility (Saikat et al., 2013). The EPA recently published an interim health advisory on PFOS (USEPA, 2022a) and proposed a National Primary Drinking Water Regulation (NPDWR) to establish a legally enforceable level for PFOS based on evidence of its carcinogenic likelihood (2023).

In summary, for NMeFOSE, the EPA identified hazards for acute toxicity and specific target organ toxicity, and related concerns for health effects from its biotransformation products, including PFOS.

Exposure for 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide (NMeFOSE)

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. 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide is listed as "active" on the TSCA Inventory, as a result of this reporting, indicating a potential for exposure. The listing of NMeFOSE on the TSCA Inventory also includes a flag for a Significant New Use Rule (SNUR). In 2002 due to concerns for certain PFAS and their pervasive use, the EPA promulgated a SNUR that required persons to notify the EPA before commencing or recommencing any manufacture (including import) of certain PFAS (including NMeFOSE) for a use that is not exempted under 40 CFR 721.9582(a)(3) such as certain aviation, photoresist, or imaging film uses (67 FR 72854 (Dec. 9, 2002)). This SNUR was amended in 2013 so that any person would be required to notify EPA prior to processing NMeFOSE for any use except certain uses (78 FR 62443 (Oct. 22, 2013)). There may be exposure from the exempted uses as well as from the disposal of any exempted activities. Concern for NMeFOSE's exposure potential is discussed further below.

Based on modeled estimates of physical-chemical property values for NMeFOSE using the EPA's model, Open (Quantitative) Structure-activity/property Relationship App (OPERA v 2.9), the EPA tentatively concludes it is a soluble solid with the following properties:

- Vapor pressure range: 1×10^{-5} mmHg (estimated by OPERA)
- Water solubility: 0.82 mg/L (estimated by OPERA)
- Melting point: 65 °C (estimated by OPERA)
- Boiling point: 169 °C (estimated by OPERA)

Estimated physical-chemical properties tentatively indicate NMeFOSE is a soluble solid, and exposure via all routes of exposure, including oral, dermal, and inhalation are of concern for this substance and are data needs addressed in this TO. In addition to estimated physical-chemical properties, experimental data are available for water solubility, *n*-octanol/water partition coefficient (K_{ow}) and melting range (**Appendix F, Table F1**). However, these available studies did not meet the requirements of this Order on the basis of explicit statements within the provided reports that the data were unreliable. Information deficiencies and unreliability included uncharacterized test substance purity and nonspecific analytical methods. The EPA is considering this information qualitatively rather than quantitatively, as these data tentatively confirm the physical state and potential bioaccumulation of NMeFOSE. Manufacturing, processing, use, disposal, and/or distribution in commerce of soluble solid substances may lead to dermal and inhalation exposures to workers in addition to potential oral, dermal, and inhalation to the general population and to consumer exposure concerns.

Inhalation is a concern for PFAS in a solid state as these substances have been measured in indoor air and dust, corroborating known and/or past consumer uses including treated apparel, use in furniture as coatings, paints, varnishes and wood processing, as well as use in carpeting (NLM, 2023). Specifically for the data needs of this Order, NMeFOSE has been measured in indoor air and

dust internationally (Norway,(Padilla-Sánchez et al., 2017; Haug et al., 2011)) and in North America (Eichler et al., 2023; Zheng et al., 2020; Goosey and Harrad, 2011; Dinglasan-Panlilio and Mabury, 2006; Shoeib et al., 2005). For instance, Shoeib et al., (2005) reported a mean indoor air NMeFOSE concentration from over 50 homes in Ottawa, Canada to be 1,970 pg/m^3, reaching up to 8,190 pg/m^3. A study by Eichler et al., (2023) measured NMeFOSE concentrations in air and cotton cloth in 11 homes in North Carolina and reported a mean concentration of 600 pg/m^3 in air. In addition, among nine neutral PFAS monitored, NMeFOSE was shown to accumulate most significantly on cotton cloth over the period of 9 months, reaching a concentration of up to 0.26 ng/cm^2. Zheng et al., (2020) further reported NMeFOSE indoor exposure data showing that it was the most abundant PFAS detected in nap mat samples from 8 childcare centers (7 in Seattle, Washington and 1 in West Lafayette, Indiana) with a median concentration of 56 ng/g and a contribution of 48% to total PFAS concentration. Dermal exposure is a data need for PFAS, generally (Ragnarsdóttir et al., 2022; ATSDR, 2021). Methods for estimating transdermal uptake directly from air, and estimations for dermal-to-inhalation exposure ratios were recently applied to NMeFOSE (Weschler and Nazaroff, 2014). Kissel et al., (2023) calculated a dermal-to-inhalation uptake ratio, using SPARC-estimated physical-chemical properties, indicating that '… potential for transdermal uptake is at least 5 times greater and may be more, compared to intake through inhalation'.

Oral exposure to NMeFOSE can occur through multiple scenarios. Typical exposure pathways considered for industrial chemicals include: drinking water ingestion from surface water sources, drinking water ingestion from wells impacted by landfill leachate, and fish ingestion when a chemical is bioaccumulative (USEPA, 2012). For instance, NMeFOSE has been detected in fish tissues (Guo et al., 2023; Ali et al., 2021; Board, 2020; Åkerblom et al., 2017; 3M Environmental Lab, 1979). Further, it has been detected in biosolids at an average concentration of 0.18 µg/kg (McNamara et al., 2023), and the application of biosolids can lead to releases to surface and groundwater as well as uptake into fertilized crops, which can later contribute to oral exposures. Hand-to-mouth activity can also lead to oral exposures, especially to infants, which may be relevant for treated objects (USEPA, 2011).

NMeFOSE may be subject to long-range transport. Previous research has quantified NMeFOSE in outdoor air gas and particulate phases at mean concentrations up to 359 pg/m^3 across North America, Europe, and the North Atlantic Ocean (Jahnke et al., 2007; Piekarz et al., 2007; Shoeib et al., 2006; Shoeib et al., 2004; Stock et al., 2004). NMeFOSE was also the most frequently detected perfluoroalkane sulfonamide (26%) reported in Wisconsin (USA) precipitation over a 5-month period (Pfotenhauer et al., 2022) and represented 11% of total PFAS detected in snowpack sampled from Arctic glaciers in Norway (Xie et al., 2015). It was also detected in 27% of ambient air samples collected by the Minnesota Pollution Control Agency in a recent year-long study (median concentration of 12 pg/m^3 (MPCA, 2022)), and in the most rural monitoring site (Grand Portage), chosen as a reference site, it was detected in 67% of ambient air samples. It is conjectured that NMeFOSE may be degraded under atmospheric conditions prevalent in urban areas and more persistent in areas with lower NO_2 air concentrations (MPCA, 2022).

Because of the potential for adverse effects and exposure via all routes (oral, inhalation and dermal), there is a potential for risk. In evaluating potential exposures to NMeFOSE, the Agency considered: (a) its status on the TSCA Inventory and (b) reported monitoring information in outdoor and indoor environmental media, as well as (c) presence in biosolids.

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

The testing required by this Order addresses only the insufficient data that has been identified in the process of developing this 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.

Experimental data are available for water solubility, *n*-octanol/water partition coefficient (K_{ow}) and melting range (**Appendix F, Table F1**). However, these available studies did not meet the best available science standards on the basis of explicit statements within the provided reports that the data were unreliable. Information deficiencies and unreliability included uncharacterized test substance purity and nonspecific analytical methods.

For NMeFOSE, the *N*-methyl-*N*-hydroxyethylsulfonamide "head" group is hydrophilic while the perfluorooctane "tail" group is hydrophobic; molecules that contain distinct hydrophilic and hydrophobic regions are potential surfactants (Davidovits, 2019). Surfactants, including certain categories of PFAS, may pose potential hazards to humans, depending on their conditions of use, chemistry, or size characteristics, since surfactants can disrupt the epithelial linings and other portal-of-entry concerns, or perturb cell membranes (Henry et al., 2021).

Data from eleven toxicity studies were reviewed (**Appendix F, Table F2**) and determined to provide evidence of health concerns, but these studies were insufficient to predict the specific health effects of concern the EPA has identified for PFAS, and for NMeFOSE in particular (**Unit II.B.1**). EPA's analysis and determination that these studies are insufficient is discussed in Appendix F.

Further, the EPA lacks information to identify the most relevant rodent species for *in vivo* testing. There is also insufficient information to estimate the half-life and identify metabolites of NMeFOSE. *Tier 2.1* consists of a toxicokinetics study in two species to inform species applicability and provide absorption, distribution, metabolism and excretion information for oral exposures to NMeFOSE. EPA further lacks toxicokinetic information for NMeFOSE exposure via the inhalation route which will be provided in the Tier 2.2 toxicokinetics study (in the most sensitive species as determined by the Tier 2.1 study). *Tier 2.2* also consists of an OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, which covers a large number of endpoints known to be relevant to PFAS in a single guideline and can be used as the basis for follow-up, definitive toxicity testing. Structurally similar PFAS have shown effects on neonates at lower exposure levels than the corresponding liver effects in adults(ATSDR, 2021); a reproduction study where animals are exposed and mated and the offspring examined for adverse effects is therefore an outstanding data need.

Data from four environmental fate and behavior studies were also reviewed (**Appendix F, Table F3**). The reported data in most of these studies lacked detailed methodological information, analytical specificity, appropriate laboratory techniques, and/or chemical identification, thus, did not meet the best available scientific standards. One review study qualitatively indicates that NMeFOSE is persistent within the environment and sorbs strongly to soils. Another sludge sorption study does not provide a carbon/water partition coefficient (Koc) and has several deficiencies. For example, the use of Teflon tubes in the sludge sorption study is not suitable for PFAS analytes, sludge samples did not have masses balanced, and proper controls were lacking for the lowest concentrations. The investigation of the uptake and bioaccumulation of NMeFOSE also remains a data need, as available studies have not reported both media concentrations and whole body/tissue concentrations.

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

C. Other Uses of This Data: PFAS Terminal Categories

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

The Testing Strategy categorizes PFAS based on the information on chemical structure and certain physical-chemical properties. 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 of over 10,000 PFAS into nine primary categories and one additional category denoted as "Others." This was further refined by the presence/absence of a ring substructure (cyclic/acyclic), with additional subcategorization based on carbon chain length and similarity of chemical fingerprinting, resulting in "terminal categories" of PFAS.

Using this approach, the EPA categorized NMeFOSE as belonging to the "'FASA based PFAA precursors,' 'gte 7'" terminal category. An additional factor in the initial categorization approach is substance volatility, as predicted by OPERA (Mansouri, 2022). For NMeFOSE, it is not predicted to be volatile under ambient conditions although inhalation concerns exist as described above.

This Order pertains to 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctane-1-sulfonamide (NMeFOSE; CASRN 24448-09-7). The EPA's concerns related to NMeFOSE, and its decision to issue this Order pursuant to TSCA Section 4(a)(1)(A)(i), may also exist for other PFAS in its terminal category. As the EPA iteratively improves its understanding of PFAS, categorization of these chemical substances will evolve. Further, the EPA may determine that testing is required on other PFAS in the same terminal category as NMeFOSE.

D. ADDITIONAL TSCA SECTION 4 CONSIDERATIONS

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

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

2. The EPA is using a tiered testing strategy

This Order includes a tiered testing approach, consistent with Section 4(a)(4) of TSCA. Developing certain information, such as physical-chemical property information (*i.e.*, water solubility, boiling point, hydrolysis, vapor pressure, and surface tension), initially ensures higher-tier testing is applicable to the chemical substance, exposure routes are feasible, and testing on vertebrate animals are appropriate.

NMeFOSE has structural alerts for surfactancy which can be definitively measured via testing for surface tension and determination of the critical micelle concentration/assembly. No existing information met this data need for NMeFOSE.

Additional testing to determine the environmental fate, transport, and potential of NMeFOSE to bioaccumulate is also needed. Results from hydrolysis, *n*-octanol/water partition coefficient and absorption coefficient will inform bioaccumulation testing in fish with aqueous and dietary exposures (OECD, 2012).

The results of the *Tier 2.1* toxicokinetic study ("TK study") via oral route of exposure will be used to select the most sensitive rodent species for subsequent tiered *in vivo* testing in *Tier 2.2*. This approach to tiered testing thereby reduces vertebrate animal use by performing the TK study via the inhalation route of exposure in only one rodent species. TK information via all routes is critical for enabling route-to-route extrapolation (OECD, 2010).

Section 4(a)(4) states that tiered testing regimes may bypass earlier tiers 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." For this Order, the EPA is implementing a tiered testing regime that includes screening-level testing to inform whether additional tests are necessary. Given that later tiers of testing are dependent on the results from earlier tiers, some testing outlined in this Order may ultimately not be required.

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, the EPA reviewed OCSPP test methods and data evaluation reports, OECD test guidelines and guidance, and other peer-reviewed and/or publicly available methodology/protocol repositories. In this Order, the EPA is including an *in vitro* dermal absorption test as a non-vertebrate alternative test to evaluate the importance of the dermal route of exposure for this substance. The information

from the *in vitro* study may eliminate the need for additional *in vivo* testing via the dermal route of exposure.

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 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 toxicokinetic 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 in rats and mice from oral, dermal, and inhalation exposures. 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 NMeFOSE 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 initial *Tier 2.1* TK test via the oral route of exposure within this Order to select the most appropriate rodent species (*i.e.*, rat or mouse). Because inhalation is also a concern for NMeFOSE, a subsequent toxicokinetic study via the inhalation route of exposure is also required, but only in the most sensitive species (the species in which NMeFOSE has the longer half-life, as determined by the oral TK test).

A subsequent phase of testing (post- toxicokinetics study by the oral route) also includes the OECD 422 screen. This data need requires vertebrate testing because there are currently no adequate substitutes for the reproductive endpoints. Also, reasonably available study information, including acute and repeated dose toxicity studies via the oral and inhalation routes of exposure either did not meet study quality requirements (Appendix F) and/or lacked reproductive and developmental outcome measurements and observations. In addition, data needs for this Order requires measured TK data both for planning subsequent toxicity testing, including critically to select the most sensitive rodent species.

Because PFAS are found in aquatic systems worldwide (Kurwadkar et al., 2022; Sims et al., 2021), and are known to bioaccumulate (Brase et al., 2022; Pickard et al., 2022) and biomagnify (George et al., 2023; Miranda et al., 2022; Munoz et al., 2022) in aquatic species, the OECD TG 305, bioaccumulation in fish (OECD, 2012), is also required testing. PFAS are known to bioaccumulate by means other than traditional lipid partitioning (Evich et al., 2022), so bioaccumulation and bioconcentration predictive models based on logKow or logP values are not adequate for understanding accumulation behavior of PFAS. Monitoring NMeFOSE concentrations in fish tissues has had limited utility due to low recovery rates (< 20%) (Ali et al., 2021; Åkerblom et al., 2017), combined analytical results (3M Environmental Lab, 1979), and concentrations below detectable limits (Androulakakis et al., 2022; Pickard et al., 2022). While Guo et al., (2023) reported a mean NMeFOSE tissue concentration of 0.1 µg/kg (wet weight) in marine shellfish, fish, crustaceans, cephalopods, and sea cucumbers, NMeFOSE was detected in only 0.29% of samples. Moreover, none provide steady-state or kinetic bioconcentration factors (BCF/BMF) needed to assess the uptake and depuration of NMeFOSE in an aquatic vertebrate species. Thus, results for bioaccumulation in fish (i.e., OECD TG 305) remains a data need.

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 1.1 Study Plans and Test Report Deadlines

Tier 1.1 tests: • **Melting point/ melting range (OECD 102)** • **Boiling point (OECD 103)** • **Vapor pressure (OECD 104) as applicable to liquids** • **Water solubility (OECD 105)** • **Hydrolysis as a Function of pH (OECD 111)** • **Determination of pH, Acidity and Alkalinity (OECD 122)** • **Dissociation constants in water (OECD 112)** • **Surface Tension of Aqueous Solutions (OECD 115)**	**Recipient's Deadline (Days after the effective date of the Order)**	**The EPA Response Deadline* (Days after the effective date of the Order)**
Submit Pre-Draft Study Plan Check-in (via email)**	95	110
Submit Draft Study Plan	125	140
Submit Final Study Plan	170	185
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

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

The EPA will notify Test Order recipients in writing of their Tier 1.2 testing obligations after the evaluation of specific Tier 1.1 test results. Tier 1.2 deadlines will use the same structure as the Tier 1.1 tests. However, Tier 1.2 submission deadlines will be calculated based on the date of the EPA's

notification to proceed with Tier 1.2 tests rather than the effective date of the NMeFOSE Test Order. Multiple Tier 1.2 notifications may be presented to Test Order recipients, based on the timing of the EPA's approval of the Tier 1.1 submissions.

Tier 1.2 Study Plans and Test Report Deadlines

Tier 1.2 tests: • **Assembly of Micelles or the Critical Micelle Concentration (CMC) (ISO 4311)** • ***In vitro* skin absorption (OECD 428)**	**Recipient's Deadline (Days after the EPA notification to proceed with the Tier 1.2 Testing)**	**The EPA Response Deadline* (Days after the EPA notification to proceed with the Tier 1.2 Testing)**
Submit Pre-Draft Study Plan Check-in (via email)**	30	45
Submit Draft Study Plan	60	75
Submit Final Study Plan	105	120
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

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

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

Tier 1.3 Study Plans and Test Report Deadlines

Tier 1.3 tests: • **n-octanol/water Partition Coefficient HPLC Method, or Kow (OECD 117)** • **Estimation of the Adsorption Coefficient, or Koc, on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) (OECD 121)**	**Recipient's Deadline (Days after the EPA notification to proceed with the Tier 1.3 Testing)**	**The EPA Response Deadline* (Days after the EPA notification to proceed with the Tier 1.3 Testing)**
Submit Pre-Draft Study Plan Check-in (via email)**	30	45
Submit Draft Study Plan	60	75
Submit Final Study Plan	105	120
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

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

The EPA will notify Test Order recipients in writing of their Tier 2.1 testing obligations after the evaluation of specific Tier 1.3 test results. Tier 2.1 deadlines will use the same structure as the Tier 1.1 tests. However, Tier 2.1 submission deadlines will be calculated based on the date of the EPA's notification to proceed with Tier 2.1 tests. Multiple Tier 2.1 notifications may be presented to Test Order recipients, based on the timing of the EPA's approval of the Tier 1.3 submissions.

Tier 2.1 Study Plans and Test Report Deadlines

Tier 2.1 tests: • **Bioaccumulation in Fish: Aqueous and**	**Recipient's Deadline (Days after EPA notification to**	**The EPA Response Deadline* (Days after the**

Dietary Exposure (OECD 305) • **Toxicokinetics (OECD 417)**	**proceed with the Tier 2.1 Testing)**	**EPA notification to proceed with the Tier 2.1 Testing)**
Submit Pre-Draft Study Plan Check-in (via email)**	30	45
Submit Draft Study Plan	60	75
Submit Final Study Plan	105	120
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

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

The EPA will notify Test Order recipients in writing of their Tier 2.2 testing obligations after the evaluation of specific Tier 2.1 test results. Tier 2.2 deadlines will use the same structure as the Tier 2.1 tests. However, Tier 2.2 submission deadlines will be calculated based on the date of the EPA's notification to proceed with Tier 2.2 tests rather than the effective date of the NMeFOSE Test Order. Multiple Tier 2.2 notifications may be presented to Test Order recipients, based on the timing of the EPA's approval of the Tier 2.1 submissions.

Tier 2.2 Study Plans and Test Report Deadlines

Tier 2.2 tests: • **Toxicokinetics (OECD 417)** • **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422) with Functional observation battery (OECD 424)**	**Recipient's Deadline (Days after the EPA notification to proceed with the Tier 2.2 Testing)**	**The EPA Response Deadline* (Days after the EPA notification to proceed with the Tier 2 .2 Testing)**
Submit Pre-Draft Study Plan Check-in (via email)**	30	45
Submit Draft Study Plan	60	75
Submit Final Study Plan	105	120
Submit Final Test Report	Deadline varies per Test Requirement (See **Unit V** and **Appendix E**)	

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

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 no later than by the date of the next status update/check-in with 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.

For multi-tier Orders, individual responses are required for each tier of testing. After the EPA's notification that a subsequent tier is required in which the prescribed testing is confirmed, the EPA will provide Test Order Numbers to access the CDX reporting application module for the corresponding tier of testing of the Order. These additional Test Order Numbers will only be provided to the entities that have submitted in the first tier the response of "Develop the Information", "Submit Existing Information", or "Request an Exemption". Thus, entities that had their "Claim that You Are Not Subject to the Order" submission granted by the EPA in the first, or

prior, tier will not need to resubmit a response to subsequent tiered testing requirements. Entities that are subject to subsequent tier testing must re-submit their Identification Response and submit an Initial Response to the subsequent tier testing. For subsequent tier testing, the deadline for the Identification Response and Initial Response is the deadline provided for the given tier's Pre-Draft Study Plan Check-in deadline.

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 5 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 5 years prior to the effective date of this Order and does not intend to manufacture (including import) or process the chemical within the period of testing required by this Order (see **Unit V.B**). However, certain companies may have unique case-specific situations that present a compelling case that they are not "manufacturers" of the chemical substance that is subject to the action and may submit such information for the EPA's consideration. For example, a company may have gone into bankruptcy and be in the hands of receivers who do not seek to continue the company's manufacturing activities involving the chemical substance subject to the testing requirements. Such situations are anticipated to be uncommon and will be highly fact-determinant; decisions for such situations will be made on a case-by-case basis.

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

If based on the evidence you provide and other evidence available to the EPA, the Agency deems your claim to be inadequately substantiated, the EPA will deny your claim, and the original requirements 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 the EPA requires supporting documentation to demonstrate that consultations with laboratories was timely (e.g., correspondence with the laboratory).

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

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

Option 3: Request an Exemption

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The EPA's grant of an exemption is conditional upon the completion of the required tests according to the specifications of this Order (or other applicable rule, order, or consent agreement), including any modifications approved by the EPA. If the Agency subsequently determines that equivalent data has not been submitted in accordance with the applicable rule, order, or consent agreement, the Agency will provide notice through CDX of its preliminary decision to terminate the exemption. Within 30 days after receipt of such notice, the exemption holder may submit information in the

CDX portal to either rebut the EPA's preliminary decision to terminate the exemption or notify the EPA of its intent to develop the required information pursuant to the specifications established in this Order and any modifications approved by the EPA. If the exemption holder submits information to rebut the EPA's preliminary decision to terminate the exemption, then the EPA will provide the exemption holder an opportunity to request a hearing prior to issuing a final decision to terminate the exemption. Following the receipt of information to rebut the EPA's preliminary decision and any subsequent hearing, the EPA will render a final decision on whether to terminate the exemption, taking into account information submitted to rebut the EPA's preliminary decision and information presented at any hearing, as applicable. The Agency may, at its discretion, make use of procedures and standards applicable to exemptions regarding TSCA Section 4 rules, contained in 40 CFR part 790, subpart E.

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

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

As explained in **Appendix B** on Cost Sharing, persons who receive exemptions from testing have an obligation to reimburse the person(s) who perform the required testing and submit the required information for a portion of the costs incurred in complying with the requirement to submit such information, and any other person required to contribute to a portion of such costs. Entities that have incurred costs in complying with a testing requirement in this Order may seek reimbursement from exemption holders as soon as they receive the EPA's notification that the applicable testing requirement has been satisfied by the submitted Final Test Report. Normally, reimbursement allocation is worked out by the parties involved 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). Note that 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.

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, 2018a). **Appendix E** provides additional sources for guidelines and/or other requirements associated with specific testing.

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

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

A. OVERVIEW OF TEST REQUIREMENTS

NMeFOSE is predicted to be a soluble solid (which is supported by available qualitative information for melting point, water solubility, and *n*-octanol partition coefficient (**Table F1**)). Therefore, oral, dermal, and inhalation routes of exposure are relevant. For human health effects, this chemical has existing inhalation, oral, dermal, and ocular toxicity data (**Table F2**). This chemical also had some studies available for environmental fate and behavior, including absorption/desorption properties and degradation and accumulation potential testing (**Table F3**), as well as ecotoxicological studies (**Table F4**). These available studies (**Table F5**) were used to inform the testing requirements in this Order.

Initial measurements of physical-chemical properties ensure subsequent testing is applicable, exposure routes are relevant and feasible, and testing on vertebrate animals are appropriate.

1. Physical-Chemical Properties

Estimated physical-chemical properties suggest NMeFOSE is a soluble solid, and exposure via all routes of exposure, including oral, dermal, and inhalation are of concern for this substance and are data needs addressed in this TO. In addition to estimated physical-chemical property testing information, reasonably available experimental information, including testing for water solubility, *n*-octanol/water partition coefficient (Kow), and melting range, did not meet the requirements of this Order (Appendix F). The EPA is considering this information qualitatively rather than quantitatively as these data tentatively confirm the physical state and potential bioaccumulation of NMeFOSE. All physical chemical property testing remain data needs for this Order and the measured results are required to prepare the subsequent tiers of testing study plans. The rate of hydrolysis, as measured in the Hydrolysis as a function of pH (OECD 111; (OECD, 2004a)), influences test substance stability and therefore applicability for later testing (*e.g.*,applicability for *in vitro* dermal absorption testing).

NMeFOSE has characteristics of surfactants, as described above in Unit IIB, which has implications for subsequent testing applicability and study plan requirements. The surface tension test, and the follow-up critical micelle concentration test, if applicable, will determine if NMeFOSE is a surfactant and if so, how strongly surface active it is. If NMeFOSE is determined to be a surfactant, the two tests in *Tier 1.3* will not be required.

Tier 1.1 Physical-chemical property testing includes the following:

- Melting Point/Melting Range (**OECD 102 (1995)**)(OECD, 1995b)
- Boiling Point (**OECD 103 (1995)**)(OECD, 1995c)
- Vapor Pressure (**OECD 104 (2006)**)(OECD, 2006)
- Water Solubility (**OECD 105 (1995)**)(OECD, 1995a)
- Hydrolysis as a Function of pH (**OECD 111 (2004)**)(OECD, 2004a)
- Determination of pH, Acidity and Alkalinity (**OECD 122 (2013)**)(OECD, 2013)
- Dissociation constants in water **(OECD 112 (1981)) (**OECD, 1981**)**
- Surface tension of aqueous solutions: test method applicability may depend on the viscosity of the test substance and/or the testing solvent/vehicle **(OECD 115 (1995))** (OECD, 1995d) **or** (ASTM D1331, Methods A and C) (ASTM, 2021) (or DIN 14370) (DIN, 2004)

Tier 1.2 Required testing dependent on results of Tier 1.1 surface tension test:

- Assembly of Micelles or the Critical Micelle Concentration (CMC) **(ISO 4311)**(ISO, 2022)

Tier 1.3

- *n*-octanol/water Partition Coefficient HPLC Method, or K_{ow} **(OECD 117 (2022))** (OECD, 2022)

2. Health Effects: *In Vitro* Dermal Route

Tier 1.2

- Skin Absorption: *In Vitro* Method (**OECD 428 (2004)**)(OECD, 2004b))

3. Environmental Fate and Behavior: Adsorption/Desorption

Tier 1.3

- Estimation of the Adsorption Coefficient, or K_{oc}, on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) **(OECD 121 (2001))**(OECD, 2001)

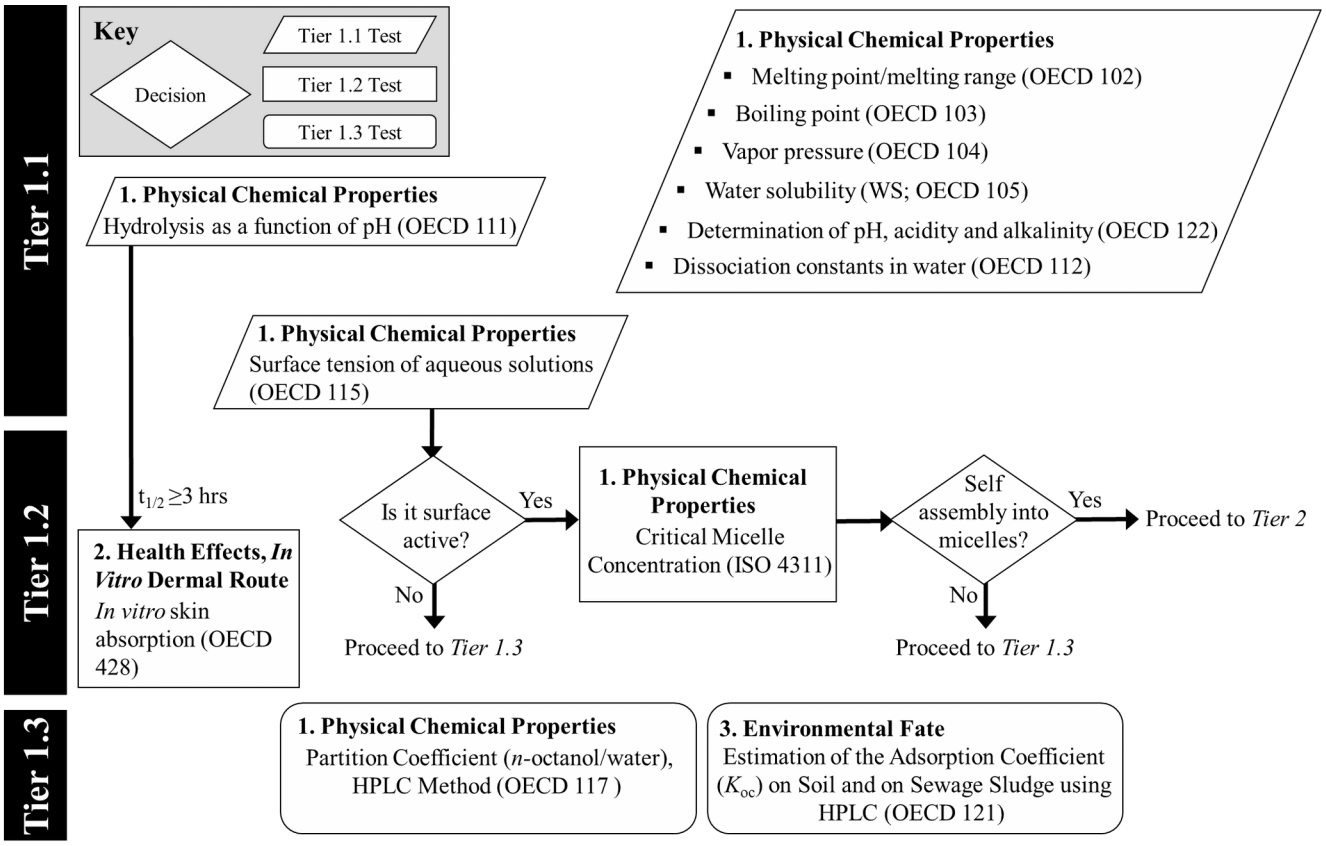

Figure 1. Tiering of tests in the Order: *Tier 1*. Testing in this Order is sequential. Results of *Tier 1.1* tests must be known before study plans can be developed for sub-tier tests in *Tier 1.2* and *1.3*. Each sub-tier is a checkpoint where the Agency and the recipients subject to this Order will confer regarding the design of later studies. *Tier 1.1* tests are shown in parallelograms, *Tier 1.2* tests in rectangles, and *Tier 1.3* tests in rounded-corner rectangles (see 'Key' top left corner of Figure 1). Decision points are in diamonds.

The hydrolysis as a function of pH is important for several reasons, including but not limited to: 1) it is a key parameter when assessing route-specific exposure pathways (i.e., inhalation, oral, dermal) and extrapolating between routes; 2) it is a measure of stability in environmental media (e.g., drinking water, air); 3) it is relevant to the design of later *in vitro* tests carried out in aqueous media (e.g., skin absorption); 4) rapid hydrolysis to other degradants, including other PFAS-/PFOS-related products, may determine whether subsequent testing is needed or if read-across is feasible and appropriate. Study plans should track the parent test substance and avoid loss of more than 50% of the parent compound NMeFOSE due to hydrolysis during the course of *in vitro* testing in aqueous media, which may cause a false negative result due to deactivation of the test chemical. While worth noting, these loss concerns may be minimal given that the one *in vitro* test in *Tier 1* testing for this Order, dermal absorption, allows for the application of the parent test substance as a solid or semi-solid. Rather, to address the predicted/expected solid state of NMeFOSE, study plans should address the homogeneous application of the test substance, its uniformity within the applied formulation and its stability, consistent with the Series on Testing and Assessment No. 156 for the conduct of skin absorption studies (Iomc, 2022).

Additional importance of *Tier 1* physical-chemical property testing includes characterizing the environmental fate, transport, and potential of NMeFOSE to bioaccumulate. Required testing includes the partition coefficient in *n*-octanol/water and the absorption coefficient.

Available *in vitro* and *in vivo* genotoxicity data on NMeFOSE had study endpoints rated with high confidence (Table F2), reducing concerns for this mode of action for cancer, though non-genotoxic modes of action may still be possible. As such, genotoxicity is not a requirement for testing in this Order.

Based on predicted physical and chemical properties and published exposure information, dermal exposure is a relevant route of exposure. Although the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals marks NMeFOSE as an irritant (ECHA, 2023; NLM, 2023; UN, 2023), available studies on skin and eye irritation with acceptable quality indicated NMeFOSE is a non-irritant (See Appendix F). As such, additional skin and eye irritation studies will not be required at the time of this initial Order for NMeFOSE. Corrosion was not evident in reasonably available *in vivo* toxicity testing information, nor classified in GHS, as a hazard and is not expected to impact the feasibility of *Tier 2* testing.

4. *In Vivo* Environmental Fate and Behavior: Degradation and Accumulation

Tier 2.1

- Bioaccumulation in Fish: Aqueous and Dietary Exposure **(OECD 305 (2012))**(OECD, 2012)

  This test evaluates the potential for bioaccumulation of substances in an aquatic species through direct aqueous or dietary exposure. The two-phase controlled laboratory test assesses the uptake and depuration of the test substance over time in fish. Most importantly, this test aims to minimize animal use (305 II) and can accommodate test substances with low water solubility by providing methods for dietary exposure (305 III). The study plan must include a control group and exposure group which will be subsampled at various time points in the update and depuration phases. Each treatment group should contain, at minimum, enough individuals for four (aqueous exposures) or five (dietary exposure) fish at each sampling event to be assessed for growth (mass and length), lipid content, and tissue analysis (i.e., whole-body concentration). Appropriate test design, exposure duration, dose concentration (i.e., subchronic), and analytical techniques can be derived using available toxicity and kinetic data. A dietary exposure (305 III) with flow-through design may be appropriate if toxicity and kinetic data indicate the test substance is not stable in water or has low water solubility. Following uptake and depuration, fish (i.e., whole body), food, and water concentrations, including concentrations for the test substance and major metabolites, steady-state and kinetic bioconcentration factors (BCF_{ss} and $BCF_{k,}$ respectively), and both growth- and lipid-corrected BCFs will be reported to evaluate the potential bioaccumulation of the test substance.

  The Agency is amenable to discussions regarding test design or test species (Annex 3) to limit the number of animals used and make more efficient use of other resources.

Such discussions must be proposed to EPA when the pre-draft study plan check-in is due.

5. *In Vivo* Health Effects: Oral and Inhalation Routes

Tier 2.1

- Toxicokinetics, oral exposure **(OECD 417 (2010))** (OECD, 2010)

  There was no available TK study data by any route of exposure. Toxicokinetic studies are used to determine test substance absorption, distribution, biotransformation (i.e., metabolism) and excretion to aid in the investigation into mechanisms of toxicity; oral exposure is one of such routes for a toxicokinetic study. In the absence of evidence that either rats or mice are more human-relevant for NMeFOSE exposure, experimental data are needed from both species to understand interspecies differences in accumulation, metabolism, and re-uptake and/or clearance of these substances. A pilot study must inform the parameters for the full oral TK study plan. Oral exposures should be carried out with oral gavage, ensuring test substance concentration is no more than 1,000 mg/kg body weight and gavage volume is below 10 mL/kg body weight. A minimum of four animals per species (of each sex) should be used for each concentration that is tested. Test organisms should be housed individually in separate metabolic units. All excreta (i.e., urine, feces, expired air) should be assessed for test substance and metabolite concentrations at each sampling point. Metabolites represent those found at 5% or greater of the administered dose. Following exposure, excreta collection should be conducted at least twice on Day 1 (at 24 hr post-exposure and at least once prior [e.g., at hour 6, 12, 18]) and daily thereafter for 7 days or until 90% of the administered dose has been recovered, whichever occurs first. Blood and plasma samples should be obtained at appropriate intervals following oral exposure and should be analyzed for each individual animal. When no substance is detected in tissues at study termination (e.g., because the substance might have been eliminated before study termination due to a short half-life), care should be taken in order to prevent misinterpretation of the data. In this type of situation, tissue distribution should be investigated at the time of test substance (and/or metabolite) peak plasma/blood concentration (Tmax) or peak rate of urinary excretion, as appropriate (see paragraph 38 of the Test Guideline). Metabolic units should be rinsed with the appropriate solvent to collect remaining excreted test substance or metabolites. All excreta and tissue concentrations and percent recoveries, bioavailability, AUC, C_{max}, T_{max}, clearance, half-life ($t_{1/2}$), and study organism information should be reported at the conclusion of the study.

  The Agency is amenable to discussions regarding changes to the timing of excreta sampling for Day 1, the number of orally administered doses, and the gavage vehicle to limit the number of animals used and make more efficient use of other resources. Such discussions must be proposed to EPA when the pre-draft study plan check-in is due.

Tier 2.2

- Toxicokinetics, inhalation exposure **(OECD 417 (2010))**(OECD, 2010)

Toxicokinetic studies are used to determine test substance absorption, distribution, biotransformation (i.e., metabolism) and excretion to aid in the investigation into mechanisms of toxicity; inhalation is one such route for a toxicokinetic study. Because inhalation is also a health concern for NMeFOSE, only the most sensitive species (in which NMeFOSE has the longer half-life) identified by the above outlined oral TK test will be used for the inhalation exposure. A pilot study must inform the parameters for the full TK study plan. To examine toxicokinetic responses following inhalation, at least four individuals (of each sex) should be outfitted with a "nose-cone" or "head-only" apparatus to prevent absorption through alternate routes. Inhalation exposure studies are typically conducted over 4-6 hr, but duration should be supported through pilot study results. The concentration and percent recovery of the test substance and metabolites and their tissue distributions should be collected as outlined above for the oral TK, with the addition of sampling the lungs and nasal tissues of exposed organisms. Following exposure, excreta collection should be conducted at least twice on Day 1 (at 24 hr post-exposure and at least once prior [e.g., at hour 6, 12, 18]) and daily thereafter for 7 days or until 90% of the administered dose has been recovered, whichever occurs first. Tissue distribution at the time of test substance (and/or pre-determined and relevant metabolite(s)) peak plasma/blood concentration (T_{max}) or peak rate of urinary excretion.

The Agency is amenable to discussions regarding changes to the headgear used to administer the test substance and duration of inhalation exposure to limit the number of animals used and make more efficient use of other resources. Such discussions must be proposed to EPA when the pre-draft study plan check-in is due.

- TK-derived half-life < 7 days: Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Screening Test **(OECD 422 (1996))**(OECD, 1996)

  This TG is designed to generate limited information concerning the effects of the test substance on male and female rodent reproductive performance, such as gonadal function, mating behavior, conception, embryonic development and parturition. The rodent species tested will be identified by the above outlined oral TK test as the most sensitive species (in which NMeFOSE has the longer half-life). All test organisms will be housed by sex in groups of no more than five individuals, with the exception of pregnant (housed individually) or lactating females (housed with offspring). N-MeFOSE exposure should be administered using oral gavage, not exceed 1000 mg N-MeFOSE/kg body weight/day or 1 mL gavage volume/100g of body weight. For males, repeated dosing should be conducted for at least four weeks (28 d), including two weeks prior to mating, during mating, and, approximately, two weeks post mating up to and including the day prior to the scheduled sacrifice. Females should be dosed throughout the duration of the study, including two weeks prior to mating, over conception, the duration of pregnancy, and at least thirteen days following delivery, up to and including the day before the scheduled sacrifice. While this TG outlines the female exposure schedule (e.g., approximately 63 days [14 days pre-mating, (up to) 14 days mating, 22 days gestation, and 13 days of lactation]), female dosing is dependent upon performance. The experimental design should include at least three test (exposure) groups and a control group. At least eight pregnant females per group are required, with 10 pregnant females preferred, thus, it is recommended each group starts with 12-13 females and 10 males. Litters should include four to five pups of each sex, and surplus pups will be used to assess serum T4 levels on Day 4 after birth. This TG includes

adult rodent fertility and pregnancy data, growth and development of offspring, and enables the examination of differences among sex. Functional observation battery endpoints must also be recorded, as described in OECD 424.

The rodent species identified in the oral TK study will be used in this combined repeated dose toxicity study that includes reproductive/developmental screening. 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.

If the TK-derived half-life is greater than or equal to 7 days, the OECD 422 study may require modifications under Agency advisement. Anticipated modifications may include extending the pre-mating exposure period. Extending the pre-mating exposure period may better compensate for the longer half-life of the test substance and achieve steady state of the test substance before mating occurs, in order to observe potential exposure-related reproductive and developmental effects.

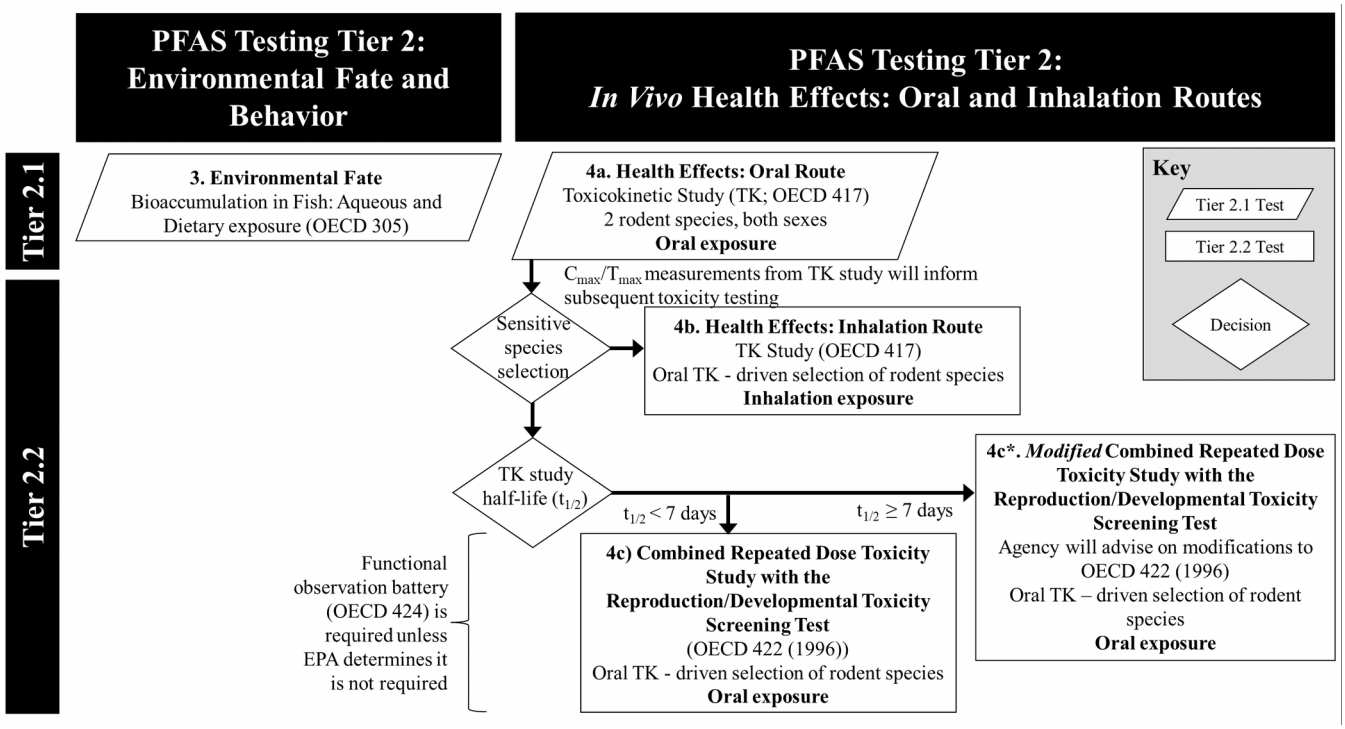

Figure 2. Tiering of tests in the Order: *Tier 2*. Testing in this Order is sequential. *Tier 2.1* testing is informed by *Tier* 1 results, and results of *Tier 2.1* tests must be known before study plans can be developed for sub-tier tests in *Tier 2.2*. Each sub-tier is a checkpoint where the Agency and the recipients subject to this Order will confer regarding the design of later studies. *Tier 2.1* tests are shown in parallelograms, and *Tier 2.2* tests in rectangles (see 'Key' top right corner of Figure 2). Decision points are in diamonds.

To address potential fate, transport and bioaccumulation concerns related generally to PFAS, and specifically NMeFOSE, environmental and aquatic toxicity testing are required, and study plans are dependent on the results of related physical-chemical property testing results from *Tier 1*, specifically *Tier 1.3* to inform the availability of the test substance in environmental media.

There was no available TK study data by any route of exposure. Thus, *Tier 2.1* human health effects testing is a TK study via oral route of exposure in both rodent species and sexes. Results from *Tier 2.1* will inform the sensitive rodent species for performing subsequent *Tier 2.2 in vivo* toxicity testing, including rodent species selection for the TK study via the inhalation route of exposure.

Available studies on skin and eye irritation with acceptable study quality indicated NMeFOSE is a non-irritant. As such, this Order will not require additional skin and eye irritation testing. Corrosion was not evident in reasonably available *in* vivo toxicity testing information, and it not expected to impact the feasibility of performing *Tier 2* testing.

The reasonably available oral repeated dose toxicity study, including range finding for dose selection, may be used to inform the dose selection of the required combined repeated dose toxicity study with the reproduction/developmental toxicity screening test. There was no available study information to meet the data needs for reproductive and developmental outcomes for NMeFOSE.

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

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

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

Test Names	Protocols/ Methodologies	Deadlines to Submit Tier 1.1 Final Test Reports, Tier 1.2 Final Test Reports, and Tier 1.3 Study Plans and Final Test Reports
Required Physical/Chemical Properties		
Tier 1.1: Melting Point/Melting Range	OECD 102 (1995)	365 days after effective date of the Order
Tier 1.1: Boiling Point	OECD 103 (1995)	365 days after effective date of the Order
Tier 1.1: Vapor Pressure	OECD 104 (2006)	365 days after effective date of the Order
Tier 1.1: Water Solubility	OECD 105 (1995)	365 days after effective date of the Order

Tier 1.1: Determination of pH, Acidity and Alkalinity	OECD 122 (2013)	365 days after effective date of the Order
Tier 1.1: Hydrolysis as a Function of pH	OECD 111 (2004)	390 days after effective date of the Order
Tier 1.1: Dissociation constants in water	OECD 112 (1981)	365 days after effective date of the Order
Tier 1.1: Surface tension of aqueous solutions	OECD 115 or ASTM D1331	365 days after effective date of the Order
Tier 1.2: Micelle assembly (CMC)	ISO 4311	365 days after EPA notification to proceed with the Tier 1.2 Testing
Tier 1.3: Partition Coefficient (*n*-octanol/water), HPLC Method	OECD 117 (2022)	365 days after EPA notification to proceed with the Tier 1.3 Testing
To pursue discussions with the EPA to combine aspects of the Tier 1.2 or Tier 1.3 tests, Order recipients must initiate discussion with the EPA within 30 days of submitting the final test report for the Tier 1.1 or Tier 1.2 tests, respectively.		
Required Health Effect Dermal Route		
Tier 1.2: *In vitro* skin absorption	OECD 428 (2004)	455 days after EPA notification to proceed with the Tier 1.2 Testing
Environmental Fate and Behavior		
Tier 1.3: Estimation of the Adsorption Coefficient (*K*oc) on Soil and on Sewage Sludge using HPLC	OECD 121 (2001)	255 days after EPA notification to proceed with the Tier 1.3 Testing

Test Names	**Protocols/ Methodologies**	**Deadlines to Submit Tier 2.1 Final Test Reports and Tier 2.2 Study Plans and Final Test Reports**
Health effects – Oral Route and Inhalation		
Tier 2.1: Toxicokinetic Study	OECD 417 (2010)	665 days after EPA notification to proceed with the Tier 2.2 Testing
Tier 2.2: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test	OECD 422 (2016)	365 days after EPA notification to proceed with the Tier 2.2 Testing
To pursue discussions with the EPA to combine aspects of the Tier 2.2, Order recipients must initiate discussion with EPA within 30 days of submitting the final test report for the Tier 2.1		
Degradation and Accumulation		

Tier 2.1: Bioaccumulation in Fish: Aqueous and Dietary exposure	OECD 305 (2004)	390 days after EPA notification to proceed with the Tier 2.2 Testing

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

C. DRAFT AND FINAL STUDY PLAN REQUIREMENTS

1. Study Plan Requirements for All Categories of Tests

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

A study plan within the Test Order context refers to a document that robustly describes the testing parameters and specific details with regards to how the study will be conducted and can be easily

used by another party to replicate the study with minimal additional guidance. Such a study plan will be more detailed than a test protocol because it will also address considerations for the specific test substance, testing facility, and any other conditions that are specific to the required testing such as simulating a particular condition of use that is the focus of the study.

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. The test sponsor must describe how to address any uncertainties that may remain. The study plan should address all required details of the protocol/methodology, including the requirements enumerated below as well as those listed in **Appendix E** for the applicable testing requirement. The draft study plan must document any uncertainties and indicate where EPA feedback is required. 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:

9. 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.

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

11. 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.

12. 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.

13. 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.

14. 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.

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

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

17. 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.

18. 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.

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

    If pilot/preliminary testing is necessary pursuant to a pre-defined (e.g. OECD, EPA, ISO, NIOSH, etc.) protocol, start and end dates must be provided for the pilot/preliminary testing as well as for the definitive/main study.

20. Where a pre-defined (e.g., OECD, EPA, ISO, NIOSH, etc.) protocol incorporates certain preliminary testing as part of its process, EPA requires such testing be incorporated and described in the submitted Draft Study Plan for the given testing requirement.

21. The test protocols/guidelines prescribed within this Order describe all necessary ancillary testing, any additional pilot/preliminary testing must be justified as to its need and how it will inform the definitive/main Study Plan. Thus, if it is anticipated that any additional, separate pilot/preliminary testing will be required (e.g., in the event of novel testing methods), such testing must be proposed to the EPA no later than 15 days before the Pre-Draft Study Plan Check-In deadline. Any request for an extension to forthcoming deadlines due to the addition of such ancillary testing must also be provided by this same milestone.

22. 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 the EPA to combine aspects of the subsequent tier of tests, you must initiate discussion with the EPA within 30 days of submitting the final test report for the current tier of tests). 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.

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

a. Study Plans

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

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

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

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

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

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

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

b. Final Test Reports

Once the EPA has completed its initial review and accepted data for all test reports subject to this Order for a given testing requirement, the EPA will notify the designated contact for the company subject to this Order and any designated consortium that this testing requirement has been satisfied, which in turn will close out the testing requirement of this Order for the companies and participants in any consortium subject to this Order. Failure to file a final test report meeting all the requirements in this Order by the deadline in **Unit 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, 2018b):

i. Melting Point/Melting Range OECD 102 (1995) (OECD, 1995b)
   - *Harmonized Template Identifier: OHT 2 (Melting point/freezing point)*

ii. Boiling Point OECD 103 (1995)(OECD, 1995c)
   - *Harmonized Template Identifier: OHT 3 (Boiling point)*

iii. *Vapor Pressure OECD 104 (2006)(OECD, 2006)*
   - *Harmonized Template Identifier: OHT 7 (Vapor pressure)*

iv. Water Solubility OECD 105 (1995)(OECD, 1995a)
   - *Harmonized Template Identifier: OHT 9 (Water solubility)*

v. Hydrolysis as a Function of pH OECD 111 (2004)(OECD, 2004a)
   - *Harmonized Template Identifier: OHT 25 (Hydrolysis)*

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

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

vii. Dissociation Constants in Water OECD 112 (1981)(OECD, 1981)

- *Harmonized Template Identifier: OHT 21 (Stability: Dissociation constant)*

viii. Surface Tension of Aqueous Solutions OECD 115 (1995) (OECD, 1995d)

- *Harmonized Template Identifier: OHT 10 (Surface tension)*

ix. Surfactancy Potential: Assembly of Micelles or the Critical Micelle Concentration (CMC) ISO 4311 (2022)(ISO, 2022)

- *Harmonized Template Identifier: OHT 23-1 (Additional physico-chemical information)*

x. n-octanol/water Partition Coefficient HPLC Method, or K_{ow} OECD 117 (2022) (OECD, 2022)

- *Harmonized Template Identifier: OHT 7 (Partition Coefficient)*

xi. Estimation of the Adsorption Coefficient, or K_{oc}, on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) OECD 121 (2001)(OECD, 2001)

- *Harmonized Template Identifier: OHT 34 (Adsorption/Desorption)*

xii. Bioaccumulation in Fish: Aqueous and Dietary Exposure OECD 305 (2012) (OECD, 2012)

- *Harmonized Template Identifier: OHT 32 (Bioaccumulation: aquatic/sediment)*

xiii. Skin Absorption: In Vitro Method (OECD 428 (2004)) (OECD, 2004b))

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

xiv. Toxicokinetics (OECD 417 (2010))(OECD, 2010), oral route

- *Harmonized Template Identifier: OHT 58 (Basic toxicokinetics)*

xv. Toxicokinetics (OECD 417 (2010))(OECD, 2010), inhalation route

- *Harmonized Template Identifier: OHT 58 (Basic toxicokinetics)*

xvi. TK-derived half-life < 7 days: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test OECD 422 (1996) (OECD, 1996), oral route

- *Harmonized Template Identifier: OHT 67 (Repeated dose toxicity: oral) and OHT 73 (Repeated dose toxicity: oral)*

If the TK-derived half-life is greater than or equal to 7 days, the OECD 422 via oral route, study may require modifications under Agency advisement. Anticipated modifications may include extending the pre-mating exposure period. Extending the pre-mating exposure period may better compensate for the longer half-life of the test substance and achieve steady state of the test substance before mating occurs, in order to observe potential exposure-related reproductive and developmental effects. Functional observation battery must be performed in at least 5 animals/sex/dose, as applicable and as described in OECD 424 (OECD, 1997).

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). (USEPA, 2021e)The procedures for assertion and substantiation of CBI claims can be found at 40 CFR 703.

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.

Dated: Click or tap to enter eSignature date.

Michal Freedhoff

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. Entities that have incurred costs in complying with the testing requirement may seek reimburse from exemption holders as soon as they receive the EPA's notification that the testing requirement has been satisfied. 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 NMeFOSE from the EPA Chemical Information System (CIS) within recent 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 Inventory Update Reporting (IUR), Chemical Data Reporting (CDR), Pre-manufacture Notifications, and Notice of Activity forms. Based on such submissions, the EPA has included entities associated with this chemical substance.

APPENDIX E – Specific Requirements and Guidance for This Order

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

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

1. Physical-Chemical Properties

Tier 1.1

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

i. Study Plans

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

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due 415 days after the effective date of the Order and must include the following, as applicable:

1. Harmonized Template OHT 2 (Melting point/Freezing Point)

2. Harmonized Template URL: https://www.oecd.org/env/ehs/testing/OHT%202%20-%20ENDPOINT_STUDY_RECORD.Melting_v5.2%20-Dec%202018.doc

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

i. Study Plans

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

ii. Test Reports

In addition to the requirements provided by **Unit VI**, test reports submitted to the EPA for this test are due 415 days after the effective date of the Order and must include the following, as applicable:

1. Harmonized Template OHT 3 (Boiling Point)

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

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

i. Study Plans

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

ii. Test Reports

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

1. Harmonized Template OHT 6 (Vapour Pressure)

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

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

i. Study Plans

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

ii. Test Reports

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

1. Harmonized Template OHT 8 (Water Solubility)

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

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

i. Study Plans

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

1. Follow the test performance criteria in OECD 111, including 'optional' testing at pH 1.2 for physiological conditions and reporting relevant intermediary hydrolysis products including and may not be limited to perfluorooctane sulfonamido acetate (FOSAA; CAS #2806-24-8), perfluorooctane sulfonamide (FOSA; CAS #754-91-6), and perfluorooctane sulfonate (PFOS; CAS #1763-23-1).

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

ii. Test Reports

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

1. Harmonized Template OHT 25 (Hydrolysis)

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

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

i. Study Plans

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

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

ii. Test Reports

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

1. Harmonized Template OHT 20 (pH)

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

g. Dissociation Constants in Water OECD 112 (1981) (OECD, 1981**)**

i. Study Plans

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

ii. Test Reports

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

1. Harmonized Template OHT 21 (Stability: Dissociation constant)

2. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2021%20-%20ENDPOINT_STUDY_RECORD.DissociationConstant_v8.2%20-Jul2023.docx

h. Surface Tension of Aqueous Solutions OECD 115 (1995) (OECD, 1995d)

i. Study Plans

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

ii. Test Reports

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

1. Surface tension ≤ 45 mN/m at conc. 0.5 wt% in water, and 20°C, would be the first of two testing requirements to definitively confirm NMeFOSE is a surfactant and study plans for *in vivo* toxicity testing should account for this property.

2. Harmonized Template OHT 10 (Surface Tension)

3. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2010%20-%20ENDPOINT_STUDY_RECORD.SurfaceTension_v8.3%20-Jul2023.docx

Tier 1.2- required testing dependent on results of Tier 1.1 surface tension test

i. Assembly of Micelles or the Critical Micelle Concentration (CMC) ISO 4311 (2022) (ISO, 2022**)**

i. Study Plans

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

ii. Test Reports

1. CMC value ≤ 0.5 wt% in water would be the second of two testing requirements to definitively confirm NMeFOSE is a surfactant and study plans for *in vivo* toxicity testing should account for this property.

   Subsequent *in vivo* testing of the test substance must be performed below the measured CMC to ensure the test organism(s) are exposed to the freely dissolved chemical species and not the micelle which may affect uptake behavior of the test substance in test organisms and micelles are less likely to occur in the environment (OECD GD no. 23; (OECD, 2019a)).

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

1. Harmonized Template OHT 23-1 (Additional physico-chemical information)

2. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2023-1%20%20ENDPOINT_STUDY_RECORD.AdditionalPhysicoChemical_v8.1%20-Jul%202023.docx

Tier 1.3

j. *n*-octanol/water Partition Coefficient HPLC Method, or K_{ow} OECD 117 (2022) (OECD, 2022**)**

i. Study Plans

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

ii. Test Reports

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

1. Harmonized Template OHT 7 (Partition Coefficient)

2. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%207%20-%20ENDPOINT_STUDY_RECORD.Partition_v8.1%20-Jul2023.docx

2. Health Effects: *In Vitro* Dermal Route

Tier 1.2- required testing dependent on results of Tier 1.1 Hydrolysis as a Function of pH test

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

i. Study Plans

1. Refer to Series on Testing & Assessment No. 156 (Iomc, 2022) for performing this testing.

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

ii. Test Reports

In addition to the requirements provided by **Unit VI.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. Harmonized Template Identifier: OHT #59 (Dermal absorption).

2. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2059%20-%20ENDPOINT_STUDY_RECORD.DermalAbsorption_v9.1-%20Jul2023.docx

3. Environmental Fate and Behavior: Adsorption/Desorption

Tier 1.3

a. Estimation of the Adsorption Coefficient, or K_{oc}, on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) OECD 121 (2001) (OECD, 2001**)**

i. Study Plans

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

ii. Test Reports

In addition to the requirements provided by **Unit VI.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. Follow OECD TG 121

2. Harmonized Template Identifier: OHT #34 (Adsorption/Desorption).

3. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2034%20-%20ENDPOINT_STUDY_RECORD.AdsorptionDesorption_v8.2%20-Jul%202023.docx

Tier 2.1

b. Bioaccumulation in Fish: Aqueous and Dietary Exposure OECD 305 (2012) (OECD, 2012**)**

This test evaluates the potential for bioaccumulation of substances in aquatic species through direct aqueous (305 I & 305 II) or dietary (305 III) exposure.

i. Study Plans

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

1. *In vivo* testing of the test substance must be performed below the measured CMC to ensure the test organism(s) are exposed to the freely dissolved chemical species and not the micelle which may affect uptake behavior of the test substance in test organisms and micelles are less likely to occur in the environment (OECD GD no. 23; (OECD, 2019a)).

2. Must include the following: fish lipid content, as well as the lipid normalization factor (L_n), fish weight (whole body), fish total length, and growth rate (k_g). Test substance concentration in fish (C_f) and test substance concentration in water (C_w) at all sampling times. Moreover, as the bioconcentration factor (BCF) is to be based on the test substance, the major metabolites should be characterized with concentrations reported; major metabolites are those representing ≥ 10% of total residues in fish tissues, those representing ≥ 5% at two consecutive sampling points, those showing increasing levels throughout the uptake phase, and those of known toxicological concern. Curves for fish growth, uptake and depuration, and time to steady-state should include both raw data and fitted models. Bioconcentration factors for steady-state (BCF_{SS}) and kinetic (BCF_K), with uptake (k_1) and depuration rate constants (k_2). Further, the depuration rate constant (k_{2g}), kinetic BCF (BCF_{Kg}), and half-life ($t_{1/2g}$) should be presented as growth-corrected. Likewise, include lipid-corrected values for the steady-state BCF (BCF_{SSL}) and kinetic BCF (BCF_{KL}), as well as a growth- and lipid-corrected kinetic BCF (BCF_{KLG}). Must be performed in both sexes.

   Must include flow-through test design and the following additional values for dietary exposures: measured time zero concentration ($C_{0,m}$), derived time zero concentration ($C_{0,d}$), and chemical concentration in the food (C_{food}). Calculate the growth-corrected half-life ($t_{1/2g}$), lipid correction factor (L_c), ingestion rate (I), effective feeding rate (adjusted for growth; I_g), and the substance assimilation efficiency (α), When conducting dietary exposure, the above BCF are referred to as biomagnification factors (BMF). Provide the indicative lipid-corrected steady-state BMF (BMF_{SS-L}) and the kinetic dietary BMF (BMF_K), as well as its growth- (BMF_{Kg}) and lipid- and growth-corrected values (BMF_{KgL}).

3. Must include the following: test design and duration used with justification, lipid content testing, uptake and depuration phase sampling schedule with justification, water sampling schedule, tissue, food, and water analytical test methods, and gross necropsy including malformation identifications and absolute fish weights.

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 all husbandry data, including the number of fish used, mortality, and abiotic data, range-finder and preliminary test results, and any observed abnormal behaviors.

3. Harmonized Template Identifier: OHT #32 (Bioaccumulation: aquatic/sediment).

4. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2032%20-%20ENDPOINT_STUDY_RECORD.BioaccumulationAquaticSediment_v9.3%20-Jul%202023.docx

4. Health Effects: Oral and Inhalation Routes

Tier 2.1- required testing

a. Toxicokinetics OECD 417 (2010) (OECD, 2010), oral route

i. Study Plans

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

1. Must be conducted in both sexes of rats and mice. Requested values and data should be represented by species and sex.

2. Must perform a pilot study to inform study plan parameters, including and may not be limited to the pre-determination of relevant metabolites, mass balance, analytical procedures, dose finding, exhalation of CO_2. The pilot may also inform whether radiolabeling of the test substance is required.

3. Must include the following: Must be performed in both sexes of rats and mice test organism information, including age, sex, and mass. Concentrations and identities of the test substance and metabolites in the test solution, tissues (including blood and plasma), and excreta. When reporting concentrations, include measured value (µg/kg) and as percent recovered of administered dose. Calculate the rate of absorption, material balance, bioavailability (F), AUC, C_{max}, T_{max}, clearance, and half-life ($t_{1/2}$).

4. In the case that no substance is detected in tissues at study termination (e.g., because the substance might have been eliminated before study termination due to a short half-life), care should be taken in order to prevent misinterpretation of the data. In this type of situation, tissue distribution should be investigated at the time of test substance (and/or metabolite) peak plasma/blood concentration (Tmax) or peak rate of urinary excretion, as appropriate (see paragraph 38 of the Test Guideline). Justification and rationale for sample selection (i.e., which organs/tissues are collected at sacrifice) should be provided, except that whole blood and plasma or red blood cells and plasma must be included.

5. Must include justification and descriptions for the following: experimental design, including the inclusion of expired air testing, number and frequency of oral doses and concentrations, gavage vehicle, and excreta sampling timeline (including proposed Day 1 collections). The feeding schedule with focus on the administration/restriction of feeding prior to dosing. Must also provide analytical techniques for testing of test substance and metabolites in the test solution, tissues, and excreta.

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 all husbandry data, including feeding schedules and mortality, pilot study data, including testing expired air and excreta to coordinate appropriate Day 1 sampling, and any observed abnormal behaviors.

3. Harmonized Template Identifier: OHT #58 (Basic Toxicokinetics).

4. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2058%20-%20ENDPOINT_STUDY_RECORD.BasicToxicokinetics%20_v10.2%20-Jul%202023.docx

Tier 2.2- required testing in a single rodent species dependent on TK oral study results; in no specific tiered order

a. Toxicokinetics OECD 417 (2010) (OECD, 2010), inhalation route

i. Study Plans

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

1. *In vivo* testing of the test substance must be performed below the measured CMC to ensure the test organism(s) are exposed to the freely dissolved chemical species and not the micelle which may affect uptake behavior of the test substance in test organisms and micelles are less likely to occur in the environment (OECD GD no. 23; (OECD, 2019a)).

2. Must perform a pilot study to inform study plan parameters, including and may not be limited to the pre-determination of relevant metabolites, mass balance, analytical procedures, dose finding, exhalation of CO_2. The pilot may also inform whether radiolabeling of the test substance is required.

3. Must be conducted in the rodent species in which NMeFOSE has the longer half-life (identified by the above outlined oral TK test). Requested values and data should be represented by sex.

4. Must include the following: test organism information, including age, sex, and mass. Concentrations and identities of the test substance and metabolites in the test solution, tissues (including lungs and nasal tissues), and excreta. When reporting concentrations, include measured value (µg/kg) and as percent recovered of administered dose. Calculate the rate of absorption, material balance, bioavailability (F), AUC, C_{max}, T_{max}, clearance, and half-life ($t_{1/2}$).

5. Must sample tissue distribution at the time of test substance (and/or pre-determined and relevant metabolite(s)) peak plasma/blood concentration (T_{max}) or peak rate of urinary excretion. Tissue-to-plasma (blood) ratios should also be reported. Justification and rationale for sample selection should be provided. Rationale should be provided if any of these are omitted from the study plan.

6. Must include justification and descriptions for the following: experimental design, including the information for headgear, duration of inhalation exposure and concentrations, and excreta sampling timeline (including proposed Day 1 collections). The feeding schedule with focus on the administration/restriction of feeding prior to dosing. Must also provide analytical techniques for testing of test substance and metabolites in the test solution, tissues, and excreta.

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 all husbandry data, including feeding schedules and mortality, pilot study data, and any observed abnormal behaviors.

3. Report any portal-of-entry effects.

4. Harmonized Template Identifier: OHT #58 (Basic Toxicokinetics).

5. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2058%20-%20ENDPOINT_STUDY_RECORD.BasicToxicokinetics%20_v10.2%20-Jul%202023.docx

a. TK-derived half-life < 7 days: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test OECD 422 (1996) (OECD, 1996), oral route

i. Study Plans

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

1. *In vivo* testing of the test substance must be performed below the measured CMC to ensure the test organism(s) are exposed to the freely dissolved chemical species and not the micelle which may affect uptake behavior of the test substance in test organisms and micelles are less likely to occur in the environment (OECD GD no. 23; (OECD, 2019a)).

2. Must perform functional observation battery (FOB) to inform later data needs, including potential developmental data needs. FOB is favored over (expanded) clinical observations, since FOB has been widely used and validated across laboratories (Gauvin et al., 2016; Moser, 2011, 2000). FOB in at least 5 animals, per sex, per species, and per dose group should be evaluated, consistent with OECD (1997). Minimal list for FOB include and potentially not limited to: a) any unusual bodily responses, e.*g.*, position, activity level, movement and coordination and gait; b) any unusual behavior including but not limited to head flicking, head searching, compulsive biting or licking, self-mutilation, circling, and walking backwards; c) presence of (1) convulsions, (2) tremors, (3) increased levels of lacrimation and/or red-colored tears, (4) increased levels of salivation, (5) piloerection, (6) pupillary dilation or constriction, (7) unusual respiration (shallow, labored, dyspneic, gasping, and retching) and/or mouth breathing, (8) diarrhea, (9) excessive or diminished urination, and (10) vocalization; d) forelimb/hindlimb grip strength (Meyer et al., 1979); e) sensory

function including reflex and pain perception (Deuel, 1977), paragraph (f) of Code of Federal Regulations (1987).

3. Must include the following; F0 masses at first dose, and once weekly to termination, date of pregnancy, duration of pregnancy (calculated from Day 0 of pregnancy); litter size, with offspring sex and mass. Offspring mass should be taken Day 0-1 and on Day 4 and 13 post-partum. Measure anogenital distance (AGD), and male offpsring nipples/areolae counts. Food consumption measured weekly; once during study, 5 males/5 females used for haematocrit, haemoglobin concentrations, erythrocyte count, reticulocytes, total and differential leucocyte count, platelet count, measure of blood clotting time/potential. Histological results of male testes. Full necropsies (at time of death and termination) for all individuals. All concentrations of test solutions, food, gavage, blood and tissues must be provided.

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. Report all husbandry data, including mortalities and feeding schedules and abnormal behaviors.

3. Report FOB

4. Harmonized Template Identifier: OHT #67 (Repeated dose toxicity: oral).

5. Harmonized Template URL: https://www.oecd.org/ehs/templates/OHT%2067%20-%20ENDPOINT_STUDY_RECORD.RepeatedDoseToxicityOral_v9.2%20-Jul2023.docx

If the TK-derived half-life is greater than or equal to 7 days, the OECD 422 study may require modifications under Agency advisement. Anticipated modifications may include extending the pre-mating exposure period. Extending the pre-mating exposure period may better compensate for the longer half-life of the test substance and achieve steady state of the test substance before mating occurs, in order to observe potential exposure-related reproductive and developmental effects.

APPENDIX F – SUMMARY OF AVAILABLE DATA

Available toxicity studies on NMeFOSE were reviewed in accordance with the draft TSCA Systematic Review Protocol (USEPA, 2021a). Data quality was 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.

Physical-chemical properties. Reasonably available studies included two sources that contained physical-chemical property information, see Ref ID 1 & 2, Table F1. One primary study (Ref ID 2) was performed/designed to measure *n*-octanol/water partition coefficient and also measure water solubility during the course of performing the testing. This primary source explicitly states that '… the data are unreliable' and goes on to state the reasoning, including uncharacterized purity of the test substance, compensation for potential test substance losses throughout testing duration, and '… nonspecific analytical techniques.' The other source was secondary (Ref ID 1), as in it was a summary report with no primary study references that would provide the required analytical methods and experimental conditions such as temperature, to meet the data needs of this Order. Taken together, all physical chemical property testing in the Order, *Tier 1* testing, remain data needs.

Health Effects. Reasonably available data on NMeFOSE included both *in vitro* and *in vivo* genotoxicity, *in vivo* skin and eye irritation testing, acute oral and inhalation studies, a short-term range-finding study, and one subchronic repeated-dose study.

In vitro and *in vivo* genotoxicity data on NMeFOSE reduced concerns for this mode of action for cancer, though non-genotoxic modes of action may still be possible.

Available studies on skin and eye irritation with acceptable study quality indicated NMeFOSE is a non-irritant. Corrosion was not evident in reasonably available *in* vivo toxicity testing information.

While the outcome assessment for the one available acute inhalation study included outcomes for liver, lungs renal, nutritional/body weights, and mortality; the quality of the study was found to be uninformative and are not useful towards fulfilling the requirements of this Order. The uninformative rating was on the basis of the test substance purity and characterization as well as the exposure frequency, duration and dose selection. The information of this study is unlikely to be useful towards the design of the required TK study via the inhalation route of exposure.

There was no available TK study data by any route of exposure.

The study quality of the oral toxicity testing including acute and repeated dose data, while of acceptable study quality and across a range of health outcomes, it lacked reproductive and developmental study plans and outcome observations needed by the EPA to understand the reproductive and developmental effects from NMeFOSE. The repeated dose rangefinder and 13-week oral study can be used to inform dose selection and critical observations related to outcomes for liver, nutritional/metabolic, and clinical pathology and biochemistry (i.e., red blood cell count, lower hemoglobin and hematocrit levels, lower absolute eosinophil count, and cholesterol). In the range finding study performed for dose selection for the 13-week repeated dose study, six groups of rats were exposed to NMeFOSE for at least 4 weeks. Each group contained 6 males and 6 females. The dose levels tested were 0, 10, 30, 100, and 500 ppm. The 500 ppm treatment was associated with several effects on clinical pathology test results including moderately lower red blood cell

count, lower hemoglobin and hematocrit levels, lower absolute eosinophil count, and markedly lower cholesterol. Mean absolute and relative liver weights from all males and females given the 100 and 500 ppm were significantly increased over control values. In the subsequent 13-week repeated dose study in rats, the higher dose at 100 ppm, produced liver effects including increased liver weights, hepatocyte hypertrophy, and hepatocellular vacuolation. Lower cholesterol and triglycerides were found in the animals treated with 100 ppm and 30 ppm. Neither liver nor cholesterol/triglyceride changes were found in the low dose (3 ppm) animals. Significantly reduced body weights were present in the high dose animals beginning at week 4 and continuing until end of study.

Ecotoxicological data. Reasonably available studies were deemed unacceptable, as discussed below, and included a fate study for determining adsorption coefficients (Table F3) and an acute aquatic toxicity test in bluegill sunfish (*L. macrochirus*) and zooplankton (*D. magna*) (Table F4). The aforementioned fate study was not acceptable to determine adsorption coefficients, based on it being a secondary source with no analytical details, cited solubility and 'reliability' concerns, and the identity nor purity of the test substance was definitive (e.g., no CASRN reported). The acute toxicity test in fish, was cited to be 'modeled' after EPA-660/3-75-009 (1975) (NWQL, 1975), and similar to OECD TG 203 Fish Acute Toxicity Test (2019) (OECD, 2019b). This acute toxicity test was also rated as unacceptable based on unresolved challenges with test substance solubility and reported precipitation of the test substance during the duration of the study. As such, LD50/LC50 value(s) could not be calculated.

Table F1. Physical Chemical Property Study Characteristics and Quality Review Results (H = High Confidence, M = Medium Confidence, L = Low Confidence, U = Uninformative, NA = Not Applicable)

Physical chemical property	Reported value/range	Reported units	Type (E= experimental, NR= not reported)	T (°C)	Quality rating	Source Type	Ref ID
Melting point	75-95	°C	NR	--	U	Secondary	1
n-octanol/water partition coefficient, log Kow	4.75*	--	E	approx. (~) 22	L	Primary	2
Water solubility	0.82	mg/L	NR	NR	U	Secondary	1
	4.72 (1000pm), 4.78 (2000ppm)	ppm	E	approx. (~) 22	L	Primary	2

*average between 1000ppm and 2000ppm test solution and erroneously reported as 56800 in the original test report, log transformed value.

Table F2. 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	3	4	5	6	7	8	9	10	11	12	13
	Duration (A= acute, SC = Subchronic, C = Chronic, ST = Short Term) *assumed	A	A	A	A	A	ST	SC	A	A	A	A
	Species (D=dog, R= rat, Rb= rabbit M=mouse, H= human)	R	R	R	R	R	R	R	R	R	Rb	Rb

Study	Route (I= inhalation, D= dermal, Or= Oral, O= occupational, E= eye)	Or	Or	Or	Or	I	Or	Or	Or	Or	D	E
	Gastrointestinal			M								
	Immunological/hematological			M			H					
	Kidney			M		U	H	H				
	Liver	M	H	H		U	H	H				
	Mortality	M	H	H	H		H	H	M	M		
	Nutritional/Metabolic	H	H	H			H	H	M	M		
	Reproductive/Developmental						H	H				
	Respiratory					U	H	H		M		
	Skin										M	
	Eye							H				M
	Thyroid						H	H				
	Other - Clinical Signs of Toxicity				H				M	M		
	Other - Unspecified Gross Necropsy								M	M		

Health Out	Other - Genotoxicity	H			H								

Table F3. Environmental Fate Characteristics and Quality Review Results (H = High Confidence, M = Medium Confidence, L = Low Confidence, U = Uninformative, NA = Not Applicable)

Environmental fate characteristic	Reported value/range	Reported units	Type (E= experimental, NR= not reported)	T (°C)	Quality rating	Source Type	Ref ID
Soil adsorption coefficient (*K*)	77	--	NR	--	U	Secondary	1
Organic carbon adsorption coefficient (K_{oc})	3,500	--	NR	--	U	Secondary	1
Photodegradation	--	--	E	--	U	Primary	14
Photolysis (in aqueous solution)	0	%	E	21±3	H	Primary	15
Sludge Sorption	--	--	E	25±1	U	Primary	16

Table F4. Ecotoxicological Data Quality Review Results (H = High Confidence, M = Medium Confidence, L = Low Confidence, U = Uninformative, NA = Not Applicable) Related testing and potentially informative for the requirements in this Order

Study Info	Study ID	1	1	17	17
	Duration (A= acute, SC = Subchronic, ST = Short Term) *assumed	A	A	A	A
	Species (D=dog, R= rat, Rb= rabbit M=mouse, H= human, BG = bluegill sunfish, Z = zooplankton)	BG	Z	BG	Z
	Exposure route (I= inhalation, D= dermal, O=occupational, E= eye, A = aqueous)	A	A	A	A
	Exposure method (F = flow-through, SR = static renewal, S = static)	S	S	S	S

Health Outcomes	Mortality	U	U	U	U

Table F5. Reference ID key

Studies are available in the docket at regulations.gov specific for this Order.

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	4745062	3M White Paper: Sulfonated Perfluorochemicals in the Environment: Sources, Dispersion, Fate, and Effects 2000	8EHQ-0300-0373 8EHQ-1180-373 8EHQ-1180-374
2	11350067	3M CO 3M Environmental Lab Project No. 9970012600 Distribution Coefficient of FM 3925 in *n*-octanol/water Preliminary Report 1979	OTS0215034_19449
3	7553708	3M General Offices Hazleton Washington, Inc. Haskell Laboratory Study No. 15515-0-494 Genotoxicity Test on T-5711.1, The *in vivo/in vitro* unscheduled DNA Synthesis and Cell Proliferation Assays in Rat Liver Cells 1993	FYI-0500-1378 85000000010
4	11350052	3M General Offices Hazleton Washington, Inc. Haskell Laboratory Study No. 154-207 Analysis of T-5794 in a Cell Proliferation Assay in Rat Liver Cells 1994	FYI-0500-1378 85000000010
5	7561259	3M General Offices	FYI-0500-1378

		Hazleton Washington, Inc. Haskell Laboratory Study No. 154-209 Analysis of T-5878 in a Cell Proliferation Assay in Rat Liver Cells 1994	85000000010
6	7553713	3M General Offices Hazleton Washington, Inc. Haskell Laboratory Study No. 15515-0-454 Mutagenicity Test on T-5711 in an *in vivo* Rat Micronucleus Assay 1993	FYI-0500-1378 85000000010
7	11350061	3M Bio/dynamics Inc. Project No. 78-7145 An Acute Inhalation Toxicity Study of T-2108 CoC in the Rat 1982	8EHQ-0792-6006 OTS0537633_423637
8	7617167	3M Covance Laboratories Inc. Covance 6329-224 4-Week Range-Finding Dietary Toxicity Study with N-Methyl Perfluorooctanesulfonamido Ethanol (N-MeFOSE, T-6314) in Rats 2000	FYI-0700-1378 85000000031
9	7692892	3M Covance Laboratories Inc. Covance 6329-225 13-Week Dietary Toxicity Study with N-Methyl Perfluorooctanesulfonamido Ethanol (N-MeFOSE, T-6314) in Rats 2000	FYI-0700-1378 85000000031
10	11350063	3M General Offices /o Biosearch Inc. Project No. 78-1161A Acute Oral Toxicity – Rats 1978	FYI-0500-1378 85000000010
11	7577976	3M General Offices Riker Laboratories Inc. Experiment No. 0979AR0037 Acute Oral Toxicity Screen with T-2574CoC in Albino Rats 1979	FYI-0500-1378 85000000010
12	11350064	3M General Offices /o Biosearch Inc. Project No. 78-1161A Primary Skin Irritation Study – Rabbits 1978	FYI-0500-1378 85000000010

13	11350066	3M General Offices /o Biosearch Inc. Project No. 78-1161A Primary Eye Irritation Study – Rabbits 1978	FYI-0500-1378 85000000010
14	11350342	3M 3M Environmental Engineering and Pollution Control Project No. 9970012600 Report No. 043 Photodegradation Study on FM-3925 1980	Comms 24-0022
15	11350341	3M 3M Environmental Laboratory (EE & PC) Project Number 9970012600 Report Number 045 Photolysis of FM3925 in Aqueous Solutions 1980	Comms 24-0022
16	11350343	3M 3M Environmental Laboratory Preliminary Sludge Sorption Studies of Selected 3M Fluorochemicals 2000	Comms 24-0010
17	11350065	3M 3M Environmental Lab Project Number 9970012600 Aquatic Toxicity Studies: FM 3925 1979	8EHQ-0206-15865B 89060000221