

40 CFR Part 799

(OPTS-42002C; BH-FRL 2909-4)

Fluoroalkenes; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: This document proposes a rule to require testing for certain health effects for the fluoroalkenes vinyl fluoride (VF; CAS No. 75-02-5), vinylidene fluoride (VDF; CAS No. 75-38-7), hexafluoropropene (HFP; CAS No. 116-15-4) and tetrafluoroethene (TFE; CAS No. 116-14-3). This proposed testing consists of reproductive effects testing for VDF, subchronic toxicity testing for HFP, chronic oncogenicity bioassays for VF and VDF, tiered mutagenicity testing for VF, VDF, HFP, and TFE and, depending on the outcome of the mutagenicity testing, chronic oncogenicity bioassays for HFP and TFE. Interested persons are invited to comment on this proposal.

DATE: Comments must be submitted by January 6, 1986.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42002C), in triplicate to: TSCA Public Information Office (TS-783), Office of Pesticides and Toxic Substances, Environmental Protection Agency, room E-108, 401 M Street SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, room E-543, 401 M Street SW., Washington, DC 20460. Toll Free: (800-424-9065). In Washington, D.C.: (554-1404). Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION: EPA is issuing a proposed rule to require health effects testing of vinylidene fluoride, vinyl fluoride, hexafluoropropene, and tetrafluoroethene.

I. Introduction

A. ITC Recommendation and EPA's Previous Actions

TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et seq.*) established an Interagency Testing Committee (ITC) under section 4(e) to recommend to the EPA a list of chemicals to be considered

for the promulgation of test rules under section 4(a) of the Act.

The ITC designated the chemical category "fluoroalkenes" for priority testing consideration in its Seventh Report, published in the Federal Register of November 25, 1980 (45 FR 78432). The ITC recommended testing for the health effects of oncogenicity, mutagenicity, teratogenicity, reproductive and other toxic effects. The Agency responded to the ITC's designation, as required by section 4(e) of TSCA, by issuing an Advance Notice of Proposed Rulemaking (ANPR) in the Federal Register of October 30, 1981 (46 FR 53704). In the ANPR, EPA stated its intention to develop a test rule for vinylidene fluoride (VDF), vinyl fluoride (VF), hexafluoropropene (HFP), trifluoroethene and tetrafluoroethene (TFE) and its decision not to require further testing of 3,3,3-trifluoro-1-propene. In response to the ANPR, the Fluoroalkenes Industry Group (FIG) submitted a proposed testing program for VF, VDF, HFP and TFE and arguments why 3,3,3-trifluoro-1-propene and trifluoroethene should not be made subject to a test rule. Following publication of the ANPR, the Agency also received data under sections 8(a) and 8(d) of TSCA on the fluoroalkenes. In the Federal Register of June 4, 1984 (49 FR 23112), EPA solicited public comment on a proposed negotiated testing agreement (NTA) for VF, VDF, TFE and HFP and published its decision not to require testing of trifluoroethene because of very low exposures to that substance. Subsequent legal action (*NRDC v. EPA*, 595 F. Supp. 1255 (S.D.N.Y. 1984)) found that NTA's such as that proposed for the fluoroalkenes are not a legally adequate alternative to test rules in obtaining needed test data on ITC-designated chemicals. On October 30, 1984 the court ordered EPA to reevaluate the testing needs for the fluoroalkenes and by October 31, 1985 either propose a test rule for the fluoroalkenes or publish the Agency's reasons for not so doing. Therefore, the Agency is now proposing a test rule for vinylidene fluoride (VDF), vinyl fluoride (VF), hexafluoropropene (HFP) and tetrafluoroethene (TFE).

B. Test Rule Development Under TSCA

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

(A) (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 are insufficient 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, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or

(B) (i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture.

(ii) there are insufficient data and experience upon which the effects of the 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 data.

EPA uses a weight-of-evidence approach in making section 4(a)(1)(A)(i) findings; both exposure and toxicity information are considered in determining whether available data support a finding that the chemical may present an unreasonable risk. For the findings under section 4(a)(1)(A)(i), EPA considers only production, exposure and release. For the findings under sections 4(a)(1)(B)(ii) and 4(a)(1)(B)(iii), EPA examines toxicity and fate studies to determine whether existing information is adequate to reasonably determine or predict the effects of human exposure to or environmental release of the chemical. In making the finding under section 4(a)(1)(A)(iii) or 4(a)(1)(B)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's process for determining when these findings apply is described in detail in EPA's first and second proposed test rules. The section 4(a)(1)(A) findings are discussed in the Federal Register of July 18, 1980 (45 FR 48528) and June 5, 1981 (46 FR 30300) and the section 4(a)(1)(B) findings are discussed in the Federal Register of June 5, 1981 (46 FR 30302).

In evaluating the ITC's testing recommendations concerning the fluoroalkenes, EPA considered all available relevant information including the following: information presented in the ITC's report recommending testing consideration; production volume, use, exposure, and release information

reported by manufacturers of the fluoroalkenes under the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR Part 712); health and safety studies submitted under the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 712); health and safety data studies submitted under the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 718) concerning the fluoroalkenes; and published and unpublished data available to the Agency. Based on its evaluation, as described in this proposed rule, EPA is proposing health effects testing requirements for vinylidene fluoride, vinyl fluoride, hexafluoropropene and tetrafluoroethene under section 4(a)(1)(A).

II. Review of Available Data

A. Profile

The ITC (Ref. 1) defined the designated fluoroalkenes to include those compounds having the general chemical formulas $C_xH_{2-x}F_x$, where x equals 2 or 3 and x equals 1 to 6. Six fluoroalkenes meeting this category definition were identified from the TSCA Chemical Substances Inventory. Two of the six chemicals, trifluoroethene and 3,3,3-trifluoro-1-propene, were considered by the Agency not to warrant additional testing at this time. The reasons relating to this decision have been discussed in the ANPR and proposed NTA for fluoroalkenes. The remaining four compounds, VF, VDF, TFE and HFP are the subject of this proposed rulemaking. All of these chemicals are gases at room temperature.

B. Production and Use

Fluoroalkenes in this category are produced and processed in closed systems for economic reasons and, in the case of vinyl fluoride, vinylidene fluoride and tetrafluoroethene, also because of an explosion hazard if the substances are not well contained.

The four fluoroalkenes under consideration for testing are used exclusively as precursors in the manufacture of highly specialized polymers and elastomers. Production levels in 1977 were less than 7 million pounds for VF, 10 million pounds for VDF, 10 to 50 million pounds for TFE and 1 to 10 million pounds for HFP (Refs. 2 through 4 and 9).

C. Exposure and Release

According to information provided by industry, product loss is minimal (Ref. 5). Actual measurements of exposure to the various chemicals were described in

the ANPR. Subsequent to the ANPR, and as reported in the proposed NTA, the FIG reported on human and area monitoring studies conducted for vinyl fluoride, tetrafluoroethene, hexafluoropropene and vinylidene fluoride in the workplace. All data indicated average human exposure levels are less than 1 part per million (ppm). Area monitoring levels were reported as not exceeding 10 ppm. Individual personal monitors did not exceed a 5 ppm peak level. Estimates of the numbers of workers exposed follow:

WORKER EXPOSURE ESTIMATES

Chemical	Manu- facturer	Refer- ence	NIOSH assess- ment	Refer- ence
Vinyl Fluoride	100	(2)	1,400	(6)
Vinylidene fluoride	460	(3)	1,900	(7)
Tetrafluoroethene	<900	(4)	5,000	(8)
Hexafluoropropene	<900	(5)		

D. Health Effects

1. *Chronic Effects.* The ITC reported renal damage was found in tests conducted with tetrafluoroethene and hexafluoropropene (Refs. 5, 10 through 12). The ITC report included citations of changes in blood potassium and urinary potassium after inhalation exposure of test animals to HFP, VDF, TFE and VF (Refs. 13 through 15). The ITC believed these changes in potassium levels reflected a metabolic pathway which released fluoride ions in the animal. The ITC postulated that the fluoride could bind with potassium, thereby causing the reported renal dysfunction and possibly cardiovascular effects.

A subchronic toxicity study on TFE was submitted by the Society of Plastics Industry, Inc. (Ref. 16) and reported in the Proposed Negotiated Test Program FEDERAL REGISTER Notice. This study was reviewed by Agency scientists and was found to provide a well-defined, no-observed-effect-level of 200 ppm for kidney effects; it was deemed adequate. Another study (Ref. 17) submitted by the FIG, a 14-day subacute study with HFP, demonstrated kidney effects similar to those seen in the TFE study. The results of these two studies tend to confirm the renal effects of this class of compounds. While the 90-day TFE study is valid as a predictor for toxic endpoints, the Agency does not consider the 14-day study on HFP sufficient to predict the long-term no-effect level of HFP on the kidneys.

In preliminary results of a subchronic study sponsored by the Association of Plastics Manufacturers in Europe (APME), and submitted to the Agency by Pennwalt Corporation, VDF-exposed

rats demonstrated a greater than 50 percent decrease in testis weight in the high dose group (40,000 ppm, by inhalation) after 13 weeks of exposure (Ref. 26). Pennwalt notes that these results are contrary to a similar study on VDF in rats and mice performed by the National Toxicology Program (NTP). NTP's study yielded no compound related effects, even at a 50,000 ppm dose level (Ref. 24). Pennwalt stated that it believes non-compound related factors (e.g., stress, diet, disease) may have influenced the results of the APME study, but that additional data are needed to clarify the APME study results.

2. Carcinogenicity. The ITC reported on a carcinogenicity study on VDF (Ref. 18). While the study did show malignancies in rats, the test methods were considered questionable by the Agency. However, a second study with VDF (Ref. 19) demonstrated that VDF produced premalignant hepatocellular lesions in rats.

The ITC also reported that in studies with VF, liver toxicity similar to that of vinyl chloride (VC) was seen (Refs. 20 and 21). The ITC further stated that additional analysis of this study revealed that the toxic effects may have been initiated or promoted by other chemicals used in the experiment, PCB and trichloropropane epoxide. However, the ITC did believe that the lesions reported by the study were from the treatment with the vinyl halides and that the toxicity of VF may be mediated through epoxide intermediates. Based on these suggestive findings of the oncogenic potential of VDF and VF, and the structural similarities of these substances to the oncogens vinylidene chloride and vinyl chloride (Ref. 23), EPA believes that both VDF and VF should be tested for oncogenicity. Oncogenicity testing of VDF in the rat, including subchronic toxicity testing, is currently ongoing in Europe under the auspices of the Association of Plastics Manufacturers in Europe. The protocols for this testing (Refs. 24 and 25) were submitted to EPA by the FIG, reviewed and approved as adequate by EPA, and considered as part of the NTA for the fluoroalkenes, as described in the June 4, 1984 Federal Register (49 FR 23112). However, this study does not include oncogenicity testing in a second species, a characteristic generally considered by EPA, NTP and others to be necessary to fully evaluate a chemical's oncogenic potential.

3. Mutagenicity. The ITC reported several mutagenicity studies for VF and VDF. Additional information was

reviewed and reported by the Agency in its Proposed Negotiated Test Program (June 4, 1984; 49 FR 23112). These data indicate that in mutagenicity tests with *E. coli* both VF and VDF gave positive mutagenic results. In addition, when VDF was tested in the *Salmonella* reverse mutation assay (Ames) this compound was positive in one test strain both with and without metabolic activation. Neither VF nor HFP gave positive results in the *Salmonella* assay. There are no mutagenicity data on TFE at present.

4. Metabolism. A member company of the FIG (ICI Americas) submitted a metabolism study of TFE in rats (Ref. 22). The test indicated that the major metabolic pathway of TFE was through glutathione, not through the cytochrome P450 pathway as in other haloalkene metabolites, notably vinyl chloride. This group also tested the TFE-cysteine conjugate and the HFP-cysteine conjugate metabolite in the *Salmonella* assay and reported negative findings for the metabolites. They did not test the parent compounds TFE or HFP in the assay. The report speculated that the metabolites found in the lower carbon fluoroalkenes (i.e., VF and VDF) which do follow the cytochrome P450 metabolic pathway could be more biologically active since they could form epoxides in the cytochrome metabolic pathway.

5. Developmental Toxicity. As discussed in the Agency's previous proposed NTA (45 FR 23112), EPA has found no evidence to suggest that VF, VDF, TFE or HFP may cause teratogenicity or other developmentally toxic effects. Industry has submitted a teratogenicity study for VDF which has been reviewed by EPA and found to be adequately performed; it showed no evidence of teratogenic effects.

III. Findings

EPA is basing its proposed health effects testing of VF, VDF, TFE and HFP on the authority of section 4(a)(1)(A) of TSCA.

EPA finds that the manufacture of these fluoroalkenes may present an unreasonable risk of chronic health effects, oncogenicity or mutagenicity to humans exposed to these substances, based on data presented in Unit II.D. which indicate that VF and VDF may have potential oncogenic effects, that VF, VDF, TFE and HFP may have potential chronic renal effects, that VDF may have potential reproductive effects and that VF, VDF, TFE and HFP may have mutagenic effects.

Available data indicate that VDF may produce oncogenic effects, as evidenced

by positive mutagenicity in *E. coli* and a strain of *Salmonella*, preneoplastic changes observed in the liver cells of rats treated with VDF, and positive oncogenicity results in a study submitted by the FIG. Although this letter study was performed using methodology considered questionable by the Agency, the results are nonetheless considered suggestive of oncogenic potential for VDF. VDF is also structurally similar to vinylidene chloride, which has shown evidence of oncogenicity in some studies.

The Agency also finds that the data available for VF indicate that VF may produce oncogenic effects, based on positive mutagenicity in *E. coli*; liver toxicity similar to that seen for vinyl chloride (a known human oncogen), and the structural similarity of VF to vinyl chloride. Additionally, both TFE and HFP have produced renal function impairment, although without a no-observed effect level being established for HFP. Both VF and VDF and induce similar changes in blood and urine chemistry as HFP and TFE when administered to test animals, suggesting the possibility for similar renal toxicity. Newly available data, showing testicular effects in rats exposed to VDF, are suggestive of possible reproductive effects due to VDF exposure. Finally, as reported by the ITC, the fluoroalkenes may metabolize to form reactive epoxides which can result in genotoxicity. Although the TFE and HFP metabolite data do not indicate mutagenic potential in the *Salmonella* test system, this test alone is insufficient evidence of non-mutagenicity of a compound. Therefore the Agency considers that the individual chemicals VF, VDF, TFE and HFP may have genotoxic potential and present a mutagenic risk to humans exposed to these chemicals. Data available on these effects are inconclusive and further testing is needed.

EPA also finds that there is sufficient potential for human exposure to VF, VDF, TFE and HFP, as discussed in Unit II.C., to support section 4(a)(1)(A) findings for these chemicals, although the exposures may not be great enough to make the findings required under section 4(a)(1)(B). The Agency also finds that the available data are insufficient to reasonably predict or determine the effects the manufacture of VF, VDF, TFE and HFP on human health in the areas noted above and, thus, EPA finds that testing is necessary to develop such data.

IV. proposed rule and test standards

A. Proposed Testing and Test Standards

The Agency is proposing that health effects testing be conducted on the fluoroalkenes in accordance with specific test guidelines set forth in Title 40 of the Code of Federal Regulations as enumerated below. Test methods under new Parts 796, 797, and 798 were published in the Federal Register of September 27, 1985 (50 FR 39252). The Agency is proposing that HFP be tested in the rat and mouse for inhalation subchronic toxicity as specified in § 798.2450 and as modified in § 799.1700(c)(3)(i)(B). Subchronic toxicity testing is not being proposed for TFE because adequate data are currently available as noted in Unit I.D.1. above. Separate subchronic testing is not being required for VF and VDF because it is included as part of the oncogenicity testing being required for those substances. The Agency is proposing that inhalation oncogenicity tests be conducted in rats and mice for VF and VDF. The test guidelines in § 798.3300 are proposed as the test standards for the oncogenicity testing of VF in both species and for VDF in mice. For testing of VDF in rats, EPA proposes that the test protocols submitted earlier by the FIG (Refs. 24 and 25) be adopted as the test standards under this rule. These protocols were reviewed and approved by the Agency as part of the previous proposed NTA. The oncogenicity testing for VF and VDF is an immediate requirement. The Agency believes that the data now available on these two compounds support a section 4(a)(1)(A)(i) finding that the manufacture of these substances may present an unreasonable risk of oncogenicity. There is substantially less evidence at the present time which would indicate that either TFE or HFP may be potential oncogens. The structural similarity among the fluoroalkenes and between the fluoroalkenes and the chloroalkenes provides limited suggestive evidence that there may be potential for TFE and HFP to exert oncogenic effects. However, other data suggest that the metabolism of TFE and HFP may be different from that of VF and VDF. Overall, the Agency believes that the weight of evidence is insufficient to propose oncogenicity testing at this time for TFE and HFP. Therefore, oncogenicity testing for TFE and HFP is being proposed only if triggered by the results of the mutagenicity testing being proposed in this rule. It is proposed that the test guidelines in § 798.3800 be used as the test standards for such testing if it is triggered. Positive test results for TFE or HFP in any of the following tests will

trigger the oncogenicity testing requirement for that chemical: *in vitro* cytogenetics assay, *in vivo* cytogenetics assay, mammalian cells in culture assay and sex-linked recessive lethal assay in *Drosophila melanogaster*.

Based on data recently submitted to the Agency showing significant testicular effects on rats to subchronic exposure of VDF (Ref. 28), the Agency is also proposing a 2-generation reproduction study in rats for VDF, to be conducted according to the test guidelines specified in § 798.4700

To assess the potential for the fluoroalkenes to cause gene mutations, the Agency is proposing mutagenicity testing in the *Salmonella* reverse mutation assay as specified in § 798.5285 and as modified in § 799.1700(c)(1)(i)(A)(2) for TFE. EPA has adequate data on the other three compounds in this test. EPA is also proposing that mutagenicity testing for cells in culture be conducted for VF and HFP on subclones of CHO cells as specified in § 798.5300 and as modified in § 799.1700(c)(1)(i)(B)(2). The same test must also be performed for TFE should that substance produce negative results in the *Salmonella* assay. If the results of cells in culture test are positive for any individual fluoroalkene or if the results of the *Salmonella* test for TFE are positive, then a *Drosophila* sex-linked recessive lethal (SLRL) assay shall be conducted as specified in § 798.5275 and as modified in § 799.1700(c)(1)(C)(2) for that chemical. Based on positive results from the testing of VDF in the *Salmonella* assay, as discussed in Unit I.D., the Agency is proposing that VDF be tested in the SLRL assay. A positive result in the SLRL for any chemical tested will trigger a mouse specific locus test, specified in § 798.5200 and as modified in § 799.1700(c)(1)(i)(D)(2), in the same chemical. If the cells in culture test is negative then no further gene mutations testing will be required for that fluoroalkene. If the SLRL assay is negative then the mouse specific locus test will not be required.

To assess the potential for fluoroalkenes to cause chromosomal aberrations, the Agency is proposing that *in vitro* cytogenetic assays be conducted on VF, VDF, TFE and HFP as specified in § 798.5375 and as modified in § 799.1700(c)(2)(i)(A)(2). If the results of the *in vitro* test are positive then a dominant lethal assay will be required as specified in § 798.5450 and as modified in § 799.1700(c)(2)(i)(C)(2). A positive result in the dominant lethal assay will trigger a heritable translocation assay as specified in

§ 798.5480 and as modified in § 799.1700(c)(2)(i)(D)(2). If the *in vitro* cytogenetic assay is negative than an *in vivo* cytogenetic assay will be required (as specified in § 798.5385 and as modified in § 799.1700(c)(2)(i)(B)(2), that fluoroalkene. Should the *in vivo* cytogenetic results prove negative, then no further chromosomal aberration testing would be required for that substance. A positive result in the *in vivo* cytogenetic assay for any fluoroalkene would trigger the dominant lethal assay for that fluoroalkene. Again, if the dominant lethal assay is positive for any fluoroalkene a heritable translocation assay shall be conducted for that fluoroalkene.

If the results from the dominant lethal assay and/or the SLRL assay are positive, EPA will hold a public program review prior to initiating the heritable translocation and/or mouse specific locus testing. Public participation in this program review will be in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting will be published in the Federal Register. Should the Agency determine, based on the weight of the evidence then available, that proceeding to the heritable translocation test and/or mouse specific locus test is no longer warranted, the Agency would propose to repeal that test requirement and, after public comment, issue a final amendment to rescind the requirement.

For a more detailed discussion concerning mutagenicity tiered testing and program review see the final test rule for the C9 aromatic hydrocarbon fraction (50 FR 20882, May 17, 1985).

The Agency is proposing that the above referenced TSCA Health Effects Test Guidelines be considered the test standards for the purposes of the proposed tests for the fluoroalkenes. The specified TSCA guidelines for Health Effects Testing provide general accepted minimal conditions for ensuring that any required testing will result in reliable and adequate data for evaluating the health effects of VDF, V TFE and HFP. The Agency reviews the TSCA test guidelines once a year in accordance with the process described in the Federal Register of September 2: 1982 (47 FR 48157). In reviewing the applicability of certain of the mutagen effects and subchronic test guidelines the fluoroalkenes, EPA has determined that certain modifications should be made to these guidelines in order to ensure that the resulting data are reliable and adequate.

EPA intends to propose shortly in a separate Federal Register notice certain

revisions to these TSCA Test Guidelines to provide more explicit guidance on the necessary minimum elements for each study. In addition, these revisions will avoid repetitive chemical-by-chemical changes to the guidelines in their adoption as test standards for chemical-specific test rules. EPA is proposing that these modifications be adopted in the test standards for VF, VDF, HFP, and TFE.

B. Test Substance

EPA is proposing testing of VDF, VF, TFE and HFP of at least 99 percent purity. EPA believes that test materials of this purity are available at reasonable cost. EPA has specified relatively pure substances for testing because the Agency is interested in evaluating the effects attributed to the subject compounds themselves. This requirement would increase the likelihood that any toxic effects observed are related to the subject fluoroalkenes and not to any impurities.

C. Persons Required to Test

Section 4(b)(3)(B) of TSCA specifies that the activities for which the Agency makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determines who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "import"). Processors are required to test if the findings are based on processing. Both manufacturers and processors are required to test if the exposures giving rise to the potential risk occur during use, distribution, or disposal. Because EPA has found that there are insufficient data to reasonably determine or predict the effects of the manufacture of the fluoroalkenes on human health, EPA is proposing that persons who manufacture or intend to manufacture VF, VDF, TFE or HFP at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the specific health effects testing requirements for each individual fluoroalkene which they manufacture. Thus, those persons who manufacture or intend to manufacture all four fluoroalkenes will be subject to the entire set of testing requirements set forth in this rule. However, those persons who manufacture or intend to manufacture a subset of those four chemicals will only be responsible for the particular testing requirements for the subset of fluoroalkenes which they manufacture. The end of the reimbursement period will be 5 years after the last final report is submitted or

an amount of time after the submission of the last final report required under the test rule equal to that which was required to develop data, if more than 5 years.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to EPA for an exemption from the requirement. EPA promulgated procedures for applying for TSCA section 4(c) exceptions in 40 CFR Part 790.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for the fluoroalkenes. As noted in Unit IV.B., EPA is interested in evaluating the effects attributable to the fluoroalkenes subject to this rule themselves, and has specified a relatively pure substance for testing.

Manufacturers subject to this test rule must comply with the test rule development and exemption procedures in 40 CFR Part 790 for single-phase rulemaking.

D. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its TSCA Good Laboratory Practices (GLP) standards which appear in 40 CFR Part 792.

In accordance with 40 CFR Part 790 under single-phase rulemaking procedures, test sponsors are required to submit individual study plans at least 30 days prior to the initiation of each study.

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. The Agency is proposing specific reporting requirements for each of the proposed test standards as follows:

1. The subchronic toxicity test shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final test rule. Progress reports shall be submitted quarterly.

2. The reproductive effects test shall be completed and final results submitted to the Agency within 29 months of the effective date of the final rule. Progress reports shall be submitted quarterly.

3. The mutagenicity studies shall be completed and final results submitted to the Agency within 36 months of the effective date of the final test rule if the

criteria necessary to trigger all of the mutagenicity testing are met. Deadlines for submission of results for individual tests are specified in the rule. Progress reports shall be submitted quarterly.

4. The oncogenicity tests shall be completed and the final results submitted to the Agency within 53 months of the effective date of the final rule for VF and VDF, and within 67 months for HFP and TFE, if required by the mutagenicity testing. Progress reports shall be submitted quarterly.

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, the Agency will publish a notice of receipt in the Federal Register as required by section 4(d) of TSCA.

Persons who export a chemical or mixture which is subject to a section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final regulations interpreting the requirements of section 12(b) are in 40 CFR Part 707 (December 16, 1980; 45 FR 82844). In brief, as of the effective date of the final test rule, an exporter of the fluoroalkenes covered by this rule (VF, VDF, HFP and TFE) must report to EPA the first annual export or intended export of a fluoroalkene to any one country. EPA will notify the foreign country concerning the test rule for the chemical.

E. Enforcement Provisions

The Agency considers failure to comply with any aspects of a section 4 rule to be a violation of section 15 of TSCA. Section 15(1) of TSCA makes it unlawful for any person to fail or refuse to comply with any rule on order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to: (1) Establish or maintain records, (2) submit reports, notices, or other information, or (3) permit access to or copying of records required by the Act or any regulation or rule issued under TSCA.

Additionally, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection required by section 11. Section 11 applies to any "establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce . . ." The Agency considers a testing facility to be a place where a chemical is held or stored and, therefore, subject to inspection. Laboratory audits/inspections will be conducted periodically in accordance with the authority and procedures

outlined in TSCA section 11 by duly designated representatives of the EPA for the purpose of determining compliance with any final rule for the fluoroalkenes. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data and interpretations thereof, and that the TSCA GLP standards and the test standards established in the rule are being complied with.

EPA's authority to inspect a testing facility also derives from section 4(b)(1) of TSCA, which directs EPA to promulgate standards for the development of test data. These standards are defined in section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and such other requirements as are necessary to provide such assurance. The Agency maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirements of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provision of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to \$25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers that fail to submit a letter of intent or an exemption request and that continue manufacturing after the deadlines for such submissions. Knowing or willful violations could lead to the imposition of criminal penalties of up to \$25,000 for each day of violation and imprisonment for up to 1 year. In determining the amount of penalty, EPA will take into account the seriousness of the violation and the degree of culpability of the violator as well as all the other factors listed in section 16. Other remedies are available to EPA under section 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Sections 15 and 16 of TSCA apply to "any person" who violates various provisions of TSCA. EPA may, at its discretion, proceed against individuals as well as companies themselves. In particular, this includes individuals who report false information or who cause it

to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

V. Issues for Comment

This proposed rule specifies TSCA test guidelines with certain modifications as the test standards for health testing of fluoroalkenes. The Agency is soliciting comments as to whether these health effects test guidelines and modifications are appropriate for the testing of fluoroalkenes. Also regarding the testing of fluoroalkenes, the Agency requests comments on:

1. The adequacy of this testing.
2. The reporting times for the identified health effects tests.
3. Whether there are any other testing approaches which should be considered.

Two further issues for comment arise from the fact that oncogenicity testing is being proposed for VDF in both rats and mice even though oncogenicity testing (in rats alone) is ongoing in Europe under the auspices of the Association of Plastics Manufacturers in Europe and testing is also planned for VDF in rats and mice by the National Toxicology Program (NTP). NTP is also considering TFE for oncogenicity testing in rats and mice. The Agency believes that both rats and mice should be tested as required by the TSCA Health-Effects-Guidelines for oncogenicity. The Agency also believes that by proceeding with this rulemaking to require testing now, timely development of the data will be assured, in case the ongoing and planned testing efforts are not brought to completion. The Agency is, however, requesting comment on how best to ensure that this testing is obtained in a timely manner while avoiding duplicative testing.

VI. Economic Analysis of Proposed Rule

To evaluate the potential economic impact of test rules, EPA has adopted a two-stage approach. All candidates for test rules go through a Level I analysis. This consists of evaluating each chemical or chemical group on four principal market characteristics: (1) Demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The results of the Level I analysis, along with the consideration of the costs of the required tests indicate whether the possibility of a significant adverse economic impact exists. Where the indication is negative, no further economic analysis is done for the chemical substance or group. However, for those chemical substances or groups where the Level I analysis indicates a

potential for significant economic impact, a more comprehensive and detailed analysis is conducted. This Level II analysis attempts to predict more precisely the magnitude of the economic impact.

Total testing costs for the proposed rule are estimated to range from \$4,768,900 to \$7,830,100. This estimate includes the costs for both the required minimum series of tests as well as the conditional tests. The annualized test costs (using a cost of capital 25 percent over a period of 15 years) range from \$1,235,600 to \$2,028,800. Based on the estimated production volumes of these four chemicals (between 48 and 77 million lbs), the unit test costs range from \$0.016 to \$0.042 per pound. Relative to the current price range of \$4.30 to \$8.50 per pound for these four chemicals, these units costs are equivalent to 0.19 to 0.98 percent of price.

Based on these costs and the market characteristics of these four chemicals, the economic analysis indicates that the potential for significant adverse economic impact as a result of this test rule is low. This conclusion is based on the following observations:

1. The annual unit cost of the testing required in this rule is low.
2. The demand for these four chemicals appears relatively price inelastic due to their exclusive use as precursors in the manufacture of highly specialized polymers and elastomers.

The preceding analysis and conclusions are based on the assumption that the four chemicals in this category will be treated as one for reimbursement purposes, and that the total cost of testing these chemicals will be divided among the producers on the basis of each producer's total production of these chemicals.

The TSCA Reimbursement Rule allows affected private parties to negotiate amongst themselves an equitable cost reimbursement scheme; therefore, while this reimbursement assumption is reasonable, other reimbursement approaches are also possible. The opposite assumption from that used above is one in which each chemical in the category is treated individually; the cost of testing that chemical will be borne only by the manufacturers of that chemical. Under this assumption, the annualized test cost for each chemical is divided by the annual production of that chemical; the increased cost is then compared with the selling price of that chemical. Thus some chemicals will have higher test costs than others, but given the uses of these four chemicals, and their fairly inelastic demand, it is reasonable to

assume that these chemicals will not be significantly affected.

Refer to the economic analysis available in the public record for this rulemaking for a complete discussion of the test cost estimation and the potential for economic impact resulting from these costs.

VII. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules and test programs negotiated with industry in place of rulemaking. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing (PB 82-140773)", can be obtained through the National Technical Information Service (NTIS).

On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing in this proposed rule.

VIII. Public Meeting

If persons indicate to EPA that they wish to present comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting in Washington, D.C. Persons who wish to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll-Free: (800-424-9065); in Washington, DC: (554-1404); Outside the U.S.A. (operator 202-554-1401), by December 23, 1985. The meeting will not be held if members of the public do not indicate that they wish to make oral presentations. This meeting will be scheduled after the deadline for submission of written comments, so that issues raised in the written comments can be discussed by EPA and the public commenters. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether the meeting will be held.

Should a meeting be held, the Agency will transcribe the meeting and include the written transcript in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will

become part of EPA's record for this rulemaking.

IX. Rulemaking Record

EPA has established a record for this rulemaking (OPTS-42002). This record includes basic information considered by the Agency in developing this proposal and appropriate Federal Register notices. The Agency will supplement the record with additional information as it is received.

This record includes the following information:

A. Support Documentation

(1) Federal Register notices pertaining to this rule consisting of:

(a) Notice containing the ITC designation of fluoroalkenes to the Priority List (45 FR 78432).

(b) Notice of the Agency's initial response to the ITC on fluoroalkenes (46 FR 53704).

(c) Notice of the Agency's second response to the ITC on fluoroalkenes (49 FR 23112).

(d) Notice of interim final rule on single-phase test rule development and exemption procedures (50 FR 20652).

(e) Notice of final rulemaking on data reimbursement (48 FR 31786).

B. References

(1) Seventh Report of the Interagency Testing Committee to the Administrator, Nov. 25, 1980: 45 FR 78432.

(2) Fluoroalkenes Industry Group. Unpublished Report on Potential Exposure to Vinyl Fluoride During Manufacture of Monomer Vinyl Fluoride. Submitted to USEPA June 26, 1981.

(3) Fluoroalkenes Industry Group. Unpublished Report on Vinylidene Fluoride (VDF) Exposure. Submitted to USEPA June 28, 1981.

(4) Halocarbon Products Corporation. Letter from L. Ferstending to A. Keller, June 25, 1982.

(5) Fluoroalkenes Industry Group. Unpublished report on potential exposure to tetrafluoroethene during manufacture of monomer tetrafluoroethene. Submitted to USEPA August 13, 1981.

(6) NIOSH (National Institute for Occupational Safety and Health). Vinyl Fluoride Industrial Hygiene Survey Report. October 1977.

(7) NIOSH-OSHA (National Institute for Occupational Safety and Health/ Occupational Safety and Health Administration). Current Intelligence Bulletin 28. Vinyl Halides Carcinogenicity. September 21, 1978. DHEW (NIOSH) Publication No. 79-102.

(8) NIOSH. SIC/NIOSH Survey. Computer printout of surveys covering 1972-74. Retrieved by USEPA 1980.

(9) TSCA Chemical Substances Inventory (EPA 1977).

(10) Fluoroalkenes: Response to the interagency Testing Committee. Oct. 30, 1981: 46 FR 53704.

(11) Clayton, J.W. "The Toxicity of fluorocarbons with special reference to chemical constitution." *Journal of Occupational Medicine* 4:262-272. 1962.

(12) Clayton, J.W. "Fluorocarbon toxicity and biological action." *Fluorine Chemistry Review* 1:197-252. 1967.

(13) Clayton, J.W. "Fluorocarbon toxicity and biological action." In Fink, B.R. ed. "Toxicity of Anaesthetics." The Williams and Wilkins Co., Baltimore pp. 77-104. 1968.

(14) Clayton, J.W. "Toxicology of the Fluoroalkenes: Review and Research Needs." *Environmental Health Perspectives* 21:255-267. 1977.

(15) Dilley, J.V., L.C. Vernon, and E.S. Harris. "Fluoride ion excretion by male rats after inhalation of one of several fluoroethylenes or hexafluoropropene." *Toxicology and Applied Pharmacology* 27:582-590. 1974.

(16) The Society of Plastics Industry, Inc. "Ninety-day inhalation toxicity study with tetrafluoroethylene (TFE) in rats and hamsters." Haskell Laboratory Report No. 208-82, July 7, 1982.

(17) Society of the Plastics Industry, Inc. "Subchronic inhalation toxicity of hexafluoropropylene." Study submitted by E.L. du Pont de Nemours and Company under section 8(d) of TSCA, February 20, 1985. Ref. 878215099.

(18) Maltoni, D. and D. Tovoli. "First experimental evidence of the carcinogenic effects of vinylidene fluoride." *La Medicina del Lavoro* 70:363-368. 1979.

(19) Stockle, G.R., J. Laib, J.C. Fisher, and H.M. Bolt. "Vinylidene Fluoride Metabolism and induction of preneoplastic hepatic foci in relation to vinyl chloride." *Toxicology Letter* 3:337-342. 1979.

(20) Conolly, R.B. and R.J. Jaeger. "Acute hepatotoxicity of ethylene and halogenated ethylenes after PCB pretreatment." *Environmental Health Perspectives* 21:131-135. 1977.

(21) Conolly, R.B., R.J. Jaeger and S. Szabo. "Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride and vinyl bromide after Arochlor 1254 pretreatment." *Experimental Molecular Pathology* 28:25-33. 1978.

(22) Lyons, James. Letter with study addressed to Richard Troast, TRDB, ECAD. 1985.

(23) International Agency for Research on Cancer. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement* 4:260-284. 1982.

(24) CIVO Institutes TNO. Protocol for a sub-chronic (13-week) inhalation study of vinylidene fluoride vapour in rats. Submitted to USEPA August 1, 1984.

(25) CIVO Institutes TNO. Protocol for a chronic toxicity/carcinogenicity inhalation study of vinylidene fluoride vapour in rats. Submitted to USEPA August 1, 1984.

(26) Hopkins, John E. Letter with preliminary study results addressed to Dr. John Moore, OPTS, USEPA. 1985.

X. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "Major" and, therefore, subject to the requirement of a Regulatory Impact Analysis. This test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order. First, the total cost of all the proposed testing for fluoroalkenes is \$4,788,900 to \$7,830,100 over the testing and reimbursement period. Second, the cost of the testing is not likely to result in a major increase in users' costs or prices. Finally, based on our present analysis, EPA does not believe that there will be any significant adverse effects as a result of this rule.

This proposed regulation was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (15 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 18, 1980), EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses because: (1) They are not expected to perform testing themselves, or to participate in the organization of the testing effort; (2) they will experience only very minor costs in securing exemption from testing requirements; and (3) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The Office of Management and Budget (OMB) has approved the information collection requirements contained in the proposed rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.* and has assigned OMB control number 2070-0033. Comments on these requirements should be submitted to the Office of Information and Regulation Affairs of OMB marked, "Attention: Desk Officer for EPA". The final rule package will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous substances, Chemicals, Recordkeeping and reporting requirements.

Dated: 31 October 1985.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

PART 799—[AMENDED]

Therefore, it is proposed that 40 CFR Part 799 be amended as follows:

1. The authority citation for Part 799 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

2. Section 799.1700 is added, to read as follows:

§ 799.1700 Fluoroalkenes.

(a) Identification of test substances.

(1) Vinyl fluoride (VF; CAS No. 75-02-5), vinylidene fluoride (VDF; CAS No. 75-38-7), tetrafluoroethene (TFE; CAS No. 116-14-3) and hexafluoropropene (HFP; CAS No. 116-15-4) shall be tested in accordance with this section.

(2) VF, VDF, TFE and HFP of at least 99 percent purity shall be used as the test substances.

(b) Persons required to submit study plans, conduct tests and submit data.

All persons who manufacture VF, VDF, TFE or HFP from the effective date of this section (44 days from the publication date of the final rule in the Federal Register) to the end of the reimbursement period shall submit letters of intent to conduct testing or exemption applications, submit study plans, conduct tests and submit data as specified in this section. Subpart A of this Part, and Part 790 of this chapter for single-phase rulemaking, for the substances they manufacture.

(c) Health effects testing—(1)

Mutagenic effects—Gene mutation—(i) Required testing. (A) (1) Gene mutation assays in the *Salmonella typhimurium* histidine reversion system shall be conducted with TFE in accordance with § 798.5265 of this chapter.

(2) Modifications to § 798.5265 of this chapter. The following modifications to § 798.5265 of this chapter for testing TFE are required.

(i) *Reference substances.* The requirement under § 798.5265(c) of this chapter regarding reference substances is not applicable for TFE.

(ii) *Test Method—Description.* The requirement under § 798.5265(d)(2) of this chapter is modified for TFE so that the desiccator method shall be used for this study.

(iii) *Control groups.* The requirement under § 798.5265(d)(5)(i) of this chapter is modified for TFE so that concurrent positive and negative (untreated and filtered air) controls shall be included in each experiment. In experiments with

metabolic activation, the positive control shall be known to require such activation. Methyl bromide is an example of a positive control for experiments without activation and vinyl chloride is an example of a positive control for experiments with metabolic activation. Filtered air shall serve as the negative control.

(iv) *Test performance.* The requirement under § 798.5265(e) of this chapter is modified for TFE so that for tests without metabolic activation, 0.5 ml of phosphate-buffered-saline (PBS) and 0.1 ml of bacteria shall be added to 2.0 ml of overlay agar. For tests with metabolic activation, 0.5 ml of activation mixture containing an adequate amount of post-mitochondrial fraction shall be added to the agar in place of the PBS and after the addition of the bacteria. Contents of each tube shall be mixed and poured over the surface of a selective agar plate. The overlay agar shall be allowed to solidify and plates without lids shall be placed in glass chambers. Test gas mixed with filtered air at several concentrations shall be introduced into the chambers through a flow-meter system. Gas-air mixture shall flow through the chambers for five volume changes after which the chambers shall be closed and placed in an incubator at 37 °C for 48 hours. At the end of the exposure period, chambers shall be flushed with five volumes of air. After chambers have been flushed, air, plates shall be removed and revertant colonies counted.

Concentrations of test gas in the chambers shall be determined 2 to 3 hours after initiating treatment and just prior to the termination of exposure. All plating shall be done at least in triplicate. All results shall be confirmed in an independent experiment.

(v) *Test report.* The requirement under § 798.5265(f)(5)(iii) of this chapter is modified for TFE so that test gas concentration in the chambers at each sampling period and the rationale for selection of each concentration shall be reported.

(B) (2) a specific locus mutation assay in mammalian cells in culture shall be conducted with VF and HFP in accordance with § 798.5300 of this chapter. TFE shall also be tested in this assay in accordance with § 798.5300 of this chapter if the *Salmonella* assay conducted on TFE pursuant to paragraph (c)(1)(i)(A) of this section produces a negative result.

(2) Modification of § 798.5300 of this chapter. The following modification to § 798.5300 of this chapter for testing V TFE and HFP are required.

(i) *Reference substances.* The requirement under § 798.5300(c) of this chapter regarding reference substances is not applicable to VF, TFE and HFP.

(ii) *Test method—Type of cells used in the assay.* The requirement under § 798.5300(d)(3)(i) of this chapter is modified for VF, TFE and HFP so that mutation induction at the Hprt locus shall be measured in Chinese hamster ovary (CHO) cells. Cells shall be checked for *Mycoplasma* contamination and may also be checked for karyotype stability.

(iii) *Test Method—Metabolic activation.* The requirement under § 798.5300(d)(4) of this chapter is modified for VF, TFE and HFP so that cells shall be exposed to test substance both in the presence and absence of a metabolic activation system. The metabolic activation system shall be derived from the post-mitochondrial fraction (S-9) of livers from rats pretreated with Aroclor 1254.

(iv) *Test method—Control groups.* The requirement under § 798.5300(d)(5) of this chapter is modified for VF, TFE and HFP so that positive and negative controls shall be included in each experiment. In assays with metabolic activation, the positive control substance shall be known to require such activation. Filtered air shall serve as the negative control.

(v) *Test method—Test chemicals.* The requirement under § 798.5300(d)(6) of this chapter is modified for VF, TFE and HFP so that the test should be designed to have a predetermined sensitivity and power. The number of cells, cultures, and concentrations of test substance used should reflect these defined parameters. The number of cells per culture is based on the expected background mutant frequency; a general guide is to use a number which is ten times the inverse of this frequency. Several concentrations (usually at least 4) of the test substance shall be used. These shall yield a concentration-related toxic effect. The highest concentration shall produce a low level of survival (approximately 10 percent) and the survival in the lowest concentration shall approximate that of the negative control. Cytotoxicity shall be determined after treatment with the test substance both in the presence and in the absence of the metabolic activation system.

(vi) *Test performance.* The requirement under § 798.5300(e)(1) of this chapter is modified for VF, TFE and HFP so that cells in treatment medium with and without metabolic activation shall be exposed to varying concentrations of test gas-air mixtures by flushing treatment flasks with 10

volumes of test gas-air mixture at a rate of 500 mL/min or that rate which will allow complete flushing within one minute. Each flask shall be closed with a cap with a rubber septum. Headspace samples shall be taken at the beginning and end of the exposure period and analyzed to determine the amount of test gas in each flask. Flasks shall be incubated on a rocker panel at 37 °C for 18 hours for experiments without metabolic activation and 5 hours for experiments with metabolic activation.

(vii) *Test performance.* The requirement under § 798.5300(e)(2) of this chapter is modified for VF, TFE and HFP so that at the end of the exposure period, cells treated without activation shall be washed and subcultured immediately to determine viability and to allow for expression of mutant phenotype. Cells treated with metabolic activation shall be washed and incubated in culture medium for 24 to 28 hours prior to subculturing for viability and expression of mutant phenotype. Appropriate subculture schedules (generally twice during the expression period) shall be used.

(viii) *Test performance.* The requirement under § 798.5300(e)(3) of this chapter is modified for VF, TFE and HFP so that at the end of the expression period, which shall be sufficient to allow near optimal phenotypic expression of induced mutants (generally 7 days for this cell system); cells shall be grown in medium with and without selective agent for determination of numbers of mutants and cloning efficiency respectively. This last growth period is generally 7 days at 37 °C.

(C)(1) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with VDF in accordance with § 798.5275 of this chapter. This test shall also be conducted with TFE in accordance with § 798.5275 of this chapter if the *Salmonella* assay conducted on TFE pursuant to paragraph (c)(1)(i)(A) of this section produces a positive result. This test shall also be performed with VF, HFP and TFE for whichever of these substances produces a positive result in the specific locus mutation assay conducted pursuant to paragraph (c)(1)(i)(B) of this section.

(2) Modifications to § 798.5275 of this chapter. The following modifications to § 798.5275 of this chapter for testing VDF, VF, TFE and HFP are required.

(i) *Test chemicals—Vehicle.* The requirement under § 798.5275(d)(5)(i) of this chapter regarding vehicle is omitted for VDF, VF, TFE and HFP.

(ii) *Test chemicals—Dose levels.* The requirement under § 798.5275(d)(5)(ii) of this chapter is modified for VDF, VF,

TFE and HFP so that it is sufficient to test a single dose of the test substance. This dose shall be the maximum tolerated dose or that which produces some indication of toxicity.

(iii) *Test chemicals—Route of administration.* The requirement under § 798.5275(d)(5)(iii) of this chapter is modified for VDF, VF, TFE and HFP so that exposure shall be by inhalation.

(D)(1) A mouse specific locus assay shall be conducted with VF, VDF, TFE and HFP in accordance with § 798.5200 of this chapter for whichever of these substances produces a positive result in the sex-linked recessive lethal test in *Drosophila melanogaster* conducted pursuant to paragraph (c)(1)(i)(C) of this section.

(2) Modifications to § 798.5200 of this chapter. The following modifications to § 798.5200 of this chapter for testing VF, VDF, HFP and TFE are required.

(i) *Test chemicals—Vehicle.* The requirement under § 798.5200(d)(5)(i) of this chapter regarding vehicle is omitted for VF, VDF, HFP and TFE.

(ii) *Test chemicals—Dose levels.* The requirement under § 798.5200(d)(5)(ii) of this chapter is modified for VF, VDF, HFP and TFE so that a minimum of two dose levels shall be tested. The highest dose tested shall be the highest dose tolerated without toxic effects, provided that any temporary sterility induced due to elimination of spermatogonia is of only moderate duration, as determined by a return of males to fertility within 14 days after treatment, or shall be the highest dose attainable.

(iii) *Test chemicals—Route of administration.* The requirement under § 798.5200(d)(5)(iii) of this chapter is modified for VF, VDF, HFP and TFE so that animals shall be exposed to the test substance by inhalation. Exposure shall be for 6 hours a day. Duration of exposure shall be dependent upon accumulated total dose desired for each group.

(ii) *Reporting requirements.* (A) Mutagenic effects gene mutation tests shall be conducted and the final result submitted to the Agency after the effective date of the rule as follows: gene mutation in *Salmonella*, 4 month specific locus mutagenicity assay, 9 months; *Drosophila* sex-linked recessive lethal, 24 months; mouse specific locus 36 months.

(B) Progress reports shall be submit to the Agency quarterly beginning 90 days after the effective date of the final rule.

(2) *Mutagenic effects—Chromosomal aberrations—(i) Required testing.* (A) An *in vitro* cytogenetics test shall be conducted with VF, VDF, TFE and HFP

in accordance with § 798.5375 of this chapter.

(2) Modifications to § 798.5375 of this chapter. The following modifications to § 798.5375 of this chapter for testing VF, VDF, TFE and HFP are required.

(i) *Test method—Type of cells used in the assay.* The requirement under § 798.5375(d)(3)(i) of this chapter is modified for VF, VDF, TFE and HFP so that these compounds shall be tested in Chinese hamster ovary (CHO) cells. Cells shall be checked for *Mycoplasma* contamination and may be checked for karyotype stability.

(ii) *Test chemicals—Vehicle.* The requirement under § 798.5375(d)(6)(i) of this chapter regarding vehicle is omitted for VF, VDF, TFE and HFP.

(iii) *Test performance—Treatment with test substance.* The requirement under § 798.5375(e)(3) of this chapter is modified for VF, VDF, TFE and HFP so that cells in the exponential phase of growth shall be treated with test substance both in the presence and absence of metabolic activation. Fluoroalkene-air mixtures in varying concentrations shall be flushed with 10 volumes of treatment mixture at a rate of 500 mL/min. Flasks shall be closed with a cap with a rubber septum. Samples shall be removed with a gas-tight syringe at the beginning and end of the exposure period and analyzed for gas content. Incubation shall be at 37°C on a rocker panel to insure maximum contact between cells and treatment mixture. For experiments without metabolic activation, treatment shall be for 10 hours (including treatment with spindle inhibitor). For experiments with metabolic activation, treatment shall be for 2 hours after which cells shall be washed, refed with culture medium and incubated for an additional 8 hours (including treatment with spindle inhibitor). Alternative treatment schedules may be justified by the investigator.

(iv) *Test performance—Culture harvest time.* The requirement under § 798.5375(e)(5)(i) of this chapter is modified for VF, VDF, TFE and HFP so that multiple harvest times shall be used. If cell cycle length is changed by treatment, the fixation intervals shall be changed accordingly.

(B)(1) For each respective test substance an *in vivo* cytogenetics test shall be conducted with VF, VDF, TFE or HFP in accordance with § 798.5385 of this chapter, if the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(2)(i)(A) of this section produces a negative result.

(2) Modifications to § 798.5385 of this chapter. The following modifications to

§ 798.5385 of this chapter for testing VF, VDF, TFE and HFP are required.

(i) *Test method—Vehicle.* The requirement under § 798.5385(d)(5)(i) of this chapter regarding vehicle is omitted for VF, VDF, TFE and HFP.

(ii) *Test method—Dose levels.* The requirement under § 798.5385(d)(5)(ii) of this chapter is modified for VF, VDF, TFE and HFP so that three dose levels shall be used. The highest dose tested shall be the maximum tolerated dose, that dose producing some indication of cytotoxicity (e.g. partial inhibition of mitosis), or the highest dose attainable.

(iii) *Test method—Route of administration.* The requirement under § 798.5385(d)(5)(iii) of this chapter is modified for VF, VDF, TFE and HFP so that animals shall be exposed by inhalation for 6 hours/day for 5 consecutive days.

(iv) *Test performance.* The requirement under § 798.5385(e) of this chapter is modified for VF, VDF, TFE and HFP as follows: Animals shall be treated with the test substance for 5 days at the selected dose(s). Bone marrow samples shall be taken 6 and 24 hours after the termination of the last treatment. Prior to sacrifice, animals shall be injected IP with an appropriate dose of a spindle inhibitor (e.g. colchicine or Colcemid®) to arrest cells in c-metaphase. Immediately after sacrifice, the bone marrow shall be obtained, exposed to hypotonic solution, and fixed. The cells shall then be spread on slides and stained. Chromosome preparations shall be made following standard procedures. The number of cells to be analyzed per animal shall be based upon the number of animals used, the negative control frequency, the predetermined sensitivity and the power chosen for the test. Slides shall be coded before microscopic analysis.

(C) (1) For each respective test substance a dominant lethal assay shall be conducted with VF, VDF, TFE or HFP in accordance with § 798.5450 of this chapter, if either the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(2)(i)(A) of this section or the *in vivo* cytogenetics test conducted pursuant to paragraph (c)(2)(i)(B) of this section produces a positive result.

(2) Modifications to § 798.5450 of this chapter. The following modifications to § 798.5450 of this chapter for testing VF, VDF, HFP and TFE are required.

(i) *Test method—Description.* The requirement under § 798.5450(d)(2)(i) of this chapter is modified for VF, VDF, TFE and HFP so that several treatment schedules are available. The most widely used schedule require single administration of test substance. However, for this assay, fluoroalkenes

shall be administered by inhalation for 5 consecutive days for 6 hours/day.

(ii) *Test method—Concurrent controls.* The requirement under § 798.5450(d)(4)(i) of this chapter is modified for VF, VDF, TFE and HFP so that concurrent positive and negative (vehicle) controls shall be included in each experiment.

(iii) *Test method—Test chemicals.* The requirement under § 798.5450(d)(5) of this chapter is modified for VF, VDF, TFE and HFP so that exposure shall be by inhalation for 5 consecutive days for 6 hours/day. Three dose level shall be used. The highest dose shall produce signs of toxicity (e.g. slightly reduced fertility) or shall be the highest attainable.

(iv) *Test performance.* The requirement under § 798.5450(e)(1) of this chapter is modified for VF, VDF, TFE and HFP so that individual males shall be mated sequentially to 1 or 2 virgin females. Females shall be left with the males for at least the duration of one estrus cycle or alternatively until mating has occurred as determined by the presence of sperm in the vagina or by the presence of a vaginal plug. In any event, females shall be left with the males for no longer than 7 days.

(v) *Test performance.* The requirement under § 798.5450(e)(2) of this chapter is modified for VF, VDF, TFE and HFP so that the number of matings following treatment shall ensure that germ maturation is adequately covered. Mating shall continue for at least 6 weeks.

(vi) *Test performance.* The requirement under § 798.5450(e)(3) of this chapter is modified for VF, VDF, TFE and HFP so that females shall be sacrificed in the second half of pregnancy and uterine contents shall be examined to determine the number of implants and live and dead embryos. The examination of ovaries to determine the number of corpora lutea is left to the discretion of the investigator.

(D)(1) For each respective test substance a heritable translocation assay shall be conducted with VF, VDF, TFE or HFP in accordance with § 798.5460 of this chapter, if the dominant lethal assay conducted pursuant to paragraph (c)(2)(i)(C) of this section produces a positive result.

(2) Modifications to § 798.5460 of this chapter. The following modifications to § 798.5460 of this chapter for testing VF, VDF, TFE and HFP are required.

(i) *Test method—Animal selection.* The requirement under § 798.5460(d)(3)(i) of this chapter is modified for VF, VDF, TFE and HFP:

that the mouse shall be used as the test species.

(ii) *Test method—Vehicle.* The requirement under § 798.5480(d)(5)(i) of this chapter regarding vehicle is omitted for VF, VDF, TFE and HFP.

(iii) *Test method—Dose levels.* The requirement under § 798.5460(d)(5)(ii) of this chapter is modified for VE, VDE, TFE and HFP so that at least two dose levels shall be used. The highest dose level shall result in toxic effects (which shall not produce an incidence of fatalities which would present a meaningful evaluation) or shall be the highest dose attainable.

(iv) *Test method—Route of administration.* The requirement under § 798.5480(d)(5)(iii) of this chapter is modified for VF, VDF, TFE and HFP so that animals shall be exposed by inhalation.

(v) *Test performance—Treatment and mating.* This requirement under § 798.5460(e)(1) of this chapter is modified for VE, VDE, TFE and HFP so that the animals shall be dosed with the test substance 6 hr/day, 7 days/week over a period of 35 days. After treatment, each male shall be caged with 2 untreated females for a period of 1 week. At the end of 1 week, females shall be separated from males and caged individually. When females give birth, the day of birth, litter size and sex of progeny shall be recorded. All male progeny shall be weaned and all female progeny shall be discarded.

(ii) *Reporting requirements.* (A) Mutagenic effects—chromosomal aberration testing shall be completed and final results submitted to the Agency after the effective date of the rule as follows: *in vitro* cytogenetics, 4 months; *in vivo* cytogenetics, 12 months; dominant lethal assay, 24 months; heritable translocation assay, 36 months.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(3) *Subchronic toxicity—(i) Required Testing.* (A) Inhalation subchronic toxicity tests shall be conducted with HFP in accordance with the TSCA Test Guidelines specified in § 798.2450 of this chapter.

(B) Modifications to § 798.2450 of this chapter. The following modifications to § 798.2450 of this chapter for testing HFP are required.

(1) *Test procedures—Exposure conditions.* The requirement under § 798.2450(d)(5) of this chapter is modified so that the animals shall be exposed to the test substance 6 hours per day, 5 days per week for 90 days.

(2) *Test procedures—Observation of animals.* The requirement under § 798.2450(d)(10)(v) of this chapter is modified so that animals shall be weighed weekly, and so that food and water consumption shall also be measured weekly.

(3) *Test report—Individual animal data.* The requirement under § 798.2450(e)(3)(iv)(D) of this chapter is modified to read "Food and water consumption data."

(ii) *Reporting requirements.* (A) The required subchronic toxicity tests shall be completed and final results submitted to the Agency within 12 months of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(4) *Reproductive toxicity—(i) Required testing.* A reproductive toxicity test shall be conducted with VDF by inhalation in accordance with § 798.4700 of this chapter.

(ii) *Reporting requirements.* (A) The reproductive toxicity test shall be completed and final results submitted to the Agency within 29 months of the effective date of the final test rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(5) *Oncogenicity—(i) Required testing.* Oncogenicity tests shall be conducted in both rats and mice by inhalation with VF and in mice with VDF in accordance with § 798.3300 of this chapter. Oncogenicity testing by inhalation shall be conducted in rats with VDF in accordance with the protocols submitted by Fluoroalkenes Industry Group (FIG), One Customs House Square, Suite 314, Wilmington, Del. 19801, and previously approved by the Agency which are incorporated by reference. These protocols are available for inspection at the Office of the Federal Register Information Center, Rm. 8301, 1100 L Street, NW., Washington, DC 20408. A copy of these protocols has also been included in the public record for this rule (docket no. OPTS-42002C) and is available for inspection in the OPTS Reading Rm., E-107, 401 M St., SW., Washington, DC 20460, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays. This incorporation by reference was approved by the Director of the Federal Register. These materials are incorporated as they exist on the date of approval and a notice of any change in these materials will be published in the Federal Register. Oncogenicity tests shall also be conducted by inhalation in both rats and mice with TFE and HFP in accordance

with § 798.3300 of this chapter for whichever of these substances yields a positive test result in any one of the following mutagenicity tests: The *in vitro* cytogenetics assay conducted pursuant to paragraph (c)(2)(i)(A) of this section, the *in vivo* cytogenetics assay conducted pursuant to paragraph (c)(2)(i)(B) of this section, the mammalian cells in culture assay conducted pursuant to paragraph (c)(i)(1)(B) of this section or the sex-linked recessive lethal assay in *Drosophila melanogaster* conducted pursuant to paragraph (c)(2)(i)(C) of this section. Criteria for positive test results are established in 46 CFR 798.5375, 798.5385, 798.5300 and 798.5275 of this chapter, respectively.

(ii) *Reporting requirements.* (A) The oncogenicity testing shall be completed and final results submitted to the Agency within 53 months of the effective date of the final rule for VF and VDE and 67 months for TFE and HFP.

(B) Progress reports shall be submitted quarterly beginning 90 days after the effective date of the final rule.

(Information collection requirements have been approved by the Office of Management and Budget under control number 2070-0033.)

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