Coasters Harbor Island, Newport, Rhode Island, and swim to Potter Cove, Jamestown, Rhode Island, and will cross the East Passage of Narragansett Bay just north of the Newport Bridge. Risk of boat/swimmer collision and large wake hazards to escorting row boats constitute the primary threats to the participants. Vessel traffic and speed will be restricted within a safety zone established in the regulated area. One Coast Guard Cutter and several Coast Guard Auxiliary vessels will be assisting the race sponsor in patrolling the safety zone. The purpose of this regulation is to limit the distance to which nonparticipating vessels may approach the participants and to restrict vessel speeds to a no-wake speed as set forth below. The restrictions are necessary to provide for the safety of life on navigable waters during the event.

List of Subjects in 33 CFR Part 100

Marine safety, Navigation (water).

Regulations

In consideration of the foregoing, Part 100 of Title 33, Code of Federal Regulations, is amended as follows:

1. The authority citation for Part 100 continues to read as follows:

Authority: 33 U.S.C. 1233; 49 CFR 1.46 and 33 CFR 100.35.

2. A temporary § 100.35-1-14, is added to read as follows:

§ 100.35-1-14

(a) *Regulated Area:* East passage of Narragansett Bay, bank to bank bounded to the south by the Newport Bridge, and to the north by a line drawn from Bishop Rock (41-31'05"N, 71-19'54"W), Newport, Rhode Island to Fowler Rocks (41-32'00"N, 71-21'48"W), Conanicut Island, Jamestown, Rhode Island.

(b) Special Local Regulations: All vessels operating in the regulated area or in the vicinity of participants in this event shall:

(1) Approach no closer than 200 yards from any participant. The participants will be swimming from Coaster's Harbor Island, Newport Rhode Island, to Potter Cove, Jamestown, Rhode Island. Each swimmer will be accompanied by a rowboat crewed by at least two persons.

(2) Observe a maximum speed limit of five (5) knots, or "No Wake Speed", whatever is less.

(3) Exercise extreme caution when operating in this area.

Dated: May 22, 1987.

R.L. Johanson,

Rear Admiral (Lower Half), U.S. Coast Guard Commander, First Coast Guard District.

[FR Doc. 87-12981 Filed 6-5-87; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 799

[OPTS-42002E; FRL-3214-8]

Fluoroalkenes; Final Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: Pursuant to the Toxic Substances Control Act (TSCA), EPA is issuing a final rule to require testing for certain health effects for the following 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). By this action, EPA is also withdrawing its proposed reproductive effects testing for VDF.

DATES: In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 12 p.m. eastern standard time on June 22, 1987. This rule shall become effective on July 22, 1987.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-543, 401 M St., SW., Washington, DC 20460, (202) 554-1404.

SUPPLEMENTARY INFORMATION: In the Federal Register of November 6, 1985 (50 FR 46133), EPA issued a proposed test rule under section 4(a) of TSCA to require health effects testing of vinyl fluoride, vinylidene fluoride, hexafluoropropene, and tetrafluoroethene. This proposed testing consisted 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. EPA is now issuing a final test rule to require the above-mentioned health effects testing of VF, VDF, HFP, and TFE, except that the Agency is withdrawing its reproductive effects testing requirement for VDF.

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 "fluoro alkenes" for priority testing consideration in its Seventh Report, published in the Federal Register of November 25, 1980 (45 FR 78432). 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 response to the ANPR, the Fluoroalkenes Industry Group (FIG) submitted a proposed testing program for VF, VDF, HFP, and TFE. 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 another fluoroalkene, 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 to either propose a test rule for the fluoroalkenes or publish the Agency's reasons for not doing so. The Agency, therefore, issued a notice of proposed rulemaking (NPRM) for VF, VDF, HFP, and TFE on October 31, 1985 (50 FR 46133; November 6, 1985). In response to the proposed rule, the Agency received written comments from the Fluoroalkenes Industry Group and its member companies. The FIG also requested a public meeting, which was held April 1, 1986. There, the FIG presented both written and oral comments on the proposed rule. All of the FIG's written comments and the transcript of the public meeting are contained in the record for this action. Having examined these comments, the Agency is now issuing a final test rule for VF, VDF, HFP, and TFE.

B. Test Rule Development Under TSCA

Under section 4(a)(1) of TSCA, EPA must require testing of a chemical substance or mixture 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 determinined 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 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 neccessary to develop such data.

In making section 4(a)(1)(A) findings, EPA considers both exposure and toxicity information to make the finding that the chemical may present an unreasonable risk. For the second finding under section 4(a)(1)(A), 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 third finding 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 as published in the Federal Register of July 18, 1980 (45 FR 48528) and June 5, 1981 (46 FR 30300). The section 4(a)(1)(A) findings are discussed in the Federal Register of July 18, 1980 and June 5, 1981 publications, and the section 4(a)(1)(B) findings are discussed in the June 5, 1981 publication.

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 716) concerning the fluoroalkenes; and published and unpublished data available to the Agency, including that submitted as public comment. From its evaluation, as described in this final rule, EPA is requiring health effects testing for VF, VDF, HFP, and TFE 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 $C_nH_{(2n-x)}F_x$, where n 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 (49 FR 23112). 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 rulemaking. All of these chemicals are gases at room temperature. The production, use, exposure and release of these compounds are discussed in the proposed rule.

B. Review of Toxicity Studies Submitted After Proposal

Subsequent to the fluoroalkenes proposed rule, the FIG submitted a number of toxicity studies to the Agency which are reviewed in this preamble. For a review of earlier studies relevant to the Agency's rulemaking efforts on the fluoroalkenes, the proposed rule should also be consulted.

1. Mutagenicity

Additional mutagenicity data submitted by the FIG gave positive mutagenic results in two studies on HFP and in two studies for VF. A third study in HFP is considered equivocal by the Agency. Three different mutagenicity assays on TFE were also completed by industry. Two were clearly negative, while the third is considered negative by the FIG, but because of experimental problems is considered inconclusive by the Agency. Two studies on VDF were also recently completed by industry; both are negative.

HFP was tested in an *in vitro* cytogenetics assay in Chinese hamster ovary (CHO) cells both with and without activation (Ref. 2). In both cases, HFP was positive, with responses greater than those of the concurrent positive control (vinyl chloride). HFP in the mouse micronucleus test (preliminary data) yielded weakly positive results in the males, and negative results in the females (Ref. 3). HFP was also tested in the CHO hypoxanthine guanine phosphoribosyltransferase (HPRT) gene mutation assay. In this cells-in-culture test, HFP is reported to be a negative mutagen by industry (Ref. 4). However, the Agency has identified a number of problems in the test; namely, substantial between-culture variability within single treatments, isolated increases in individual cultures, high negative controls in some instances, and a failed positive control in one of the trials (Ref. 38). Because of these problems, the Agency believes that the results of this testing are equivocal and cannot be accepted as indicative of the nongenotoxicity of HFP for gene mutations. Therefore, the Agency is requiring that this test be repeated, both with and without activation.

VF, tested in the CHO/HPRT gene mutation assay, was negative without activation, but positive with activation (Ref. 5). The response of VF was much weaker than the positive control, vinyl chloride. VF was also tested in an *in vitro* cytocenetics assay (CHO cells). Although the results without activation were equivocal, the test was positive for cytogenetic activity with activation (Ref. 6). VDF was also tested in these same two assays but was negative in both cases (Refs. 32 and 33).

TFE was tested in the Ames *Salmonella* assay with four strains of bacteria, TA1535, TA97, TA98, and TA100 both with and without activation. TFE was negative in this assay (Ref. 7). Likewise, TFE tested in an *in vitro* cytogenetics assay (CHO cells) was negative, both with and without activation (Ref. 39).

TFE was also tested in the CHO/HPRT gene mutation assay and was concluded by industry to be negative, both with and without metabolic activation (Ref. 8). However, the assay with activation suffered from a lack of significant response in the positive controls in the first of two trials, and a problem with equipment failures and the

subsequent loss of two experimental dose levels (the 80 and 100 percent levels), in the second trial. Therefore, despite arguments by the FIG to the contrary, the Agency believes that the assay with activation should be repeated before a conclusion of negative results can be drawn for TFE in this test (Refs. 34 and 35).

2. Subchronic Toxicity

The Agency has reviewed data from two inhalation subchronic studies of VDF on rats, sponsored by the Association of Plastics Manufacturers in Europe (APME). Results from the first study show testicular and systemic effects at the two highest dose levels, 40,000 and 7,000 ppm (Ref. 9). The second study, which had a highest dose of 7,000 ppm showed no effects (Ref. 10). A simple fertility study was also conducted as part of the second study, wherein male and female rats that had been exposed to VDF in the 13-week subchronic portion of the study were mated with untreated animals. This fertility study was evaluated by EPA. No effects of potential reproductive significance were observed.

The Agency also reviewed the results of an inhalation subchronic study with VDF performed by the National Toxicology Program on male and female F344 rats (Ref. 11). In this study, VDF caused minor testicular effects (decrease in weight, no lesions) at doses which caused liver, kidney, and blood toxicities. No effects of potential reproductive significance were observed for females. The testicular effects were most pronounced at the highest dose level, 50,000 ppm. NTP reported there was a significant decrease in right testis weight relative to controls. There was also a significant decrease in right testis weight relative to body weight at 5,000 ppm but not 15,000 ppm. Systemic, but not testicular effects, were also seen at 1,500 ppm and 500 ppm, the two lowest doses. These included increases in group mean liver weights and increases in right kidney to body weight ratios.

III. Response to Public Comments

In response to the proposed rule, the Agency received written comments from the FIG and its member companies. The FIG also requested a public meeting, which was held April 1, 1986. There, the FIG presented written and oral comments on the rule. The FIG's written comments and the transcript of the public meeting are contained in the record for this action. The substantive issues raised by industry are discussed below.

A. Worker Exposure

The EPA finding that fluoroalkenes may pose an unreasonable risk of adverse health effects under section 4(a)(1)(A)(i) of TSCA is based in part on the potential for inhalation exposure of workers to the fluoroalkenes. However, the FIG contends that the fluoroalkenes have insufficient exposure potential to pose an unreasonable risk of injury, and without the potential for exposure the Agency does not have the regulatory authority to require testing. In support of this claim, the results of a FIG-sponsored industrial hygiene survey of its manufacturing operations for monomer production and for polymer production involving processing of the fluoroalkenes were submitted to the Agency. The survey results are the basis for the claim that there is no significant exposure to fluoroalkenes in the workplace.

An examination of the FIG survey raises several concerns. One concern is that only full work shift personal measurements were taken, and thus the monitoring results were expressed as time-weighted average concentrations. Although this sampling strategy is appropriate for demonstrating compliance with permissible exposure limits, it obscures the evaluation of peak exposures resulting from short-term release of contaminants in the atmosphere. The results of the FIG survey indicate that worker exposure to fluoroalkenes typically takes the form of brief episodes of relatively high exposure followed by extended periods of little or no exposure.

The FIG survey results include several explanations of how exposure to fluoroalkenes typically occurs. For example, it is stated that, "A detectable sample occurs when a plugged line must be corrected * * *" and, "The detectable sample occurred because of a reactor pluggage." Since the time-weighted average concentration measured for operators who corrected pluggage problems or were exposed to an "unusual pressure relief valve release * * *" was in the range of 10 to 38 ppm, the peak level existing at the time of the problem was likely much higher. The lack of area measurements taken with fixed-location continuous monitors makes it difficult to assess which areas of the plant are most likely to be associated with significant worker exposures.

For many years warnings have been expressed against the use of single values, such as the TWA, as an index of exposure (Ref. 12). Whereas the integration of concentration over time produces a convenient measure of workplace conditions, toxic responses cannot be expected to vary as a linear function of time and concentration. That is, the amplitude and frequency of variation from the mean due to peaks during the day may be very important.

In addition, for at least one job category (polymer operator) an air-supplied respirator is routinely worn. This type of precaution is not typically taken in situations where engineering controls are adequate to ensure against significant release of contaminants into the atmosphere. Area measurements would have been very useful in evaluating potential exposures for this job category. Also, since the fluoroalkenes are said to be odorless, workers are not likely to be aware of situations where high concentrations are present. Thus, they are much more likely to be subjected to brief periods of intense exposure, such as when a maintenance mechanic performs emergency repairs or when a sample valve is bled to the atmosphere.

Furthermore, the FIG's claim that worker exposure to fluoroalkenes is insignificant relies heavily on the concept of a "level of concern." By their definition, a worker can be said to have no exposure when air samples reveal concentrations less than 1 percent of the level of concern. This unconventional approach to industrial hygiene monitoring has little value in the quantitative assessment of worker exposure to chemicals. By introducing the concept of a level of concern, the FIG has made certain assumptions about the toxicity of the fluoroalkenes. From four unpublished animal studies involving exposures lasting for 2 to 13 weeks, the FIG concluded that exposure concentrations that elicited "minimal" adverse effects would be appropriate to adopt as levels of concern for worker exposure. These "minimal" effects included respiratory tract irritation (VF), testicular and kidney pathology (TFE), and kidney pathology alone (HFP). The Agency does not believe there is any scientific justification for incorporating such assumptions concerning health risks when attempting to evaluate worker exposure to chemicals. In light of the acknowledged lack of chronic toxicity data for the fluoroalkenes, the FIG's approach totally ignores the potential for development of adverse effects (e.g., cancer) following long-term low level exposures. Moreover, the approach taken by the FIG in arriving at a level of concern is not supported by any currently accepted risk assessment methodology.

Current risk assessment practice for non-carcinogens (see for example 51 FR

34028; September 24, 1986) indicates that no-effect levels for chronic exposure may be derived from the highest no-observed-adverse effect level (NOEL) or the lowest-observed-adverse effect level (LOEL) taken from an animal study by applying an appropriate uncertainty factor. However, the Agency considers this approach of using uncertainty factors to be valid only in the case where the substance under consideration is a non-carcinogen, an assumption which has not been documented for the fluoroalkenes. Evaluation of true worker exposure to the fluoroalkenes is much less ambiguous if one chooses simply to examine the actual results of the workplace monitoring presented in the FIG survey. Approximately 17 percent of the total measurements taken gave positive results for the presence of fluoroalkenes. However, this percentage may have been much higher if short-term or area samples had been taken in addition to the time-weighted average personal measurements. For most job categories, the FIG survey results indicated that time-weighted average personal exposures are quite low. Exceptions are evident, however. Vinylidene fluoride polymer operators experienced time-weighted average exposures of 4.5 and 6.5 ppm on what was said to be a * * * "very typical day. No unusual events during the day." Measurements in excess of 30 to 50 ppm (time-weighted average) were reported for several other workers included in the FIG survey.

Supporting evidence for the occurrence of occupational exposure to fluoroalkenes is available in the report of an industrial hygiene survey conducted by NIOSH, the National Institute for Occupational Safety and Health (Ref. 13). Worker exposures to VF were measured at a VF manufacturing facility and a VF polymerization plant. Plant operator exposure levels for VF production were typically less than 2 ppm (time-weighted average), although exposure of an operator during start-up was 21 ppm (time-weighted average). Exposure to VF in the polymerization plant varied from 1 to 5 ppm (time-weighted average).

The results of the FIG survey and the NIOSH survey do not support the conclusion that "* * * there is no significant exposure to the fluoroalkenes in the workplace." The critical issue in evaluating exposure to fluoroalkenes is whether the concentrations reported in the surveys are indeed significant from a public health standpoint. Neither the currently available toxicological data nor the results of the FIG survey are adequate to resolve this question. Therefore, until more extensive toxicological studies are conducted, it is inappropriate to conclude that current worker exposures to fluoroalkenes are of no concern. EPA believes that the FIG survey, together with other exposure information discussed above, shows that workers are potentially exposed to levels of various fluoroalkenes which may present unreasonable risks of injury to human health.

B. Structure-Activity Relationship (SAR)

The Agency used the structural similarities of VF and VDF to vinyl chloride (VC) and vinylidene chloride (VDC) to support the Agency's conclusion that VF and VDF may present unreasonable risks and need immediate testing for oncogenicity. In addition, similar structure activity relationships were used to support the required mutagenicity testing for TFE and HFP and the conditional oncogenicity testing triggered by the results of those mutagenicity tests. The FIG responded that the physical, chemical, and biological properties of the chlorinated and fluorinated alkenes are vastly different and do not support the analogies drawn by the Agency. The FIG believes that the available data suggest that it is, in fact, unlikely that the fluoroalkenes will behave similarly to the chloroalkenes and, hence, the Agency's conclusion is unjustified.

The FIG contended that it is extremely unlikely that VF or VDF will behave anything like their chlorinated analogues with regard to physical and chemical properties. They reasoned that fluorine's high electronegativity, short crystal and covalent radii, and the short C–F bond length and high bond strength make fluoroalkenes unique and hence any analogies to chloroalkenes are inappropriate. They went on to compare a number of physical and chemical properties of fluoro- and chloroalkenes that exemplify these differences. They concluded by stating that "structure-activity relationships in the haloalkenes demonstrate that it is unlikely that there will be any similarity between fluoroalkenes and chloroalkenes."

While there are a number of properties that distinguish fluoro compounds from their chloro analogs, and also the bromo analogs, the FIG has not demonstrated why or how these differences would affect the biological activity (e.g., the epoxidation of the C=C double bond).

In certain chemical reactions, such as electrophilic addition to the double bond, the reactivity in fluoroalkenes will be reduced because of the inductive withdrawal of electron density due to the high electronegativity of the fluorine (Ref. 14), but the reaction will not be stopped altogether; moreover, the toxicological significance of such rate differences is not obvious. For the same reason, nucleophilic addition reactions will be faster for the fluoroalkenes. Radical reactions will also take place in both chloro- and fluoroalkenes. While the FIG pointed out that some gas phase radical reactions are slower for fluoroalkenes than for chloroalkenes by an unspecified factor, no details of the kinetics were provided, and no mention was made of enzyme mediated or solution reactions. In general, however, radical reactions proceed at similar rates regardless of the substrate. In biological systems, all of these reactions (electrophilic, nucleophilic, and radical) are important and will take place with both fluoroalkenes and chloroalkenes, although probably at different rates. Since epoxides have been implicated in the mechanism of carcinogenesis for some alkenes and arenes, their formation is of special interest, and it appears that this reaction can proceed by both radical and ionic mechanisms in biological systems (Ref. 15). Therefore, in the case of the fluoroalkenes, the potential for epoxide formation *in vivo* is present, and it appears that similar reactions can take place for both chloro- and fluoroalkenes and that the expected differences in physical and chemical properties cannot be used to rule out similar toxicities in biological systems.

The FIG also states that the available data on the biologic effects of the chloro- and the fluoroalkenes are very different and do not support the analogies that the Agency has drawn. The experimental evidence presented by the FIG indicates that the fluorinated compounds have a lower potential to be sequestered in body tissues or fluids, have a much higher acute lethal level, and affect different target organs. With regard to the latter point, it is stated that the chlorinated compounds generally affect the liver as the primary target organ, while the kidneys are the primary target organ for the fluoroalkenes, and that this implies a different mechanism of action for these two classes of compounds. In support of this the FIG cites data submitted by the industry indicating that the fluorinated compound TFE is metabolized entirely by a glutathione pathway, whereas the biologically active metabolite of the chlorinated alkenes is produced by a cytochrome P–450 enzyme system. The FIG believes the available biological data indicate that the fluoroalkene compounds have different biologic fates than the chlorinated alkenes, and hence

there is little justification in making analogies between these two classes of compounds.

TFE and tetrachloroethylene (TCE) apparently have qualitatively different metabolic routes as demonstrated in the study by Odom and Green (Ref. 16). However, this is not true for VF and VDF compared to VC and VDC. Furthermore, all of the haloalkenes apparently are metabolized by an oxidative mechanism involving microsomal monooxygenases (cytochrome P-450), although the rates vary widely (Ref. 17). Bolt et al. (Ref. 18) showed interaction with P-450 by measuring the degree of inhibition of aniline hydroxylation and aminopyrene demethylation. They found that VC which is rapidly metabolized, exerted a weak effect as did VF, while VDF was substantially stronger. Presumably the VC interaction is shorter because it is rapidly oxidized, probably to chloroethylene oxide, and quickly released. VDF remains bound longer since it is oxidized slower, and thus interferes more strongly with the P-450 enzyme activities.

VC, VF, and VDF have also been shown to metabolize similarly *in vivo*, and concomitantly produce acetonemia in rats (Refs. 19 and 20). The increases of acetone production were concentration (dose) dependent and showed saturable kinetics. Interestingly, VDF was found to be more potent than VC for this toxic effect.

This acetonemia was shown to be caused by reactive metabolites formed by oxidative interaction with cytochrome P-450. Pretreatment with the inducers phenobarbital and DDT increased the effect, while the inhibitors pyrazole and dithiocarb caused a reduction, as did reducing the oxygen concentration in the atmosphere. Since VC is known to be oxidized to chloroethylene oxide, it is believed that corresponding fluorooxiranes are formed from VF and VDF. All such epoxides can act as direct alkylators, or can rearrange to precursors of chloro- and fluoroacetic acids.

Filser et al. (Ref. 20) also found that infusion of chloro- and fluoroacetate at the rates they would be formed by VC and VDF did produce acetonemia, probably by interfering with the citric acid cycle. This shows that the oxidative metabolites formed analogously from VC, VF, and VDF can cause the same toxic effect. Since the fluoroacetate treatment did not cause as much acetone formation as did the corresponding dose of VDF, they thought that an epoxide intermediate may have directly alkylated cytosolic coenzyme A to account for the excess production of ketone bodies.

In contrast also to the FIG position, Conolly et al. (Ref. 21) have shown that VF is hepatotoxic, like VC, by an oxidative mechanism. Furthermore, Stockle et al. (Ref. 22) and Conolly et al. (Ref. 23) have also shown that VDF is hepatotoxic by an oxidative mechanism, like VDC and VC.

Therefore, EPA believes that the Agency's conclusions on the need for testing, to the extent that they are based on SAR between the fluoroalkenes and their chlorinated analogs, are appropriate and supported by the available data.

C. Genotoxicity Screening Tests and the Use of Automatic Triggers

The Agency proposed a tiered mutagenicity testing program for the fluoroalkenes in the proposed test rule. Positive results in certain Tier I test systems (mammalian cells in culture assay, *in vitro* cytogenetics assay, *in vivo* cytogenetics assay, mouse micronucleus assay) would automatically trigger Tier II testing (*Drosophila* sex-linked recessive lethal assay, dominant lethal assay). Positive results in Tier II test systems would trigger Tier III (mouse specific locus assay, heritable translocation assay). However, prior to requiring the Tier III tests the Agency proposed to hold a public program review to determine if continued testing would serve a scientific and regulatory need. If Tier III tests are conducted, the results would permit the Agency to perform quantitative risk assessments for genetic effects. Also, under the proposed rule for TFE and HFP positive results in any one of the following: *In vitro* cytogenetic assay, *in vivo* cytogenetic assay, mammalian cells in culture assay, and sex-linked recessive lethal assay in *Drosophila melanogaster*, would trigger oncogenicity testing.

The FIG disagreed with many aspects of the Agency's proposed genotoxicity testing program for the fluoroalkenes. Many of the points of contention are identical to those brought up during comments concerning the EPA-proposed test rule for the C_6 aromatic hydrocarbon fraction (50 FR 20662). Since the response to these comments has not substantially changed, the Agency is providing only a brief summary of the response as presented in the C_{6a} test rule with reference to the C_6 rule for greater detail of discussion.

The FIG believes that greater weight should be placed on negative *in vivo* findings rather than positive *in vitro* cytogenetic test results. Using this philosophy, a positive *in vitro* cytogenetic test would require further testing *in vivo* to confirm the results, rather than negative *in vitro* results requiring further testing *in vivo* as described in the present test rule. In addition, negative results in the *in vivo* test would indicate that no further testing should be required regardless of the results of the *in vitro* assay. As the Agency stated in the C_6 rule, the intent of the Agency is to maximize the detection of clastogenic agents. It should therefore be noted that *in vitro* assays may detect genotoxicity via alternative mechanisms, target tissues or species, and thus in part potentially complement *in vivo* assays for the same endpoint. Since it is considered that the *in vitro* data by themselves are predictive of both potential germ cell mutagens and carcinogens, positive results in the *in vitro* assay would require no further Tier I genotoxicity testing, while the recognized limitations associated with all *in vitro* test systems make it prudent to conduct further *in vivo* studies to confirm any negative findings.

The FIG asserts that all tests required by the Agency should be validated for routine use, have recognized scientific guidelines, be capable of being performed according to Agency-mandated Good Laboratory Practice (GLP) standards, and serve a useful purpose in the context of developing regulations. This comment was made with specific reference to the sex-linked recessive lethal assay in *Drosophila* and the dominant lethal test in rats, and concerned the scientific usefulness of the information provided by these assays and the relevance of this information to the development of regulations. As outlined in the C_6 final test rule, the Agency considers both the sex-linked recessive lethal assay and the dominant lethal assay to be validated tests. Because they are whole animal tests, the Agency also believes that they provide information not duplicated by other tests in this battery before proceeding with more costly Tier III tests. However, the Agency recognizes that there is some debate among scientists concerning the relative standing of certain mutagenicity tests as predictors of mutagens in humans or predictors of carcinogenicity. Recognizing this, the Agency has decided in the case of the fluoroalkenes to hold a public meeting after the Tier II mutagenicity testing is completed. At the meeting, the Agency will discuss its assessment of the weight of the evidence for proceeding (or not) with Tier III mutagenicity testing (for VF, VDF, HFP, and TFE) or with oncogenicity testing (for TFE and HFP).

The proposed requirement for the mouse specific locus and heritable translocation tests were opposed by the FIG on the grounds that they would provide no useful information beyond that already obtained by Tier I and II *in vitro* and *in vivo* tests, and would not assist in defining acceptable exposure levels. In addition, the FIG commented that adequate laboratory facilities in the United States are not generally available for conducting these assays using the GLP standards required by the Agency. The FIG maintains that the heritable translocation test is considered a valid research tool, but is not an assay to be employed in routine testing. It further maintains that this assay would provide no additional information beyond that obtained by a positive dominant lethal test. For these reasons, the FIG believes that the Agency cannot justify requiring either the mouse specific locus test or the heritable translocation test in the proposed test rule for the fluoroalkenes.

Regarding the issue of available test facilities, there are commercial laboratories readily available which can perform the heritable translocation assay. Testing facilities for the mouse specific locus assay are admittedly much more limited at the present time. The availability of testing facilities for the mouse specific locus assay is dealt with in detail in the final test standards and reporting requirements rule for diethylenetriamine (DETA), which has been published in the Federal Register (52 FR 3230; February 3, 1987). The DETA rule and the summary of a meeting held in October 1986 between the U.S. Department of Energy and the Agency on this subject should be consulted for a full discussion of this issue (Ref. 36).

The Agency stated in the C_9 rule that these two assays are not to be considered screening tests, but rather are intended for human risk assessment. Therefore, the Agency does not consider their cost, which is estimated to be less than half that of a 2-year assay for oncogenicity, to be unreasonable. The strategy for use of these tests in human risk assessment has been outlined by the Agency in the Final Guidelines for Mutagenicity Risk Assessment published in the Federal Register (51 FR 34006; September 24, 1986). The FIG, however, asserts that quantitative estimates of human genetic risk from these assays are of only limited value. They state the reasons for these limitations as follows: The studies are limited to male gametes (premeiotic stem cells in the case of the mouse specific locus test); there are species, age, and sex variability in DNA repair processes; and accurate calculations of germ cell risk as it relates to all aspects of human exposure would be impossible. The Agency recognized the limitations of risk assessment with regard to genetic endpoints in their response presented in the C_9 test rule. Although there are limitations, it is believed that estimating risk is an important aspect in protecting the public from chemicals which may have adverse effects on future generations. Risk assessment, regardless of whether it is for chronic toxicity, carcinogenicity, or genetic end-points, inherently has limitations, many of which are similar to those stated by the FIG. These limitations stem from the extrapolation from animal models to humans where data necessary for extrapolation, exact relations, and correlations between the animal model and humans, are not usually available. Development of methods for risk assessment is an ongoing process with modifications made to the existing procedures as new information becomes available. The Agency's (now final) Guidelines for Mutagenicity Risk Assessment reflect the best approach available at this time, and EPA considers it inappropriate to postpone the effort to assess human genetic risk until a definitive methodology has been developed.

Although the FIG concurs with the philosophy of using short-term tests to screen compounds for potential mutagenic and carcinogenic effects, the FIG is opposed to the use of these screening tests as automatic triggers for further testing. Rather than using automatic triggers, the FIG proposes that scientific reviews occur during critical stages of testing to determine if the results generated warrant the conducting of further tests. There are two separate sets of automatic triggers proposed in the test rule on fluoroalkenes. The first would allow certain Tier I genotoxicity tests to trigger Tier II genotoxicity testing. The second set of automatic triggers would initiate an oncogenicity study if positive results were obtained from any of certain specified short-term tests. With regard to the latter, the FIG believes a weight of evidence approach is necessary in the evaluation of these short-term tests and that it is not scientifically justified to permit the positive results of a single short-term test to initiate oncogenicity testing.

In addressing the use of automatic triggers with regard to mutagenic potential in the C_9 test rule, the Agency stated that scientific judgement is required in assessing the need for a test where reference data are limited or the test is controversial. This is the case with Tier III tests, and the Agency will provide opportunity for public comment prior to initiating these tests. With Tier I tests, however, the Agency considers it appropriate for positive results to automatically require further Tier II testing. The available reference data and past experience with Tier I tests indicate that scientific review of any positive data would likely support further Tier II testing, and EPA believes that the public interest in promptly obtaining appropriate test data on suspected hazardous chemicals would not best be served by incorporating a public review between Tiers I and II. Regarding the use of automatic triggers for oncogenicity testing, the Agency has stated in the C_9 test rule that negative results in this battery of short-term assays, in the absence of other evidence for oncogenic potential, indicate a small likelihood that a compound will be a chemical carcinogen. Regarding the use of automatic triggers for oncogenicity testing, the Agency believes that clearly positive results in one of the designated assays is suggestive of a carcinogenic potential, and the only way to empirically support or refute this suggestive evidence is by conducting a chronic oncogenicity test. It is, therefore, the Agency's opinion that automatic triggers as proposed in the fluoroalkenes test rule for TFE and HFP are justified on scientific grounds. However, the Agency agrees with the FIG that a review of the testing results is appropriate before proceeding with oncogenicity testing and therefore the Agency will have a public review before requiring the triggered oncogenicity testing for TFE and HFP.

D. Immediate Testing for Oncogenicity of VF and VDF

Based on data available on VF and VDF indicating that these two chemicals may present an unreasonable risk for oncogenic effects, the Agency proposed that both VF and VDF be tested immediately for oncogenic effects in both rats and mice for VF, and in mice for VDF. (Because there is presently an ongoing bioassay of VDF in rats, being conducted using a protocol EPA has reviewed and found to be adequate, only a test in mice will need to be conducted under this rulemaking for VDF.) The FIG considers the data on VF and VDF inadequate to support the Agency's requirement for immediate oncogenicity testing of these two compounds.

In support of the Agency position on VF, the Agency cites the structural

similarity between VF and the known human carcinogen VC, along with positive mutagenicity results from an assay using *E. coli* reported by the Agency in its Proposed Negotiated Testing Program (June 4, 1984; 49 FR 23112). Recent *in vitro* studies have also shown VF to be positive in Chinese hamster ovary cells for both mutagenicity and cytogenicity endpoints. The FIG contends that the physical, chemical, and biologic properties of VF are not sufficiently similar to those of vinyl chloride to permit extrapolation between these two compounds. In addition, the FIG states that a single mutagenicity test in a prokaryotic assay system is not sufficient evidence to support a finding of potential unreasonable risk.

The relevance of the structure activity relationship between the fluoroalkenes and chloroalkenes has been discussed previously in Unit II.B. of this document. As discussed there, EPA believes there is sufficient similarity between VF and its chloro analog to justify at least a qualitative extrapolation with regard to oncogenic potential. The structural similarity between VF and vinyl chloride in itself would support a finding of potential unreasonable risk for VF. The positive mutagenicity data, therefore, are mainly additional supportive data.

The Agency agrees with the FIG that if there were only data from a single prokaryotic mutagenicity test a finding of potential unreasonable risk for VF would be less justified. The data base on VF is more extensive, however. The evidence includes not only the positive tests in *E. coli*, but also the structural similarity with vinyl chloride. It is this entire weight of evidence which constituted the basis for the finding of potential unreasonable risk and the need for immediate testing. Furthermore results from additional mutagenicity testing received after proposal, and discussed in Unit II.B., support the Agency's testing decision for VF. Therefore, there is no reason to delay the carcinogenicity testing of VF, since the results of additional short term screening tests (if negative) would not negate the Agency's concern.

The FIG presented similar objections to the requirement that VDF be immediately tested for oncogenicity. The Agency considers that the response to comments pertaining to VF (above) are also applicable to VDF. It should also be noted that there are two positive mutagenicity tests of VDF, one in *E. coli* and a second in *S. typhimurium*. Positive tests in two different species of bacteria provide confirmatory evidence that VDF is active in short-term tests predictive for oncogenicity.

In addition to the above objections to the immediate testing of VDF for carcinogenicity, the FIG further contended that additional data presented by the Agency concerning VDF did not support the conclusion that VDF had a potential for being either an animal or human carcinogen. These additional objections related to the Agency's conclusions that VDC is a proven chemical carcinogen, that the results of the Maltoni and Tovoli (Ref. 22) study demonstrated a carcinogenic potential for VDF, and that the altered foci of enzymatic activity in the liver observed by Stockle et al. (Ref. 24) following exposure to VDF were indicative of preneoplastic lesions.

The issues concerning whether the data on VDC support the conclusion that VDC is a potential human carcinogen are very complex. These issues have been addressed by the Agency's Carcinogen Assessment Group (CAG) (Ref. 25). According to CAG's appraisal the animal data for VDC are "limited" and the human data "inadequate" with regard to carcinogenicity. The weight of evidence places this compound in Group C, which represents chemicals that are "possible" human carcinogens. The CAG calculated an incremental cancer risk estimate for human exposure to VDC. In making this determination for VDC, CAG not only considered the animal bioassay data, but also considered "supporting evidence from mutagenicity studies, and related biochemical and toxicity considerations" before making the final determination. Because of the structural similarities between VDF and VDC the Agency believes that CAG's carefully conducted and detailed assessment can be justifiably factored into the weight of evidence decision on whether VDF should be tested immediately for carcinogenicity.

The FIG has a number of reservations regarding the experimental design and interpretation of results in the study by Maltoni and Tovoli (Ref. 24) which described the first bioassay of VDF. Deficiencies in study design included the use of group sizes which were too small, the use of only one species (the rat), and administration of the test compound by gavage in an oily vehicle rather than by inhalation. The FIG provided data demonstrating that VDF was easily lost from oily solutions, with as much as a 50 percent decrease from the original concentration in an open container measured during one hour. The major deficiency in the [illegible] interpretation of the results relates to the pooling of incidence data for lipomas and liposarcomas which arose at different anatomical sites. The FIG concludes that the deficiencies in this study preclude the use of these data for supporting the finding that VDF should be tested immediately for carcinogenicity.

The study by Maltoni and Tovoli (Ref. 24) has the design deficiencies the FIG described. Most of these deficiencies, however, would tend to make the study less sensitive for the detection of potential carcinogens. The 30 to 35 animals per sex, per group, is less than the 50 animals of each sex specified in current National Toxicology Program protocols; however, this number of animals is not inconsistent with the group size used by many investigators conducting basic research into carcinogens. Similarly, the use of only one species is typical in studies that are not conducted to support regulatory action. The possible loss of test material through volatilization from the vehicle is a limiting factor in this study which would tend, particularly if the magnitude was as large as suggested by the FIG, to result in a negative finding. The suggestion of positive results using a protocol which is less powerful than that required by TSCA test guidelines is a strong indication that a more extensive study, as required in this test rule, will confirm the potential for VDF to be a carcinogen, as well as providing the necessary data to determine potential human risk.

The pooling of tumor data nearly always results in some controversy, since the appropriateness of the groupings is difficult to justify without a complete understanding of the underlying mechanisms of the tumorigenic response. The FIG maintains that without the pooling of the lipomas and liposarcomas the data from the Maltoni and Tovoli (1979) study indicate that there was no increase in tumors. The Agency considers the results of the study to be highly suggestive of a tumorigenic response regardless of whether the data are pooled. The authors of this study indicated that these two tumor types are very rare in the Sprague-Dawley rat used in their laboratory, with a combined historical incidence of 0.5 percent. Considering the limitations of this study, the Agency believes that the reported increase in lipomas and liposarcomas above historic control values suggests a positive response and indicates a need for further testing. If the Maltoni and Tovoli (Ref. 24) study was adequate, no further testing would be required. However, because of

deficiencies in study design and an indication of a tumorigenic response, we believe this study provides a sound rationale for requiring further testing of VDF.

As further justification for the need for oncogenicity testing of VDF, the Agency cited a report by Stockle et al. (Ref. 22) demonstrating that inhalation exposure of newborn rats to VDF resulted in ATP-ase deficient foci in the liver. The FIG maintains that these enzyme altered foci are not preneoplastic changes, that the newborn rat is an inappropriate animal model since many hepatic enzymes are not developed at this stage of life, and that acute and subchronic toxicity studies have failed to demonstrate VDF-induced hepatotoxicity and hence the "appearance of foci does not necessarily mean that carcinomas will occur". The FIG believes that for the above reasons the study by Stockle et al. (Ref. 22) provides no substantiation for the conclusion that VDF may present an unreasonable risk for oncogenicity.

The Agency believes that the available data on chemically induced enzyme-altered foci in the liver can be used to support the assessment of oncogenic potential of VDF. The data do not indicate the exact relationship that enzyme-altered foci have with regard to hepatocellular carcinoma, and hence the terminology used by Stockle et al. (Ref. 22) of preneoplastic hepatic foci may provide for some confusion. Sirica et al. (Ref. 26) demonstrated a correlation between the extent of development of enzyme altered foci and chemical treatment regimes which resulted in the development of hepatocarcinomas. They suggested that these altered foci are the progeny of initiated cells. A difficulty with the concept that the altered foci are direct precursors to neoplastic cells is that alterations such as decreases in ATP-ase activity are often reversible after cessation of exposure to the chemical carcinogen (Ref. 27). Peraino et al. (Ref. 28) provide three alternative explanations for the relationship of altered enzyme foci to neoplasia as follows: (1) The altered foci evolve directly into tumors by progressive cellular deviation, (2) the member cells of a focus have enhanced sensitivity, and (3) a chemical carcinogen independently produces enzyme-altered cells and tumor cells by action at separate genetic loci (Ref. 28). Regardless of which of the current theories prevail, the present data clearly indicate that enzyme foci in the liver are associated with exposure to chemical carcinogens and the subsequent development of hepatocellular carcinomas. Therefore, the fact that VDF produced ATP-ase deficient foci is additional supportive evidence for the finding that VDF may present an unreasonable risk of oncogenicity.

The Agency does not consider the other objection presented by the FIG as relevant to the interpretation of the study by Stockle et al. (1979). The metabolic capability of newborn mammals is different than that of the adult with regard to both Phase I and II reactions in the liver. This results in differences in the ratio of oxidative to conjugative reactions. This difference in ratio could make newborn animals particularly sensitive to the induction of certain tumor types, while adult animals appear to be more sensitive to the induction of other tumor types (Ref. 29). Particularly for a test that is used as a qualitative indicator of neoplastic potential, it is not scientifically justified to exclude data generated from newborn animals. The FIG also commented that hepatotoxicity has not been observed in either acute or subchronic studies with VDF, which would indicate that enzyme altered foci do not necessarily precede the development of carcinomas. The Agency disagrees that VF and VDF are not hepatotoxic. This is discussed above in Unit III.B.

The findings that VF and VDF may present an unreasonable risk for oncogenic effects is based on the weight of evidence from all the studies cited in the proposed test rule and additional studies subsequently obtained by EPA as described above. As pointed out by the FIG, some of these studies have deficiencies, but taken together, the evidence from all the data indicates a potential for these two compounds to be carcinogens. Moreover, negative results in the short term assays of VF and VDF proposed by the FIG would not provide sufficient evidence to prove that VF and VDF are not carcinogenic. Because of the strength of the entire data set, the Agency is requiring immediate oncogenicity testing.

E. Two-Generation Study With VDF

The Agency had proposed that a two-generation reproductive toxicity test be conducted to evaluate the potential hazard from exposure to VDF. This proposal was based on preliminary results from a 13-week toxicity study submitted by the industry in which the absolute weights of the epididymides and testes were reduced after 4 and 13 weeks of exposure to VDF (Ref. 9). The FIG contends that a two-generation reproductive test is unjustified, stating that the presently available data do not indicate a potential for VDF to result in adverse effects on reproduction.

The Agency agrees. The Agency notes that VDF caused testicular toxicity in the industry study and in the NTP study, described in Unit II.B., only at relatively high dose levels (7,000 and 5,000 ppm, respectively) and only in the presence of other significant systemic effects. Furthermore, the Agency finds that given the weight of the evidence, including the present low exposure of VDF relative to the observed testicular effects, that there is no indication of potential unreasonable risk associated with VDF for reproductive toxicity. Therefore, the Agency is withdrawing its proposed requirement for reproductive effects testing for VDF.

F. Tests and Test Species

The FIG, in its comments, argued that the mouse micronucleus cytogenetics assay be used in place of the *in vivo* cytogenetics assay required in the proposed rule. The FIG has already tested one fluoroalkene (HFP) in this assay. The end-points of both assays are comparable. The Agency agrees that the mouse micronucleus assay is a reasonable alternative to the *in vivo* cytogenetics assay for the purposes of testing the fluoroalkenes. The Agency is requiring that the Agency's test standards for the mouse micronucleus assay be used to test the fluoroalkenes where that testing is required. However, a repetition of the mouse micronucleus assay is not being required for HFP.

The FIG also argued in its public comments that the hamster, rather than the mouse, should be the second species of choice (after the rat) in any required oncogenicity testing of the fluoroalkenes. The FIG stated concern that the mouse exhibits a high susceptibility to spontaneous development of adenomatous lung tumors. The FIG also noted that the tracheobronchial epithelium of the hamster is more similar to that of humans and therefore is possibly a better model for examining compounds which may be respiratory carcinogens. The Agency does not agree that the hamster should be used in place of the mouse in the case of the fluoroalkenes. The historical data and laboratory experience in handling the mouse in the oncogenicity bioassay are much superior to that of the hamster. Furthermore, not all mouse strains are susceptible to the problems cited by the FIG. Also, the Agency's concern for oncogenic effects for the fluoroalkenes is based largely on effects observed in the liver and possibly also the kidneys, not the respiratory system. There is no evidence that the fluoroalkenes may be respiratory carcinogens. This, of course,

does not mean that oncogenicity may not be observed in other organs or organ systems, including the respiratory system. Therefore the Agency sees no necessity to test the hamster in place of the mouse.

C. Reporting Deadlines

The FIG concurs with the proposed reporting schedule for the subchronic toxicity testing for HFP and the oncogenicity tests for VF and VDF. The FIG commented, however, that the reporting deadlines for the other proposed tests were unrealistic. The FIG commented that the reporting deadlines for these latter tests failed to take into account the logistics of such an extensive testing program. In addition, the FIG believes that special consideration should be given to the reporting schedule of the fluoroalkenes since these substances are gases which require special test facilities. For the sake of reproducibility, the FIG believes that all tests should be performed at one facility, which would impose the limitation that only one substance could be tested at a given time. Also, the FIG points out that TFE is highly hazardous and is normally not shipped off-site because of its explosive potential. When shipping is required, the TFE is diluted with inert material which would have to be removed prior to testing. It is claimed that the purchase and installation of the appropriate separation equipment at a testing facility would add several months to the time required for developing test results.

The Agency believes that although there are fewer testing facilities capable of performing tests on gaseous materials, sufficient facilities will be available, as discussed in the proposed test rule, for conducting the required tests on the fluoroalkenes. The issue of test facilities is primarily limited to the *in vivo* studies, which require extended exposure periods, while the other test procedures can be performed using exposure techniques available to most testing laboratories. The Agency disagrees with the FIG that all tests have to be performed in the same facility in order to assure reproducibility. The basic contention of this argument is that comparisons of tests results are relevant only when the tests are conducted within one facility; and that comparisons of results between facilities is difficult. The body of data available to evaluate the toxicological properties of most compounds has been derived not only from different facilities, but from studies conducted during different time periods, and these studies, if conducted with acceptable state-of-the-art procedures, have proved adequate.

Furthermore, the Agency has taken into account that additional time may be necessary to perform testing by inhalation. For the short-term *in vivo* mutagenicity assays (e.g., mouse micronucleus, *Drosophila* SLRL and rodent dominant lethal assays) an additional 2 months time was provided for set-up and standardization. For the longer term studies (e.g., mouse specific locus and oncogenicity assays) an additional 3 months was provided.

The Agency also disagrees that additional time is needed in testing TFE to allow for the installation of special equipment for reconstituting the TFE at the testing facility. Although TFE does present an explosive hazard as a result of the formation of polymeric peroxides, these peroxides can be chemically inhibited (Ref. 14). Terpene inhibitors are considered effective and are used to protect against polymerization during storage. The level of inhibitor recommended for stabilization of TFE is 0.5 percent (Ref. 31), which would provide material of sufficient quality for the recommended tests. We believe that the relatively small amounts of material used in biological testing, as compared to manufacturing uses, will not present a severe safety problem if handled with appropriate care. In addition, the gas at a purity of 99 percent has been available from specialty gas distributors. Also, in the proposed rule, the reporting requirement for the subchronic toxicity study on TFE is 18 months. This is 3 months longer than the Agency's usual requirement for an inhalation subchronic study. The 18-month reporting requirement will remain in the final rule. The Agency considers this sufficient additional time to resolve any handling issues for TFE.

The FIG further claimed that the Agency did not take into account the logistics of such extensive testing when considering the reporting deadlines. The Agency disagrees. The reporting deadlines set by the Agency take into account the longest possible sequential route of testing and the added time necessary for each test when formulating the reporting deadline for the last test in a series. The FIG suggested that greater time should be allowed for certain required tests; however, no substantial rationale was provided for the necessity of further time allotments. The Agency believes that the deadlines set forth for the fluoroalkenes in this rule are [illegible] reasonable, and that the special considerations of testing these [illegible] compounds, which are gases, have sufficiently been taken into account.

IV. 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, carcinogenicity and/or mutagenicity to humans exposed to these substances, based on data presented in the ANPR, the proposed rule, and in Unit II.B. of this notice, which indicate that VF, VDF, and HFP may have potential oncogenic effects, that VF, VDF, TFE, and HFP may have potential chronic renal 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 latter 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 VDC which has shown evidence of oncogenicity in some studies.

The Agency also finds that the data available indicate that VF may produce oncogenic effects, based on positive mutagenicity in *E. coli.*, positive results in the CHO/HPRT gene mutation assay, and the CHO cytogenicity assay, liver toxicity similar to that seen for VC (a known human oncogen), and the structural similarity of VF to VC. More recently, as discussed in Unit II.B., HFP has been found to be a positive mutagen in *in vitro* cytogenicity testing and in the mouse micronucleus assay. The Agency considers both of these tests to be correlative with oncogenicity, and therefore finds that these data indicate that HFP may also produce oncogenic effects and that further testing is needed to assess HFP's oncogenic potential. Additionally, both TFE and HFP have produced renal function impairment; however, because a no-observed effect level has not been established for HFP, subchronic testing for that compound is necessary. Both VF and VDF induce similar changes in blood and urine chemistry as HFP and TFE when [illegible] administered to test animals, suggesting the possibility for similar renal toxicity.

As reported by the ITC, the fluoroalkenes may metabolize to form reactive epoxides which can result in genotoxicity. In the NPRM, EPA noted that although the TFE and HFP metabolite data do not indicate mutagenic potential in the *Salmonella* test system, these results alone are insufficient evidence of non-mutagenicity of a compound. Since that time, HFP has been tested with positive results in the *in vitro* cytogenetics mutagenicity assay and weakly positive results in the mouse micronucleus test. TFE was also tested in the CHO/HPRT gene mutation assay, but the Agency considers the results of that test to be inconclusive, as discussed in Unit II.B. Therefore, the Agency considers that the individual chemicals VF, VDF, TFE, and HFP may have genotoxic potential and may 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 the NPRM and Unit III.A. of this notice, to support section 4(a)(1)(A) findings for these chemicals. As discussed in the NPRM and in Units II. and III. of this rule, the Agency also finds that the available data are insufficient to reasonably predict or determine the effects of the manufacture of VF, VDF, TFE, and HFP on human health in the areas noted above in this section and, thus, EPA finds that testing is necessary to develop such data. EPA believes that the data resulting from this testing will be relevant to a determination as to whether the manufacture, processing, or use of VF, VDF, TFE, and HFP does or does not present an unreasonable risk of injury to human health.

V. Final Rule and Test Standards

A. Testing and Test Standards

The Agency is requiring that health effects testing be conducted on the fluoroalkenes in accordance with specific test guidelines set forth in Title 40 CFR Part 798. The Agency is requiring 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). The Agency is also requiring that inhalation oncogenicity tests be conducted in rats and mice for VF and in mice for VDF. The test guidelines in § 798.3300 are required as the test standards for the oncogenicity testing of VF in both species and for VDF in mice. Oncogenicity testing of VDF in rats is being performed under the sponsorship of the Association of Plastics Manufacturers in Europe using test protocols submitted earlier by the FIG (NPRM Refs. 24 and 25). These protocols were reviewed and approved by the Agency as part of the previous proposed NTA. Should this testing not be performed in accordance with protocols and laboratory practices approved by EPA, or if the data are not submitted in a timely fashion, then EPA will issue a final rule for the VDF oncogenicity testing requirement in rats. 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. Furthermore, recent mutagenicity results for HFP, discussed in Unit II.B. of this rule, also suggest that HFP has potential to be oncogenic. Therefore, in accordance with the Agency's triggers from mutagenicity to oncogenicity as described in the Fluoroalkenes Proposed Test Rule (50 FR 46133), HFP is required to be tested in mice and rats for oncogenicity. Oncogenicity testing for HFP shall be conducted according to § 798.3300. However, oncogenicity testing for HFP will not be required to begin until after the Agency holds a public program review on HFP, which will be held shortly after completion of the subchronic toxicity testing and Tier II mutagenicity testing required for HFP in this rule-making. After the public review and an Agency determination that either testing must begin, or that testing is not necessary, the Agency will notify industry by certified letter or Federal Register notice either affirming or proposing to rescind the oncogenicity testing requirement for HFP.

There is much less evidence at the present time to indicate that TFE may be a potential oncogen. Therefore, oncogenicity testing for TFE is required only if triggered by the results of the mutagenicity testing required in this rule. The test guidelines in § 798.3300 shall be used as the test standards for such testing if it is triggered. Positive test results for TFE in any of the following tests will trigger the oncogenicity testing requirement for that chemical: *In vitro* cytogenetics assay, mouse micronucleus assay, mammalian cells in culture assay, or sex-linked recessive lethal assay in *Drosophila melanogaster*. However, prior to initiation of oncogenicity testing for TFE, the Agency will have a public review of all the relevant data, before requiring commencement of oncogenicity testing. This review will be held soon after completion of Tier II of the tiered mutagenicity testing required for TFE in this notice. Official notice, in the form of a certified letter II.8. of this rule, the Agency is requiring that both VF and VDF be tested in the SLRL assay. A positive result in the SLRL assay for any chemical tested will trigger a mouse specific locus test, as specified in § 798.5200 and as modified in § 799.1700(c)(1)(i)(D)(*2*), in the same chemical. 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 requires that an *in vitro* cytogenetic assay be conducted. This test has been completed for each of the subject fluoroalkenes, as discussed in Unit II.B.1. If the results of the *in vitro* test are positive then a dominant lethal assay is required. Both VF and HFP were tested and found to be positive in the *in vitro* cytogenetics assay, thus requiring the dominant lethal assay for these compounds as specified in § 798.5450 and as modified in § 799.1700(c)(2)(i)(B)(*2*). A positive result in the dominant lethal assay will trigger a heritable translocation assay as specified in § 798.5460 and as modified in § 799.1700(c)(2)(i)(D)(*2*). If the *in vitro* cytogenetic assay is negative then a mouse micronucleus assay will be required (as specified in § 798.5395 and as modified in § 799.1700(c)(2)(i)(B)(*2*)) for that fluoroalkene. (This is a requested change from the *in vivo* cytogenetics assay specified in the proposed rule; see Unit III.F. for a discussion of this change.) Both VDF and TFE were negative in the *in vitro* cytogenetics assay and thus, the mouse micronucleus test is required for VDF and TFE. Should the mouse micronucleus results prove negative, then no further chromosomal aberration testing would be required for that substance. A positive result in the mouse micronucleus cytogenetic assay for any fluoroalkene would trigger the dominant lethal assay for that fluoroalkene. HFP, which was positive in both the mouse micronucleus test and the *in vitro* cytogenetics assay, is required to be tested in the dominant lethal assay. 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 requiring the initiation of 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 C_6 aromatic hydrocarbon fraction (50 FR 20662, May 17, 1985).

The Agency is requiring that the above-referenced TSCA Health Effects Test Guidelines be the test standards for the testing of the fluoroalkenes. The specified TSCA guidelines for health effects testing provide generally accepted minimal conditions for ensuring that any required testing will result in reliable and adequate data for evaluating the health effects of VDF, VF, 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 22, 1982 (47 FR 41857). In reviewing the applicability of the mutagenic effects and subchronic test guidelines to the fluoroalkenes, EPA has determined that certain modifications are necessary in order to ensure that the resulting data are reliable and adequate.

EPA has issued a separate Federal Register notice containing certain revisions to these TSCA Test Guidelines to provide more explicit guidance on the necessary minimum elements for each study published in the Federal Register of (May 20, 1987). These modifications are adopted in the test standards for VF, VDF, HFP, and TFE. EPA has also responded to comments concerning these guideline revisions in the record for that rulemaking and these are contained in the docket for this rulemaking (Ref. 37).

B. Test Substance

EPA is specifying that VDF, VF, TFE, and HFP of at least 99 percent purity be used as test substances. 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) determine 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 requiring that persons who manufacture or intend to manufacture VF, VDF, TFE, or HFP at any time from the effective date of this 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 are 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 are responsible only for the particular testing requirements for the subset of fluoroalkenes which they manufacture. The end of the reimbursement period for each substance is 5 years after the last final report is submitted for that substance 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 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) exemptions in 40 CFR Part 790.

EPA did not propose to require the submission of equivalence data as a condition for exemption from the 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 relatively pure substances for testing.

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

D. Reporting Requirements

The Agency is requiring that all data developed under this rule be reported in accordance with the TSCA Good Laboratory Practice standards (40 CFR Part 792).

The Agency is required by TSCA section 4(b)(1)(C) to specify the time periods during which persons subject to a test rule must submit test data. On the basis of the Agency's regulatory experience for the tests required for the fluoroalkenes, as well as in response to public comments, EPA is adopting the reporting requirements for these tests and which are presented in the following table.

REPORTING REQUIREMENTS FOR THE FLUOROALKENES

Test	Reporting deadline for final report (months after the effective date of final rule, except as indicated and, in parentheses, number of interim 6-month reports required)			
	VF	VDF	TFE	HFP
Gene mutation cells in culture assay			6	6
Sex-linked recessive lethal test in *Drosophila*	9(1)	9(1)	15(2)	15(2)
Mouse specific locus assay [1]	51(8)	51(8)	51(8)	51(8)
In vitro cytogenetics test				
Mouse micronucleus cytogenetics test		10(1)	10(1)	
Dominant lethal test	9(1)	19(1)	19(1)	9(1)
Heritable translocation assay [1]	25(4)	25(4)	25(4)	25(4)
Oncogenicity (inhalation) [2]	56(9)	56(9)	56(9)	56(9)
Subchronic toxicity (inhalation)				18(2)

[1] Figures indicate the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or FEDERAL REGISTER notice that, following public program review of all of the then existing data for the fluoroalkenes fraction, the Agency has determined that the required testing must be performed.

[2] For TFE and HFP, the figures indicate the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or FEDERAL REGISTER notice that, following public program review, the Agency has determined that the required testing must be performed. For VF and VDF, the figures indicate the reporting deadline, in months, calculated from the effective date of the Fluoroalkenes Final Rule.

In regards to interim reports, the Agency has decided that interim reports for the testing required under section 4 of TSCA should be submitted at 6-month intervals, rather than at 3-month intervals, as was previously proposed for the fluoroalkenes. This reporting frequency will be sufficient to keep EPA informed of the current status of required testing and of any difficulties which the testing facility may encounter during testing. This change also lessens the reporting burden of test sponsors. Accordingly, the final reporting requirements for the testing required for the fluoroalkenes reflect a requirement for 6-month, rather than 3 months, interim reports.

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 substance 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. 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 aspect 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 or 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 as 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 the chemical is held or stored and, therefore, subject to inspection. Laboratory audits/inspections may 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)(D) 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 requirement 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.

VI. Economic Analysis of Final Rule

To assess the potential economic impact of this rule, EPA has prepared an economic analysis (Ref. 30) that evaluates the potential for significant economic impacts on the industry as a result of the required testing. The economic analysis estimates the costs of conducting the required testing and evaluates the potential for significant adverse economic impact as a result of these test costs by examining four market characteristics of the fluoroalkenes: (1) Price sensitivity of demand, (2) industry cost characteristics, (3) industry structure, and (4) market expectations. If there is no indication of adverse effect, no further economic analysis will be performed; however, if the first level of analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted which more precisely predicts the magnitude and distribution of the expected impact.

Total testing costs for the final rule for the fluoroalkenes are estimated to range from $4,783,500 to $6,196,200. In order to predict the financial decision-making practices of manufacturing firms, these costs have been annualized. Annualized costs are compared with annual revenue as an indication of potential impact. The annualized costs represent equivalent constant costs which would have to be recouped each year of the payback period in order to finance the testing expenditure in the first year.

The annualized test costs (using a cost of capital of 25 percent over a period of 15 years) range from $1,239,800 to $1,605,600. Based on the total combined

1977 estimated production volumes for the four fluoroalkenes of 48 to 77 million pounds, the unit test costs will be about 2.6 to 3.3 cents per pound. (However, for TFE, the 1984 production volume was available and this more recent figure was used in this combined estimate.) In relation to the 1985 list prices for the fluoroalkenes, these costs are equivalent to 0.3 to 0.8 percent of price. On an individual chemical basis, these costs represent 0.5 to 0.6 percent of price for TFE, 0.3 to 0.4 for HFP, and 0.6 to 0.8 for VDF. Although a list price is not available for VF, it can reasonably be assumed to be in the same range as those of the other fluoroalkenes, and thus cost in relation to price is probably less than one percent.

Based on these costs and the uses of the fluoroalkenes, 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 estimated unit test costs are low—3.3 cents per pound for the category.

2. The overall demand for the fluoroalkenes appears relatively inelastic due to their exclusive use as precursors in the manufacture of highly specialized polymers and elastomers.

3. The market expectations for the fluoroalkenes are very optimistic.

The TSCA Reimbursement Rule allows affected private parties to negotiate among 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. On an individual chemical basis, using this assumption, these costs represent 0.2 to 0.3 percent of price for TFE, 4.9 to 6.4 percent for HFP, and 0.9 to 1.2 percent for VDF. Again, although a list price is not available for VF, it can reasonably be assumed to be in the same range as those of the other fluoroalkenes; with costs likely to be similar to, or perhaps slightly higher than those of VDF. Thus, some chemicals will have higher test costs than others, but given the uses of these four chemicals, and their fairly inelastic demand and the favorable market expectations, it is reasonable to assume that none of these chemicals will be significantly affected.

Refer to the economic analysis (Ref. 30) 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 test facilities and personnel are available to perform the testing in this final rule.

VIII. Rulemaking Record

EPA has established a record for this rulemaking, (OPTS-42002E). This record includes basic information considered by the Agency in developing this final rule and appropriate Federal Register notices.

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 Proposed Decision to Adopt a Negotiated Testing Program on Fluoroalkenes (49 FR 23112).

(d) Notice of the Agency's Proposed Rulemaking on Fluoroalkenes (50 FR 46133).

(e) Notice of Interim Final Rule on Single-phase Test Rule Development and Exemption Procedures (50 FR 20652).

(f) Notice of Final Rulemaking on Data Reimbursement (48 FR 31786).

(g) Written comments on the Fluoroalkenes Proposed Test Rule Submitted to USEPA by the Fluoroalkenes Industry Group.

(h) Transcript of Proceedings of the Public Meeting of April 1, 1986 on the Proposed Rule for Fluoroalkenes and Material Submitted by the Fluoroalkenes Industry Group as Presented in the Public Meeting.

(i) Notice of the Agency's Final Rulemaking on the C9 Aromatic Hydrocarbon Fraction (50 FR 20662).

(j) Notice of the Agency's Final Guidelines for the Health Assessment of Suspect Developmental Toxicants (51 FR 34028).

(k) Notice of the Agency's Final Guidelines for Mutagenicity Risk Assessment (51 FR 34006).

(l) Notice of the Agency's Final Test Standards and Reporting Requirements for Diethylenetriamine (52 FR 3230).

(m) Notice of the Agency's Final Rulemaking on Revision of TSCA Test Guidelines (52 FR 19056).

B. References

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

(2) E.I. duPont de Nemours & Company. Evaluation of Hexafluoropropylene in the *In Vitro* Assay for Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. Submitted to USEPA. (July 23, 1986).

(3) E.I. duPont de Nemours & Company. Mouse Micronucleus Test with Hexafluoropropylene. Preliminary Information Submitted to USEPA. (August 7, 1986).

(4) E.I. duPont de Nemours & Company. Mutagenicity Evaluation of Hexafluoropropylene in the CHO/HPRT Assay. Submitted to USEPA. (February 3, 1986).

(5) E.I. duPont de Nemours & Company. Mutagenicity Evaluation of Vinyl Fluoride in the CHO/HPRT Assay. Submitted to USEPA. (August 22, 1986).

(6) E.I. duPont de Nemours & Company. Evaluation of Vinyl Fluoride in the *In Vitro* Assay for Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. Submitted to USEPA. (October 22, 1986).

(7) Fluoroalkenes Industry Group. Mutagenicity Evaluation of Tetrafluoroethylene in *Salmonella typhimurium* (Final Report). Submitted to USEPA. (July 10, 1986).

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(9) Fluoroalkenes Industry Group. Sub-Chronic (13-Week) Inhalation Toxicity Study of Vinylidene Fluoride in Rats (Final Report). Submitted to USEPA. (June 12, 1986).

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(33) Fluoroalkenes Industry Group. Evaluation of Vinylidene Fluoride in the *In Vitro* Assay for Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. Submitted to USEPA. (December 18, 1986).

(34) Fluoroalkenes Industry Group. Letter with attachment from R.E. Stahl to Richard Troast. (December 2, 1986).

(35) USEPA (United States Environmental Protection Agency). Memorandum from David S. Klauder to Gary E. Timm. "Response to industry's disagreement with EPA Critique of CHO/HPRT assay on tetrafluoroethylene (TFE)." (December 30, 1986).

(36) USEPA (United States Environmental Protection Agency). Summary of Meeting with U.S. Department of Energy on availability of Oak Ridge National Laboratory to conduct the mouse visible specific locus assay at Industry's expense for chemicals subject to a TSCA section 4 Test Rule requirement. (October 1986).

(37) USEPA (United States Environmental Protection Agency). "Response to Public Comments, Proposed Revision of TSCA Test Guidelines as published in 51 FR 1522." (April, 1987).

(38) USEPA (United States Environmental Protection Agency). Memorandum from David S. Klauder to Gary Timm. "Review of Mutagenicity Testing Results on Fluoroalkenes." (December 4, 1986).

(39) Fluoroalkenes Industry Group. Evaluation of Tetrafluoroethylene in the *In Vitro* Assay for Chromosomes Aberrations in Chinese Hamster Ovary (CHO) Cells. Submitted to USEPA. (April 3, 1987).

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection in the OPTS Reading Room NE–G004, 401 M Street, SW., Washington, DC, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays. The Agency will supplement this record periodically with additional relevant information received.

IX. 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 $4,720,000 to $6,114,000 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 its present analysis, EPA does not believe that there will be any significant adverse effects as a result of this rule.

This 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 19, 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

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.

List of Subjects in 40 CFR Part 799

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

Dated: May 28, 1987.

Victor J. Kimm,

Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR Part 799 is 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, other than as an impurity, from July 22, 1987 to the end of the reimbursement period shall submit letters of intent to conduct testing or exemption applications, submit study plans, conduct tests in accordance with the TSCA Good Laboratory Practice Standards (40 CFR Part 792), 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*) A detection of gene mutations in somatic cells in culture assay shall be conducted with TFE and HFP in accordance with § 798.5300 of this chapter except for the provisions in paragraphs (c), (d)(3)(i), (4), (5) and (6) and (e).

(*2*) For the purposes of this section, the following provisions also apply:

(i) Reference substances. No reference substance is required.

(ii) Test method—Type of cells used in the assay. 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. Cells shall be exposed to the test substance only in the presence of a metabolic activation system for TFE, and in both the presence and absence of a metabolic activation system for HFP. 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. 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 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 10 times the inverse of this frequency. Several concentrations (usually at least four) 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. 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 1 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 5 hours for tests with metabolic activation. At the end of the exposure period, cells treated with metabolic activation shall be washed and incubated in culture medium for 21 to 26 hours prior to subculturing for viability and expression of mutant phenotype. Cells treated without metabolic activation shall be washed and subcultured immediately to determine viability and to allow for expression of mutant phenotype. Appropriate subculture schedules (generally twice during the expression period) shall be used. 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. Results of this test shall be confirmed in an independent experiment.

(B) (*1*) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with VDF and VF in accordance with § 798.5275 of this chapter except for the provisions in paragraph (d)(5). This test shall also be performed with TFE or HFP if the somatic cells in culture assay conducted pursuant to paragraph (c)(1)(i)(A) of this section produces a positive result.

(*2*) For the purposes of this section the following provisions also apply:

(i) Test chemicals. 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. Exposure shall be by inhalation.

(ii) [Reserved]

(C) (*1*) A mouse specific locus assay shall be conducted with VF, VDF, TFE, and HFP in accordance with § 798.5200 of this chapter, except for the provisions of paragraph (d)(5), for whichever of these substances produces a positive result in the sex-linked recessive lethal test in *Drosohila melanogaster* conducted pursuant to paragraph (c)(1)(i)(B) of this section if, after a public program review, EPA issues a **Federal Register** notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

(*2*) For the purposes of this section, the following provisions also apply:

(i) Test chemicals. 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 spermatagonia is of only moderate duration, as determined by a return of males to fertility within 80 days after treatment, or shall be the highest dose attainable. 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) [Reserved]

(ii) Reporting requirements. (A) Mutagenic effects-gene mutation tests shall be completed and the final results submitted to the Agency as follows: Somatic cells in culture assay, within 6 months after the effective date of the final rule; Drosophila sex-linked recessive lethal, within 9 months (for VF and VDF) and within 15 months (for TFE and HFP) after the effective date of the final rule; mouse specific locus assay, within 51 months after the date of EPA's notification of the test sponsor by certified letter or **Federal Register** notice that testing shall be initiated.

(B) Progress reports shall be submitted to the Agency every 6 months beginning 6 months after the effective date of the final rule or receipt of notice that testing shall be initiated.

(2) *Mutagenic effects—Chromosomal aberrations*—(i) *Required testing.* (A) (*1*) A mouse micronucleus cytogenetics test

shall be conducted with VDF and TFE in accordance with § 798.5395 of this chapter except for the provisions in paragraphs (d)(5) (i), (ii), and (iii).

(2) For the purposes of this section, the following provisions also apply:

(i) Test method—Vehicle. No vehicle is required.

(ii) Test method—Dose levels. 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., a change in the ratio of polychromatic to normochromatic erythrocytes, or the highest dose attainable).

(iii) Test method—Route of administration. Animals shall be exposed by inhalation for 6 hours per day for 5 consecutive days.

(B) (1) For each respective test substance, a dominant lethal assay shall be conducted with VF and HFP in accordance with § 798.5450 of this chapter except for the provisions in paragraphs (d)(2)(i), (4)(i), (5) and (e). This test shall also be performed with TFE or VDF if either the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(2)(i)(A) of this section or the mouse micronucleus cytogenetics test conducted pursuant to paragraph (c)(2)(i)(B) of this section produce a positive result.

(2) For the purposes of this section, the following provisions also apply:

(i) Test method—Description. For this assay, the test substance shall be administered by inhalation for 5 consecutive days for 6 hours per day.

(ii) Test method—Concurrent controls. Concurrent positive and negative (vehicle) controls shall be included in each experiment.

(iii) Test method—Test chemicals. Exposure shall be by inhalation for 5 consecutive days for 6 hours per day. Three dose levels 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. 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. The number of matings following treatment shall ensure that germ cell maturation is adequately covered. Mating shall continue for at least 6 weeks. 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.

(C) (1) A heritable translocation assay shall be conducted with VF, VDF, TFE, or HFP in accordance with § 798.5460 of this chapter except for the provisions in paragraphs (d)(3)(i), (5), and (e)(i), if the dominant lethal assay conducted for that substance pursuant to paragraph (c)(2)(i)(C) of this section produces a positive result and if, after a public program review, EPA issues a Federal Register notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

(2) For the purposes of this section, the following provisions also apply:

(i) Test method—Animal selection. The mouse shall be used as the test species.

(ii) Test method. No vehicle is required. 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 preclude a meaningful evaluation) or shall be the highest dose attainable. Animals shall be exposed by inhalation.

(iii) Test performance—Treatment and mating. The animals shall be dosed with the test substance 6 hours per day, 7 days per 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 date 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: mouse micronucleus cytogenetics, within 10 months for VDF and TFE after the effective date of the final rule; dominant lethal assay, within 9 months (for VF and HFP), and within 19 months (for VDF and TFE), after the effective date of the final rule; heritable translocation assay, within 25 months after the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing shall be initiated.

(B) Progress reports shall be submitted to the Agency every 6 months beginning 6 months after the effective date of the final rule or receipt of notice that testing shall be initiated.

(3) *Subchronic toxicity*—(i) *Required Testing.* (A) An inhalation subchronic toxicity test shall be conducted with HFP in accordance with the TSCA Test Guideline specified in § 798.2450 of this chapter except for the provisions in paragraphs (d)(5), (10)(v), and (e)(3)(iv)(D).

(B) For the purpose of this section the following provisions also apply:

(1) *Test procedures—Exposure conditions.* 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.* Animals shall be weighted weekly, and food and water consumption shall also be measured weekly.

(3) *Test report—Individual animal data.* Food and water consumption data shall be reported.

(ii) *Reporting requirements.* (A) The required subchronic toxicity test shall be completed and final results submitted to the Agency within 18 months after the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency every 6 months beginning 6 months after the effective date of the final rule.

(4) *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 tests shall be conducted in both rats and mice with HFP if, after a public program review, EPA issues a Federal Register notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

Oncogenicity tests shall also be conducted by inhalation in both rats and mice with TFE in accordance with § 798.3300 of this chapter if TFE 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 mouse micronucleus cytogenetics assay conducted pursuant to paragraph (c)(2)(i)(B) of this section, the mammalian cells in culture assay conducted pursuant to paragraph (c)(1)(i)(A) of this section or the sex-linked recessive lethal assay in *Drosophila melanogaster* conducted pursuant to paragraph (c)(1)(i)(B) of this section if, after a public program review, EPA issues a Federal Register notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated. Criteria for positive test results are established in 40 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 the final results submitted to the Agency within 56 months after the

effective date of the final rule for VF and VDF. For TFE and HFP, the oncogenicity testing shall be completed and final results submitted to the Agency within 56 months after the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing shall be initiated.

(B) Progress reports shall be submitted every 6 months beginning 6 months after the effective date of the final rule for VF and VDF and beginning 6 months after notification by certified letter or Federal Register notice that testing is to begin for TFE and HFP.

(d) *Effective date.* The effective date of this final rule is July 22, 1987.

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

42 CFR Part 34

Medical Examination of Aliens (AIDS)

AGENCY: Centers for Disease Control, Public Health Service, HHS.

ACTION: Final rule.

SUMMARY: This rule amends the Medical Examination of Aliens regulations (42 CFR Part 34). The final rule requires that a finding of acquired immunodeficiency syndrome (AIDS) be reported by the medical examiner to the consular or immigration officer. This Final Rule cites AIDS as a "dangerous contagious disease" which makes an alien inadmissible under provisions of section 212(a)(6) of the Immigration and Nationality Act (8 U.S.C. 1182(a)(6)).

EFFECTIVE DATE: July 8, 1987.

FOR FURTHER INFORMATION CONTACT: Dr. Laurence S. Farer, Director, Division of Quarantine, Center for Prevention Services, Centers for Disease Control, Atlanta, GA, 30333, telephone (404) 329-1286, or FTS 236-1286.

SUPPLEMENTARY INFORMATION: Notice of Proposed Rulemaking (NPRM) published in the Federal Register on April 23, 1986 (5 FR 15354) proposed that AIDS be added to the list of "dangerous contagious diseases" in the Medical Examination of Aliens regulations (42 CFR 34.2(b)). The NPRM proposed that aliens be excluded from entering the United States for permanent residence under the authority of section 212(a)(6) of the Immigration and Nationality Act (8 U.S.C. 1182(a)(6)). After reviewing the comments received in response to the NPRM, and further consideration of the matter, the Department has decided to add AIDS to the list of "dangerous contagious diseases" in these regulations. The Department is also publishing elsewhere in this issue of the Federal Register an NPRM proposing to substitute HIV infection for AIDS on the above-cited list, since individuals who are so infected, but do not actually have AIDS, are also contagious.

Discussion of Comments

Comments were received from 116 individuals and 16 organizations. A summary of the substantive comments and our response follows.

Comment—Comments were received from 107 sources favoring the exclusion of aliens with AIDS. Most of these comments were brief, but supported the proposal. Four commenters thought that all aliens seeking admission to the United States should be screened for AIDS.

Response—These comments demonstrated general public sentiment for the concept of exclusion of aliens with AIDS.

42 CFR Part 34 outlines all aspects of the medical examination of aliens, including those medical conditions which may cause an alien to be inadmissible. This Final Rule specifically cites AIDS as a "dangerous contagious disease." It does not change who is required to have a medical examination. A medical examination is mandatory for applicants for permanent resident status, fiance(e)s of U.S. citizens and/or their children, and refugees. For aliens seeking temporary admission, a medical examination may be required at the discretion of a consular officer overseas or an immigration inspector at a U.S. port of entry if there is reason to suspect that an excludable condition exists.

Comment—Comments were received from 25 sources opposing the rule. The majority of these commenters expressed concern about possible discrimination against aliens falling into "high-risk" groups for AIDS, and the possibility of inappropriate referrals for medical examination. Several commenters thought the proposal did not reflect current knowledge about AIDS and its transmission and would promote further misunderstanding about the condition. Three commenters expressed concern that exclusion would subvert a humanitarian responsibility to accept persons with AIDS who want to enter the U.S. for medical care. Five commenters expressed concern about possible reciprocal actions by foreign governments which could hinder international travel by U.S. citizens.

Response—The final rule does not change who is required to have a medical examination. The same aliens will continue to be subject to a medical examination, under the same conditions, and by the same medical examiners. This final rule requires that the medical examiner, if there is clinical suspicion of AIDS, establish a diagnosis and report the findings to the consular or immigration officer. The PHS provides medical examiners with technical guidance for conducting the medical examination in accordance with applicable law and regulations. Instructions will be provided to the medical examiners regarding obtaining the medical history and clinical signs to look for and how to diagnose AIDS.

The current overall fatality rate is greater than 50% and exceeds 90% 3 to 5 years following onset of illness. AID is *not* spread by casual contact which is the usual public concept of "contagious," but it is spread by sexual contact, needle-sharing, transfusion of blood or blood products, and perinatally from infected mother to newborn. The spread of AIDS by certain high risk sexual practices is not unlike several other diseases currently on the list of "dangerous contagious diseases" in the regulations implementing our responsibilities under the Immigration and Nationality Act. Accordingly, in the context of the Immigration and Nationality Act, AIDS is being added to the existing list of "dangerous contagious diseases."

It should be stressed that the designation is being made specifically in the context of the requirement of the Immigration and Nationality Act. This designation has not been made on the basis of any new scientific knowledge about the transmission or natural history of AIDS, nor should any such interpretation be drawn. Also, this designation alone should in no way alter existing AIDS prevention and control activities in this country. All existing Public Health Service recommendations and guidelines on the prevention and control of AIDS remain in full effect as currently written.

Further, this Final Rule will not interfere with the ability of an alien with AIDS, who wishes medical care in the U.S., to seek a nonimmigrant (temporary) visa under the authority of section 212(d)(3) of the Immigration and Nationality Act (8 U.S.C. 1182(d)(3)).

The Secretary has determined that this amendment will not significantly impact on a substantial number of small entities and therefore does not require