

TSCA TEST RULES

Background for all three case studies

Under Section 4 of the Toxic Substances Control Act (TSCA), EPA may issue specific “test rules” that require manufacturers of a particular risky chemical to conduct prescribed testing, often under relatively short deadlines. 15 U.S.C. § 2603. The International Testing Commission (ITC) first identifies individual risky chemicals for which testing is insufficient. EPA is then required “with respect to [the designated] chemical substance or mixture either initiate a rulemaking proceeding [to impose testing requirements] or if such a proceeding is not initiated within such period, publish in the Federal Register the Administrator’s reason for not initiating such a proceeding.” TSCA § 4(c)(1)(B), 15 U.S.C. § 2603(c)(1)(B).

In a test rule, EPA first determines the nature of the risks or hazards that are most in need of research for each chemical and then specifies the precise tests and protocols that need to be conducted by the manufacturers within set timeframes. The results of these tests must then be provided to the agency to enable it to assess whether added restrictions and controls are needed for the chemical.

EPA did not issue many TSCA test rules during the 1980’s and 1990’s, when this program was particularly active, but the rules EPA did issue comprise our dataset for the study. In the three case studies that follow, we trace the revisions that were made to the test rules after they were promulgated as final. We discovered that the vast majority of EPA’s revisions to final test rules take the form of a somewhat unique interim rule that EPA terms a “Technical Amendment[] to Test Rules and Consent Order.” In these “Technical Amendments,” there is no context or explanation of the change itself; EPA provides only the changed text of the rule. Moreover, in most cases, EPA has already signed an agreement with one or more manufacturers to the changes, sometimes as much as nine months earlier. As a result, by the time revisions to test rules are ultimately published, at least some are moot since the tests have been run or the original deadlines have expired.

First Case Study (lightest revisions): Cumene

Case

Cumene is a chemical that the Interagency Testing Committee (ITC) identified for priority health testing in November 1984. This prioritization was based in part on the potential hazards of Cumene, the quantity of production (4-5 billion pounds is produced annually), and the insufficient understanding of the risks of the chemical. See EPA, Cumene; Final Test Rule, 53 FR 28195, 28196 (1988).

EPA's proposed rule, published in the Federal Register on November 6, 1985, 50 Fed. Reg. 46104 (1985), "would require that cumene be tested for oral and inhalation comparative pharmacokinetics, oral and inhalation subchronic toxicity, mutagenicity, developmental toxicity, neurotoxicity, oncogenicity, acute and chronic toxicity to saltwater and freshwater fish and invertebrates, biodegradation in an aquatic system, volatilization from an aquatic system, and, if triggered, a two-generation reproductive effects study." Cited in EPA, Final Rule, 53 Fed. Reg. at 28196 (1988).

EPA received written comments on its proposed rule from "the Chemical Manufacturers Association's (CMA) Cumene Program Panel (the Panel) The Panel includes manufacturers and processors of cumene. Panel members are Texaco Chemical Company, Chevron Chemical Company, Dow Chemical Company, Champlin Petroleum Company, Koch Refining, Inc., Ashland Oil Company, US Steel Corporation, and Georgia Gulf Corporation. Dow Chemical Company (Dow) also submitted written comments separately on an earlier date (February 13, 1986) that dealt specifically with the Agency's proposed guidelines for oral and inhalation pharmacokinetic studies." *Id.*

EPA issued a final test rule that required manufacturers to conduct approximately twenty different tests on health effects, environmental effects, and chemical fate studies. *Id.* at 28200.

Revisions

First Revision in 1990

On March 1, 1990, the test rule for Cumene was revised through a generic "Technical Amendment and Consent Order." 55 Fed. Reg. 7322 (1990). The changes to the Final Rule had actually been finalized by letter with industry earlier, between Oct. 1, 1988 and Sept. 30, 1989. Yet the publication of the changes in the Federal Register was not made until March 1, 1990. By that time, at least some of the changes had become moot.

The nature of the changes made in this interim rule are difficult to assess since EPA only publishes the changed text and not the context or even the original text that has been changed.

For illustrative purposes, we have copied the revisions published in the Federal Register in the text box below. This is the only information EPA provides on the changes:

§ 799.1285 Cumene.

* * * * *

(d) * * *

(1) * * *

(i) Required testing. (A) Saltwater and freshwater invertebrate and vertebrate tests, in a flow-through system, shall be conducted with **cumene** on the following organisms: *Daphnia magna*, to be conducted in accordance with § 797.1300 of this chapter; *Mysidopsis bahia* to be conducted in accordance with § 797.1930 of this chapter, and *Salmo gairdneri* and *Cyprinodon variegatus* to be conducted in accordance with § 797.1400 of this chapter except for the provisions in paragraph (d)(3)(iii) of § 797.1400. The total and dissolved (e.g. filtered) concentrations of the test substance shall be measured in each test chamber and delivery chamber before the test and in each test chamber at 0, 24, and 48 hours (*Daphnia magna*) and 0, 48, and 96 hours (*Mysidopsis bahia*, *Salmo gairdneri*, and *Cyprinodon variegatus*) to ascertain whether it is in solution.

(B)(1) For the purpose of this section, the following provisions also apply:

(2) Temperature. The test temperature shall be 12° C for rainbow trout. Excursions from the test temperature shall be no greater than 2° C. The temperature shall be measured at least hourly in one test chamber.

(ii) * * *

(A) The acute toxicity tests shall be completed and the final reports submitted to EPA within 18 months of the effective date of the final rule.

* * * * *

(e) * * *

(1) * * *

(ii) Reporting requirements. (A) The biodegradation test in an aquatic system shall be completed and the final report submitted to EPA within 15 months of the effective date of the final rule.

* * * * *

(g) Effective date. (1) The effective date of this final rule for **cumene** is September 9, 1988, except for paragraphs (d)(1)(i) and (d)(1)(ii)(A), and (e)(1)(ii)(A) of this section. The effective date for paragraphs (d)(1)(i), (d)(1)(ii)(A), and (e)(1)(ii)(A) of this section is March 1, 1990.

(2) The guidelines and other test methods cited in this rule are referenced as they exist on the effective date of the final rule.

* * * * *

To better understand the implications of these changes, we traced back to the original text of the rule published in 1988 and compared it to the revisions. Yet even after making this effort, we found that unless one is an expert in this area, it is difficult to know whether the changes are scientifically important. Specifically, the one substantive change to the test protocol is a revision relating to temperature in the study.

Original requirement in 53 Fed. Reg. 28195: “(iii) Temperature. The test temperature shall be 22 °C for bluegill and fathead minnow and 12 °C for rainbow trout. Excursions from the test temperature shall be no greater than ±2 °C. The temperature shall be measured at least hourly in one test chamber.”

Revised requirement in 1990: “Temperature. The test temperature shall be 12° C for rainbow trout. Excursions from the test temperature shall be no greater than 2° C. The temperature shall be measured at least hourly in one test chamber.”

There were also several time extensions in the 1990 Technical Amendment. Specifically:

- a) EPA added 6 more months for completing the acute toxicity test [Note: the deadline would have occurred after the EPA’s approval but before publication of the extension in 1990].
- b) EPA added a 3 month extension for biodegradation test.
- c) In another part it appears that EPA extended the dates for several other tests by another 18 months. Even this later date (all tests done by March 1, 1990) would have lapsed by the time EPA published the extension.

Second Revision in 1991

In a second Technical Amendment, published one year later, there were additional extensions to some of the Cumene test deadlines. See EPA, Technical Amendments to Test Rules and Consent Orders, 56 FR 23228, 23229 (1991). A comparison of the revised deadlines with the original 1988 requirements reveal that reporting requirements for acute toxicity tests appeared to add another few months for one test (given the delayed publication, this deadline lapsed about about 9 months before the Final rule was published). The deadline for another test was extended another 1½ years or so.

General Thoughts

These two revisions to the original Cumene test rule are likely minor. Through two interim rules, EPA extends some testing deadlines by about 1 ½ years and perhaps 2+ years at the outside. Yet, despite what might otherwise be perfectly reasonable adjustments, EPA’s method of publishing and explaining these changes causes one to be suspicious. Moreover, with respect to deadlines, EPA’s delayed publication effectively moots out the ability of the public to object to extensions. Perhaps this is sensible since the extensions were at most two years; still the approach of publishing these cryptic “interim rules,” often after the tests have been done, makes the prospect of meaningful public oversight difficult if not impossible.

Second (Medium Revised) Case Study: Anthraquinone

The Case

On June 4, 1987, EPA issued a final test rule for Anthraquinone. EPA, Anthraquinone; Final Reporting and Recordkeeping Requirements and Test Rule, 52 Fed. Reg. 21018 (1987). The ITC had listed Anthraquinone as high priority for testing in 1984. EPA responded in a proposed rule, published on Nov. 6, 1985 and identified a two tier system of testing. EPA, Anthraquinone; Proposed Rule, 50 Fed. Reg. 46090. In the first tier, manufacturers would conduct research on water solubility and acute toxicity of Anthraquinone on a number of species. If the first tier of testing revealed hazards, EPA would then require a second tier of tests on chronic toxicity on the most sensitive species. Final Rule, 52 Fed. Reg. at 21018.

In EPA's final rule, EPA found that there were high levels of production and release of Anthraquinone into the environment, particularly by paper mills, and EPA further concluded that there was insufficient research available to assess these risks. EPA also concluded that even the water solubility features of the chemical were imperfectly understood. To address these gaps, EPA required tests on water solubility and provided industry with choices for acute toxicity testing with regard to the species it could use (from a larger list of candidate species). EPA also established the possibility for a second tier of studies based on the findings in the first tier.

The Revisions

First Revision: 1989

The first revision to the 1987 Final Rule, published in 1989, extended the deadline for 3 separate tests by 3 months (the original deadline was 12 months). EPA, Technical Amendments to Test Rules and Consent Orders, 54 FR 27352 (1989). This extension was clearly explained in a summary in the Technical Amendment. Consistent with other Technical Amendments published by EPA for TSCA test rules, however, the extension itself had been granted almost 8 months before publishing the change in the Federal Register, making it effectively moot. *Id.* at 27352.

Second Revision: 1990

The second change, published in 1990, was more difficult to decipher. EPA, Technical Amendments and Consent Orders, 55 Fed. Reg. 7322 (1990). EPA published only the changes themselves, but even after tracing these changes back to the original rule, it is difficult to tell what to make of some of them. Again, for illustrative purposes the revision published by EPA is copied verbatim below out of the Federal Register.

§ 799.500 Anthraquinone.

* * * * *

(c) * * *

(2) * * *

(i) * * *

(A) Fish acute toxicity tests shall be conducted with Anthraquinone using chinook salmon, *Oncorhynchus tshawytscha*, or coho salmon, *Oncorhynchus kisutch* (cold water species); bluegill, *Lepomis macrochirus* (warm water species); and rainbow trout, *Salmo gairdneri* (cold water species) in accordance with the test guideline specified under § 797.1400 of this chapter, except for paragraphs (c)(4)(i) and (6)(iii)(A)(2) of § 797.1400.

* * * * *

(B) * * *

(4) In each chamber at 4, 7, and 14 days. If no dose-dependent mortality is observed by days 7 and 14, the concentration of dissolved test substance shall be measured in the chambers with the two highest concentrations only.

* * * * *

(ii) * * *

(A) The fish acute toxicity tests for chinook salmon, *Oncorhynchus tshawytscha*, or coho salmon, *Oncorhynchus kisutch*, and rainbow trout, *Salmo gairdneri*, shall be completed and the final results submitted to EPA within 12 months of the effective date of the final rule. The fish acute toxicity test for bluegill, *Lepomis macrochirus*, shall be completed and the final results submitted to EPA within 14 months of the effective date of the final rule.

* * * * *

(3) * * *

(ii) * * *

(A) The invertebrate acute toxicity tests shall be completed and the final results submitted to EPA within 14 months of the effective date of the final rule.

* * * * *

(5) * * *

(ii) * * *

(A) The bioconcentration test shall be completed and the final results submitted to EPA within 21 months of the effective date of the final rule.

* * * * *

(e) Effective date. (1) The effective date of this final rule is July 20, 1987, except for paragraphs (c)(2)(i)(A), (c)(2)(i)(B)(4), (c)(2)(ii)(A), (c)(3)(ii)(A), and (c)(5)(ii)(A) of this section. The effective date for paragraphs (c)(2)(i)(A), (c)(2)(i)(B)(4), (c)(2)(ii)(A), (c)(3)(ii)(A), and (c)(5)(ii)(A) of this section is March 1, 1990.

(2) The guidelines and other test methods cited in this rule are referenced as they exist on the effective date of the final rule.

* * * * *

3. In § 799.925, by revising paragraphs (c)(3)(iii) and (e) to read as follows:

As best as we can tell after comparing these changes to the original rules, the following two changes were made:

- a. There appears to be a modest substantive change to the measurements taken during the acute tests. EPA deleted the requirement that after 96 hours, the concentration of the substance in each test chamber has to be measured at 4 hour intervals. (see 55 FR 7322, deleting 797.1400(d)(iii)(A)(2)). In the same

section, EPA inserted as a technical amendment a requirement that measurements of the substance are generally required in each chamber at 4, 7, and 15 days. This seems like a weakening of the test protocol, but perhaps it wasn't necessary to do all the measurements and perhaps they were very expensive. It is not possible to tell the reason for the change or its significance.

- b. There are also extensions to several testing deadlines:
 - 1. EPA provided an additional 2 month extension for one of the fish tested in the acute fish toxicity test.
 - 2. EPA extended the invertebrate toxicity (above) by another 2 months.
 - 3. EPA extended another test – to measure bioaccumulation – by 6 months.

It appears that all of these deadlines would have passed by the time the “Technical Amendment” was actually published in the Federal Register.

General Thoughts

Much like Cumene, it is clear that some changes are occurring to the original test rules, but the implications of the changes are difficult to determine. The extensions are not terribly significant, although EPA's method of publishing the extensions well after the fact makes them effectively outside the ambit of public notice. It would be easy to write off these changes as uniformly trivial, but because EPA is so cryptic about the changes it is difficult to afford the agency with the benefit of the doubt.

Third Case Study (heavily revised): Fluoroalkenes

The Case

On June 8, 1987, EPA issued a final test rule requiring manufacturers to conduct a number of tests on a set of chemicals (consisting of 4 different chemicals) in the fluoroalkenes family. The ITC had recommended fluoralkenes for testing in 1980. EPA issued an Advanced Notice of Proposed Rulemaking in 1981, and in response the industry proposed a testing regime. In June 4, 1984, 49 Fed. Reg. 23112, EPA published its proposed rule, which consisted of a negotiated testing agreement with industry. In a subsequent challenge, the Southern District of New York held the negotiated test rules were not a permissible alternative to rulemaking, and ordered the EPA to start over (under deadline). *NRDC v. EPA*, 595 F. Supp. 1255 (S.D.N.Y. 1984).

On October 31, 1985, EPA issued a proposed test rule for fluoroalkenes. Proposed Rule, 50 Fed. Reg. 46133 (1985). The EPA received comments from the Fluoroalkenes Industry Group and its member companies, and they requested a public meeting, which was held on April 1, 1986. The EPA published its final rule setting forth testing requirements about 14 months later. EPA, Fluoroalkenes, Final Test rule, 52 Fed. Reg. 21516 (1987).

In the final rule, EPA required tiered testing (triggered by the findings of earlier testing) for a variety of health effects. The tests included subchronic inhalation studies and inhalation oncogenicity tests on specific fluoralkenes, as well as an *in vitro* cytogenetic assay to test for the potential for fluoroaklenes to cause chromosomal aberrations. *Id.* at 21525.

The Revisions

First Revision: 1987

EPA's first revision to the Final Test Rule occurred only four months later, on Nov. 16, 1987, as a "Technical Amendment". EPA, Fluoroalkenes; Technical Amendment to Test Rule, 52 FR 43762 (1987). In the amendment, EPA removes referrals to certain types of test requirements and indicates that they were "inadvertently included". The tests are "in vitro cytogenetics and other mutagenicity and oncogenicity test requirements". We spent some time trying to figure this out by comparing the changes against the original rule, since EPA only published the changes without explaining what they did or their implications.

By comparing the amendments against the original, we discovered the following specific changes but are unsure of their scientific significance or implications:

- a. At one section, EPA substituted the "VDF" test in place of "HFP" test.
- b. At another section, EPA substituted this (see underlined for the changes:

“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 of paragraph (d)(3)(i), (5), and (e)(1), if the dominant lethal assay conducted for that substance pursuant to paragraph (c)(2)(i)(B) 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.”

In place of this original text:

“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 *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.”

- c. Finally, EPA cut “The in vitro cytogenetics assay conducted pursuant to paragraph (c)(2)(i)(A) of this section,” but there does not appear to be mention of the assay at that section in the original rule, so this indeed appeared to be an error.

Second Revision: 1989

The 1989 revisions to the Federal Register again take the form of a “Technical Amendments to Test Rules and Consent Orders” and the changes appear to a response by EPA to various requests by manufacturers for modifications to the test standard and schedules. 54 Fed. Reg. 27352 (1989). The changes published on June 29, 1989 in this rule were approved earlier by EPA “by letter”, thus making them moot or partly moot by the time they were published in the Federal Register.

The specific changes made to the Fluoroalkenes rule in this 1989 set of Technical Amendments consisted of the following (again based on a comparison of the listed changes to the text of original rule):

- a. Three extensions of testing deadlines by 6 months; and 2 other deadlines by 1 and 5 months respectively.
- b. Two substantive changes that are difficult to locate (EPA doesn’t identify the original section and word searches don’t work) and nearly impossible to assess in terms of the significance:
 - (i) “EPA approved use of nitrogen as the negative control and diluting gas, a 10 L/min flow rate, and an 18- to 19-hour treatment time for the non-activated portion of the test.” [it is not clear what this means]

- (ii) “In the mouse micronucleus cytogenetics assay, EPA approved the use of a single exposure of 6 hours with three sampling times in the testing regimen for tetrafuloroethene and vinylidene fluoride.”
Id. at 27352.

Third Revision (Generic Test Change): 1990

On April 5, 1990, EPA significantly modified the actual test protocol for a health effects test; the test had been required for several chemicals, including fluoroalkenes. EPA, Mouse Visible Specific Locus Test Requirement; Final Amendment in Test Rules, 55 Fed. Reg. 12639 (1990). The protocol modification was subjected to earlier notice and comment, although it appears from the preamble that only industry commented on the proposed test change. In the final rule, EPA provides two alternative tests for manufacturers to use in assessing “heritable gene mutations in mammals”.

Although the scientific implications are again difficult to discern, the crux is that EPA added an alternative test called the MBSL (mouse biochemical specific locus test) that could be used by a manufacturer instead of the mandated mouse visible specific locus test (MVSL). The final rule not only makes this option official but provides the methods for testing if a manufacturer wants to use the second, new test (MBSL).

The backdrop for this rule may be important. Apparently CMA and Texaco challenged the original MVSL rule in court, arguing that it would be impossible to perform because of the unavailability of labs. In the interim, it turned out that for their substance, the MVSL wasn’t triggered and they dropped the case. “However, because EPA believed that the MVSL issue still needed to be addressed, EPA issued the MVSL proposed rule on Dec. 23, 1988.” Comments on the proposed were received from Am. Industrial Health Council, CMA, DuPont, Monsanto, API, and SOCMA.

In the final rule, EPA amends the test rules individually for a number of substances, including fluoroalkenes. It inserts both test options at the relevant part of the fluoroalkene rule. It also rolls back the deadline by 3 years for running this test.

Fourth Revision: 1991

On May 21, 1991, EPA issued another set of “Technical Amendments to Test Rules and Consent Orders,” 56 Fed. Reg. 23228 (1991). Once again, it is difficult to understand the nature of the revisions since EPA does not provide the original rule text or explain the reason or nature of the changes. From what we can piece together by comparing the changes with the original rule, the following revisions were made:

- a. There appears to be another 1 year extension for one or more tests (a total of 4 years extension on the oncogenicity testing.

- b. The testing requirement in the original rule also changes. See side-by-side text boxes below. The changes again raise questions with regard to the reason and nature of the changes.

Original Rule Text, 52 Fed. Reg. at 21530	Revised Rule Text, 56 Fed. Reg. at 23230-31
<p>“(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.</p> <p>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 <i>Drosophila melanogaster</i> 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.”</p>	<p>“(4) Oncogenicity— (i) Required testing. (A) (1) Oncogenicity tests shall be conducted in both rats and mice by inhalation with VF in accordance with § 798.3300 of this chapter, except for the provisions in paragraph (b)(7)(vi) of § 798.3300.</p> <p>(2) For the purposes of this section, the following provisions also apply:</p> <p>(i) Test procedures—observations of animals. All mice of test groups in which survival is approximately 25 percent of mice at risk (approximately 25 percent of 70, or approximately 18 mice) will be sacrificed near the time that 25 percent survival is achieved. All mice surviving the 18-month test period will be sacrificed and necropsied. The order of sacrifice for mice at all pathological evaluations will be random among all exposure groups within a sex. Moribund animals should be removed and sacrificed when noticed.</p> <p>(ii) [Reserved]</p> <p>(B) Oncogenicity testing shall be conducted in mice with VDF in accordance with § 798.3300 of this chapter.</p> <p>(C) 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.</p> <p>(D) 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</p>

	<p>section or the sex-linked recessive lethal assay in <i>Drosophila melanogaster</i> 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.</p> <p>* * * * *</p> <p>(d) Effective date. (1) The effective date of the final rule is July 22, 1987, except for paragraphs (c)(1)(i)(C)(1), (c)(1)(ii)(A), and (c)(4)(i), of this section. The effective date of paragraphs (c)(1)(i)(C)(1), and (c)(1)(ii)(A) is May 21, 1990. The effective date of paragraph (c)(4)(i) of this section is May 21, 1991.”</p>
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Fifth Revision: 1992

In another Technical Amendments to Test Rules and Consent Orders, 57 Fed. Reg. 24958 (1992), EPA rolls back the deadlines for several tests another year (for a total of 5 years roll back in one case).

EPA also added an amendment to address the specifications for sacrificing rats. The requirement parallels the requirement for mice, so it was probably just an oversight in the original rule.

Sixth Revision: 1993.

EPA published another Technical Amendments to Test Rules and Consent Orders in May 1993, 58 Fed. Reg. 30989 (1993). The change appears to provide another, one-year extension on a test deadline. Initially the rule was effective 1987 and all deadlines ran from that. After this last amendment, the latest effective date of the rule is 1993. So the total deadline extension in some cases was 6 years.

General Thoughts

There is a lot of incremental tweaking going on with both the tests and the deadlines. It is difficult to tell substantively how important they are, but it appears that the pressure for the changes is coming uniformly from industry. The industry’s motives may be primarily to cut testing costs, but that is hard to know.

To gain a birds’ eye view of the incremental revisions, we have put together a complete track-change version of the original rule against the final rule that captures all of the cumulative

revisions. The track version (with all revisions marked in track) of the test rule is provided in the remainder of this document.

~~§ 799.1700 Fluoroalkenes.~~

§ 799.1700 Fluoroalkenes.

All changes made to the first final rule are in track.

Currentness

(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 ~~Partpart~~ 792), and submit data as specified in this section, ~~Subpartsubpart~~ A of this ~~Partpart~~, and ~~Partpart~~ 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)~~ (1) A detection of gene mutations in somatic cells in culture assay shall be conducted with TFE and HFP in accordance with ~~§ 798.5300~~ § 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~~Nitrogen shall serve as the negative control and diluting gas.

(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 (or chambers) 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. In the case of a test chamber volume of 1.67 L, a flow rate of 10 L/min is appropriate. 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. For the non-activated portion of the test, the incubation time shall be 18 to 19 hours at 37 °C. 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~~the 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)~~ (1) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with VDF and VF in accordance with ~~§ 798.5275~~ § 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)~~ (1) A mouse visible specific locus assay (MVSL) shall be conducted with VF, VDF, TFE, and HFP in accordance with ~~§ 798.5200~~ § 798.5200 of this chapter, except for the provisions of ~~paragraph (d)(5); paragraph (d)(5) of § 798.5200, or a mouse biochemical-specific locus assay (MBSL) shall be conducted with VF, VDF, TFE, and HFP in accordance with § 798.5195 of this chapter, except for the provisions of paragraph (d)(5) of § 798.5195,~~ for whichever of these substances produces a positive test result in the sex-linked recessive lethal test in

~~Drosophila~~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.

(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 spermatogonia 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~~reports shall be submitted to ~~the Agency~~EPA 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~~MVSL or MBSL, 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 ~~*21531~~ shall be conducted with VDF and TFE in accordance with ~~§ 798.5395~~ § 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~~route of administration. Animals shall be exposed by inhalation ~~for with a single 6-hour exposure, with three sampling times between 20 and 72 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~~ § 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~~produces 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~~ § 798.5460 of this chapter except for the provisions ~~in~~ of paragraphs (d)(3)(i), (5), and (e)~~(1)~~, if the dominant lethal assay conducted for that substance pursuant to paragraph (c)(2)(i)~~(CB)~~ 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~~EPA after the effective date of the rule as follows: mouse micronucleus cytogenetics, ~~for VDF by November 22, 1988, and for TFE~~ 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); by October 22, 1988, and for VDF and TFE 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~~ § 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.

(A)(1) Oncogenicity tests shall be conducted in both rats and mice by inhalation with VF and in mice with VDF in accordance with § 798.3300 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, except for the provisions in paragraph (b)(7)(vi) of § 798.3300.

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

(i) Test procedures--observations of animals. All mice of test sponsor specifying groups in which survival is approximately 25 percent of mice at risk (approximately 25 percent of 70, or approximately 18 mice) will be sacrificed near the time that the 25 percent survival is achieved. All mice surviving the 18-month test period will be sacrificed and necropsied. The order of sacrifice for mice at all pathological evaluations will be random among all exposure groups within a sex. Moribund animals should be removed and sacrificed when noticed.

(ii) All rats of test groups in which survival is approximately 25 percent of rats at risk (approximately 25 percent of 60, or approximately 15 rats) will be sacrificed near the time that 25 percent survival is achieved. All rats surviving the 24-month test period will be sacrificed and necropsied. The order of sacrifice for rats at all pathological evaluations will be random among

all exposure groups within a sex. Moribund animals should be removed and sacrificed when noticed.

(B) Oncogenicity testing shall be initiated conducted in mice with VDF in accordance with § 798.3300 of this chapter.

(C) [Reserved]

(D) Oncogenicity tests shall also be conducted by inhalation in both rats and mice with TFE in accordance with ~~§ 798.3300~~ § 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~~ 40 CFR 798.5375, ~~798.5385~~ 798.5385, ~~798.5300~~ and ~~798.5275~~ 798.5300 and 798.5275 of this chapter, respectively.

(ii) Reporting requirements. ~~(A) The~~

(A) The oncogenicity testing for VDF shall be completed and the final results submitted to the Agency by March 23, 1992. The oncogenicity testing for VF shall be completed and the final results submitted to the Agency by July 22, 1992. For TFE and HFP, the oncogenicity testing shall be completed and the final results submitted to the Agency within 56 months after the ~~*21532~~ 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)~~

~~[FR Doc. 87-12828 Filed 6-5-87; 8:45 am]~~

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(1) The effective date of the final rule is July 22, 1987, except for paragraphs (c)(1)(i)(C)(1), (c)(1)(ii)(A), (c)(4)(i) and (c)(4)(ii)(A) of this section. The effective date of paragraphs (c)(1)(i)(C)(1) and (c)(1)(ii)(A) of this section is May 21, 1990. The effective date of paragraphs (c)(4)(i)(A)(1) (c)(4)(i)(A)(2)(i), (c)(4)(i)(B) and (c)(4)(i)(D) of this section is May 21, 1991. The effective date for paragraphs (c)(4)(i)(A)(2)(ii) and (c)(4)(i)(C) of this section is June 12, 1992. The effective date of paragraph (c)(4)(ii)(A) of this section is May 28, 1993.

(2) The guidelines and other test methods cited in this rule are referenced as they exist on the effective date of the final rule.

Credits

[52 FR 21530, June 8, 1987; 52 FR 43762, Nov. 16, 1987; 54 FR 27357, June 29, 1989; 54 FR 33148, Aug. 11, 1989; 55 FR 12643, April 5, 1990; 56 FR 23230, May 21, 1991; 57 FR 24960, June 12, 1992; 58 FR 30992, May 28, 1993]

SOURCE: 49 FR 39817, Oct. 10, 1984; 50 FR 20676, May 17, 1985; 53 FR 49822, Dec. 11, 1988, unless otherwise noted.