(B) The route of administration for the reproduction and fertility testing for 1,2,4,5-TCB shall be dietary.

(C) A rodent test species shall be used and shall be the Sprague-Dawley rat.

(ii) *Reporting requirements.* (A) The reproduction and fertility test shall be completed and the final results submitted to EPA within 32 months of the effective date of this final rule.

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

(2) *Developmental toxicity*—(i) *Required testing.* (A) A test of developmental toxicity shall be conducted with 1,2,4,5-TCB in accordance with §798.4900 of this chapter.

(B) The route of administration for the developmental toxicity testing for 1,2,4,5-TCB shall be via oral gavage.

(C) Two rodent species shall be used in the study. One shall be the Fischer-344 rat and the second the New Zealand white rabbit.

(ii) *Reporting requirements.* (A) The developmental toxicity testing shall be completed and the final results submitted to the Agency within 16 months of the effective date of the test rule.

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

[51 FR 24667, July 8, 1986, as amended at 52 FR 10378, Apr. 1, 1987; 52 FR 26477, July 15, 1987; 54 FR 27355, June 29, 1989; 58 FR 34205, June 23, 1993]

§799.1250 Cresols.

(a) *Identification of test substances.* (1) *ortho*-Cresol (CAS No. 95-48-7), *meta*-cresol (CAS No. 108-39-4), and *para*-cresol (CAS No. 106-44-5) shall each be tested in accordance with this section.

(2) *ortho-*, *meta-*, and *para*-Cresol of at least 99 percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests, and submit data.* (1) All persons who manufacture or process or intend to manufacture or process cresols from the effective date of this rule (June 11, 1986) to the end of the reimbursement period shall submit letters of intent to conduct testing or exemption applications, study plans, and/or shall conduct tests and submit data as specified in this section, subpart A of this part, and part 790 of this chapter.

(2) Persons subject to this section are not subject to the requirements of §§790.50(a)(2), (5), and (6) and (b), and 790.87(a)(1)(ii) of this chapter.

(3) Persons who notify EPA of their intent to conduct tests in compliance with the requirements of this section must submit study plans for those tests no later than 30 days before the initiation of each of those tests.

(4) In addition to the requirements of §790.87(a)(2) and (3) of this chapter, EPA will conditionally approve exemption applications for this rule if EPA has received a letter of intent to conduct the testing from which exemption is sought and EPA has adopted test standards and schedules in a final Phase II test rule.

(c) *Health effects testing*—(1) *Mutagenic effects—chromosomal aberrations*—(i) *Required testing.* (A) *In vitro* cytogenetics tests shall be conducted individually with *ortho-*, *meta-*, and *para*-cresol;

(B) An *in vivo* cytogenetics test shall be conducted for each isomer which produces a negative result in the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(1)(i)(A) of this section.

(C) A dominant lethal assay shall be conducted for each isomer which produces a positive result in either the *in vitro* or the *in vivo* cytogenetics test conducted pursuant to paragraphs (c)(1)(i)(A) and (B) of this section.

(ii) *Test standards.* (A)(*1*) *In vitro mammalian cytogenetics test.* This test shall be conducted individually with *ortho-*, *meta-*, and *para*-cresols in accordance with §798.5375 of this chapter, except for the provisions in paragraphs (d)(3)(i) and (4) and (6) (i) and (ii).

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

(*i*) *Type of cells used in the assay. Ortho-*, *meta-*, and *para*-cresols shall be tested in established cell lines. The cell lines or strain shall be checked for *Mycoplasma* contamination.

(*ii*) *Metabolic activation.* The metabolic activation system for this assay shall be derived from Aroclor-1254 induced rat liver S-9 preparations.

(*iii*) *Test substance—Vehicle. Ortho-*, *meta-*, and *para*-cresols shall be dis-

solved in DMSO prior to treatment of the cells.

(*iv*) *Exposure concentrations.* At least three concentrations of the test substance over a range adequate to define the response curve shall be tested. The highest test concentration tested with and without metabolic activation shall be 5 milligrams per milliliter or that dose which shows evidence of cytotoxicity or reduced mitotic activity.

(B) (*1*) *In vivo mammalian bone marrow cytogenetics test.* This chromosomal analysis test shall be conducted with each *ortho-*, *meta-*, or *para*-cresol isomer which produces a negative result in the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(1)(i)(A) of this section. This test shall be conducted in accordance with § 798.5385 of this chapter, except for the provisions in paragraphs (d) (3)(i) and (5) (ii) and (iii).

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

(*i*) *Animal selection—Species and strain.* The mouse shall be used. Commonly used laboratory strains should be employed. The test sponsor should provide justification/reasoning for its selection.

(*ii*) *Dose levels.* At least three dose levels shall be used. The highest dose tested shall be the maximum tolerated dose or that producing some indication of cytotoxicity, e.g., partial inhibition of mitosis, or shall be the highest dose attainable.

(*iii*) *Route of administration.* The test substance shall be administered only once by oral gavage.

(C) (*1*) *Rodent dominant-lethal assay.* This assay shall be conducted with *ortho-*, *meta-*, or *para*-cresols in accordance with § 798.5450 of this chapter, except for the provision in paragraphs (d) 3)(i) and (5)(iii) and (e)(1). The rodent dominant-lethal assay shall be conducted for each isomer which produces a positive result in either the *in vitro* or the *in vivo* cytogenetics test conducted pursuant to paragraphs (c)(1)(i) (A) and B) of this section.

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

(*i*) *Animal selection—Species.* The mouse shall be used. Commonly used laboratory strains should be employed. The test sponsor should provide justification/reasoning for its selection.

(*ii*) *Route of administration.* The test substance shall be administered by oral gavage.

(*iii*) *Test performance.* Each male shall be mated to no more than two, and preferably to only one, female per mating interval. Females shall be left with the males for no longer than 7 days, and mating shall continue for at least 6 weeks.

(iii) *Reporting requirements.* (A) The chromosomal aberration tests shall be completed and the final results submitted to the Agency as follows:

(*1*) The *in vitro* and *in vivo* (conditional) tests shall be completed and the final results submitted to EPA within 12 and 19 months, respectively, of the effective date of the final Phase II test rule.

(*2*) The dominant lethal assay (conditional) within 24 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the *in vitro* and *in vivo* cytogenetics assays and the dominant lethal assay at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(2) *Mutagenic effects—gene mutations*—(i) *Required testing.* (A) A DNA damage assay shall be conducted with *meta*-cresol.

(B) A gene mutation in somatic cells assay shall be conducted individually with *meta-* and *para*-cresol.

(C) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted individually with *ortho-* and *para*-cresol.

(D) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with *meta-* cresol if it produces a positive result in the DNA damage assay or gene mutation in somatic cells assay conducted pursuant to paragraphs (c)(2)(i)(A) and (B) of this section.

(ii) *Test standards.* (A)(*1*) *Unscheduled DNA synthesis in mammalian cells in culture assay.* This assay shall be conducted with *meta*-cresol in accordance with § 798.5550 of this chapter, except for provisions in § 798.5550(d) (3)(i) and (6)(i).

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

(*i*) *Cells—Types of cells used in the assay.* Primary cultures of rat hepatocytes shall be used.

(*ii*) *Test chemical—Vehicle. Meta*-cresol shall be dissolved in DMSO prior to treatment of cells.

(B)(*1*) *Detection of gene mutations in somatic cells in culture.* This assay shall be conducted individually with *meta*- and *para*-cresols in accordance with § 798.5300 of this chapter, except for provisions in § 798.5300(d)(3)(i), (4), (6)(i), and (e)(1).

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

(*i*) *Cells—Type of cells used in the assay.* L5178Y mouse lymphoma cells shall be used. Cells shall be checked for *Mycoplasma* contamination.

(*ii*) *Metabolic activation.* The metabolic activation system shall be derived from the postmitochondrial fraction (S–9) of rat livers pretreated with Aroclor 1254.

(iii) Test chemical—Vehicle. Meta- and *para*-cresols shall be dissolved in DMSO prior to treatment of the cells. The final concentration of the vehicle shall not interfere with cell viability or growth rate.

(iv) Test performance—Exposure. Exposure shall be for 4 hours unless a different exposure time is justified by the investigator.

(C) *(1) Sex-linked recessive lethal test in Drosophila melanogaster.* This test shall be conducted with *meta*-cresols in accordance with § 798.5275 of this chapter, except for the provisions in § 798.5275(d)(5)(iii). This sex-linked recessive lethal test shall be conducted with *meta*-cresol if it produces a positive result in either one of the assays conducted pursuant to paragraphs (c)(2)(i) (A) and (B) of this section.

(*2*) For the purposes of this section the following provision also applies: *Route of administration.* The oral route of administration shall be used.

(iii) *Reporting requirements.* (A) The genetic toxicity tests shall be completed and final results submitted to the Agency as follows:

(*1*) The unscheduled DNA synthesis in mammalian cells in culture assay within 12 months of the effective date of the final Phase II test rule.

(*2*) The detection of gene mutations in somatic cells in culture assay within 12 months of the effective date of the final Phase II test rule.

(*3*) The sex-linked recessive lethal test in *Drosophila melanogaster*, if required, within 24 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the unscheduled DNA synthesis in mammalian cells in culture assay, gene mutation in mammalian cells in culture assay, and the *Drosophila* sex-linked recessive lethal test at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(3) *Mutagenic effects—cellular transformation*—(i) *Required testing.* (A) A Balb/c-3T3 cellular transformation test performed without metabolic activation shall be conducted individually with *meta*- and *para*-cresol.

(B) A Balb/c-3T3 cellular transformation test performed with metabolic activation shall be conducted with each isomer which produces a negative result in the cellular transformation test without metabolic activation conducted pursuant to paragraph (c)(3)(i)(A) of this section.

(C) A Balb/c-3T3 cellular transformation test performed with metabolic activation shall be conducted with *ortho*-cresol.

(ii) *Test standards.* (A) *Morphologic transformation of mammalian cells in culture.* This test shall be conducted individually with *ortho-*, *meta-*, and *para*-cresols in accordance with § 795.285 of this chapter, except for provisions in § 795.285(d)(4).

(B) For the purposes of this section the following provision also applies: *Metabolic activation. Meta-* and *para*-cresol shall initially be tested in this assay performed without metabolic activation. Only if they produce negative results in the assay performed without activation will *meta-* and *para*-cresol then be tested in the assay with metabolic activation. *Ortho*-cresol shall only be tested in this assay performed with metabolic activation.

(iii) *Reporting requirements.* (A) The morphologic transformation of mammalian cells in culture assay shall be completed and final results submitted

to EPA within 17 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the morphologic transformation assay at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(4) *Developmental toxicity*—(i) *Required testing.* A developmental toxicity study shall be conducted individually with *ortho-*, *meta-*, and *para*-cresol.

(ii) *Test standards.* (A) *Developmental toxicity.* This study shall be conducted individually with *ortho-*, *meta-*, and *para*-cresols in accordance with § 798.4900 of this chapter, except for provisions in § 798.4900(e)(5).

(B) For the purposes of this section the following provision also applies: *Administration of test substance.* The test substance shall be administered by oral gavage.

(iii) *Reporting requirements.* (A) The developmental toxicity study shall be completed and final results submitted to the Agency within 12 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the developmental toxicity study at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(5) *Reproductive effects—(i) Required testing.* A two-generation reproductive effects study shall be conducted individually with *ortho-*, *meta-*, and *para*-cresol.

(ii) *Test standards.* (A) *Reproduction and fertility effects.* This study shall be conducted individually with *ortho-*, *meta-*, and *para*-cresols in accordance with § 798.4700 of this chapter, except for provisions in § 798.4700(c)(5)(i)(A).

(B) For the purposes of this section the following provision also applies: *Administration of the test substance—Oral studies.* The test substance shall be administered by oral gavage.

(iii) *Reporting requirements.* (A) The reproduction and fertility effects study shall be completed and final results submitted to the Agency within 29 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the reproduction and fertility effects study at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(d) *Effective date.* The effective date of the final Phase II rule for cresols is July 6, 1987.

[51 FR 15782, Apr. 28, 1986, as amended at 52 FR 19087, May 20, 1987; 54 FR 27355, June 29, 1989; 58 FR 34205, June 23, 1993]

§ 799.1285 Cumene.

(a) *Identification of test substance.* (1) Cumene (isopropylbenzene, CAS No. 98–82–8) shall be tested in accordance with this section.

(2) Cumene of at least 99 percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests, and submit data.* All persons who manufacture (including import or byproduct manufacture) or process or intend to manufacture or process cumene, other than as an impurity, after September 9, 1988, to the end of the reimbursement period shall submit letters of intent to conduct testing, submit study plans, conduct tests, and submit data, or submit exemption applications, as specified in this section, subpart A of this part, and parts 790 and 792 of this chapter for single-phase rulemaking.

(c) *Health effects*—(1) *Oral and inhalation pharmacokinetic test*—(i) *Required testing.* Pharmacokinetic testing using the oral and inhalation routes shall be conducted with cumene in accordance with § 795.230 of this chapter.

(ii) *Reporting requirements.* (A) The pharmacokinetic testing shall be completed and the final report submitted to EPA within 15 months of the effective date of the final rule.

(B) Interim progress reports shall be submitted to EPA at 6-month intervals beginning 6 months after the effective date of the final rule, until the final report is submitted to EPA.

(2) *Subchronic inhalation toxicity*—(i) *Required testing.* (A) A subchronic inhalation toxicity test shall be conducted with cumene in accordance with § 798.2450 of this chapter except for the provisions of paragraphs (d)(1)(iv), (5), (6), (9), (12)(iii), (13)(i), and (e)(3)(iv)(D) of § 798.2450.

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