(D)(*1*) A neuropathology test shall be conducted with commercial hexane in accordance with § 798.6400 of this chapter except for the provisions in paragraphs (d)(4)(i), (5), and (6) of § 798.6400.

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

(*i*) *High dose level.* The highest dose shall produce clear behavior effects or life-threatening toxicity. In addition, the highest dose should not exceed the lower explosive limit of commercial hexane.

(*ii*) *Duration and frequency of exposure.* Animals shall be dosed for 6 hours/day, 5 days/week for 90 days.

(*iii*) *Route of exposure.* Animals shall be exposed to commercial hexane by inhalation.

(ii) *Reporting requirements.* (A) The schedule-controlled operant behavior, functional observation battery, motor activity, and neuropathology tests shall be completed and the final reports submitted to EPA within 15 months of the effective date of the final rule.

(B) Interim progress reports for each test shall be submitted to EPA for the schedule-controlled operant behavior, functional observation battery, motor activity, and neuropathology tests at 6-month intervals beginning 6 months after the effective date of the applicable final rule, until the applicable final report is submitted to EPA.

(8) *Pharmacokinetics*—(i) *Required testing.* (A) Pharmacokinetics testing shall be conducted in rats in accordance with § 795.232 of this chapter, except for paragraph (c)(1)(ii) of § 795.232.

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

(*1*) *Test animals.* Adult male and female rats shall be used for testing. The rats shall be 9 to 11 weeks old and their weight range should be comparable from group to group. The animals shall be purchased from a reputable dealer and shall be permanently identified upon arrival. The animals shall be selected at random for the testing groups, and any animal showing signs of ill health shall not be used.

(*2*) *Species and strain.* The rat strain used shall be the same as the strain used in the subchronic and chronic tests required under § 798.2450(d)(1)(i) and § 798.3300(b)(1)(i).

(ii) *Reporting requirements.* (A) The inhalation and dermal pharmacokinetics tests shall be completed and the final report submitted to EPA by August 21, 1992.

(B) Interim progress reports shall be submitted to EPA for the inhalation and dermal pharmacokinetics tests at 6-month intervals, beginning 6 months after the effective date specified in paragraph (d)(1) of this section, until the final report is submitted to EPA.

(d) *Effective date.* (1) The effective date of this final rule is November 17, 1988, except for the provisions of paragraphs (c)(5)(i)(D), (c)(5)(ii)(A)(*4*), (c)(5)(ii)(C), (c)(8)(i) and (c)(8)(ii)(A) of this section. The effective date for paragraphs (c)(5)(i)(D), (c)(5)(ii)(A)(*4*) and (c)(5)(ii)(C) of this section is May 21, 1990. The effective date for paragraphs (c)(8)(i) and (c)(8)(ii)(A) of this section is June 12, 1992.

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

[53 FR 3392, Feb. 5, 1988, as amended at 53 FR 38953, Oct. 4, 1988; 55 FR 634, Jan. 8, 1990; 55 FR 7325, Mar. 1, 1990; 55 FR 12643, Apr. 5, 1990; 57 FR 24961, June 12, 1992; 58 FR 34205, June 23, 1993]

§ 799.2175 C9 aromatic hydrocarbon fraction.

(a) *Identification of chemical substance.* The C9 aromatic hydrocarbon fraction obtained from the reforming of crude petroleum shall be tested in accordance with this part.

(b) *Identification of test substance.* A C9 substance consisting of *ortho-*, *meta-* and *para*-ethyltoluene (minimum 22 percent), and 1,2,4-, 1,2,3,- and 1,3,5-trimethylbenzene minimum 15 percent) that is representative of a typical C9 aromatic hydrocarbon fraction obtained from the reforming of crude petroleum (minimum total ET–TMB content 75 percent) and intended for use as a solvent end product shall be prepared and used as the test substance in all tests.

(c) *Persons required to submit study plans, conduct tests and submit data.* All persons who manufacture or process, or intend to manufacture or process, the C9 aromatic hydrocarbon fraction, other than as an impurity, from July 1,

985, to the end of the reimbursement eriod shall submit letters of intent to est, exemption applications, and study lans, and shall conduct tests and sub- nit data as specified in this section, ubpart A of this part, and part 790 of his chapter.

(d) *Health Effects Testing*—(1) *Mutagenic effects—Chromosomal aberrations*—) *Required testing.* (A) An in vitro cytogenetics test shall be conducted with he C9 test substance.

(B) An in vivo cytogenetics test shall e conducted for the C9 test substance the in vitro cytogenetics test conucted pursuant to paragraph l)(1)(i)(A) of this section produces a egative result.

(C) A dominant lethal assay shall be onducted with the C9 test substance nless the in vitro cytogenetics test onducted pursuant to paragraph l)(1)(i)(A) of this section and the in ivo cytogenetics test conducted purant to paragraph (d)(1)(i)(B) of this ection (if required) produce negative esults.

(D) A heritable translocation assay hall be conducted with the C9 test ubstance if the dominant lethal assay onducted pursuant to paragraph l)(1)(i)(C) of this section produces a ositive result.

(ii) *Reporting requirements.* (A) The utagenic effects testing for chromoomal aberrations as contained in the rst tier of testing, which consists of n *in vitro* cytogenetics test and an *in ivo* cytogenetics test shall be comleted and the final results submitted o the Agency within 12 months of the ffective date of the final Phase II rule.

(B) The mutagenic effects testing for hromosomal aberrations as contained n the second tier of testing, which onsists of a dominant lethal assay, hall be completed and the final results ubmitted to the Agency within 24 onths of the effective date of the nal Phase II rule.

(C) The mutagenic effects testing for hromosomal aberrations as contained n the third tier of testing, which consts of a heritable translocation assay, hall be completed and the final results ubmitted to the Agency within 24 onths of the date of EPA's notificaon of the test sponsor by certified letter or FEDERAL REGISTER notice that testing should be initiated.

(D) 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.

(E) Progress reports shall be submitted to the Agency for the heritable translocation assay at 6-month intervals, the first of which is due within 6 months of the date of EPA's notification of the test sponsor that testing should be initiated.

(2) *Mutagenic effects—Gene mutation*—(i) *Required testing.* (A) A *Salmonella typhimurium* mammalian reverse mutation microsomal assay shall be conducted with the C9 test substance, both with and without activation.

(B) A sister chromatid exchange (SCE) assay shall be conducted with the C9 test substance.

(C) A gene mutation in mammalian cells in culture assay shall be conducted with the C9 test substance.

(D) A second gene mutation in mammalian cells in culture assay, using a different cell line from that used in the first assay, shall be conducted with the C9 test substance if the first gene mutation in cells in culture assay, conducted pursuant to paragraph (d)(2)(i)(C) of this section, produces a negative result, unless the *Salmonella* microsomal assay, conducted pursuant to paragraph (d)(2)(i)(A) of this section, and the SCE assay, conducted pursuant to paragraph (d)(2)(i)(B) of this section, produce negative results.

(E) A *Drosophila* sex-linked recessive lethality test shall be conducted with the C9 test substance unless the *Salmonella* microsomal assay conducted pursuant to paragraph (d)(2)(i)(A) of this section and the gene mutation in cells in culture assays conducted pursuant to paragraphs (d)(2)(i)(C) and (D) of this section produce negative results.

(F) A mouse specific locus assay shall be conducted with the C9 test substance if the *Drosophila* sex-linked recessive lethality test, conducted pursuant to paragraph (d)(2)(i)(E) of this section produces a positive result.

(ii) *Reporting requirements.* (A) The mutagenic effects testing for gene mutations as contained in the first tier of testing, which consists of a *Salmonella typhimurium* mammalian reverse mutation microsomal assay, a sister chromatid exchange (SCE) assay, and a gene mutation in mammalian cells in culture assay, shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final Phase II rule.

(B) The mutagenic effects testing for gene mutations as contained in the second tier of testing, which consists of a second gene mutation in mammalian cells in culture assay and a *Drosophila* sex-linked recessive lethal test, shall be completed and the final results submitted to the Agency within 24 months of the effective date of the final Phase II rule.

(C) The mutagenic effects testing for gene mutations as contained in the third tier of testing, consisting of a mouse specific locus assay, shall be completed and the final results submitted to the Agency within 48 months of the date of EPA's notification of the test sponsor by certified letter or FEDERAL REGISTER notice that testing should be initiated.

(D) Progress reports shall be submitted to the Agency for the *Salmonella typhimurium* mammalian reverse mutation microsomal assay, SCE assay, gene mutation in mammalian cells in culture assays, and *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.

(E) Progress reports shall be submitted to the Agency for the mouse specific locus assay at 6-month intervals, the first of which is due within 6 months of the date of EPA's notification of the test sponsor that testing should be initiated.

(3) *Oncogenicity*—(i) *Required testing.* A 2-year inhalation oncogenicity bioassay shall be conducted with the C9 test substance unless it produces negative results in all of the following tests: In vitro cytogenetics test, in vivo cytogenetics test (if required), first gene mutation in cells in culture assay, second gene mutation in cells in culture assay (if required), and *Drosophila* sex-linked recessive lethality test (if required) conducted pursuant to paragraphs (d)(1)(i)(A) and (B) and (d)(2)(i)(C), (D) and (E) of this section.

(ii) *Reporting requirements.* (A) The oncogenicity testing shall be completed and the final results submitted to the Agency within 53 months after the date of EPA's notification of the test sponsor by certified letter or FEDERAL REGISTER notice that testing should be initiated.

(B) Progress reports shall be submitted to the Agency at 6-month intervals, the first of which is due within 6 months after the date of EPA's notification of the test sponsor that testing should be initiated.

(4) *Developmental Toxicity*—(i) *Required testing.* An inhalation developmental toxicity study shall be conducted with the C9 test substance.

(ii) *Reporting requirements.* (A) The developmental toxicity testing shall be completed and the final results submitted to the Agency within 18 months of the effective date of the final Phase II rule.

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

(5) *Reproductive Effects*—(i) *Required testing.* An inhalation reproductive effects study shall be conducted with the C9 test substance.

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

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

(6) *Neurotoxicity*—(i) *Required testing.* A neurotoxicity test battery consisting of a 90-day subchronic inhalation exposure incorporating the following tests shall be conducted with the C9 test substance:

(A) A neuropathology test;

(B) A motor activity test; and

(C) A functional observation battery.

(ii) *Reporting requirements.* (A) The neurotoxicity test battery consisting

f a motor activity test and functional bservational battery shall be completed and the final results submitted o the Agency within 15 months from he effective date of the final Phase II ule.

(B) The neuropathology test shall be ompleted and the final results submitted to the Agency within 25 months om the effective date of the final hase II rule.

(C) Progress reports shall be submitted to the Agency at 6-month intervals, he first of which shall be due within 6 nonths from the effective date of the nal Phase II rule.

(e) *Test standards*—(1) *General.* (i)(A) he required testing specified in paragraphs (d) (1), (2), (3), and (4) of this ection shall be conducted in accordnce with the study plans for testing he C9 fraction developed by the Amerian Petroleum Institute (API), subnitted to EPA on September 30, 1985, nodified in a submission dated Janury 10, 1986, and the additional requirements specified in this paragraph.

(B) The required testing specified in aragraph (d)(5) of this section shall be onducted in accordance with the tudy plans for testing the C9 fraction eveloped by the American Petroleum nstitute (API), submitted to EPA on eptember 30, 1985, and modified in ubmissions dated January 10, 1986, and eptember 13, 1988.

(ii) The required testing specified in aragraph (d)(6) of this section shall be onducted in accordance with the tudy plan for testing the C_9 fraction eveloped by API, and submitted to the gency on November 4, 1986.

(iii) Copies of the API study plans are ocated in the public record for this ule (Docket No. OPPTS–42034) and are vailable for inspection in EPA's PPTS Reading Room, NE–G004, 401 M t., SW., Washington, DC 20460, from 8 .m. to 4 p.m., Monday through Friday, xcept legal holidays.

(2) *Mutagenic effects.* (i) For each tudy specified in paragraphs d)(1)(i)(A) and (2)(i) (A), (B), (C), and D) of this section, the study shall be epeated over a narrow range of conentrations if a single, statistically ignificant positive effect for at least ne of the test points is produced here no statistically significant dose-related increase in the number of mutagenic events was found.

(ii) For each study specified in paragraph (d) of this section, in addition to the criteria for determining a positive result given in the study plans specified in paragraph (e)(1) of this section, the detection of a reproducible and statistically significant response for at least one of the test substance concentrations shall be interpreted as a positive result. In the absence of a repeat assay, a statistically significant response for at least one of the test substance concentrations shall be interpreted as a positive response.

(iii) For the mouse heritable translocation assay specified in paragraph (d)(1)(i)(D) of this section, the following are required.

(A) If the laboratory's historical control data base is inadequate, concurrent positive and negative controls shall be conducted which conform to the requirements specified in §798.5200(d)(4)(i) of this chapter.

(B) Control data shall be presented, whether they are historical or concurrent, in the final report of the study and shall be identified as either the one or the other.

(3) *Oncogenicity*—(i) *Dose levels and dose selection.* The lowest dose shall not be lower than 10 percent of the high dose.

(ii) *Duration.* Each study shall last the majority of the normal lifespan of the strain of animals to be used. This time period shall not be less than 24 months for rats and 18 months for mice, and ordinarily not longer than 30 months for rats and 24 months for mice.

(iii) *Histopathology.* Target organs (including but not limited to lungs and respiratory tract) in all animals shall be subject to a histopathological examination.

(iv) *Individual animal data.* (A) Food and water consumption data shall be reported, when measured.

(B) Ophthalmological data shall be recorded when the examination is performed.

(4) *Developmental toxicity.* (i) Testing in one mammalian species other than the rat is required.

(ii) Dams shall be killed before parturition.

(5) *Test substance*—(i) *Identity and source.* The remaining components, which may be as high as 25 percent of the test mixture, shall be characterized.

(ii) *Stability under test and storage conditions.* The atmosphere being inhaled by the animals shall be characterized with regard to concentration and identification of the components inhaled.

(f) *Effective date.* The effective date of the final Phase II rule for the C_9 aromatic hydrocarbon fraction is March 9, 1987.

[50 FR 20676, May 17, 1985, as amended at 52 FR 2527, Jan. 23, 1987; 54 FR 27357, June 29, 1989; 58 FR 34205, June 23, 1993]

§ 799.2200 Hydroquinone.

(a) *Identification of test substance.* (1) Hydroquinone (CAS No. 123–31–9) shall be tested in accordance with this section.

(2) Hydroquinone 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 hydroquinone, other than as an impurity, from January 13, 1986 to the end of the reimbursement period shall submit letters of intent to test, exemption applications, and shall conduct tests and submit data as specified in this section, subpart A of this part and part 790 of this chapter for two-phase rulemaking.

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

(3) Persons who notify EPA of their intent of conduct tests in compliance with the requirements of this section must submit 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) *Toxicokinetic studies*—(i) *Required testing.* Skin and oral dosing studies, which will provide data regarding both rate and extent of absorption, shall be conducted with hydroquinone.

(ii) *Test standard.* (A) The toxicokinetic testing shall be conducted in accordance with § 795.235 of this chapter except for the provisions in paragraph (c)(1)(iii)(C) of § 795.235.

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

(*1*) During the acclimatization period, rats shall be housed in polycarbonate cages on hardboard chip bedding, or suspended steel cages with no bedding material.

(*2*) [Reserved]

(iii) *Reporting requirements.* (A) The toxicokinetic tests shall be completed and the final results submitted to the Agency within 1 year of the effective date of the Phase II final test rule.

(B) A progress report shall be provided 6 months from the effective date of the final Phase II rule.

(2) *Developmental Toxicity*—(i) *Required testing.* Developmental toxicity studies in both a rodent and nonrodent species shall be conducted with hydroquinone. These tests must be conducted using the oral route of exposure.

(ii) *Test standards.* The developmental toxicity testing shall be conducted in accordance with § 798.4900, as revised July 1, 1987.

(iii) *Reporting requirements.* (A) The Developmental toxicity tests shall be completed and the final results submitted to the Agency within 18 months of the effective date of the final Phase II rule.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months from the effective date of the final Phase II rule.

(3) *Reproductive Effects*—(i) *Required testing.* A two-generation reproductive effects study in a rodent species shall be conducted with hydroquinone. This test must be conducted using the oral route of exposure.

(ii) *Test standards.* The reproductive effects testing shall be conducted in accordance with § 798.4700, as revised July 1, 1987.

(iii) *Reporting requirements.* (A) The two-generation reproductive effects toxicity test shall be completed and