Electronic Supplementary Material (ESI) for Environmental Science: Nano.

Testing Rules Under TSCA 1984-2016

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Identification of Specific Chemical Substance and Mixture Testing Requirements; 1,1,1-Trichloroethane	49 FR 39810	10-Oct-84	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
For Developmental Toxicity: The Agency believes that developmental toxicity testing should be performed via inhalation in the rat and a non-rodent mammalian species and that some sign of maternal toxicity should be demonstrated at the highest dose in each species. The EPA is requiring that a developmental toxicity study or studies on TCEA be conducted by the inhalation route. Although the Agency is currently preparing a guideline for inhalation developmental toxicity, which is expected to be available by Fall, 1984, at the present time there is no TSCA Guideline for this test and EPA suggests using a modified version of the protocol submitted by the Chemical Manufacturers Association (CMA) for inhalation teratogenicity of isophorone in the rat and mouse. Should the TSCA Guideline for inhalation developmental toxicity become available at a time consistent with the time requirements for submission of study plans, then the Guideline should also be consulted for appropriate study design. (p. 39814) **For Chronic effects/Oncogenicity**: The Agency is awaiting the final report from the NTP study. Should the Agency decide that a data insufficiency exists after Agency review of the final NTP report then EPA reserves the right to require an additional oncogenicity study **Mutagenicity** Both Proctor and Gamble and Atlantic Richfield noted that EPA intended to perform certain tests (i.e., mutagenicity) for which test standards had not yet been adopted by EPA. They questioned how the Agency will be able to perform the tests itself if it is unable to provide suitable guidance to others. Subsequent to the proposal, the Agency developed guidelines for conducting mutagenicity testing, including triggers to go from lower to higher tier testing. However, in the case of TCEA a separate proposal would be required if the Agency wanted to have industry conduct the mutagenicity testing. Because it wanted at least preliminary mutagenicity results sooner than would be possible through rulemaking, the Agency decided to proceed with EPA-sponsored testing. After the Agency has evaluated the results of the lower-tiered mutagenicity tests, EPA may propose a test rule to require higher tiered mutagenicity tests if needed. **Environmental Effects**: No testing required because already have sufficient information.	in vivo	beyond filling information gap-> none given	

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Identification of Specific Chemical Substance and Mixture Testing Requirements; Ethyltoluenes, Trimethylbenzenes, and the C9 Aromatic Hydrocarbon Fraction	50 FR 20662	5/17/1985	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
The EPA is requiring that the C9 aromatic hydrocarbon fraction be tested for neurotoxicity, developmental toxicity, mutagenicity, and reproductive effects, and for oncogenicity unless specific mutagenicity test results are negative. In the case of the C9 fraction, composed primarily of high percentages of ET and TMB isomers, the Agency agrees that testing the C9 fraction alone would most likely elucidate any potential problems that may result from exposures to the C9 fraction or solvents containing significant concentrations of the C9 fraction. Testing of the individual isomers does not appear necessary at this time in order to evaluate the risk posed by exposure to the C9 fraction and solvents containing it. EPA is exempting from these testing requirements those manufacturers and processors which produce and process the C9 aromatic hydrocarbon fraction only as an impurity. The test protocols contained in the approved study plans for the C9 fraction for mutagenicity, oncogenicity, developmental toxicity in mice, and reproductive effects testing (Refs. 3 and 4) and for neurotoxicity testing (Ref. 6) and the additional requirements specified in 40 CFR 799.2175 are the test standards for the testing of the C9 fraction required under 40 CFR 799.2175. The Agency believes that the conduct of the required tests in accordance with the approved study plans will ensure that the resulting data are reliable and adequate. The testing must be conducted in accordance with the EPA's TSCA Good Laboratory Practice Standards (40 CFR Part 792). (52 FR 2522 (Jan 23, 1987)) Testing Required: **Mutagenicity.** (p. 20669-20671, also 48 FR 23088) EPA has decided to utilize automatic triggers between the first and second tier tests, and a “presumptive automatic trigger and opt-out” approach between second tier tests and the final or “end-point” tests in this final test rule for C9 aromatic hydrocarbons. Under this approach, EPA is promulgating a tiered testing scheme for mutagenicity for the C9 fraction with automatic triggers to additional mutagenicity testing. Before the last tier, EPA will hold a public program review if the results of the previous tier test are positive. Chromosoal aberration: First Tier: *Cytogenetic assays: Tiered testing sequence with in vivo assay only required upon a negative finding in the in vitro test.	in vivo, tiered (in vitro +in vivo)	beyond filling information gap-> none given	Sex-linked recessive lethal (SLRL) assay in Drosophila: CMA is correct in stating that there are metabolic differences between insects and humans. However, the Agency considers these differences to be no greater than those between bacteria and humans such as in the Ames assays, and further believes that the in vivo metabolism afforded by Drosophila with intact enzyme systems and repair mechanisms is superior to the artifically manipulated in vitro metabolic activation systems used with bacterial and in vitro cell culture systems (p. 20699-70) Dosimetry is a generic problem in toxicology and is not unique to studies with Drosophila. Good toxicologic practices help to minimize this problem which is not a valid reason for eliminating the SLRL assay from the proposed testing scheme. Also, it should be remembered that results from this assay will not be used for quantitative risk assessment, but rather as a qualitative indication of potential mammalian mutagenicity which will be confirmed by subsequent testing. (p. 20670) e. Cytogenetic assays: An in vitro cytogenetics assays precedes the in vivo cytogenetics assay because it is a easier to perform than the in vivo cytogenetics assay and is conservative of time, resources, money and animals. Further, the Agency is of the opinion that in vitro cytogenetics assays are sufficiently predictive of both carcinogenicity and potential germ-cell mutagenicity that further testing can be triggered as a result of positive results in this assay. However, the Agency also believes that the in vitro test is subject to sufficient limitations, particularly in the use of in vitro metabolic activation systems,

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Identification of Specific Chemical Substance and Mixture Testing Requirements; Diethylenetriamine	50 FR 21398	23-May-85	A	health	The EPA finds that the manufacture, processing, use, and disposal of DETA may present an unreasonable risk of injury to human health due to potential mutagenic, oncogenic, and subchronic effects. EPA did not propose testing for reproductive and teratogenic effects, because, in the Agency's judgment, the available data (although limited) did not suggest a potential for these effects. (p. 21399)	in vitro, in vivo, SAR, chemical fate (non-cellular), exposure

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
The test protocols contained in the revised EPA-approved modified study plans for DETA (Ref. 5) shall be the test standards for the testing of DETA required under 40 CFR 799.1575. The Agency believes that the conduct of the required tests in accordance with the revised EPA-approved modified study plans for DETA will insure that the resulting data are reliable and adequate. [Diethylenetriamine; Final Test Standards and Reporting Requirements, 52 FR 3230, 3236 (Feb. 3, 1987)]. consisting of (1) oral subchronic (90-day) toxicity in at least one mammalian species, (2) dermal absorption in the same mammalian species used for the subchronic testing, (3) chemical fate under aerobic conditions, and (4) mutagenicity (including tests for both gene mutations and chromosomal aberrations). (p. 21398, 21408) In vivo Gene Mutations-> Sex-linked recessive lethal test in Drosophila: if negative no further testing, if positive then mouse visible specific locus assay; chromosomal aberrations-> (1) In vitro cytogenetics test: if negative then no further testing, if positive then dominant lethal test. (2) In vivo cytogenetics test: if negative no further testing, if positive then dominant lethal test. Dominant lethal test, if negative then on further testing, if positive then Heritable translocation assay. 90-Day subchronic toxicity test; Dermal absorption test; Chemical fate test. (p. 21408, Diethylenetriamine; Final Test Standards and Reporting Requirements, 52 FR 3230, 3236 (Feb. 3, 1987)).	in vivo, tiered (in vitro, in vivo), chemical fate	testing necessary to develop insufficient data	In the proposed test rule for DETA, the Agency also requested comments on EPA's selection of the oral route of exposure as the route of choice for the required 90-day subchronic toxicity testing of DETA. Although the Agency believes that exposures to DETA will occur primarily by the dermal route, the difficulties associated with determining the actual doses of the test substance received by the animals in studies utilizing this route of administration, together with the fact that preliminary pharmacokinetics data submitted to EPA by Union Carbide indicate that DETA is absorbed following oral administration, led the Agency to conclude that the oral route of administration should be required for the subchronic testing of DETA. Only Dow and Union Carbide commented on this issue. These manufacturers agreed with the Agency that oral studies of DETA would allow the adequate evaluation of the systemic toxicity of this substance without the difficulties of determining the effective doses received by treated animals which would arise in dermal studies. In addition, these manufacturers pointed out that the known skin irritancy and sensitization potentials of DETA would likely lead to stressful conditions in animals receiving DETA by the dermal route, making the evaluation of the systemic toxicity observed in such studies difficult. These difficulties would not arise in oral feeding studies. Therefore, the Agency is requiring oral 90-day subchronic toxicity testing in the final Phase I test rule for DETA. (p. 21401). The general sequences of tiered tests usually employed by EPA in assessing the mutagenic (both gene mutation and cytogenetic) potential of chemical substances, portions of which are required in this final Phase I test rule for DETA [see Unit

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Toxic Substances; Biphenyl Test Rule	50 FR 37182	12-Sep-85	A	environment	EPA finds that environmental release of biphenyl from the chemical's use and disposal may present an unreasonable risk of adverse effects to aquatic organisms because of the existing data which suggest that biphenyl may have the potential to produce chronic effects in aquatic vertebrates and invertebrates and because of detected concentrations of biphenyl in the aquatic environment. In addition, EPA believes that such releases of biphenyl may present an unreasonable risk of adverse effects to sediment organisms. This belief is based on detected levels of biphenyl in sediments and on the potential of biphenyl to partition from water into sediments, to persist and possibly accumulate in aerobic and anaerobic sediments, and to bioconcentrate and produce	in vivo; chemical fate

The Actual Test Required in the Final Rule			
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The tests for environmental effects and chemical fate, consisting of chronic testing on Daphnia magna, early life stage testing on rainbow trout, oyster toxicity, oyster bioconcentration, and aerobic and anaerobic biodegradation are required of manufacturers and processors of biphenyl under section 4(a) of the Toxic Substances Control Act (TSCA). Biphenyl; Test Standards and Reporting Requirements, 52 FR 20710, 20710 (June 3, 1987) EPA is requiring that testing of biphenyl be performed for the environmental effects and chemical fate tests listed below: 1. Chronic fish toxicity 2. Chronic daphid toxicity 3. Acute oyster toxicity 4. Oyster bioconcentration and chronic oyster toxicity 5. Aerobic and anaerobic biodegradation (p. 37185) the study plans together with the final EPA revisions, are referred to as the “revised EPA-approved modified study plans for biphenyl” and shall constitute the test standards and reporting requirements for biphenyl as required under 40 CFR 799.925 (Ref. 2). The Agency believes that the conduct of the required tests in accordance with the revised EPA-approved modified study plans for biphenyl will ensure that the resulting data are reliable and adequate. Biphenyl; Test Standards and Reporting Requirements, 52 FR 20710, 20711 (June 3, 1987) Chronic Daphnid Toxicity; Rainbow Trout Early Life Stage [FN1] (order of these two tests can be reversed) Oyster Shell Deposition Oyster Bioconcentration; Partitioning Water/Sediment Aerobic Degradation; Anaerobic Degradation. Biphenyl; Test Standards and Reporting Requirements, 52 FR 20710, 20711 (June 3, 1987)	in vivo; chemical fate		

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Propylene Oxide; Testing Requirements	50 FR 48762	27-Nov-85	A and B	health	EPA finds that the manufacture, processing, and use of propylene oxide may present an unreasonable risk of injury to human health due to developmental toxicity because (1) available animal studies suggest that propylene oxide has a developmental toxicity potential, and (2) in excess of 40,000 individuals are potentially exposed to propylene oxide as a result of its manufacture, processing, and use. (p. 48766)	in vivo

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
There are essentially no differences in the EPA-approved study plans and the Health Effects Test Guideline set forth in 40 CFR 798.4350.- inhalation developmental studies in rats. Propylene Oxide; Final Test Standards and Reporting Requirements, 52 FR 35706, 35707 (Sept. 23, 1987)	in vivo		all in vivo (not really relevant to pred tox)

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Hydroquinone; Testing Requirements	50 FR 53145	30-Dec-85	A and B	health	EPA has found that the processing and use of hydroquinone may present an unreasonable risk of injury to human health from nervous system, developmentally toxic, reproductive, and carcinogenic effects. In proposed, the Agency based its chemical fate and environmental effects testing on the authority ofsection 4(a)(1)(A) of TSCA. (1) EPA found that there was evidence of potential environmental risks to aquatic organisms resulting from the processing and use activities associated with hydroquinone. (2) While there were existing data to support this belief with respect to these effects, the data were inadequate to reasonably predict or determine the effects of these exposures to hydroquinone. (3) Testing	in vitro; in vivo

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
The TSCA test guidelines for toxicokinetic studies in 40 CFR 795.235, the neurotoxicity testing in 40 CFR 798.6050 and 798.6400 and the industry-submitted protocols for developmental toxicity and reproductive effects testing shall be the test standards for the testing of hydroquinone required under 40 CFR 799.2200.AQ24 Toxicokinetic Test § 795.235 (rat in vivo study) Absorption toxicokinetics refers to the bioavailability, i.e., the rate and extent of absorption of the test substance, and metabolism and excretion rates of the test substance after absorption. The neurotoxicity testing of hydroquinone, consisting of a functional observational battery and neuropathology shall be conducted in accordance with §§ 798.6050 and 798.6400, respectively, of this chapter. The functional-observational battery and the neuropathology assessment may be conducted sequentially on the same group of rats. Neuropathological assessment should begin with the highest dose level and work downward until a no-observable-adverse-effects dose is reached. 52 FR 19865, 19867-19870 (May 28, 1987). The reproductive effects testing shall be conducted according to the two generation reproduction unit of the study plan (in vivo) 40 CFR § 799.2200. 52 FR 19865, 19870 (May 28, 1987). The developmental toxicity testing shall be conducted according to the teratology study plans submitted to the EPA on June 15, 1983 (Eastman Kodak Company, 1983) and reviewed by the Agency as part of the study plan (rat in vivo). 52 FR 19865, 19870	in vivo		Toxicokinetics: **With regard to the dermal studies, the CMA Hydroquinone Panel has commented that EPA should require an in vitro study of the kinetics of hydroquinone penetration through rat skin in place of the proposed in vivo rat skin absorption study.** They argue that data on dermal penetration in the rat can be obtained in a more reliable, rapid, and cost-effective manner by an *19867 in vitro study and such a study would allow longer exposure periods and direct collection of quantitative data (Ref. 2).[52 FR 19865, 19866-19867 (May 28, 1987)]. Kodak supports their argument by citing a Kodak study of the percutaneous absorption of [U-14 C] hydroquinone in dogs (Refs. 2 and 6). Kodak argues that because the dog study showed very slow skin penetration (about 1.1 ug/cm2 /hr), similar tests in rats would not provide enough penetration to characterize metabolites and would provide only data on the skin penetration rate of hydroquinone through rat skin. The Panel adds that if their suggested in vitro study establishes a high rate (higher than the low rate expected by the Panel) they then can conduct an in vivo study. 52 FR 19865, 19867 (May 28, 1987). The Agency rejects the modification to the test standard as proposed by the Panel. This decision is based on the following reasons: (1) The Agency believes that the dermal penetration study, “Percutaneous Absorption of Hydroquinone in Beagle Dogs,” upon which the Panel has based its prediction of limited skin penetration in rats, has serious deficiencies. **Deficiencies, such as the failure of the study to account for large amounts of the hydroquinone administered to the test animals, make it impossible for the Agency to reasonably predict the behavior of hydroquinone applied to other test animals such as rats or to the skin of humans** exposed to hydroquinone. (2) While the

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Certain Chlorinated Benzenes; Final Test Rule	51 FR 11728	7-Apr-86	A and B; The EPA is basing the testing of monochlorobenzene, 1,2- and 1.4-dichlorobenzene and 1.2,4-trichlorobenzene on the authority of section 4(a)(1)(B) of TSCA. EPA has concluded that these chemicals are produced in substantial quantities, and may enter the	environment (for 1,2,3-trichlorobenzene)	Existing toxicity data indicate that among the mono-, di-, and trichlorobenzene, 1,2,3-trichlorobenzene is the chlorinated benzene most toxic to aquatic organisms (Ref. 3). Available information indicates that the manufacture and uses of 1,2,3-trichlorobenzene are the principal sources of its environmental release. Ware and West reported levels of 0.021 to 0.046 mg/L of 1,2,3-trichlorobenzene in municipal discharges (Ref. 5). Considering these measured levels, of 0.021 to 0.046 mg/L, an estimated 10 to 100 fold dilution by a receiving stream (Ref. 7), and 1,2,3-trichlorobenzene's reported bioconcentration factor in fish of 1,200-2,600X (Ref. 4), the potential concentration in fish is in the range of 0.25 mg/kg to 12.0 mg/kg (measured levels in municipal discharges X estimated dilution factors X BCF's for	in vivo

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1,2- and 1,4-Dichlorobenzene: (chemical fate) Soil adsorption coefficient test 1,2,4-Trichlorobenzene: : (env effects) Acute and chronic toxicity to mysid shrimp (Mysidopis bahia).1,2,3-Trichlorobenzene: (Env.l effects) 96-hour LC50 for fathead minnow (Pimephales promelas); 96-hour EC50 for one species of Gammarus;; acute toxicity to mysid shrimp (Mysidopis bahia) and silversides (Menidia menidia); chronic toxicity to mysid shrimp(Mysidopis bahia) if LC50 is <1 ppm. (p. 11730) No testing required for 1,3-Dichlorobenzene, 1,3,5-Trichlorobenzene and Pentachlorobenzene. Tetrachlorobenzenes to be addressed in a forthcoming notice. (p. 11730) No industry testing required for monochorobenzene. (p. 11730)	chemical/non-cellular, in vivo		see necessary testing cells

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Cresols; Testing Requirements	51 FR 15771	18-Apr-86	A and B	health	In addition, EPA has found that (a) there is evidence of potential unreasonable human health risks from mutagenic effects resulting from the manufacture, processing, and use activities associated with cresols, and that while there are existing data which support this belief with respect to these effects, (b) these existing data are inadequate to reasonably predict or determine the effects of these exposures to cresols, and (c) testing is necessary for these effects. Therefore, EPA believes that requiring testing of cresols for mutagenicity can also be based upon section 4(a)(1)(A) of TSCA. T	N/A

The Actual Test Required in the Final Rule			
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EPA is requiring that each of the three cresol isomers, ortho-cresol, meta-cresol, and para-cresol, shall be tested in the following health effects studies: (1) Mutagenic effects studies (including tests for chromosomal aberrations, gene mutations, and cellular transformations on specified cresol isomers), (2) developmental toxicity, and (3) two-generation reproductive effects studies. (15778-15779). Mutagenicity. Chromosomal effects. a. In vitro mammalian cytogenetics test (40 CFR 798.5375). b. In vivo mammalian bone marrow cytogenetics tests: chromosomal analysis (40 CFR 798.5385). c. Rodent dominant lethal assay (40 CFR 798.5450). 2. Mutagenicity. Unscheduled DNA synthesis in mammalian cells in culture assay (40 CFR 798.5550). 3. Mutagenicity. Gene mutations. a. Detection of gene mutations in somatic cells in culture assay (40 CFR 798.5300). b. Sex-linked recessive lethal test in Drosophila melanogaster (40 CFR 798.5275). 4. Mutagenicity. Cellular transformations. Morphologic transformation of mammalian cells in culture assay (40 CFR 795.285). 5. Developmental toxicity. Developmental toxicity study (40 CFR 798.4900). 6. Reproductive effects. Reproduction and fertility effects study (40 CFR 798.4700). [52 FR 19082, 19083 (May 20, 1987)]	in vivo, in vitro (tiered)	to fill insufficient information The Resource Conservation and Recovery Act (RCRA), as amended by the Hazardous and Solid Waste Amendments of 1984 (HSWA), requires that appropriate treatment standards must be met prior to land disposal of hazardous wastes containing cited chemical substance (Ref. 5).Cresols are constituents of wastes for which treatment standards must be set by November 8, 1986. Following a review by the Agency, it was determined that insufficient reliable information was available for cresols. As a result either EPA must obtain usable data in order to set an appropriate toxicity reference dose (RfD), or certain wasts containing cresols would be banned as of November 8, 1986 from all land disposal. (p***15773***) The subchronic toxicity studies included in EPA's proposed test rule for cresols would provide the initial data needed to establish RfDs for the cresols. However, the Agency concluded that this rulemaking to require this testing (which has been proposed under the former two-phase test rule process) could not be completed in time to obtain data within the schedule imposed by the HSWA.	Repeating Mutagenicity Assays: The Agency agrees that a generic requirement to repeat all in vivo mutagenicity assays is not routinely necessary; however, the Agency believes that under certain conditions repeats of tests are appropriate and necessary. The Agency interprets any single positive finding at one dose level, but no dose response, as a positive mutagenic response in the absence of a repeat assay. The Agency is therefore not including a generic requirement for repeats of the following assays: in vivo mammalian cytogenetics, Drosophila sex-linked recessive lethal, and rodent dominant lethal. Because of the nature of in vitro tests in comparison to in vivo systems, the Agency believes that repeats of equivocal studies are appropriate and necessary for the evaluation of the in vitro mammalian cytogenetics, the gene mutation in somatic cells in culture, and the morphologic transformation of mammalian cells in culture assays. The Agency is thus requiring repeats of these in vitro assays over a narrow range of concentrations in the event a single, statistically significant increase is produced at one dose point without a dose response. (52 FR 19082, 19083 (May 20, 1987]. Detection of Gene Mutations in Somatic Cells in Culture: The Panel recommended that cresols be tested in Chinese hamster ovary (CHO) cells rather than the L5178Y mouse lymphoma cells proposed by the Agency for this assay. The Agency specifically proposed the L5178Y cells because of the previous assays with a cresols mixture and with o-cresol using that cell line. EPA is interested in obtaining the clearest overall picture of *19084 the mutagenic effects of each of the cresol isomers. Therefore, for the two isomers, m-cresol and p-cresol, for which testing in this assay is required, the Agency disagrees with the Panel on the

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Chlorinated Benzenes; Final Test Rule	51 FR 24657	8-Jul-86	A	Health	1,2,4-TCB may present an unreasonable risk of cancer to humans. Sufficient human exposure and sufficient information to indicate that may present an oncogenic hazard to humans. EPA concludes that on the basis of the high occupational exposures to MCB, 1,2- and 1,4-DCBs, the suggestive evidence of MCB's potential to cause reproductive effects, and the close structural similarity between MCB and DCBs, both MCB and 1,2- and 1,4-DCBs may present an unreasonable risk of reproductive effects to humans. (p.24661) EPA finds that the use of 1,2,4,5-TCB may present an unreasonable risk of reproductive and teratogenic (developmental) effects to humans (p.24662)	SAR, in vivo; in vitro

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1,2,4-trichlorobenzene: oncogenicity testing; monochlorobenzene (MCB): reproductive effects testing; ortho- and para-dichlorobenzenes (1,2-and 1,4-DCBs): reproductive effects testing 1,2,4,5-tetrachlorobenzene (1,2,4,5-TCB) reproductive effects and developmental toxicity testing, and terminating its rulemaking process for subchronic/chronic and oncogenicity testing of 1,2,4,5-TCB. Therefore, the remaining health effects tests for the chlorinated benzenes shall be performed in accordance with the methodologies cited in the TSCA Health Effects Test Guidelines in 40 CFR Part 798, published in the Federal Register on September 27, 1985 (50 FR 39252). At this time the Agency is requiring that oncogenicity testing for 1,2,4-TCB be conducted by testing 1,2,4-TCB in two mammalian species (the mouse and the Fischer-344 rat). The Agency is requiring that the oncogenicity testing be performed in accordance with the methodology cited in the TSCA Health Effects Test Guideline at 40 CFR Part 798.3300 and the TSCA Good Laboratory Practice Standards in 40 CFR Part 792. EPA is requiring that 1,2,4-TCB be administered in the feed. EPA also is requiring that reproductive effects testing for MCB and 1,2- and 1,4-DCBs be conducted by testing MCB, 1,2- and 1,4-DCBs in the 2-generation reproductive and fertility study in the Sprague-Dawley rat. The Agency is requiring that the reproductive and fertility effects testing be performed in accordance with the methodology cited in the TSCA Health Effects Test Guideline at 40 CFR Part 798.4700. EPA is requiring that the route of administration for MCB, and 1,2- and 1,4-DCBs be inhalation. EPA is also requiring that reproductive effects and developmental effects testing for 1,2,4,5-TCB be conducted. The Agency is requiring that the reproductive and fertility effects testing be performed in accordance with the methodology cited in the TSCA Health Effects Test Guidelines at 40 CFR Part 798.4700. The Agency is requiring that the developmental effects testing be performed in accordance with the methodology cited in the TSCA Health Effects Test Guidelines at 40 CFR Part 798.4900. EPA is requiring that the reproductive and fertility effects testing be conducted using the Sprague-Dawley rat and that the developmental effects testing be done in the Fischer 344 rat and the New Zealand White rabbit (both species were previously used in the developmental effects testing of MCB, 1,2- and 1,4-DCB). 1,2,4,5-TCB shall be administered in the feed in the reproductive and fertility effects study and shall be administered by oral gavage in the developmental effects study. Developmental effects testing of the tetrachlorobenzenes by Kacew, et al. (Ref. 14) demonstrated the effective use of this route of administration.	in vivo		Commenters suggested that a monitoring program for male fertility and chromosomal breakage in humans occupationally exposed to the chlorinated benzenes be run in parallel with tests for the same endpoints in laboratory animals.EPA believes the reproductive effects studies being required will generate adequate information on the potential reproductive effects these chemicals may cause. The need for further studies as suggested in the comment will be considered upon evaluation of the required testing results. (p.24660). Decision To Terminate Rulemaking Process for Subchronic and Oncogenicity Testing Requirements for 1,2,4,5-Tetrachlorobenzene: Meanwhile, the National Toxicology Program (NTP) initiated activity to test the chemical for oncogenicity. Because NTP has initiated its pre-chronic testing program for 1,2,4,5-TCB, EPA has decided to terminate its rulemaking process for subchronic/chronic effects and oncogenic effects testing and is notifying the public of this decision in this notice at this time. EPA remains concerned about the reproductive and teratogenic (developmental) hazard potential, 1,2,4,5-TCB may pose to human health and is requiring this testing as described below. (p. 24660)

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Toxic Substances; 1,2-Dichloropropane; Testing Requirements	51 FR 32079	9-Sep-86	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
EPA is requiring that 1,2-dichloropropane be tested for developmental, reproductive, mutagenic (chromosomal aberrations), and neurotoxic effects, as well as acute and chronic toxicity to aquatic invertebrates and acute toxicity to algae. Also on September 9, 1986 (51 FR 32107), EPA proposed applicable TSCA guidelines as test standards. Since TSCA test guidelines were available for all the testing requirements included in the final Phase I rule, they were proposed as the test standards. (52 FR 37138). The TSCA test guidelines (40 CFR Parts 797 and 798) specified in Unit II.B. for neurotoxicity, mutagenicity (chromosomal aberrations), reproductive effects, developmental toxicity, acute toxicity to marine and freshwater algae and mysid shrimp, chronic toxicity to mysid shrimp and Daphnia magna, and oral and inhalation pharmacokinetics, as modified in this rule, shall be the test standards for the testing of DCP required under 40 CFR 799.1550. The Agency believes that the conduct of the required studies in accordance with these test standards is necessary to ensure that the results are reliable and adequate. (52 FR 37138). PA is requiring that an oral-inhalation pharmacokinetic study be conducted with DCP. (52 FR 37138)	in vivo		Dow also commented on the proposed tiered testing scheme for determination of mutagenic effects, stating their belief that "EPA has not articulated which human risks are related to this testing and furthermore has not specified or described the methodology by which the data could be used to assess those risks." Dow also believes "the scheme incorporates a rigid decision tree that precludes any scientific judgement and evaluation to determine whether further testing is necessary." The Agency disagrees with these comments for the following reasons. (p.32083) As described in detail in the final Phase I test rule for the C9 aromatic hydrocarbon fraction (50 FR 20662, 20668-71), the Agency believes that there is a consensus in the scientific community on both the need for, and the manner of, identifying mammalian mutagens, and that its proposed scheme for identifying these agents is in keeping with those recommended by experts in the field of mammalian mutagenesis. Further, while EPA recognizes that there is, as yet, no generally accepted single methodology for estimating human risk from mutagenic agents, it is the Agency's view that appropriate methodologies do exist and are usable. (p.32083) In the case of DCP, only the second tier of mutagenicity testing (dominant lethal assay) is being required at this time, without an automatic trigger to the end point test (heritable translocation assay). This decision is based on available information for a structurally similar chemical, 1,2-dibromo-3-chloropropane (DBCP), indicating that mice are not sensitive to DBCP in the dominant lethal assay (Ref. 5). The rat is therefore the

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Bisphenol A; Final Test Rule	51 FR 33047	18-Sep-86	A	health	EPA finds that the manufacture, processing, use, and disposal of BPA may present an unreasonable risk of * lung injury after chronic inhalation exposure. (33048-33049)	in vivo; exposure data (production. Manufacturing, use)

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conduct a 90-day inhalation subchronic toxicity study with particular emphasis on pulmonary effects. EPA is also terminating the test rule process for acute and chronic aquatic toxicity testing of BPA. The Agency is requiring that this testing be performed in accordance with the methodology cited in the TSCA Health Effects Test Guideline at 40 CFR 798.2450 and the TSCA Good Laboratory Practice Standards in 40 CFR Part 792. (p.33049-33050)	in vivo		SPI also commented that the requirement under § 798.2450(d)(8)(iv) for continuous monitoring of temperature and humidity and recording of these values at least every 30 minutes, is excessive. SPI believes records should only be required for the start and end of the exposure period and include one measurement approximately halfway through the exposure period. EPA believes this requirement is not excessive. Equipment for continuous monitoring and chart recording of both parameters is readily available. EPA believes toxicity data may besignificantly influenced by abrupt changes in either condition and only through continuous monitoring, as prescribed in this standard, can their influence be determined and interpreted. EPA also believes that changes in temperature and humidity may affect the BPA dust levels in the exposure chamber and that every effort should be taken to minimize such changes.(33047-33048) SPI also suggested that although the range of hematology and clinical chemistry determinations outlined in the guidelines may be appropriate under certain circumstances, a reasonable evaluation can be achieved with a clinical battery such as that used in the 2-week BPA dust inhalation study (Ref. 2). EPA agrees with this comment and is recommending in this final rule that the hematological and clinical chemistry determinations be similar to those used in the 2-week aerosol toxicity study sponsored by SPI. EPA does not believe there is a necessity to conduct urinalyses because such data are available from toxicity testing done by NTP. (p.33048)

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
2-Ethylhexanoic Acid; Final Test Rule	51 FR 40318	6-Nov-86	A	Health	EPA finds that EHA may present an unreasonable risk of oncogenicity, developmental toxicity, and subchronic toxicity. These findings are based on the strongly suggestive evidence of toxicity [] and the potential for dermal exposure of workers engaged in manufacturing, transfer, storage, and processing of EHA. Because EPA believes EHA has a high hazard potential, EPA believes the exposure potential need not be very high to justify the 4(a)(1)(A) finding. Furthermore, although current exposure may appear to be low, future exposure from the same or different uses may change. (p.40322)	in vivo; SAR; exposure data

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What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
On the basis of these findings, the Agency is requiring developmental toxicity, 90-day subchronic, and pharmacokinetic testing as a basis for determining the health risks of EHA. Pharmokinetics: in vivo (rats); Subchronic toxicity: in vivo (90 day oral); Developmental toxicity: in vivo (OECD oral developmental toxicity test). (p. 40322-40323)	in vivo		The Agency believes that the pharmacokinetic test standard developed by the Office of Toxic Substances (OTS) for this final rule is appropriate for determining and comparing the absorption, distribution, metabolism, and excretion of EHA for both the oral and dermal routes of administration. Data from these studies are necessary to aid in the evaluation of test results from other toxicology studies and to determine the comparability of oral and dermal dosing. (p. 40322). The required studies evaluate blood levels, urinary and fecal excretion, and biotransformation of EHA when administered dermally and orally. In addition, the extent to which washing removes dermally-applied EHA is also evaluated. (p. 40322-40323)…The Agency believes that this modified pharmacokinetics test methodology represents the state-of-the-art and forms the basis for a valid and scientifically acceptable test standard. This test standard was proposed under 40 CFR 798.460 published in the Federal Register of May 17, 1985 (50 FR 20689), and is published in the final rule below under 40 CFR 795.223. (p. 40322) The Agency believes that the subchronic exposure oral toxicity test standard developed by OTS for this final rule is appropriate in determining the subchronic toxicity of EHA. This test permits the determination of the no-observed-effect level, the characterization of toxic effects associated with continuous or repeated exposure for a period of 90 days, and provides information on target organs. This test standard was proposed under 40 CFR 798.75, published in the Federal Register of May 17, 1985 (50 FR 20687), and is published in the final rule below under § 795.260. (p. 40322) The Agency believes that multispecies testing is a more sensitive

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Anthraquinone; Final Reporting and Recordkeeping Requirements and Test Rule	52 FR 21018	4-Jun-87	B	N/A	N/A	N/A

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requiring manufacturers and processors of 9,10-anthraquinone (CAS No. 84-65-1), hereinafter anthraquinone, to perform testing for water solubility, bioconcentration, sediment toxicity to benthic organisms, and acute toxicity to aquatic organisms. Testing for biodegradation and chronic toxicity to aquatic organisms will be required if the acute toxicity, sediment toxicity, or bioconcentration test results suggest a hazard potential and the annual production/importation level reaches or exceeds 3 million pounds (lb). chemical fate and environmental effects testing Based on section 4(a)(1)(B) of TSCA, EPA proposed tiered testing, with the first tier including water solubility; acute toxicity to 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), acute toxicity to the invertebrates Daphnia magna or D. pulex and oyster; marine sediment toxicity to the amphipod, Rhepoxynius abronius (EPA is allowing industry a choice of either of the two above-referenced sediment toxicity tests because the Agency wishes to allow the manufacturers of anthraquinone the opportunity to conduct this testing using the species and methods required in other section 4 test rules concurrently under development or published. It also allows industry to select a species that is more representative of the streams and waters receiving effluents from pulping plants and a species that may be more available for testing.); and oyster bioconcentration. In order to evaluate the potential hazard of the median lethal concentrations (LC50's) generated by the Tier I tests, EPA is requiring that the LC50's be compared to the predicted environmental concentrations (PEC's) for anthraquinone in water and sediment, i.e., 5 ppb and 0.1 ppm respectively, which have been determined from reported discharge levels (see the proposed rule). Also proposed under section 4(a) of TSCA was a second tier of testing which would be triggered if the results of Tier I tests indicated a hazard potential (one or more of the median lethal concentrations (LC50's) generated by the Tier I tests are less than 100 times the predicted environmental concentrations.)and the reported production/importation volume reached or exceeded 3 million lb per year. The second tier of tests included chronic toxicity in the most sensitive fish, chronic toxicity in Daphnia, biodegradability in sludge systems, and biodegradation rate.	tiered testing: in vivo and non-cellular	EPA believes that the data resulting from this testing will be relevant to a determination as to whether the manufacture, processing, or use of anthraquinone does or does not present an unreasonable risk of injury to the environment.	In view of the prospect for a growing market for anthraquinone owing to its use in the pulping industry and the projected economic impact (see section IV. of this preamble, Economic Analysis of Test Rule) of the full set of aquatic tests EPA believes would be necessary to adequately assess the environmental risks of anthraquinone, the Agency is requiring that testing be conducted in two tiers. By tiering testing, EPA expects to obtain limited data now from the first tier to better assess the potential for expanded releases of anthraquinone to pose significant risks. Should the production or importation of anthraquinone expand substantially and the results of the first tier of testing meet the specified triggers, the second tier of testing will provide the more complete data needed to evaluate the possible risks associated with substantially larger aquatic releases of the chemical. (p.21021) EPA chose to trigger second tier testing with an increase in production/import level for two reasons. First, as the use of anthraquinone increases, the Agency's concerns for environmental release and the potential for unreasonable risk to the environment increase. Under such conditions, the need for further testing to fully characterize the hazard potential and chemical fate of anthraquinone becomes essential. If the data developed in the first tier of testing do not meet at least one of the hazard triggers described above, there would be no potential to trigger further testing and thus no need for continued section 8(a) reporting; EPA then would remove the section 8(a) reporting requirement and publish a notice of such action in the Federal Register. (p.21022) However, if these data suggest concern and if anthraquinone use continued to increase to 3 million lb per year, the second

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Polyhalogenated Dibenzo-p-Dioxins/Dibenzofurans; Testing and Reporting Requirements	52 FR 21412	5-Jun-87	A	health, environment	First, EPA finds that these chemicals may present an unreasonable risk of injury to health or the environment because they may be contaminated with HDDs/HDFs, which may be highly toxic even at trace levels.	in vivo, in vitro, SAR, exposure, chemical characterization

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What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
require analytical testing for certain chemicals for HDD/HDF contamination (p. 21412) EPA believes that production, processing, distribution, use, and disposal of the listed chemicals may present an unreasonable risk of injury to human health and the environment because of their potential for contamination by chlorinated and brominated dibenzo-p-dioxins and dibenzofurans. (p. 21413) EPA believes these contaminants may present a health risk at very low levels, down to 0.1 part per billion (ppb) for 2,3,7,8-TCDD, the most toxic congener, and for 2,3,7,8-tetrabromodibenzo-p-dioxin (TBDD), believed to be equally as toxic. Therefore, this target level of quantitation has been set for 2,3,7,8-TCDD and 2,3,7,8-TBDD, with higher levels for the remaining congeners based on toxicity equivalent to that of 2,3,7,8-TCDD. These levels are targets, and EPA expects testing laboratories to make a good faith effort to reach these targets. EPA's Director of the Office of Toxic Substances (OTS) will determine whether good faith efforts are made, advised by a panel of experts in analytical chemistry convened by EPA. In cases where good faith efforts are made, EPA will accept results higher than the target LOQs. (p. 21413) EPA also believes*21414 that the differences in cost to test for HDDs/HDF at 0.1 ppb or 10 ppb or even 100 ppb are very small because the major part of the cost of testing is incurred by separation of matrix and clean-up of sample, and this cost will be approximately the same for these levels. (p. 21414, p. 21419) General analytical method consideration. The analytical procedures specified in this final rule for the quantitative measurement of HDDs/HDFs in commercial products include: (1) The quantitative extraction or partitioning of the analytes from the commercial product; (2) separation of the HDDs/HDFs from interferences present in the extract; and (3) separation, identification and quantitatio.n of HDD/HDF congeners, using high-resolution gas chromatography (HRGC) and high-resolution mass spectrometry (HRMS) or low-resolution mass spectrometry (LRMS), if it can be shown to be as effective as HRMS for a particular matrix. (p.21427) Detection method. In the proposed rule, EPA chose HRGC/HRMS as the analytical method of detection (see 50 FR 51801, unit IV.B.2.b.). (p. 21427)	analytic method (non-bio)	EPA finds that this analytical testing is relevant to determining whether activities involving the 32 substances do or do not present an unreasonable risk 9p. 21416)	EPA lacks legal authority under section 4 of TSCA to require analytical testing for impurities in chemicals. Section 4 does not explicitly refer to testing for contamination, but rather limits EPA to requiring testing on “health and environmental effects.” Section 4(b)(2)(A) describes the “effects” and “characteristics” for which testing is permitted and does not mention tests for contamination. EPA disagrees with this narrow reading of TSCA. EPA interprets section 4 to allow the testing of chemicals to obtain data relevant to a determination of unreasonable risk. These data include the types of information which would be generated by testing under the proposed rule. EPA rejects the position taken by these commenters, which would limit section 4 to toxicity testing, rather than “effects” testing. (p21416). The potential for a chemical to be contaminated with dangerous impurities, such as HDDs, falls within the “effects” or “characteristics” of that chemical which would be relevant to whether the chemical may present an unreasonable risk. Requiring analytical testing of the type discussed in the proposed rule— the levels at which a particular toxic contaminant, such as HDDs, is present in a chemical substance—is an important factor in any determination of unreasonable risk because it provides EPA with information from which human and environmental exposure to the contaminant can be assessed. Moreover, information on the amount of the contaminant in a chemical substance allows the Agency to better assess the hazard of that particular chemical substance. Finally, requiring chemical manufacturers to conduct such analytical chemistry testing is consistent with the well-defined Congressional intent in enacting TSCA that “adequate

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Fluoroalkenes; Final Test Rule	52 FR 21516	8-Jun-87	A	health	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. (p. 21524) 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. (p. 21524) (inhalation)	in vitro, in vivo, SAR, exposure

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What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
Oncogenicity, mutagenicity, subchronic toxicity 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). (p. 21525) inhalation oncogenicity tests [For HFP; for VDF mice required and rat only if current testing not performed in accordance and EPA issues final rule; for HFP after public program review have notice either affirming or proposing to rescind the oncogenicity testing requirements for HFP; for TFE when triggered by positive test results in mutageniticty testing: 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.] (p. 21525) 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. (p. 21525) 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 requirinq 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	in vivo, , tiered testing (in vivo & in vitro)	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.	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. (p.21525) 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 C9 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. (p. 21520) As outlined in the C9 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

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Tetrabromobisphenol A; Final Test Rule	52 FR 25219	6-Jul-87	A	environment	EPA finds that the manufacture, processing, use, and disposal of TBBPA may present an unreasonable risk of injury to the environment because TBBPA has the potential to persist in the environment, bioconcentrate in aquatic organisms, and cause adverse effects in aquatic and benthic organisms. These findings are based on the evidence of exposure, available physical/chemical data, and available toxicity data (p. 25222)	in vivo, chemical char/non-cellular, exposure data

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On the basis of these findings, the Agency is requiring chemical fate and environmental effects testing be conducted for TBBPA in accordance with specific test guidelines set forth in 40 CFR Parts 796, 797, and 798. Revisions to these guidelines were proposed in the Federal Register of January 14, 1986 (51 FR 1522), and were promulgated in the Federal Register of May 20, 1987 (52 FR 19056).(p. 25222). 1. Chemical fate tests to be conducted for TBBPA are: (a) biodegradability in sediment/water, using the Core-Chamber Method described by Bourquin et al. (Ref. 5) and (b) aerobic and anaerobic biodegradability in soil, using the guideline at 40 CFR 796.3400. (p. 25222). 2. Environmental effects tests to be conducted for TBBPA are: (a) acute toxicity to freshwater algae, Selenastrum capricornutum, using the test guideline at 40 CFR 797.1050; (b) acute toxicity to Pimephales promelas (fathead minnow) in a flow-through system, using the guideline at 40 CFR 797.1400; (c) partial life-cycle toxicity to the midge (Chironomus tentans) conducted in a flow-through system using TBBPA-spiked clean, freshwater sediments having low, medium, and high organic carbon content in accordance with the method described by Adams et al. (Ref. 10); (d) chronic toxicity to the invertebrate Daphnia, tested in a renewal or a flow-through system, using the guideline at40 CFR 797.1330; (e) early life stage toxicity to fish conducted in a flow-through system, using the guideline at 40 CFR 797.1600 (the test species for the fish early life stage test is fathead minnow (Pimephales promelas) if the LC50 value for fathead minnow is equal to or less than 0.08 mg/L, either fathead minnow or rainbow trout if the 96-hour LC50 for fathead minnow is in the range between 0.08-2.0 mg/L, and rainbow trout if the 96-hour LC50 for fathead minnow is greater than or equal to 2.0 mg/L); (f) bioconcentration in the fathead minnow (Pimephales promelas) using the guideline at 40 CFR 797.1520; and (g) bioconcentration in the oyster (Crassostrea virginica) using the guideline at 40 CFR 797.1830. (p. 25222). The Agency is requiring that the above referenced TSCA Chemical Fate and Environmental Effects Test Guidelines and revisions and other cited methods be the test standards for the purposes of the required tests for TBBPA. The TSCA test guidelines for chemical fate and aquatic toxicity testing specify generally accepted minimum conditions for determining chemical fate and aquatic organism toxicities for substances like TBBPA to which aquatic life is expected to be exposed. (p. 25222) The required methods of Bourguin et al. (1977) for investigating the biodegradation rate of TBBPA in sediment/water and Adams et al. for investigating the toxicity of TBBPA to benthic organisms specify generally accepted minimum conditions (Refs. 5 and 10). The Agency believes that these test methods reflect the current state-of-the-science for testing the fate and effects of chemicals such as TBBPA in sediment/water systems. (p. 25222)	in vivo, chemical fate/boidegration		In the aquatic environment, TBBPA is expected to partition strongly to sediment based on its log P value of 4.5 Therefore, the Agency believes that determining the toxicity of TBBPA to benthic organisms is important in characterizing the environmental effects of TBBPA. Since the Agency did not receive any comments on the sediment bioassay methods referenced in the proposed rule or on the availability of alternate sediment bioassay methods, the Agency is requiring that testing the toxicity of TBBPA to benthic organisms be conducted in accordance with the method it has selected as being appropriate from those referenced in the proposed rule. 52 FR 25219 1. Biodegradability Test in Water The Panel commented that because of TBBPA's tendency to partition from water into sediment, testing for biodegradability in water will provide only limited useful information on the chemical fate of TBBPA. The test methodology proposed by the Agency for this test (Core-Chamber Method by Bourquin et al.), however, provides data on biodegradability (i.e., rate of carbon dioxide evolution and extent of transformation) of the chemical in a combined sediment/water environment (Ref. 5). (p. 25221) EPA believes many differences exist between soil and activated sludge which influence their bacterial composition and activity (i.e., moisture, temperature, pH, etc.). However, the review of information collected following the proposed rule shows that activated sludge is not currently being used in treatment of TBBPA process wastes. Therefore, the modified SCAS test, which provides data on biodegradability of a chemical substance in

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2-Ethylhexanol	52 FR 28698	3-Aug-87	A, B	health	The finding for potential carcinogenicity is based on studies conducted on other chemicals containing the ethylhexyl moiety which suggest that EH may possess a carcinogenic hazard.	SAR

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a 2-year oncogenicity bioassay On the basis of these findings, the Agency is requiring oncogenicity testing of EH. Data from these bioassays in rats and mice will assist the Agency in conducting risk assessments for EH and thus will be of critical importance in determining whether EH presents an unreasonable risk of cancer. . (p. 28701) The Agency is requiring the oncogenicity testing to be conducted on EH in accordance with the TSCA test guidelines for oncogenicity specified in 40 CFR 798.3300, published in the Federal Register of September 27, 1985 (50 FP 39252) and modified in the Federal Register of May 20, 1987 (52 FR 19056). EPA proposed these revisions to the guidelines in the Federal Register of January 14, 1986 (51 FR 1522), and responded to comments on the proposed revisions in the record for that rulemaking (Ref. 10). . (p. 28701) The testing required in this final rule shall be performed with the Fisher 344 rat and B6C3F1 mouse. These species and strains have demonstrated sensitivity to other ethylhexyl compounds. The route of exposure shall be oral. Based upon experience at NTP (Ref. 9), the EH can be microencapsulated in the diet or administered by gavage. A subchronic study should be conducted using the same exposure method as selected for the lifetime bioassay to determine dose levels and characterize target organ effects for the bioassay. (p. 28701)	in vivo		

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Oleylamine; Testing Requirements	52 FR 31962	24-Aug-87	A and B		The section 4(a)(1)(A) findings for developmental toxicity are as follows: EPA finds that the use of ODA may present an unreasonable risk of injury to human health from developmental toxicity because: (1) The available animal studies suggest that ODA has a developmental toxicity potential; and (2) approximately 2 million individuals in 1985 were potentially exposed to ODA as a result of its manufacture, processing, and use (Ref. 19). . (p. 31965)	in vivo; testing for subchronic risks obviated due to in vitro and SAR

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
developmental toxicity and two-tiered mutagenicity testing of ODA. The need for third tier mutagenicity testing and oncogenicity testing was to be determined by EPA following public program review of all relevant data. Oleylamine; Final Test Standards and Reporting Requirements, 53 FR 48542, 48542 (Dec. 1, 1988). 1. For specific organ/tissue toxicity under 40 CFR 798.4900 Developmental toxicity study except requiring oral route of administration by gavage. 2. For genetic toxicity: Chromosomal effects—a. First tier under 40 CFR 798.5385 In vivo mammalian bone marrow cytogenetics tests: Chromosomal analysis. b. Second tier under 40 CFR 798.5450 Rodent dominant lethal assay. c. Third tier under 40 CFR 798.5460 Rodent heritable translocation assay. 3. For genetic toxicity: Gene mutations—a. First tier under 40 CFR 798.5300 Detection of gene mutations in somatic cells in culture. b. Second tier under 40 CFR 798.5275 Sex-linked recessive lethal test in Drosophila melanogaster. c. Third tier under 40 CFR 798.5200 Mouse visible specific locus test (see Unit V.A.3. of this preamble)- not required yet. 4. For chronic exposure under 40 CFR 798.3300 Oncogenicity- not required yet. Oleylamine; Final Test Standards and Reporting Requirements, 53 FR 48542, 48544 (Dec. 1, 1988) 3. Mouse visible specific locus test. EPA proposed a tiered testing approach to evaluate whether ODA elicits heritable gene mutations. Positive results in certain lower-tier tests would trigger the requirement for conducting a mouse visible specific locus (MVSL) test. EPA believes that the MVSL is necessary, when certain lower-tier tests are positive, to establish definitively whether a substance is capable of eliciting heritable gene mutations. Under the proposed approach, EPA would consider any positive lower-tier test results in a public program review, together with other relevant information, during which interested persons would be able to give their views to EPA. If, after the review, EPA determined that the MVSL was still appropriate, EPA would notify the test sponsors by letter or Federal Register notice that they must conduct the test. If EPA determines that the test is no longer necessary, EPA would propose to amend the rule to delete the test requirement. Oleylamine; Final Test Standards and Reporting Requirements, 53 FR 48542, 48544 (Dec. 1, 1988). The final test rule for ODA includes requirements to conduct the lower-tier tests for gene mutations. However, EPA is not promulgating the Phase II requirement for the MVSL for ODA at this time. EPA had based its proposal to require the MVSL, in part, on certain information and assumptions about the cost of conducting the test and the availability of laboratories able to perform the test. The information and assumptions have since proven to be incorrect. Accordingly, EPA is reexamining this information as it applies to the MVSL requirement for this test rule as well as those for other chemical substances. In particular, EPA is reviewing whether any	in vivo, tiered (in vitro, in vivo)		discussion on oral versus dermal The Panel commented that a negative in vitro cytogenetics assay need not be followed by an in vivo mammalian bone marrow cytogenetics test to determine chromosomal aberration. This judgment is based on a review of the literature which the Panel contends shows that no chemical testing negatively in an in vitro mammalian cytogenetics assay has been found positive in in vivo cytogenetics tests. EPA has in past section 4 test rules included both in vitro and in vivo cytogenetics testing in its first tier of testing to maximize detection of potentially clastogenic agents, e.g., for cresols (51 FR 15771; April 28, 1986) and C9 aromatic hydrocarbons (50 FR 20662; May 7, 1985). The Agency believes that the in vitro assay is subject to sufficient limitations, particularly in the use of in vitro metabolic activation systems, that a negative response, especially in cases of technical difficulties with the metabolic activation system or of erratic or narrowly-defined toxicity curves, should be confirmed in an in vivo test. The information presented by the Panel or otherwise available to the Agency is not sufficient to warrant a change in this view at this time. (p. 31963)

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Commercial Hexane and Methycyclopentane Test Rule	53 FR 3382	5-Feb-88	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
EPA is issuing a final test rule requiring manufacturers and processors of commercial hexane to perform testing for subchronic toxicity, oncogenicity, reproductive toxicity, developmental toxicity, mutagencity, neurotoxicity, and inhalation and dermal pharmacokinetics and is terminating rulemaking under TSCA section 4(a) for subchronic toxicity, neurotoxicity, and inhalation and dermal pharmacokinetics testing of methylcyclopentane (MCP; CAS No. 96-37-7). Subchronic toxicity: Subchronic inhalation toxicity § 798.2450 Chronic toxicity: Oncogenicity . § 798.3300 Specific organ/tissue toxicity, Reporduction and fertility effects § 798.4700, Inhalation developmental toxicity § 798.4350, Genetic toxicity,Gene Mutations,Salmonella typhimurium § 798.5265, Mammalian cells in culture § 798.5300, Drosophila sex-linked recessive lethal § 798.5275, Chromosomal Aberrations,In vitro cytogenetics § 798.5375, In vivo cytogenetics § 798.5385, Dominant lethal assay § 798.5450, Heritable translocation assay § 798.5460, Acute neurotoxicity: Schedule-controlled operant behavior § 798.6500, Subchronic neurotoxicity, Functional observation battery § 798.6050, Motor activity . § 798.6200, Neuropathology § 798.6400	in vivo, in vitro tiered	test requirements will be relevant to a determination that the manufacture, processing, distribution in commerce, and use of commercial hexane does or does not present an unreasonable risk of injury to human health	The final test rule for commercial hexane includes requirements to conduct the lower-tier tests for gene mutations.(the proposed rule had lower-tier that would trigger mouse visible specific locus test). However, EPA is not promulgating the requirement for the MVSL for commercial hexane at this time. EPA had based its proposal to require the MVSL, in part, on information and assumptions about the cost of conducting the test and the availability of laboratories capable of performing the test. The information and assumptions have since proven to be incorrect. Accordingly, EPA is in the process of reexamining the MVSL requirement for this test rule as well as those for other chemical substances. …Once EPA completes its evaluation of this additional information, EPA will publish a notice in the Federal Register concerning the MVSL for commercial hexane and other substances subject to TSCA section 4 test rules. This notice will provide up-to-date information on the cost of MVSL testing, availability of laboratories to perform the MVSL, and possible alternative tests to the MVSL together with their costs and laboratory availability. The notice will also address EPA's intentions about any changes to the MVSL requirements in the various test rules and will provide an opportunity for public comment. If, after this exercise, EPA concludes that the MVSL is still appropriate for commercial hexane, EPA will amend this final test rule for commercial hexane to add the MVSL requirements with any appropriate modifications. (p. 3385)

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Diethylene Glycol Butyl Ether and Diethylene Glycol Butyl Ether Acetate; Test Standards and Requirements	53 FR 5932	26-Feb-88	A and B	health	Under section 4(a)(1)(A), EPA finds that the use of DGBE and DGBA in consumer goods may present an unreasonable risk of adverse hematological, reproductive, hepatic, and renal effects. These findings are based on the available toxicity data discussed in Unit II of this preamble and in Unit II.G of the preamble to the proposed rule (51 FR 27880)	in vitro, in vivo

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
On the basis of these findings, EPA is requiring that certain health effects testing of DGBE be conducted in accordance with specific guidelines set forth in 40 CFR Part 798. The Agency is also requiring that developmental neurotoxicity testing of DGBE, if required after public program review, pharmacokinetics testing of DGBE, and *5941 dermal absorption testing of DGBA be conducted in accordance with specific guidelines set forth in 40 CFR Part 795, which are published with today's final rule. (p. 5940-5941) The final rule provides for tiered testing. The following tests are in Tier I: Subchronic toxicity with particular emphasis on reproductive, hematological, and kidney effects; neurotoxicity; pharmacokinetics and dermal absorption. Developmental neurotoxicity is the only Tier II test and will be required pending the assessment of the data in the Tier I tests. (p. 5941) All of the tests are required. However, before Tier II testing is required to be initiated, EPA will hold a public program review of the Tier I data from the functional observational battery, motor activity, neuropathology, and reproductive tests. A review of these data will be conducted to determine if developmental neurotoxicity testing should be initiated. …Should EPA determine from the weight of available evidence that proceeding to the developmental neurotoxicity test is no longer warranted, the Agency will propose to repeal the appropriate testing requirement and, after public comment, issue a final amendment to rescind this requirement. Should EPA determine that developmental neurotoxicity testing is necessary, the Agency will notify the test sponsor by certified letter or Federal Register notice that testing shall be initiated. (p. 5941) Although a section 4(a)(1)(B) finding was made, oncogenicity testing is not being required because it was proposed to be triggered from positive mutagenicity findings. Negative Tier I mutagenicity tests have since been conducted by industry. However, the National Toxicology Program (NTP) is currently conducting oncogenicity studies of structurally similar glycol ethers. If these tests are positive, EPA may repropose oncogenicity testing for DGBE. (p. 5941)	Tiered in vivo	testing will be relevant to a determination as to whether the manufacture, processing, distribution, or use of DGBE and DGBA does or does not present an unreasonable risk of injury to human health. (p. 5940)	Testing for subchronic and neurotoxic effects shall be by the dermal route because it is a major route of exposure. The fertility satellite data will be obtained as a result of dermal exposure since the fertility screen is a component of the subchronic toxicity study. Acceptance of this route of exposure for DGBE should not be regarded as a precedent for the use of dermal exposure in reproductive and fertility studies, in general. Testing for developmental neurotoxicity should be by the oral route. Although inhalation is also a main route of exposure, EPA believes such a route of administration is inappropriate due to the technical difficulty of testing DGBE by this route. (p. 5940)

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Office of Solid Waste Chemicals; Final Test Rule	53 FR 22300	15-Jun-88	A	?	EPA believes that these chemicals meet the requirements for testing under section 4(a)(1)(A)(i) of TSCA. By virtue of these chemicals being identified as "hazardous constituents," the nature of potential toxicity, the presence and evidence of these chemicals in the waste streams of treatment, storage, or disposal facilities, evidence that existing landfills leak, and the potential for human exposure to these chemicals during treatment, storage, and disposal activities and through possible leaching or volatilization, the Agency has determined that the disposal of these chemicals may present an unreasonable risk of injury to human health.	scientifics studies, substantial human exposure

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
On the basis of these findings, EPA is requiring health effects testing and/or specific chemical fate testing for the chemicals subject to this final rule (see Unit III.A. of this preamble). The chemicals and the specific tests are listed in Table 4, along with a test that is recommended (biodegradation), but not required. The required tests are to be conducted in accordance with: (1) EPA's TSCA Good Laboratory Practice Standards in 40 CFR Part 792; and (2) the specific TSCA test guidelines as enumerated in 40 CFR Parts 796 and 798, as amended in this rule. The optional biodegradation test, if conducted, should be conducted in accordance with the EPA-developed guideline, 40 CFR Part 795.54, finalized in this rule. EPA is requiring that the chemicals listed in Table 4 under Subchronic Testing be tested using the guideline at 40 CFR 798.2650. The subchronic studies will be performed by the oral gavage route. The rat will be the test species. EPA requires that the chemicals listed in Table 4 under Soil Sorption Testing be tested using the guideline at 40 CFR 796.2750—Sediment and soil adsorption isotherm. EPA further requires that the chemicals listed in Table 4 under Hydrolysis Testing be tested using the guideline at 40 CFR 796.3500—Hydrolysis as a function of pH at 25 °C, as modified in this rule. These modifications do not apply to the hydrolysis test requirements of previous rules, such as for anthraquinone. To make this clear, language has been added to the codified portion of this rule stating that the guidelines and other test methods cited in the anthraquinone test rule are referenced as they existed on July 20, 1987. Persons manufacturing or processing the 32 chemicals for which biodegradation testing is recommended, as indicated in Table 4, have the option of performing the test according to the EPA-developed guideline at 40 CFR 795.54, finalized in this rule, or not performing the test and having EPA assume “zero biodegradation” when formulating regulatory requirements for land disposal of hazardous wastes.	in vivo; non-cellular	EPA's Office of Solid Waste (OSW) identified a need for health effects and/or chemical fate data on 73 chemicals in support of its effort under section 3001 of the Resource Conservation and Recovery Act (RCRA) to identify those wastes which may pose a substantial hazard to human health and the environment if improperly managed. Those chemicals were the subject of a proposed TSCA section 4 test rule (May 29, 1987; 52 FR 20336) that included testing for chemical fate and/or human health effects. Testing is required for 33 chemicals. Industry believes that the Agency's use of section 4 of TSCA to accomplish the goal is inappropriate. (p. 22301). Its belief is based primarily on the fact that the chemicals are listed on Appendix VIII of 40 CFR Part 261, a Part that governs the disposal of hazardous waste under RCRA and has not direct relationship to TSCA….TSCA was enacted in 1976 to fill in some of the regulatory gaps that then existed regarding the assessment and prevention of adverse health and environmental effects from potentially toxic substances. This test rule therefore fulfills the intent of Congress, because RCRA contains such a ‘regulatory gap’: it does not itself contain any	NRDC and USDOI concurred that the health effects testing is warranted; however, NRDC believes that the proposed 90-day subchronic toxicity study is grossly inadequate to determine the adverse health effects of the chemicals in question. NRDC recommended that a series of additional tests be performed to fully ascertain carcinogenic, mutagenic, and neurotoxic effects of these chemicals. First, NRDC advised EPA to replace the 90-day subchronic test in favor of a two-year chronic toxicity test. NRDC maintained that the 90-day test is not adequate to determine long-term effects from prolonged exposure. Second, NRDC urged the adoption of a tiered testing plan that would incorporate: a. Initial analysis of each chemical to determine whether there exist structural analogues which are carcinogens, mutagens, neurotoxins, or are associated with reproductive effects, and whether the chemical is an alkylating agent. b. A battery of mutagenicity tests for all chemicals. c. Satellite tests for carcinogenicity, adverse reproductive effects, and neurotoxicity. NRDC maintained that the plan contained in its comment would fully characterize a chemical's chronic toxicity. On the other hand, SOCMA recommended that the Agency reevaluate the requirement to perform th e90-day subchronic test in view of chemicals on the list that are not amenable to testing by this method and the impact of testing on the regulated community. EPA acknowledges NRDC's comment regarding the scope of tests required to fully characterize a given chemical's toxic potential. However, the purpose of this test rule is to obtain data in support of OSW's concentration-based (relisting) program. OSW has determined that relistings can be accomplished using toxicity data from a 90-day study. The Agency maintains that a well-designed and conducted

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Cumene; Final Test Rule	53 FR 28195	27-Jul-88	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
The health effects testing requirements include: Oral and inhalation comparative pharmacokinetics, subchronic inhalation toxicity, developmental toxicity, neurotoxicity, and, if triggered, two generation reproductive effects. The environmental effects and chemical fate testing requirements include: Acute toxicity to fish and invertebrates, biodegradation in an aquatic system, volatilization from an aquatic system, and, if triggered, chronic toxicity to fish and invertebrates. HEALTH EFFECTS TESTS: Oral and inhalation pharmacokinetics 795.230 Subchronic inhalation toxicity 798.2450, Inhalation developmental toxicity 798.4350, . Subchronic neurotoxicity: Functional observation battery 798.6050, Motor activity 798.6200, Neuropathology 798.6400, Two-generation reproductive effects 798.4700, ENVIRONMENTAL EFFECTS TESTS: Acute toxicity to Daphina magna 797.1300, Acute toxicity to Mysidopsis bahia 797.1930, Acute toxicity to Salmo gairdneri 797.1400, Acute toxicity to Cyprinodon variegatus 797.1400, Chronic toxicity to Daphnia magna 797.1330, Chronic toxicity to Mysidopsis bahia 797.1950, Early life stage toxicity to Salmo gairdneri 797. , Early life stage toxicity to Cyprinodon variegatus 797.1600 CHEMICAL FATE TESTS: Biodegradation in aquatic system, Volatilization from aquatic system	in vivo; tiered in vivo (reproductive effects); chemical fate	EPA believes that the data generated from this testing will be relevant to a determination as to whether the manufacture, processing, use, and disposal of cumene does or does not present an unreasonable risk of injury to human health or to the environment.	EPA believes that inhalation is the most relevant route of human exposure, and, for this reason, it has required testing only with this route whenever that was adequate. Nevertheless, the potential for human exposure to cumene via the oral route is also of some concern to the Agency because monitoring data for ground and surface water near cumene manufacturing and processing facilities are not available. Pharmacokinetics testing with cumene is being required by both routes, oral and inhalation. EPA will use the pharmacokinetics data for extrapolating from one route to the other. Thus, the Agency's concern regarding the potential of exposure to cumene via the oral route will also be addressed without having to require the proposed 90-day oral subchronic study. (p. 28198). The Agency does not agree with the Panel's assumption that pharmacokinetic data are only useful for evaluating toxicity. Pharmacokinetics testing is being required to generate comparative, dose-dependent, oral and inhalation absorption, tissue distribution, bioaccumulation, metabolism, and excretion data. These data are needed for high to low dose, route-to-route, and species to species extrapolation. (P.28199) Likewise, metabolism studies conducted without the benefit of a radiolabeled test compound or by state-of-the-art methods are of little value for risk assessment purposes. (p. 28199) The Panel contends that EPA's proposed method of studying biodegradation of cumene in water, the Core-Chamber Method developed by Bourquin et al., is not a standard method for degradation as outlined in TSCA guidance and was not validated for application to TSCA, and that finding qualified laboratories for testing under Good Laboratory Practice (GLP) standards may be difficult. In addition, the Panel has suggested that the

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
2- Mercaptobenzothiazole	53 FR 34514	7-Sep-88	Environmental Effects and Chemical Fate testing requiresment (A and B); Human health testing requirements (B)	Environment	Under TSCA section 4(a)(1)(A)(i), EPA finds that the manufacture, processing, use, and disposal of MBT may present an unreasonable risk of injury to organisms in the aquatic environment. EPA is basing this finding on EC50 or LC50 values that are less than 100 times the minimum, median, or maximum predicted environmental concentration (PEC) values, two LC50 values that are less than 1 mg/L, and for an LC50 value greater than 1 mg/L but less than 100 mg/L, the 24-hr to 96-hr LC50 ratio is greater than 2. EPA believes that chronic effects may occur at anticipated environmental concentrations.	in vivo; exposure/use data

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
testing for persistence and mobility, chronic aquatic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, and mutagenic effects in the dominant lethal assay. On the basis of these findings, EPA is requiring that chemical fate, environmental effects, and health effects testing be conducted for MBT in accordance with specific test guidelines set forth in 40 CFR Parts 796, 797, and 798. The tests are to be conducted in accordance with EPA's TSCA Good Laboratory Practice Standards in 40 CFR Part 792. (p. 34518) On the basis of the findings presented above for chemical fate testing, the Agency is requiring that MBT be tested for: (1) Biodegradation using the test guideline specified in40 CFR 796.3100; (2) indirect photolysis screening using the test guideline specified in 40 CFR 795.70,[FN1] promulgated with this final rule; *34519 and (3) chemical mobility using the test guideline specified in 40 CFR 796.2750.(§ 795.70 Indirect photolysis screening test: Sunlight photolysis in waters containing dissolved humic substances, was proposed as § 796.3765 in 51 FR 472; January 6, 1986.) (p. 34518-34519) For environmental effects testing, the Agency is requiring that chronic toxicity testing of MBT be conducted on (1) rainbow trout (Salmo gairdneri) using the test guideline specified in 40 CFR 797.1600; and (2) Daphnia magna using the test guidelines specified in 40 CFR 797.1330. (p.34519) For health effects testing, the Agency is requiring that MBT be tested for: (1) Developmental toxicity in two mammalian species using the test guideline specified in 40 CFR 798.4900; (2) reproductive toxicity using the test guideline specified in 40 CFR 798.4700; (3) neurotoxicity using the test guidelines specified in 40 CFR 798.6050, 798.6200 and798.6400; and (4) mutagenicity (dominant-lethal assay) using the guidelines specified in40 CFR 798.5450. A positive result in the dominant-lethal assay may, after a public program review, trigger a heritable translocation assay using the procedure specified in 40 CFR 798.5460. If the dominant-lethal assay is negative, no further chromosomal aberration testing shall be required for MBT. If the results of the dominant-lethal assay are positive, EPA will hold a public program review prior to requiring the initiation of the heritable translocation assay. Public participation in this program review will be in the form of written comments or a public meeting. Request for public comments or notification of a public meeting will be published in the Federal Register. Should EPA determine, from the available weight of evidence, that proceeding to the heritable translocation test is no longer warranted, the Agency would	in vivo, tiered in vivo, non-cellular	testing will be relevant to a determination as to whether the manufacture, processing, use, or disposal of MBT does or does not present an unreasonable risk of injury	

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Triethylene Glycol Monomethyl Ether; Final Test Rule	54 FR 13472	3-Apr-89	A and B	health	EPA finds that the use of TGME may present an unreasonable risk of developmental neurotoxicity on the basis of SAR with EGME and EGEE (Refs. 3, 6, and 7), both of which demonstrate developmental neurotoxicity, and the exposure to brake fluid which may contain TGME during use at levels up to 250 to 2,300 mg/day for up to 250 days per year by mechanics (Ref. 14). Other workplace personnel may be exposed to even higher levels (Ref. 20). (p. 13474)	SAR, exposure

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
EPA is requiring that developmental neurotoxicity be conducted on TGME in accordance with the specific guideline in 40 CFR 795.250, as published in the Federal Register of February 26, 1988 (53 FR 5947). The test substance is administered to several groups of pregnant animals during gestation and lactation, one dose level being used per group. Offspring are randomly selected from within litters for neurotoxicity evaluation. The evaluation includes observation to detect gross neurological and behavioral abnormalities, determination of motor activity, neuropathological evaluation, and brain weights. Measurements are carried out periodically during both postnatal development and adulthood. 53 FR 5932, 5947 (Feb. 26. 1988). The test substance or vehicle should be administered orally by intubation.	in vivo	Data resulting from the developmental neurotoxicity screen will help EPA determine whether TGME is developmentally neurotoxic and whether further testing is necessary, and are relevant to determining whether exposure to TGME during use does or does not present an unreasonable risk to human health. (p. 13474))	Comment: CMA also commented on the rationale for developmental neurotoxicity testing for risk assessment purposes, and concluded that “although such testing may be of academic interest, it is of no proven value to the risk assessment needs that must exist to justify section 4 testing requirements”. (p. 13473). Response: At the time of the proposal, EPA had not previously required developmental neurotoxicity testing and had never used such testing for risk assessment purposes. However, EPA has long recognized that there is a need for this testing, as is discussed below. To fulfill this need, EPA has developed a guideline for this test (40 CFR 795.250). (p. 13473). ….In addition, EPA's Scientific Advisory Panel (SAP) recently reviewed the rationale for developmental neurotoxicity testing and concluded that EPA should require that such testing be conducted in a number of instances including “strong structure-activity relationships to known neurotoxicants” (Ref. 13).

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Tributyl Phosphate; Final Test Rule	54 FR 33400	14-Aug-89	A, B	health and enevrionment	Under section 4(a)(1)(A), EPA finds that the manufacturing, processing, distribution, use, and disposal of TBP in aircraft hydraulic fluid and other uses may present an unreasonable risk of adverse oncogenic effects, neurotoxic effects, and dermal sensitization.	in vivo; In vitro (Ames-> valid negative results); chemical fate/tranport

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
Chemical fate: Vapor pressure § 796.1950; Hydrolysis rate at 25 degrees C § 796.3500; Sediment and soil adsorption isotherm . § 796.2750 **Environmental effects:** Gammarid acute toxity § 795.120; Selenastrum acute toxicity § 797.1050; Rainbow trout acute toxicity § 797.1400; Daphnid acute toxicity § 797.1300; Daphnid chronic toxicity § 797.1330; Fish early life stage § 797.1600,Sediment invertebrate bioassay Adams et al.; **Health effects**: Oral/dermal pharmacokinetics .. § 798.228; Oncogenicity § 798.3300; Reproduction and fertility effects (oral) § 798.4700; Developmental toxicity (oral) . § 798.4900; Dermal sensitization § 798.4100; Functional observation battery (acute and subchronic) § 798.6050; Motor activity (acute and subchronic) § 798.6200; Neuropathology § 798.6400; Mammalian cells in culture .... § 798.5300; Drosophila sex-linked recessive lethal§ 798.5275; In vitro cytogenetics § 798.5375; In vivo cytogenetics§ 798.5385; Dominant lethal assay§ 798.5450; Heritable translocation assay § 798.5460; (p. 33403) To assess the mutagenic effects of TBP, EPA is requring that testing be conducted in tiers. First-tier testing will consist of the detection of gene mutation in somatic cells in culture using the test guideline § 798.5300, an in vitro mammalian cytogenetics test using the test guideline in § 798.5375, and an in vivo mammalian bone marrow cytogenetics chromosomal analysis test using the test guideline in § 798.5385, as modified in § 799.4360(c)(5)(i)(B)(2). Unless the results of the gene mutation in somatic cells in culture are negative, a sex-linked recessive lethal test in Drosophila melanogaster will be required. Second-tier testing will consist of a sex-linked recessive lethal assay in Drosophila melanogaster using the test guideline in § 798.5275, as modified in § 799.4360(c)(4)(i)(B)(2), and a rodent dominant lethal test using the test guideline in § 798.5450; third-tier testing will consist of a rodent heritable translocation test using the test guidelines in § 798.5460, and as modified in § 799.4360(c)(5)(i)(D)(2). (p. 33404) Should the gene mutation in somatic cells test prove negative, no further gene-mutation tests will be required. If the sex-linked recessive lethal test is negative, no further gene-mutation test will be required of TBP. If the results of the in vitro mammalian cytogenetics test are negative, an in vivo mammalian bone	in vitro, in vivo, tiered (in vitro/in vivo)		On the basis of these findings EPA is requiring that chemical fate, environmental effects and health effects testing be conducted for TBP in accordance with specific test guidelines set forth in 40 CFR parts 796, 797 and 798, or other published test methods as specified in this test rule as listed in the following table.

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Methyl Ethel Ketoxime; Final Test Rule	54 FR 37799	13-Sep-89	A and B	health	human health due to its potential to cause oncogenic, mutagenic, reproductive, developmental, and subchronic effects.	hazard: SAR, in vivo, exposure: use, manufactring, and processing data

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
The testing requirements include oncogenicity, mutagenicity, developmental toxicity, reproductive toxicity, neurotoxicity, and pharmacokinetics. For the pharmacokinetics test only, EPA will finalize the test standard and reporting requirement in a separate final rule. EPA is requiring that health effects testing be conducted for MEKO. The tests shall be conducted in accordance with EPA's TSCA Good Laboratory Practice Standards in 40 CFR part 792 and in accordance with specific test standards based on the guidelines set forth in 40 CFR part 798, or other published test methods as specified in this test rule and enumerated in the following Table. (See FR for table) All testing is in vivo. An in vitro mammalian cytogenetics assay, and a sister chromatid exchange test on MEKO were conducted by NTP, which indicates that both of these tests were negative (Ref. 31). NTP is also conducting a gene mutation assay in Salmonella. EPA will evaluate this information along with lower-tier mutagenicity data developed through this test rule to determine if the mouse visible specific locus assay, the rodent dominant lethal assay, the rodent heritable translocation assay, or other mutagenic testing is necessary for MEKO. These upper-tier mutagenic tests are not being required at this time. (p.37803-37804)	in vivo	determine is unreasonable risk	Allied expressed general concern for the unnecessary sacrifice of animals. EPA shares this concern, and has made every effort to design studies which economize on the number of animals while providing adequate numbers for acceptable statistical analysis. Industry may further reduce the number of animals by submitting study plans which use satellite groups or the same animals for different measurements, wherever feasible. **EPA also notes that there are presently no alternatives to whole-animal testing for the toxicological endpoints required by this rule. 37800** **Because numerous comments were received on the generic pharmacokinetics guideline published in the MEKO proposed rule (53 FR 35838; September 15, 1988), EPA has decided to reevaluate the pharmacokinetics test standard and reporting requirements for MEKO. EPA plans to promulgate the pharmacokinetics test standard and related reporting requirements for MEKO in a separate rule.** **Allied proposed that a protocol combining developmental toxicity, neurotoxicity, and reproductive toxicity be devised. EPA believes that a combined protocol testing for neurotoxicity, developmental toxicity, and reproductive toxicity will compromise the results of these studies. Developmental and reproductive tests require different exposure periods and different dose levels. Neurotoxicity tests also require longer exposure times than the developmental test (Ref. 24, 25, and 40). Theoretically, the neurotoxicity and reproductive studies could be combined. However, at this time, the commenter failed to establish that it can be done**

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Isopropanol; Final Test Rule	54 FR 43252	23-Oct-89	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
To assess the degree of toxicological activity of **isopropanol upon various target organs**, EPA is requiring that isopropanol be tested for subchronic toxicity by inhalation (40 CFR 798.2450). To assess the potential for isopropanol to cause gene mutations, EPA is requiring that testing be conducted for gene mutations in **cells in culture (40 CFR 798.5300). If the results of the cells in culture test are positive,** a Drosophila sex-linked recessive lethal assay (SLRL) shall be conducted (40 CFR 798.5275). A positive result in the SLRL assay shall trigger a mouse visible specific locus (MVSL) test (40 CFR 798.5200). If the cells in culture test is negative, no further testing is required. If the SLRL assay is negative, the MVSL test is not required. (p. 43257) To assess the potential for isopropanol to cause chromosomal aberrations: tiered in vivo. (p. 43257) reproductive effects, developmental toxicity, acute neurotoxic inhalation, neurotoxic effects of repeated inhalation exposures, developmental neurotoxicity potential of isopropanol, oncogenicity: in vivo tests. **To aid in the assessment of the potential toxicity of isopropanol for risk assessment purposes,** EPA is requiring metabolism and pharmacokinetics testing by the oral and inhalation routes of exposure.	in vivo, tiered in vitro/vivo, tiered in vivo	?	**To aid in the assessment of the potential toxicity of isopropanol for risk assessment purposes, EPA is requiring metabolism and pharmacokinetics testing by the oral and inhalation routes of exposure**. EPA believes this testing [metabolism and pharmacokinetics testing by the oral and inhalation routes of exposure[of isopropanol is necessary to reduce uncertainties associated with the **43258* extrapolation of test data from high to low doses, from species to species, and from one route of exposure to another. Pharmacokinetics testing in rats is being required to develop comparative, dose-dependent, oral and inhalation absorption, tissue distribution, bioaccumulation, metabolism, and excretion data. These data are needed for extrapolation purposes. The necessary extrapolations can be made on the basis of metabolism and pharmacokinetics data obtained from studies performed by both routes of isopropanol administration. Repeated dose studies are needed to learn whether multiple exposures modify the metabolism and/or pharmacokinetics of isopropanol. Although there are some human and rat data, these are not adequate to support the required extrapolations. Mutagenicity testing. a. The Panel (CMA) agreed that additional assessment of the genotoxic potential of isopropanol is warranted; however, it recommended that the first tier tests be modified. The study of Thompson (Ref. 17) compared 181 compounds tested for induction of chromosomal aberrations in both in vitro and in vivo assays, and reported that similar results were obtained with 126 compounds while 53 were positive when tested in vitro and negative in vivo, 2 compounds were positive in vivo and negative in vitro, and 35 had equivocal

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Multi-Substance Rule for the Testing of Neurotoxicity	58 FR 40262	27-Jul-93	A, B	6 of 10 substances (injury-> health?)	neurotoxicity studies discussed in the proposed rule and Unit II of this preamble for acetone, 1-butanol, diethyl ether, 2-ethoxyethanol, ethyl acetate, and methyl isobutyl ketone, and the worker and/or consumer exposure to these substances indicate that the manufacturing, processing, use, and disposal of these substances may present an unreasonable risk of injury to human health. (p. 40282) The specific effects observed in these studies indicate that each of these substances presents a potential to cause neurotoxic effects. Acetone: human study; ddose-related functional decrements observed in rats and mice after exposure to 1,000 to 56,000 ppm acetone 1-butanol: observed impairment of motor control in rats and motor performance in mice. diethyl	in vivo; exposure data (consumer use; occupational)

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
EPA proposed that four neurotoxicity tests be conducted with each solvent. These tests are the functional observational battery, motor activity, neuropathology, and schedule-controlled operant behavior. These tests will examine neurobehavioral function in animals exposed by inhalation and will not only screen for certain neurotoxic effects of each solvent, but will also indicate the relative safety of the tested solvents for this endpoint. EPA does not consider this test program to be the most comprehensive program possible, but rather to be a start in addressing a complex and long-neglected issue.(p. 40262) The testing shall be performed in rats with inhalation as the route of administration. The duration of exposure for acute testing will be 6 hours per day for 1 day; duration of exposure for subchronic testing will be 6 hours per day for 5 days per week for 13 weeks (90 days). (p. 40283-40284)	in vivo	Given the section 4(a)(1)(B) findings for the 10 substances, EPA has the authority to require other health effects testing for which there is an insufficiency of data and for which testing is necessary. However, as a matter of policy, EPA is requiring only neurotoxicity testing for the substances included in this final rule at this time to focus on the deficiency in neurotoxicity data. EPA may, in the future, find other data deficiencies for these substances and propose other tests. (p. 40284)	These tests will examine neurobehavioral function in animals exposed by inhalation and will not only screen for certain neurotoxic effects of each solvent, but will also indicate the relative safety of the tested solvents for this endpoint. EPA does not consider this test program to be the most comprehensive program possible, but rather to be a start in addressing a complex and long-neglected issue. The testing in this rule, therefore, should not be viewed as a rigid universal template for all future test rules of solvents. Other test programs have been suggested in the past to examine solvent effects. A 1985 workshop co-sponsored by representatives from industry, academia, and government (Ref. 55) recommended batteries of neurobehavioral, electrophysiological, and neuropathological tests in rodents and primates exposed to solvents for up to several years. The ITC (Ref. 21) indicated its support for the concept of a multi-substance endpoint rule in general and particularly when such a rule targets “substantially produced chemicals” as with the proposed neurotoxicity test rule. CMA (Ref. 3) commented that the multi-substance endpoint test rule proposal was an important new initiative in the TSCA testing program noting that, in the past, EPA traditionally required in-depth testing of multiple endpoints on a single substance that was time and resource intensive for both EPA and industry. CMA and Monsanto (Ref. 17) further stated that the value of focused endpoint rules will be lost if, at a later date, EPA requires comprehensive testing on a substance that was subject to an endpoint rule.

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Office of Water Chemicals; Final Test Rule	58 FR 59667	10-Nov-93	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
A 14-day oral subacute and a 90-day oral subchronic study are required for each substance. The studies are to be conducted in accordance with EPA's TSCA Good Laboratory Practice Standards (GLPs) in 40 CFR part 792 and the specific TSCA test guideline in 40 CFR part 798. (p.59677)	in vivo	This rule also supports EPA's effort to develop Health Advisories (HAs) for unregulated drinking water contaminants that are monitored under section 1445 of the Safe Drinking Water Act (SDWA). HA levels provide guidance to Federal, State, and local officials responsible for protecting health after chemical spills. HA levels suggest acceptable concentrations of the chemical in drinking water; levels that would not be expected to result in an adverse health effect for 1-day, 10-day, longer-term, or lifetime human exposures based on data describing noncarcinogenic endpoints of toxicity, and, where available, data on carcinogenicity. In developing a HA, oral studies in one or more species are used in which the exposure duration is comparable to the HA exposure duration. HAs are intended to inform public health officials of the potential health effects associated with a chemical, as well as the concentration of the chemical that is not expected to cause an adverse effect after exposure of various durations.	EPA believes that these test methods reflect the current state of the science for testing substances such as these for the specified endpoints.

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Dermal Test Rule- In vitro Dermal Absorption Rate Testing of Certain Chemicals of Interest to the Occupational Safety and Health Administration	69 Fed. Reg. 22402	26-Apr-04	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
In vitro dermal absorption rate test standard; This test standard describes procedures for measuring a permeability constant (Kp) and two short-term dermal absorption rates for test substances in liquid form. The test standard utilizes in vitro diffusion cell techniques which allow absorption studies to be conducted with human cadaver skin. In vitro diffusion studies are necessary for measuring a Kp. This test standard specifies the use of static or flow-through diffusion cells and non-viable human cadaver skin. It also requires the use of radiolabeled test substances unless it can be demonstrated that procedures utilizing a non-radiolabeled test substance are able to measure the test substance with a sensitivity equivalent to the radiolabeled method. (40 CFR § 799.5115)	in vitro (not toxicity testing)	develop dermal absorption rate data for OSHA's data needs to support its skin designations. Although OSHA is the primary agency requesting the data that will be developed under this final rule, OSHA is not the only Federal Agency that will use the data. NIOSH is also very interested in method-related issues associated with characterizing dermal exposure and advancing improvements in occupational exposure assessments. EPA is also interested in data that may be gathered on these chemicals. The information obtained by the testing required in this final rule may be used to inform the Agency's decisionmaking process by providing data which can be used in a preliminary estimate of the potential health risk of certain chemical exposures. The 34 chemicals for which testing is required under this final rule are part of other ongoing Agency efforts. For example, all 34 chemicals are included in EPA's High Production Volume (HPV) Initiative (http:// www.epa.gov/chemrtk.htm.) In addition, EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) (Ref. 43) is designed to provide data to enable the	The standard articulated in this rulemaking makes efficient use of labor and materials and can be performed in a consistent, economical, and timely manner by different laboratories. The specification of the in vitro method as the test standard for this final rule also reflects EPA efforts to reduce the use of animals, where appropriate, in its testing programs. However, as noted previously in Unit II.A., although this in vitro method will satisfy OSHA's data needs to support its skin designations, EPA does not believe the method is an adequate substitute for all dermal absorption rate testing methods. (p. 22409). EPA disagrees with the category approach suggested by ACC as an alternative to the approach proposed by EPA for testing those chemicals. ACC has not provided specifics on the number of chemicals in each category that would need to be tested and the reason certain chemicals would be representative so that reliable structure activity predictions could be made. Twelve different structural classes were mentioned as potential categories by ACC, but additional classes would likely be needed to categorize within the group of 79 chemicals that have been designated for testing by the ITC. EPA remains unconvinced that the approach suggested by ACC will either minimize the testing burden or more efficiently develop data on the chemicals of interest. However, the results from the dermal absorption rate testing of the chemicals in this final rule could, in appropriate cases, provide additional data for more thorough QSAR analysis and better validated models for future predictions. (p. 22408) As an initial matter, EPA believes that measured Kps (i.e., those determined through well designed and conducted in vitro or in

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Testing of Certain High Production Volume Chemicals	71 FR 13708	16-Mar-06	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
conduct acute toxicity, repeat dose toxicity, developmental and reproductive toxicity, genetic toxicity (gene mutations and chromosomal aberrations), ecotoxicity (in fish, Daphnia, and algae), and environmental fate (including 5 tests for physical chemical properties and biodegradation) testing. (p. 13708) The tests are screening level tests which in combination are known as the Screening Information Data Set (SIDS) (see Unit II.D.). (p.13709). The SIDS provides an internationally agreed upon set of test data for screening high production volume chemicals for human and environmental hazards, and will allow the Agency and others to make an informed, preliminary *13710judgment about the hazards of HPV chemicals. (p. 13710) Come back to Table 2 in rule to see which chemicals required which testing. 1. Physical/chemical properties: Melting Point: American Society for Testing and Materials (ASTM) E 324 (capillary tube) (Ref. 44); Boiling Point: ASTM E 1719 (ebulliometry) (Ref. 45); Vapor Pressure: ASTM E 1782 (thermal analysis) (Ref. 46); n-Octanol/Water Partition Coefficient: Method A (40 CFR 799.6755—shake flask). Method B (ASTM E 1147—liquid chromatography) (Ref. 47). Method C (40 CFR 799.6756—generator column). Water Solubility: Method A: (ASTM E 1148—shake flask) (Ref. 48). Method B: (40 CFR 799.6784—shake flask). Method C: (40 CFR 799.6784—column elution). Method D: (40 CFR 799.6786—generator column). (p. 13714) 2. Environmental fate and pathways. Inherent Biodegradation: ASTM 1625 (semicontinuous activated sludge test) (Ref. 52) or ISO 9888 (Zahn-Wellens Method) (Ref. 53). Either method may be used, and no special conditions apply. (p. 13715) 3. Aquatic toxicity. Test Group 1: Acute toxicity to fish (ASTM E 729) (Ref. 54). Acute toxicity to Daphnia (ASTM E 729) (Ref. 54). Toxicity to plants (algae) (ASTM E 1218) (Ref. 55). Test Group 2: Chronic toxicity to Daphnia (ASTM E 1193) (Ref. 56). Toxicity to plants (algae) (ASTM E 1218) (Ref. 55). (p. 13715) 4. Mammalian toxicity—acute. Acute Inhalation Toxicity (rat): Method A (40 CFR 799.9130) Acute Oral Toxicity (rat): Method B (ASTM E 1163 or 40 CFR 799.9110(d)(1)(i)(A)) (Ref. 64). (p. 13716) 5. Mammalian toxicity—genotoxicity. Gene Mutations: Bacterial Reverse Mutation Test (in vitro): 40 CFR 799.9510. Chromosomal Damage: In Vitro Mammalian Chromosome Aberration Test (40 CFR 799.9537), or Mammalian Bone Marrow Chromosomal Aberration Test (in vivo in rodents: Mouse (preferred species), rat, or Chinese hamster) (40 CFR 799.9538), or Mammalian Erythrocyte Micronucleus Test (sampled in bone	in vivo, in vitro, chemical properties, environmental fate (sludge)	EPA found that, of those non-polymeric organic substances produced or imported in amounts equal to or greater than 1 million pounds per year based on 1990 IUR reporting, only 7% had a full set of publicly available and internationally recognized basic screening test data for health and environmental effects (Ref. 13). Of the over 2,800 U.S. HPV chemicals based on 1990 IUR data, 43% had no publicly available basic hazard data. For the remaining chemicals, limited amounts of the data were available. This lack of available hazard data compromises EPA's and others' ability to determine whether these HPV chemicals pose potential risks to human health or the environment, as well as the public's ability to know about the hazards of chemicals that may be found in their environment, their homes, their workplaces, and the products they buy. (p. 13711) As indicated in the December 26, 2000 Federal Register document (Ref. 1) describing the voluntary HPV Challenge Program, EPA intends to use rulemaking under TSCA where appropriate to help fill data gaps not addressed as part of the	EPA is focusing on Screening Information Data Set (SIDS) testing because it is comprised of a battery of tests agreed upon by the international community through the OECD, of which the United States is a member country, as appropriate for screening HPV chemical substances for toxicity and produces information relevant to*13711 understanding the basic health and environmental hazards and fate of HPV chemicals. The six basic testing endpoints comprising this battery of tests, known as the SIDS, have been adopted by the OECD as the minimum required to screen HPV chemical substances for toxicity and environmental fate. The content of SIDS was agreed upon at the 13[FNth] Joint Meeting of the OECD Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals (Refs. 7 and 8). The United States believes these are the right tests for our domestic needs, i.e., screening U.S. HPV chemicals for health and environmental effects and environmental fate. SIDS testing evaluates the following six testing endpoints (Ref. 5): • Acute toxicity.• Repeat dose toxicity. • Developmental and reproductive toxicity. • Genetic toxicity (gene mutations and chromosomal aberrations). • Ecotoxicity (studies in fish, Daphnia, and algae). • Environmental fate (including physical/chemical properties (melting point, boiling point, vapor pressure, n-octanol/water partition coefficient, and water solubility), photolysis, hydrolysis, transport/distribution, and biodegradation).While data on the six SIDS endpoints do not fully measure a chemical's toxicity, they do provide a consistent minimum set of information that can be used to determine the relative hazards of chemicals and to judge if additional testing or assessment is necessary. (p. 13711)

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Testing of Certain High Production Volume Chemicals; Second Group of Chemicals	76 FR 1067	7-Jan-11	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
For which chemicals require which testing see table p, 1093 1. Physical/Chemical Properties. Melting Point: American Society for Testing and Materials (ASTM) E 324-99 (capillary tube) (Ref. 21). (If a Freezing Point: OECD102 (melting point/melting range) (Ref. 25)). Boiling Point: ASTM E 1719-05 (ebulliometry) (Ref. 22). Vapor Pressure: ASTM E 1782-08 (thermal analysis) (Ref. 23). n-Octanol/Water Partition Coefficient: Method A (40 CFR 799.6755—shake flask). Method B (ASTM E 1147-92 (Reapproved 2005)—liquid chromatography) (Ref. 24). Method C (40 CFR 799.6756—generator column). Water Solubility: Method A (ASTM E 1148-02 (Reapproved 2008)—shake flask) (Ref. 26). Method B (40 CFR 799.6784—shake flask). Method C (40 CFR 799.6784—column elution). Method D (40 CFR 799.6786—generator column). (p. 1074) 2. Environmental Fate and Pathways Ready Biodegradation: Method A: ASTM E 1720-01 (Reapproved 2008) (Sealed vessel CO2 production test) (Ref. 30). Method B: International Organization for Standardization (ISO) 14593:1999(E) (CO2headspace test) (Ref. 31). Method C: ISO 7827:1994(E) (Method by analysis of dissolved organic carbon (DOC)) (Ref. 32). Method D: ISO 9408:1999(E) (Determination of oxygen demand in a closed respirometer) (Ref. 33). Method E: ISO 9439:1999(E) (Carbon dioxide evolution test) (Ref. 34). Method F: ISO 10707:1994(E) (Closed bottle test) (Ref. 35). Method G: ISO 10708:1997(E) (Two-phase closed bottle test) (Ref. 36). (p. 1075) 3. Aquatic Toxicity. Test Group 1: Acute toxicity to fish (ASTM E 729-96 (Reapproved 2007)) (Ref. 38), Acute toxicity to Daphnia (ASTM E 729-96 (Reapproved 2007)) (Ref. 38), and Toxicity to plants (algae) (ASTM E 1218-04[FNe1]) (Ref. 39). Test Group 2: Chronic toxicity to Daphnia (ASTM E 1193-97 (Reapproved 2004)) (Ref. 40) and Toxicity to plants (algae) (ASTM E 1218-04[FNe1]) (Ref. 39). (p. 1075) 4. Mammalian Toxicity—Acute. Acute Inhalation Toxicity (rat): Method A (40 CFR 799.9130). Acute Oral Toxicity (rat): Method B (ASTM E 1163-98 (Reapproved 2002) (Ref. 45) or40 CFR 799.9110(d)(1)(i)(A)). (p. 1076) 5. Mammalian Toxicity—Genotoxicity. Gene Mutations: Bacterial Reverse Mutation Test (in vitro): 40 CFR 799.9510. Chromosomal Damage: In Vitro Mammalian Chromosome Aberration Test (40 CFR 799.9537), or the In Vivo Mammalian Bone Marrow Chromosomal Aberration Test (rodents: Mouse (preferred species), rat, or Chinese hamster) (40 CFR 799.9538), or the In Vivo Mammalian Erythrocyte Micronucleus Test (sampled in bone marrow) (rodents: Mouse (preferred species), rat, or Chinese hamster) (40 CFR 799.9539). (P. 1076) 6. Mammalian Toxicity—Repeated Dose/Reproduction/Developmental. Combined Repeated Dose Toxicity	in vivo, in vitro, chemical properties, environmental fate (biodegration)	EPA will use the data obtained from this final rule to support development of preliminary hazard and risk assessments for the 19 HPV chemicals subject to the rule. The data will also be used by EPA to set priorities for further testing that may produce hazard information on these chemicals that may be needed by EPA, other Federal agencies, the public, industry, and others, to support adequate risk assessments. As appropriate, this information will be used to ensure a scientifically sound basis for risk characterizations and risk management actions. As such, this effort will serve to further the Agency's goal of identifying and controlling human and environmental risks as well as providing greater knowledge and protection to the public. EPA uses data from test rules to support such actions as the risk management decisions and activities under TSCA, development of water quality criteria, Toxic Release Inventory (TRI) listings, and reduction of workplace exposures. (p.1070) In addition, a key goal of the HPV Challenge Program was making basic health and environmental effects data for HPV chemicals available to the public as	

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Testing of Certain High Production Volume Chemicals; Third Group of Chemicals	76 FR 65385	21-Oct-11	B	N/A	N/A	N/A

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
1. Physical/Chemical Properties—a. Melting Point: ASTM International (ASTM) E 324-99 (capillary tube) (Ref. 21) (or, for substances liquid at room temperature, Freezing Point: OECD102 (melting point/melting range) (Ref. 22)). b. Boiling Point: ASTM E 1719-05 (ebulliometry) (Ref. 23). c. Vapor Pressure: ASTM E 1782-08 (thermal analysis) (Ref. 24). d. n-Octanol/Water Partition Coefficient: Method A (40 CFR 799.6755—shake flask). e. Method B (ASTM E 1147-92 (Reapproved 2005)—liquid chromatography) (Ref. 25). f. Method C (40 CFR 799.6756—generator column). g. Water Solubility: Method A (ASTM E 1148-02 (Reapproved 2008)—shake flask) (Ref. 26). h. Method B (40 CFR 799.6784—shake flask). i. Method C (40 CFR 799.6784—column elution). j. Method D (40 CFR 799.6786—generator column). (p. 65391) 2. Environmental Fate and Pathways—a. Ready Biodegradation: Method A: ASTM E 1720-01 (Reapproved 2008) (sealed vessel CO2 production test) (Ref. 30). (p. 65392). b. Method B: International Organization for Standardization (ISO) *6539314593:1999(E) (CO2 headspace test) (Ref. 31). c. Method C: ISO 7827:1994(E) (method by analysis of dissolved organic carbon (DOC)) (Ref. 32). d. Method D: ISO 9408:1999(E) (determination of oxygen demand in a closed respirometer) (Ref. 33). e. Method E: ISO 9439:1999(E) (carbon dioxide evolution test) (Ref. 34). f. Method F: ISO 10707:1994(E) (closed bottle test) (Ref. 35). g. Method G: ISO 10708:1997(E) (two-phase closed bottle test) (Ref. 36). (p. 65393) 3. Aquatic Toxicity—a. Test Group 1: i. Acute toxicity to fish (ASTM E 729-96 (Reapproved 2007)) (Ref. 38). ii. Acute toxicity to Daphnia (ASTM E 729-96 (Reapproved 2007)) (Ref. 38). iii. Toxicity to plants (algae) (ASTM E 1218-04 —G6 e [FN1]) (Ref. 39). b. Test Group 2: i. Chronic toxicity to Daphnia (ASTM E 1193-97 (Reapproved 2004)) (Ref. 40). ii. Toxicity to plants (algae) (ASTM E 1218-04 —G6 e [FN1]) (Ref. 39). (p. 65393) 4. Mammalian Toxicity—Acute—a. Acute Inhalation Toxicity (rat): Method A (40 CFR 799.9130). b. Acute Oral Toxicity (rat): Method B (ASTM E 1163-98 (Reapproved 2002) (Ref. 45) or 40 CFR 799.9110(d)(1)(i)(A)). (p. 65393) 5. Mammalian Toxicity—Genotoxicity—a. Gene Mutations: Bacterial Reverse Mutation Test (in vitro): 40 CFR 799.9510. b. Chromosomal Damage: In Vitro Mammalian Chromosome Aberration Test (40 CFR 799.9537), or the In Vivo Mammalian Bone Marrow Chromosomal Aberration Test (rodents: Mouse (preferred species), rat, or Chinese hamster) (40 CFR 799.9538), or the In Vivo Mammalian Erythrocyte Micronucleus Test (sampled in bone marrow) (rodents: Mouse (preferred species), rat, or Chinese hamster) (40 CFR 799.9539). (p. 65394). 6. Mammalian Toxicity—Repeated Dose/Reproduction/Developmental—a. Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test: 40 CFR 799.9365. b. Reproduction/Developmental Toxicity Screening Test: 40 CFR 799.9355. c. Repeated Dose 28-Day Oral	in vivo, in vitro, chemical properties, environmental fate (biodegration)	EPA will use the data obtained from this final rule to support development of preliminary hazard and risk assessments for the 15 HPV chemical substances subject to this final rule. The data will also be used by EPA to set priorities for further testing that may produce hazard information which may be needed by EPA, other Federal agencies, the public, industry, and others, to support adequate risk assessments. EPA uses data from TSCA section 4 test rules to support such actions as the risk management decisions and activities under TSCA, development of water quality criteria, Toxics Release Inventory (TRI) listings, and reduction of workplace exposures. (p.65388). As appropriate, this information will be used to ensure a scientifically sound basis for risk assessments and risk management actions. As such, this effort will serve to further the Agency's goal of identifying and controlling human and environmental risks as well as providing greater knowledge and protection to the public. (p.65388). In addition, a key goal of the HPV Challenge Program was making basic health and environmental effects data for HPV chemical substances available to the public as part of EPA's “Right to Know”	

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Toxic Substances; Mesityl Oxide; Final Test Rule	50 FR 51857	Decemeber 20, 1985	A	health	EPA finds that the manufacture, processing, and distribution in commerce of MO may present an unreasonable risk of injury to human health due to potential chronic, mutagenic, and oncogenic (conditional on the mutagenicity test results) effects (p.51863)	in vivo, SAR, (in vitro???? Can't indicate from study names)

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
EPA is requiring that MO be tested for chronic toxicity (via a 90-day subchronic toxicity test), mutagenicity, and for oncogenicity if specific mutagenicity test results are positive. (p. 51863-51864). 1. Subchronic exposure: Inhalation toxicity (40 CFR 798.2450). 2. Mutagenicity: Chromosomal effects. First tier: In vitro mammalian cytogenetics (40 CFR 798.5375); In vivo mammalian bone marrow cytogenetics tests: Chromosomal analysis (40 CFR 798.5385). Second tier: Rodent dominant lethal assay (40 CFR 798.5450). Third tier: Rodent heritable translocation assay (40 CFR 798.5460).3. Mutagenicity: Gene mutations. i. First tier:a. Salmonella typhimurium (40 CFR 798.5265); b. Somatic cells in culture (40 CFR 798.5300). Second tier: Sex linked recessive lethal test (40 CFR 798.5275). Third tier: Mouse specific locus test (40 CFR 798.5200). 4.Chronic Exposure: Oncogenicity (40 CFR 798.3300). 52 FR 19088, 19091 (May 20, 1987). Some variations to the above are specified in 52 FR 19088, 19091 (May 20, 1987) Before the third tier mutagenicity testing is to begin, EPA will hold a public review if the results of the previous tier tests are positive. If, after review of public comment, no change in the test sequence is deemed necessary, EPA will provide formal notification to the test sponsor that the next tier tests must be conducted. If, however, EPA believes additional testing is no longer warranted as a result of the earlier test results, public comment, scientific judgment, and/or other appropriate factors, EPA will issue a proposed amendment to rescind these requirements. 52 FR 19088, 19091 (May 20, 1987) EPA has decided not to use the public program review approach between the lower-tier mutagenicity tests for the MO test rule. EPA believes the use of automatic triggers between these tiers is suitable. It should be noted that this does not exclude the public from requesting modifications in the test program. Provisions are available under section 21 of TSCA for the public to petition EPA at any time to amend a rule under section 4. (p. 51862)	in vivo, tiered (in vivo and in vitro)		*Sex-Linked Recessive Lethal Test* : The Panel commented that the inhalation route for this test was inappropriate because arthropods (Drosophila) have totally different circulatory and respiratory systems than man. **Such differences, they commented, preclude use of the data in risk assessment. Concern over differences in physiology and morphology between mammalian and nonmammalian species can be raised for any of the routes of administration for this test.** The scientific community accepts Droso-phila as an acceptable test species to detect both point mutations and small deletions on the X chromosome which when expressed cause death to the carrier. Administration of MO via inhalation will ensure accurate quantification of dose. Furthermore, since it is technically feasible to conduct this test via the inhalation route of exposure, and since inhalation is the primary route of exposure to this chemical, the Agency believes conducting this test via inhalation is most appropriate. Therefore, the Agency does not agree with the Panel's suggested modification to allow an alternative route of exposure to be used. (p. 19090-19091) As discussed in the final Phase I test rule for the C aromaic hydrocarbon fraction (50 FR 20662, 20668-20672), the Agency believes that the use of sequences of tiered tests for mutagenicity testing and the use of automatic triggers to require chronic oncogenicity bioassays based on the results of certain mutagenicity assays are consistent with both current scientific knowledge and the regulatory approach to chemical testing established under section 4 of TSCA. Existing data show a strong correlation between positive results in certain mutagenicity tests and positive results in animal chronic oncogenicity

				Evidence for A Finding		
Final Rule	FR for Final Rule	Date of FR	A or B Finding?	If A, environmental or health?	Determination	Evidence Relied on in making Decision about A (in vitro, in vivo, SAR/QSAR, direct exposure, exposure models, etc.)
Unsubstitued Phenylenediamines; Final Test Rule	54 FR 49285	November, 30 1989	A	Health	Mutagenicity. The finding that m-pda "may present an unreasonable risk" of mutagenic toxicity is based on its positive Ames assays and a comparative study which showed m-pda to be the most potent mutagen of 11 aromatic amines tested (51 FR 472, 474), positive results in the in vivo Chinese hamster ovary chromosomal aberration test, and inhibition by m-pda of mouse testicular cell DNA synthesis in vitro (53 FR 913, 914). Neurotoxicity. The finding that these pda isomers "may present an unreasonable risk" of neurotoxicity is based on available literature reports of a consistent pattern of neurobehavioral effects resulting from exposure to pda's. Oncogenicity. The finding that m-pda may present an unreasonable risk of oncogenicity is based on a positive Chinese hamster ovary assay (53 FR 913, 914).	in vitro, in vivo , exposure

The Actual Test Required in the Final Rule			
What is the testing required/ test standard?	Type	purpose of test standard	standard for selection
m-pda be tested for mutagenic and oncogenic effects; m-, o-, and p-pda be tested for neurotoxic effects, chemical fate, and aquatic toxicity. These tests shall be conducted in accordance with specific test guidelines set forth in 40 CFR parts 795, 796, 797, and 798. The tests are to be conducted in accordance with EPA's TSCA Good Laboratory Practice (GLP) Standards in 40 CFR part 792. m-pda be tested for mutagenicity, using Drosophila sex-linked recessive lethal and mouse bone marrow micronucleus assays, as stipulated in 40 CFR 798.5275 and 798.5395, respectively. A positive bone marrow assay would trigger a dominant lethal assay in mice using the procedure in 40 CFR 798.5450. A positive result in the dominant lethal assay may, after a public program review, trigger the heritable translocation assay using the procedure in 40 CFR 798.5460. If the dominant lethal assay is negative, no further chromosomal aberration testing will be required for m-pda.If the sex-linked recessive lethal assay is positive, after a public program review, the [mouse visible specifc local test] MVSL (40 CFR 798.5200) will be triggered. If the proposed amendment for the requirement of the MSVL is promulgated prior to the onset of the MVSL testing, the test sponsor may choose to conduct either the MVSL or the [mouse biochemical specific locus test] MBSL and shall notify EPA in writing of its choice in its first interim report. If the sex-linked recessive lethal assay is negative, no further gene-mutation testing will be required. A determination of whether oncogenicity testing shall be initiated will be made at the completion of the mutagenicity testing program, at which time EPA will make a weight-of-evidence determination and conduct a public program review as referenced in Unit II.B.3 of this preamble. If the test must be initiated, EPA will propose the oncogenicity test standard for comment. m-pda, o-pda, and p-pda be tested for neurotoxic effects (acute functional observational battery and motor activity test) using the test guidelines in40 CFR 798.6050 and 798.6200. Results of the acute testing may trigger subchronic neurotoxicity testing and neuropathological examination, as specified in 40 CFR 798.6050,798.6200, and 798.6400. EPA will hold a public program review prior to requiring the initiation of the mouse specific locus assay, the heritable translocation assay, the chronic oncogenicity assay, or additional neurotoxicity testing. ….Should EPA determine, from the available weight of evidence, that proceeding to the mouse specific locus test, heritable translocation test, oncogenicity test, or neurotoxicity testing is no longer warranted, EPA would propose to repeal that test requirement(s) and, after public comment, issue a final amendment to rescind the requirement(s). If oncogenicity testing must be initiated, EPA will propose the standard for conducting such testing in a separate Federal Register notice. 2. Chemical fate. On the basis of	In vivo, tiered in vivo, non-cellular		