ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 795 and 799

[OPTS-42097B; FRL 3658-7]

RIN 2070-AB07

Isopropanol; Final Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is issuing a final test rule, under section 4 of the Toxic Substances Control Act (TSCA), requiring manufacturers and processors of isopropanol (CAS No. 67-63-0) to perform testing for health effects. The testing requirements include subchronic toxicity, reproductive toxicity, developmental toxicity, neurotoxicity, developmental neurotoxicity, mutagenicity, oncogenicity, and pharmacokinetics. The action is in response to the Interagency Testing Committee's (ITC) designation of isopropanol for priority testing consideration.

DATES: In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern (daylight or standard as appropriate) time on November 6, 1989. This rule shall become effective on December 4, 1989.

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SUPPLEMENTARY INFORMATION: EPA is issuing a final test rule under section 4(a) of TSCA to require health effects testing of isopropanol.

I. Introduction

A. Test Rule Development Under TSCA

The final rule is part of the overall implementation of section 4 of TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*, 15 U.S.C. 2601 *et seq.*), which contains authority for EPA to require the development of data relevant to assessing the risk to health and environment posed by exposure to particular chemical substances or mixtures (chemicals).

Under section 4(a) of TSCA, EPA must require testing of a chemical to develop data if the Administrator makes certain findings as described in TSCA under section 4(a)(1)(A) or (B). Detailed discussions of the statutory section 4 findings are provided in the EPA's first and second proposed test rules which were published in the **Federal Register** of July 18, 1980 (45 FR 48510) and June 5, 1981 (46 FR 30300).

B. Regulatory History

The Interagency Testing Committee (ITC) recommended isopropanol with intent to designate for health effects testing consideration in its 19th Report, published in the **Federal Register** of November 14, 1986 (51 FR 41417). The ITC designated isopropanol for priority testing consideration in its 20th Report (May 20, 1987, 52 FR 19020). The ITC recommended that isopropanol be tested for chronic toxicity including oncogenicity, and for genotoxicity including mutagenicity in mammalian systems and clastogenicity. Testing for developmental and reproductive effects was deferred from consideration pending the outcome of relevant studies that were being conducted in the United Kingdom by the British Industrial and Biological Research Association (BIBRA).

EPA responded to the ITC's recommendations for isopropanol by issuing a proposed rule (March 16, 1988, 53 FR 8638), which proposed that isopropanol be tested for subchronic toxicity, reproductive toxicity, developmental toxicity, neurotoxicity, developmental neurotoxicity, mutagenicity, oncogenicity, and pharmacokinetics. Consent order negotiations for isopropanol, attempted prior to rulemaking, were abandoned when consensus could not be reached between EPA and the Isopropanol Panel of the Chemical Manufacturers Association (CMA) on the requirements of a two-species oncogenicity bioassay.

The proposed rule for isopropanol contained the discussions on the attempted consent order, chemical profile of isopropanol, section 4(a) findings, and the proposed test standards and reporting requirements.

II. Response to Public Comments

EPA received written comments on the isopropanol proposed test rule from the Isopropanol Panel of CMA (the Panel), the Procter and Gamble Company (PGC), and the Natural Resources Defense Council (NRDC) on May 16, 1988 (Refs. 1 through 3). The Panel members are: Arco Chemical Company, Exxon Chemical Corporation, Shell Oil Company, and Union Carbide Corporation. A public meeting was also requested by the Panel and was held on June 1, 1988. The Panel submitted supplemental written comments on July 21, 1988 that reiterated the issues discussed at the public meeting (Ref. 4). A summary of the comments received on the isopropanol proposed test rule are stated in the following Units II. A. and B. along with EPA's responses to the comments.

A. Exposure Finding

The Panel stated that it does not dispute EPA's finding that there is or may be substantial exposure to isopropanol, although it does not accept all aspects of EPA's characterization of exposure (Ref. 1).

1. *Exposure during isopropanol manufacture.* The Panel expressed concern that EPA's proposed rule may have overstated worker exposure to isopropanol during its manufacture. The Panel indicated that it had initiated a survey of its four members, who produce all of the U.S. isopropanol at five manufacturing sites, to obtain data on potential and actual exposure during production of isopropanol (Ref. 1). The survey results, submitted to EPA as part of the Panel's supplemental written comments, showed that there are 395 manufacturing employees in the United States who are potentially exposed to isopropanol. The concentration of isopropanol to which employees are exposed ranged from 0.02 parts per million (ppm) to 6.41 ppm (Ref. 1).

The worker exposure level to isopropanol of 50 mg/m^3 (approximately 20 ppm) during its manufacture, stated in the proposed rule, is the upper limit of exposure derived from EPA analysis (Ref. 5). Although worker exposure to isopropanol from manufacturing operations is generally less than this value, EPA believes that worker exposure from isopropanol manufacturing operations is only a minor source of occupational exposure to isopropanol. Worker exposure from industrial use is a much greater source of occupational exposure to isopropanol (Ref. 5). Therefore, the data on exposure to workers at manufacturing facilities are of only limited use, since exposure to workers from processing and use of isopropanol, which contributes a far greater proportion of the exposure upon which the substantial exposure finding is based, was not considered by the Panel.

2. *Inhalation exposure within the general population.* The Panel suggested that isopropanol may be a naturally occurring constituent of milk, therefore, the Pellizarri mother's milk study (Ref. 6) should not be used as evidence of exposure to isopropanol in the general population. The Panel also pointed out several serious flaws with this study.

EPA agrees that there are flaws in the Pellizzari study and is not using the study to support the findings in the rule.

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B. Health Effects Testing Requirements

The Panel agreed with EPA that additional health effects testing for isopropanol is warranted. Therefore, the Panel's comments are directed principally at the scope and sequence of the required tests and the selection of appropriate methodologies (Ref. 1).

1. *Route of exposure.* a. The Panel stated that, since inhalation is the principal route of exposure to isopropanol, inhalation should be the preferred route of exposure for all of the major health effects studies conducted, including reproductive toxicity, developmental toxicity, and developmental neurotoxicity studies. The Panel envisioned no technical difficulties in conducting the required studies by inhalation. The Panel recommended that exposure be through drinking water if EPA concludes inhalation is an inappropriate route for any of the major health effects studies. The Panel further stated that gavage administration is particularly inappropriate for testing isopropanol because isopropanol demonstrates saturable metabolism.

EPA concurs with the Panel that there are no major technical difficulties with conducting developmental toxicity tests by the inhalation route. There are, however, technical difficulties with conducting both the reproductive toxicity and developmental neurotoxicity tests by inhalation. In these latter tests the animals are exposed to isopropanol both during pregnancy and through the period of weaning. During the time from just prior to birth until the end of weaning it would be difficult to transfer animals daily to the inhalation chamber for the required exposure periods. This excessive handling of the animals (particularly removal of the mother from the pups) would likely result in adverse effects on the pups which was not chemically related and would confound the interpretation of the results. This would be particularly true in assessments of developmental neurotoxicity where aberrant behavior might be easily be attributed to handling. In addition, if it was decided to expose both mothers and pups in an inhalation chamber, the nesting material required during the latter part of pregnancy and during weaning could easily absorb vapors during an inhalation exposure, and the saturated bedding could provide an important, yet unquantified, exposure to the test substance to both the mothers and the pups. For these reasons, EPA disagrees that inhalation route should be used for ducting reproductive toxicity and developmental neurotoxicity tests. Further, EPA considers it advisable, for the ability to compare reproductive performance, that the developmental toxicity, developmental neurotoxicity, and reproductive toxicity tests be conducted by similar routes.

Administration by gavage has some distinct advantages for the developmental neurotoxicity testing. The use of gavage administration permits relatively precise estimations of the dosages administered. By comparison, drinking water studies require estimates of individual water consumptions. Also, some spillage of water may occur during drinking and volatile chemicals may be lost. Furthermore, in the developmental neurotoxicity study, exposure extends through the period of weaning, and gavage administration ensures that exposure of the pups only occurs through the mother's milk. Since, as mentioned above, it is desirable to perform all the reproductive tests by the same route of administration, EPA believes that gavage administration is the most appropriate route for these studies.

b. While the Panel supported the use of inhalation exposure for most of the health effects testing, the Panel stated that the *Drosophila* assay and the in vivo cytogenetics assay should not be conducted by inhalation exposure. The Panel contended that, since the data from these assays will not be used directly for human risk assessment, the greater expense involved in inhalation studies is not justified under TSCA. In addition, the Panel contended that vapor phase exposure has provided inconclusive results in tests of glycol ethers (Ref. 7), and that tests of a similar compound, methanol, have been conducted by feeding. Finally, the Panel contended that the use of a feeding study would allow a more ready comparison with other *Drosophila* assays.

EPA does not agree that feed should be the route of administration in the *Drosophila* assay because of the relative difficulty of determining the dosages administered by feed. There is no apparent major technical obstacle to performing this study with isopropanol using vapor exposure. The study of glycol ethers by McGregor (Ref. 7) does not indicate that there is any inherent limitation to the use of vapor exposure, but, on the contrary, demonstrates that this experimental system is feasible and has been performed in the past. The inconclusive results reported in this study were attributed by the authors to the metabolic status of *Drosophila* and not to the exposure conditions. Thus, EPA is requiring that isopropanol be administered by vapor exposure or by injection.

The Panel may choose to conduct the in vivo cytogenetic assay by a route other than inhalation. EPA is requiring the other route to be either oral gavage or interperitoneal (IP).

2. *Reproductive toxicity testing.* The Panel stated that the available data on reproductive toxicity of isopropanol are adequate. The Panel cites existing reproductive toxicity data in rats to indicate that reproductive effects are more severe in the first generation. The Panel also noted that a recently completed BIBRA one- generation reproductive toxicity study, currently under review in the United Kingdom, may provide the necessary data to assess the reproductive toxicity of isopropanol.

The question of one- vs. two-generation reproductive effects studies was recently evaluated by a panel of experts in a workshop sponsored by the EPA's Risk Assessment Forum. The Panel of experts concluded that, by itself, a one-generation reproductive effects study is insufficient to identify all potential reproductive toxicants and that a two-generation study is needed for an adequate assessment (Ref. 8). Thus, EPA considers that the one-generation study conducted by BIBRA, even when it becomes available in the United States, will not provide the data needed for an adequate assessment of this endpoint. Because there is no benefit in delaying the two-generation reproductive toxicity testing for isopropanol until the BIBRA study becomes available, EPA is requiring testing for this endpoint in this rule.

3. *Developmental toxicity testing.* The Panel recommended that EPA include a two-species developmental toxicity study in its final rule but stay the requirement to conduct testing in the rat until the results of a rat developmental toxicity study conducted by BIBRA becomes available. It further recommended that at this juncture, following a public meeting, EPA could determine whether additional testing in the rat is needed.

EPA concurs with the Panel's contention that the BIBRA study may fulfill the data needs for developmental toxicity testing in rats. To assure that adequate testing is available if BIBRA data are not submitted in a timely manner, EPA is requiring a two-species developmental toxicity test in this rule. The testing requirement in the rat will be reexamined after the BIBRA data are received by EPA.

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4. *Developmental neurotoxicity testing.* a. The Panel noted that in previous test rules, developmental neurotoxicity tests have only been required when data exists to raise concern about this endpoint for the test compound, and that the tests were required as a tier-II type study. The Panel disagreed with EPA's decision to use data on other short chain alcohols, ethanol and t-butanol, to support the decision to require developmental toxicity testing of isopropanol. The Panel stated that studies by Nelson and co-workers on ethanol and 1-propanol (Refs. 9 and 10) only reported changes in neurotransmitter levels and hence can only be used to support similar types of testing rather than the more extensive tests required in the proposed rule.

EPA is concerned that data on other short chain alcohols have shown developmental neurotoxic effects. As stated in the proposed rule, EPA is basing the developmental neurotoxicity testing requirement for isopropanol on the authority of section 4(a)(1)(B), not section 4(a)(1)(A), of TSCA. Because there is a high degree of exposure to isopropanol, EPA has decided that testing should not be delayed.

b. The Panel also noted a number of technical issues with regard to the conduct of the developmental neurotoxicity tests. For instance, statistical questions concerning the number of animals required for each test and neuropathology issues regarding such questions as the type of histologic stains to be used, the techniques for examining the spinal cord and other nerve tissues, and the measurement of brain tissues need to be resolved.

The neuropathology issues were raised earlier in a July 9, 1987 letter from Dr. John L. O'Donoghue to the CMA Glycol Ethers Program concerning similar testing under a consent order for triethylene glycol ethers (Ref. 11). These issues were subsequently addressed (Refs. 12 and 13).

c. Finally, the Panel maintained that an even greater problem with regard to the developmental neurotoxicity tests is the lack of testing facilities that can perform these tests by the required Good Laboratory Practice Standards (GLPS).

On the basis of information available to EPA, it appears that some capability exists for conducting developmental neurotoxicity studies at this time and additional capability will be available in the near future (Ref. 14).

5. *Neurotoxicity testing.* a. The Panel stated that the existing study in humans by Maizlish et al. (Ref. 15) provides sufficient data to indicate that exposure to isopropanol does not result in any neurologic impairment. In this study, workers were exposed to isopropanol at an average concentration of 161 ppm, with both naphtha (50 ppm) and hexane (39 ppm) also present in the air. The Panel noted that neither hexane nor naphtha is metabolized by alcohol dehydrogenase, nor would it be anticipated that these compounds would induce this enzyme, and thus the metabolism of isopropanol should not be affected by the co-exposure. In this study, no relation was observed between solvent exposure and 10 behavioral variables. The Panel contended that the lack of observed effects in humans is supported by the animal data by Boughton (Ref. 16), who observed only slight reversible decrement in performance in rats maintained on drinking water containing sufficient isopropanol to result in weight loss in the test animals. The Panel stated that this is sufficient evidence that isopropanol has little potential to be a neurotoxic agent, and that EPA should not require further testing.

EPA disagrees that the studies cited by the Panel provide sufficient data to evaluate the neurotoxicity of isopropanol. The study of Maizlish et al. has severe limitations. The entire exposed population in this study consisted of 240 workers in four plants; however, the subgroup referred to by the Panel was made up of only 26 individuals from one plant who signed consent forms and were tested. Not only was this group small, but the authors of the study were concerned with biases since only those who volunteered were tested. Also the extent of exposure was determined through an analysis of air in the breathing zone taken only during the week that the behavioral testing was conducted. There is no data to indicate that the reported exposure was representative of exposure in this plant. Possibly the most critical limitation was with regard to study design. As the authors noted, this was a cross-sectional study which has many inherent limitations. The predominant confounders are the healthy worker effect since workers who have ill health are likely to either leave employment or be transferred to other jobs, and not be present at the time the study is conducted. In addition, subjects are not followed up with time, and this does not permit evaluation of deterioration of performance as the subjects age. Also, the early study by Boughton is inadequate, since only one dose was used, 5 percent in drinking water, and the only behavioral test performed was the activity and maze learning tests which would allow for only a limited ability to detect neurological effects. Taken together, these two studies are inadequate to predict the potential for isopropanol to produce neurologic effects, and are insufficient to justify elimination of the proposed testing.

b. The Panel stated that the subchronic neurotoxicity test should not be initiated until completion of the acute study. The benefits cited by the Panel include the ability to identify appropriate doses for the subchronic study, and the identification of potential important endpoints in the acute study which may be monitored more closely in the subchronic test.

EPA agrees that there are advantages to conducting these tests sequentially. There are, however, disadvantages which include delays in the receipt of data, and the inability to conduct the acute tests as a satellite of the subchronic test. Since it is estimated by the Panel that performing the tests sequentially would result in an extension of the reporting requirements from 15 to 30 months, EPA has decided that this would unduly delay obtaining the needed data and that the schedule as outlined in the proposed rule should be maintained.

c. The Panel stated that EPA must resolve technical issues with regard to the adult neurotoxicity tests before the tests are required. Some of these issues are the same as discussed for the developmental neurotoxicity tests and have been addressed. (Refs. 12 and 13).

In addition, the Panel notes that for each of the proposed motor activity tests, "...each test or control group must be designed to contain a sufficient number of animals at the completion of the study to detect a 40 percent change in activity of the test groups relative to the control group with 90 percent power at the 5 percent level." The Panel maintains that testing laboratories and industrial company laboratories have insufficient experience with these test protocols to be able to predict the number of animals needed. Data would not be available from published studies since published articles often underestimate variation, and these tests have been conducted by university groups which have a great deal of experience in conducting such tests. Although the Panel expects that many of these issues will be resolved by neurotoxicity testing that is now underway, the Panel wants the adult neurotoxicity testing to be stayed if unresolved issues remain at the time of promulgation of the final rule on isopropanol.

As noted in the memorandum from Rees (Ref. 13), some judgment is required in determining the parameters

to be used in the determination of sample size. The determination of sample size to allow for confidence in experimental results is not limited to neurotoxicity testing, but is an integral part of all test protocols. It is professional judgement which allows an investigator to determine the number of animals needed and doses to be used to have sufficient animals at the termination of the study for valid interpretation of the results. EPA believes that, with the information gained by ongoing testing and the use of professional judgment, it will be possible to reasonably predict the numbers of animals needed for the adult neurotoxicity tests, and that the small amount of uncertainty involved with regard to the question of number of animals does not justify a delay in testing.

6. *Mutagenicity testing.* a. The Panel 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 results. The Panel stated that this data indicates that in vitro chromosomal aberration tests are not predictive of results obtained in vivo, and hence the requirement for in vitro testing for chromosomal aberrations should be eliminated and an in vivo micronucleus test performed instead. The Panel also stated that the available data on clastogenic effects in vitro, negative tests for meiotic nondisjunction in *Neurospora crassa* and sister chromatid exchange (SCE) in cultured V79 cells, indicate that it is unlikely that isopropanol will be active in other in vitro systems. In addition, since EPA considers the in vivo chromosome aberration assay to be equivalent to the in vivo micronucleus test, the Panel requested that the rule be modified to substitute the latter for the former. Further, the micronucleus test is substantially less expensive and hence fulfills the requirement under TSCA of cost effective testing.

EPA is not requiring the in vitro chromosomal aberration assay for isopropanol. The study of Von der Hude et al. (Ref. 18), which evaluated the potential induction of SCE in vitro, has become available since the evaluation of the data for the proposed rule and fulfills the requirement for an in vitro cytogenetic assay. This recently published study reported on an assay of isopropanol at four concentrations, 3.3, 10.0, 33.3, and 100 mM, in the presence and absence of metabolic activation, and determined that isopropanol was negative. The highest concentration tested was reported to produce cytotoxicity as indicated by a delay in the cell cycle.

In regards to the Panel's arguments for elimination of the in vitro cytogenetic assay as a general rule, EPA does not agree with the Panel. The study by Thompson should not be interpreted to indicate that in vitro testing is unnecessary. In that report, the in vitro tests identified more compounds as potential genotoxic agents than did the in vivo tests. As noted by the authors, the occurrence of activity in vitro and not in vivo may result from detoxification mechanisms or barriers present in the whole animal. It should be concluded from this study that these "false positives" are only false positives as related to the in vivo bone marrow assay, while the activity observed in vitro may be expressed at other target sites.

b. The Panel agreed to perform Tier III tests if earlier results are positive; however, the Panel noted that there is some controversy over the mouse visible specific locus (MVSL) test, that EPA is reexamining the test, and that there is a question whether this relatively expensive test can actually be performed. The Panel recommended that the EPA not require any Tier III tests in the rule, but instead reopen the rulemaking proceedings if Tier III tests are to be required.

EPA is requiring the MVSL test in this rule, but plans to amend all test rules requiring the MVSL through a separate rule. EPA has proposed separately to amend the requirement for the MVSL (40 CFR 798.5200) for proposed and final test rules promulgated under section 4(a) of TSCA. EPA plans to allow test sponsors of current test rules, including this rule for isopropanol, to choose either the MVSL or the mouse biochemical specific locus test (MBSL), after it is promulgated, to test for heritable mutations in mammals. EPA believes that the MBSL and MVSL are comparable tests and are acceptable for detecting this endpoint in mammals. The test guideline for the MBSL was proposed on December 23, 1988 (53 FR 51847) to be codified at 40 CFR 798.5195. EPA is proposing a reporting requirement of 51 months for the completion of testing for either the MVSL or MBSL once triggered. The provision in this final rule for public review prior to requiring Tier III testing will permit EPA and the public to address many of the concerns raised by the Panel with regard to Tier III testing. Requiring the Tier III MVSL testing in the rule will permit a more expeditious treatment of questions concerning Tier III testing than would be obtained by requiring the reopening of the rulemaking process.

7. *Oncogenicity testing.* The Panel's comments reiterate the position it took during the consent order negotiations that the design of the oncogenicity study be determined by evaluation of data on the pharmacokinetics, subchronic, and mutagenicity testing of isopropanol. After evaluation of this data, a determination would be made as to whether a one species or two species oncogenicity study would be required.

EPA requires data from two species under its oncogenicity testing guidelines (40 CFR 798.3300) and cancer risk assessment guidelines (51 FR 33992). For chemicals of unknown activity, such as isopropanol, two mammalian species are needed to increase the power of the test to detect potential carcinogens. Also, a negative single-species bioassay would be insufficient evidence to exonerate isopropanol as a potential carcinogen (Ref. 3).

8. *Pharmacokinetics testing.* a. The Panel did not dispute that pharmacokinetics data were insufficient. The Panel argued that the reporting requirements specified in the proposed rule on isopropanol will make it necessary to initiate subchronic toxicity studies prior to completion of the pharmacokinetics studies. This would preclude use of the pharmacokinetics data for setting dose levels for the subchronic studies. The Panel suggested that it will be necessary to adjust the maximum dose level so that it does not exceed the metabolic saturation point, as defined from the results of pharmacokinetics studies. The Panel proposed that the subchronic and chronic toxicity studies be delayed to allow for completion of the pharmacokinetics studies.

The proposed reporting requirements allow 15 months from the effective date of the final rule for completion of the pharmacokinetics study and the 90-day subchronic study, and 53 months for completion of the 2-year chronic study. EPA believes that the reporting requirements allow sufficient time for completion of the pharmacokinetics study and preliminary data analysis prior to initiating the subchronic and chronic toxicity studies.

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b. The Panel suggested that an additional 9 months will be required to develop inhalation exposure methods and assay procedures for isopropanol and its metabolites, and that these tasks will be time-consuming because the metabolism departments of many testing facilities are unaccustomed to using the inhalation route for pharmacokinetics and metabolism studies.

EPA conducted a study to assess the availability of adequate test facilities and concluded that there will be test facilities and personnel to perform the testing specified in this rule. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing," can be obtained through the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (PB 82- 140773). With respect to assay procedures, the Panel's comments indicated that methods already exist for determining isopropanol and its metabolites in biological materials. Therefore, EPA believes that 15 months allows sufficient time for completion of the pharmacokinetics testing.

c. The Panel suggested that pharmacokinetics data for the mouse may be useful for interpreting mouse bioassays. The Panel indicated that it is prepared to work with EPA to initiate such testing voluntarily. EPA agrees that this data would be extremely useful and encourages the Panel to perform these studies on a voluntary basis.

d. The Panel would like EPA to specify whether inhalation exposures are to be conducted in dynamic or static exposure systems. EPA is requiring inhalation exposures to be conducted in dynamic exposure systems. Inhalation toxicity studies are generally performed under dynamic exposure conditions; guidelines for subchronic inhalation toxicity studies specify dynamic exposures (see 40 CFR 798.2450). It is also the most consistent with the goals of risk assessment extrapolations, which are based on assuming continuous exposures to a constant concentration of air-borne chemicals. Furthermore, it is the only exposure system in which exposure to volatile metabolites can be prevented.

e. The Panel expressed concern about the requirement for use of radioisotopes in the pharmacokinetics studies. The Panel suggested that very large quantities of radioactivity would be required for dynamic inhalation exposures and that incorporation of radiolabel into tissue constituents may lead to confusing or misleading data on distribution of the test substance.

EPA believes that use of radiolabel in conjunction with chromatographic techniques provides the most reliable and sensitive means for detecting metabolites and for evaluating mass balance for the carbon skeleton of the test substance. The objective of the metabolite identification requirements specified in the proposed rule is to identify the major metabolites of isopropanol in tissues and excreta, to provide data for evaluating the contribution of metabolism to detoxification or activation of isopropanol in the test species. If metabolic incorporation of the radiolabel into tissue constituents is a quantitatively significant metabolic fate of isopropanol, then this should be documented with data regarding the identity of the incorporated label. Such incorporation may represent fixation of CO_2 derived from the degradation of isopropanol or may represent a covalent interaction of tissue constituents with reactive metabolites of isopropanol. In either case, it will be important to document the nature of the incorporation. Indeed, only with the use of radiolabeled isopropanol is this kind of rigorous analysis possible.

f. The Panel expressed concern about the requirement for collection of exhaled air, urine, and feces excreta during nose-only or head-only inhalation exposures, and indicated that the latter is not technically feasible. EPA agrees that collection of multiple samples of urine and feces from such an apparatus may be very difficult and has modified the guideline accordingly.

g. The Panel expressed concern about the definition for percent absorption that is cited in the proposed rule. The definition given by EPA is "...100 times the ratio between total excretion of radioactivity following oral or inhalation administration and total excretion of radioactivity following intravenous administration of test substance." EPA agrees that for compounds administered by the oral route, this calculation may overestimate the actual percent absorption by that amount of chemical that passes through the gastrointestinal tract without absorption. Thus, EPA has modified the guideline to reflect this change.

h. The Panel expressed concern over the selection of an appropriate toxicity endpoint on which to base the selection of the high dose level to be used in the pharmacokinetics studies.

The objective of the high-dose level study is to examine the absorption, distribution, metabolism and excretion of the test substance at the highest dose level that can be achieved without severely perturbing or impairing the above mechanisms. Dose levels that produce frank effects, e.g., convulsions, coma, and death, are clearly unacceptable since the disposition mechanisms are likely to be severely perturbed or impaired in severely poisoned animals. Ideally, the high dose level should be the lowest observable effect level. This effect will vary depending on the chemical and its toxicologic characteristics. In the case of isopropanol, for which narcosis represents an important critical effect, the dose level at or just below that required to produce mild symptoms of narcosis seems appropriate. The relevant observation period in which to define the effect would include the exposure and sampling period, since it would not be productive to expose an animal to a dose that results in unconsciousness or frank effects after the exposure and before the sampling was completed. Note that toxicity will define the highest dose level acceptable for testing; however, this does not preclude testing of several levels below the high-dose level, although EPA requires that only one nontoxic dose level be examined.

C. TSCA Sections 4 and 12(B) Requirements

PGC proposed that EPA exclude small manufacturers and importers from the requirements of section 4. PGC suggested this exclusion include production or importation of 25,000 lb/yr or less. In addition, PGC suggested that EPA eliminate the requirement for all section 12(b) reporting for isopropanol, since the benefit would not be commensurate with the burden that this reporting requirement would place upon EPA. If all section 12(b) reporting is not exempted, then PGC further recommended that a small quantity exemption (shipment of 25,000 lb/yr or less) be used to eliminate the burden to small companies.

Since these issues apply to all section 4 rules and consent orders and the commenter has not distinguished how this rule is any more burdensome than other section 4 rules, EPA rejects these comments. EPA is continuing to look at the burden of section 4 and 12(b) requirements. EPA has proposed amendments to its procedural rule that would alleviate the requirement of certain manufacturers to submit letters of intent to test or submit exemption applications (54 FR 21237; May 17, 1989). EPA has also proposed amendments to its section 12(b) rules (54 FR 29524; July 12, 1989) to reduce the burden of section 12(b) notification as it relates to section 4.

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D. Summary of NRDC's Comments

In general, NRDC concurred with the testing program outlined by EPA in its proposed rule for isopropanol. Specifically, NRDC agreed that oncogenicity testing must be conducted in two species and that a two-generation study is necessary to adequately assess reproductive effects. NRDC recommended that the BIBRA study on the developmental effects be used to replace the required developmental testing in the rat only if it is submitted and reviewed in a timely fashion.

III. Final Test Rule for Isopropanol

A. Findings

EPA is basing its final health effects testing requirements for isopropanol on the authority of section 4(a)(1)(B) of TSCA.

EPA finds that isopropanol is produced in substantial quantities and that there is or may be substantial human exposure to isopropanol from its manufacture, processing, use, and disposal. The available data on isopropanol, discussed in Unit II. of the preamble to the proposed rule (53 FR 8638), show that the annual production volume of isopropanol has been in excess of 1 billion pounds since 1956, and that it was ranked 50th among chemicals produced in the United States in 1985. There is or may be a substantial number of workers exposed to isopropanol from activities related to its manufacturing, processing, distribution in commerce, and use. The National Occupational Hazard Survey (NOHS) conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974 estimated that there were 8,899,594 exposures in 357,173 plants, potentially exposing 5,483,862 people to isopropanol in the workplace in 1970. The National Occupational Exposure Survey (NOES) estimates that 1,857,972 workers, 60 percent of whom were female, were potentially exposed to isopropanol in the workplace in 1980.

Isopropanol is used as a solvent and is a component of numerous industrial products, consumer products, and commercial sprays. The above uses may result in widespread exposure to workers and consumers (Ref. 5). EPA believes that exposures associated with the manufacture, processing, use, and disposal of isopropanol and its products provide a sufficient basis for a finding that there is or may be substantial human exposure under TSCA section 4(a)(1)(B) for isopropanol.

Under TSCA Section 4(a)(1)(B)(ii) and (iii), EPA finds that existing data are insufficient to reasonably determine or predict the subchronic, reproductive, developmental, neurotoxic, developmental neurotoxic, mutagenic, and oncogenic effects of human exposure to isopropanol resulting from its manufacture, processing, use, and disposal. EPA also finds that there are insufficient data to reasonably predict and compare the absorption, distribution, metabolism, and excretion of isopropanol in the body as a result of oral or inhalation exposure due to isopropanol's manufacture, processing, use, and disposal, and that an oral/inhalation comparative pharmacokinetics study of isopropanol is necessary to develop such data. The reasons data are insufficient are further discussed in Unit II. B. of this preamble. 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 isopropanol does or does not present an unreasonable risk of injury to human health.

B. Required Testing and Test Standards

On the basis of these findings, EPA is requiring that certain health effects testing be conducted for isopropanol in accordance with scientific test guidelines set forth in 40 CFR 795 and 798.

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).

EPA is requiring that testing for reproductive effects (40 CFR 798.4700), and developmental toxicity (40 CFR 798.4900) be done by gavage.

To assess the effects of acute neurotoxic inhalation exposures to isopropanol, EPA is requiring an acute neurobehavioral toxicity evaluation consisting of a functional observational battery (40 CFR 798.6050), and measurement of motor activity (40 CFR 798.6200).

To assess the neurotoxic effects of repeated inhalation exposures to isopropanol, EPA is requiring a subchronic neurobehavioral toxicity evaluation consisting of a neuropathologic evaluation of tissues perfused in situ (40 CFR 798.6400), a functional observational battery (40 CFR 798.6050), and measurement of motor activity (40 CFR 798.6200). This required battery of neurotoxic evaluation may be combined with the subchronic test (40 CFR 798.2450).

To assess the developmental neurotoxicity potential of isopropanol, EPA is requiring a developmental neurotoxicity evaluation (40 CFR 795.250).

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.

To assess the potential for isopropanol to cause chromosomal aberrations, EPA is requiring that an in vivo bone marrow assay (40 CFR 798.5385) be conducted. Should the in vivo bone marrow test results prove negative, no further chromosomal aberrations testing is required. If the results of the in vivo bone marrow test are positive, a dominant-lethal assay is required (40 CFR 798.5450). A positive result in the dominant-lethal assay will trigger a heritable translocation assay (40 CFR 798.5460).

If the results from the dominant-lethal assay and/or the SLRL are positive, EPA will hold a public program review prior to requiring initiation of the heritable translocation and/or mouse specific locus testing. Public participation in this program review will be in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting, if one is held, will be published in the Federal Register. Should EPA determine, based on the weight of the evidence then available, that proceeding to the heritable translocation test and/or MVSL assay is no longer warranted, EPA will propose to repeal that test requirement and, after public comment, will issue a final amendment to rescind the requirement. For a more detailed discussion concerning mutagenicity tiered testing and program review, see the final test rule for the C_4 aromatic hydrocarbon fraction (50 FR 20662; May 17, 1985).

EPA believes that the oncogenicity testing is justified without waiting for the results of gene mutation tests. EPA is thus requiring a 2-year inhalation bioassay in two species (40 CFR 798.3300).

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 of isopropanol is necessary to reduce uncertainties associated with the

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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.

EPA is establishing the TSCA health effects test guidelines as the test standards for the purpose of the required tests for isopropanol. The TSCA test guidelines for health effects testing specify generally accepted minimum conditions for determining the health effects for substances like isopropanol to which humans are expected to be exposed.

C. Test Substance

EPA is requiring that isopropanol of at least 99.8 percent purity be used as the test substance. Commercial isopropanol of such purity is available according to comments received from the Panel (Ref. 1). EPA has specified a relatively pure substance for testing to best evaluate the effects attributable to isopropanol itself. In addition, radiolabeled 14C isopropanol is required for the pharmacokinetics.

D. Persons Required to Test

Section 4(b)(3)(B) of TSCA specifies that the activities for which EPA makes section 4(a) findings (manufacture, processing, distribution in commerce, use, and/or disposal) determine who bears the responsibility for testing a chemical. Because EPA has found that there are insufficient data and experience to reasonably determine or predict the effects on human health from manufacture, processing, use, and disposal of isopropanol, EPA is requiring that persons who manufacture and/or process, or who intend to manufacture and/or process, isopropanol, other than as an impurity, at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the testing requirements in this final rule. While EPA has not identified any byproduct manufacturers of isopropanol, such persons are covered by the requirements of this test rule. The reimbursement period will end 5 years after the last final report is submitted to EPA or an amount of time equal to that which was required to develop data, whichever is later.

E. Reporting Requirements

EPA requires that all data developed under this rule be reported in accordance with its TSCA GLPS, which appear in 40 CFR Part 792.

In accordance with 40 CFR Part 790 under single-phase rulemaking procedures, test sponsors are required to submit individual study plans at least 45 days prior to the initiation of each study.

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. Thespecific reporting requirements for each of the test standards for isopropanol are specified in the following table:

TABLE—REQUIRED TESTING, TEST STANDARDS, AND REPORTING REQUIREMENTS FOR ISOPROPANOL

Test	Test Standard (40 CFR Citation)	Reporting Deadline for Final Report (Months)[1]	Number of Interim (6-month) Reports Required
Health Effects:			
1. Subchronic inhalation toxicity	§ 798.2450	15	2
2. Reproduction and fertility effects	§ 798.4700	29	4
3. Developmental toxicity	§ 798.4900	12	1
Mutagenicity - gene mutations:			
4. Mammalian cells in culture	§ 798.5300	6	—
5. *Drosophila* sex-linked recessive lethal	§ 798.5275	18	2
6. Mouse visible specific locus test	§ 798.5200	51	8
Mutagenicity - chromosomal aberrations:			
7. In vivo cytogenetics: micronucleus	§ 798.5395	15	2
8. Dominant lethal assay	§ 798.5450	27	4
9. Heritable translocation assay	§ 798.5460	24[2]	3
Acute neurotoxicity:			
10. Functional observation battery	§ 798.6050	15	2
11. Motor activity	§ 798.6200	15	2
Subchronic neurotoxicity:			
12. Functional observation battery	§ 798.6050	18	2
13. Motor activity	§ 798.6200	18	2
14. Neuropathology	§ 798.6400	18	2
15. Developmental neurotoxicity	§ 795.250	21	3
Chronic toxicity:			
16. Oncogenicity	§ 798.3300	53	8
Pharmacokinetics:			
17. Oral and inhal. Pharmacokinetics	§ 795.231	15	2

[1] Number of months after the effective date of the final rule, except as indicated.
[2] Figure indicates the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or FEDERAL REGISTER notice that, following public program review of all of the then existing data for isopropanol, the Agency has determined that the required testing must be performed.

Persons who export a chemical which is subject to a final section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final rules interpreting the requirements of section 12(b) are in 40 CFR Part 707. In brief, as of the effective date of the final test rule, an exporter of isopropanol must report to EPA the first annual export or intended export of isopropanol to each country. EPA will

notify the foreign country concerning the test rule for the chemical.

F. Enforcement Provisions

EPA considers failure to comply with any aspect of a section 4 rule to be a violation of section 15 of TSCA. Section 15(1) of TSCA makes it unlawful for any person to fail or refuse to comply with any rule or order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to: (1) Establish or maintain records, (2) submit reports, notices, or other information, or (3) permit access to or copying of records required by TSCA. Section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by TSCA section 11. Section 11 applies to any "...establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce..." EPA considers a testing facility to be a place where the chemical is held or stored and, therefore, subject to inspection. Laboratory inspections and data audits will be conducted periodically in accordance with the authority and procedures outlined in TSCA section 11 by duly designated representatives of EPA for the purpose of determining compliance with the final rule for isopropanol. These inspections may be conducted for purposes which include verification that testing has begun, schedules are being met, and reports accurately reflect the underlying raw data, interpretations, and evaluations, and to determine compliance with TSCA GLPS and the test standards established in the rule.

EPA's authority to inspect a testing facility also derives from section 4(b)(1) of TSCA, which directs EPA to promulgate standards for the development of test data. These standards are defined in section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and to include such other requirements as are necessary to provide such assurance. EPA maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provisions of section 16 of TSCA, any person who violates section 15 of TSCA could be subject to a civil penalty of up to $25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers who fail to submit a letter of intent or an exemption request and who continue manufacturing after the deadlines for such submissions. This provision also applies to processors that fail to submit a letter of intent or an exemption application and continue processing after EPA has notified them of their obligation to submit such documents (see 40 CFR 790.28(b)). Knowing or willful violations could lead to the imposition of criminal penalties of up to $25,000 for each day of violation, imprisonment for up to 1 year, or both. In determining the amount of penalty, EPA will take into account the seriousness of the violation and the degree of culpability of the violator as well as all the other factors listed in TSCA section 16. Other remedies are available to EPA under section 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Sections 15 and 16 of TSCA apply to "any person" who violates provisions of TSCA. EPA may, at its discretion, proceed against individuals as well as companies themselves. In particular, this includes individuals who report false information or who cause it to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

IV. Economic Analysis of Final Rule

To assess the potential economic impact of this rule, EPA has prepared an economic analysis (Ref. 19) that evaluates the potential for significant economic impact on the industry as a result of the required testing. The economic analysis estimates that costs of conducting the required testing and evaluates the potential for significant adverse economic impact as a result of these tests costs by examining four market characteristics of isopropanol: (1) price sensitivity of demand; (2) market expectations; (3) industry cost characteristics; and (4) industry structure.

Total testing costs for the final rule for isopropanol are estimated to range from $2.6 to $3.8 million. To predict the financial decision making practices of manufacturing firms, these costs have been annualized. Annualized costs are compared with annual revenue as an indication of potential impact. The annualized costs represent equivalent constant costs which would have to be recouped each year of the payback period to finance the testing expenditure in the first year.

The annualized test costs, using a 7 percent cost of capital over a period of 15 years, range from $289,000 to $412,000. Based on 1987 production of 1.4 billion pounds, the unit test costs range from $0.00021 to $0.00029 per pound. These costs are equivalent to 0.09 to 0.13 percent of the current price of $0.23 per pound.

EPA believes that the potential for adverse economic impact resulting from the costs of testing is low. This conclusion is based on the following observations:

1. The annualized cost of testing is very low, at approximately 0.13 percent of product prices in the upper bound case.

2. Demand for isopropanol does not appear to be sensitive to a price increase in this range.

Refer to the economic analysis which is contained in the public record for this rule making for a complete discussion of test cost estimation and potential for economic impact resulting from these costs.

V. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "...the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing," can be obtained through the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (PB 82-140773). On the basis of this study, EPA believes that there will be available test facilities and personnel to perform the testing specified in this rule.

EPA has reviewed the availability of contract laboratory facilities to conduct the neurotoxicity testing requirements (Ref. 20) and believes that facilities will be made available for conducting these tests. The laboratory review indicates that few laboratories are currently conducting these tests according to TSCA test guidelines and TSCA GLPS. However, the barriers faced by testing laboratories to gear up for conducting these tests are not formidable. Laboratories will need to invest in testing equipment and personnel training, but EPA believes that these investments will be recovered as the neurotoxicity testing programs under TSCA section 4 and the Federal Insecticide, Fungicide and Rodenticide

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Act (FIFRA) continue. EPA's expectations of laboratory availability were borne out under the testing requirements of the C_9 aromatic hydrocarbon fraction test rule (50 FR 20675; May 17, 1985). Pursuant to that rule, the manufacturers were able to contract with a laboratory to conduct the testing according to TSCA guidelines and TSCA GLPS.

VI. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42097B). This record includes the following information:

A. Supporting Documentation

(1) **Federal Register** notices pertaining to this rule consisting of:

(a) Notice containing the ITC designation of isopropanol to the Priority List (51 FR 41417; November 14, 1986) and all comments on isopropanol received in response to that notice.

(b) Rules requiring TSCA section 8(a) and (d) reporting on isopropanol (51 FR 41328; November 14, 1986).

(c) Notice of final rule on EPA's TSCA Good Laboratory Practice Standards (48 FR 53922; November 29, 1983).

(d) Notice of interim final rule on single-phase test rule development and exemption procedures (50 FR 20652; May 17, 1985).

(e) Notice of final rule on data reimbursement policy and procedures (48 FR 31786; July 11, 1983).

(f) Interim Final Rule: Procedures Governing Testing Consent Agreements and Test Rules Under the Toxic Substances Control Act (51 FR 23706; June 30, 1986).

(2) Communications consisting of:

(a) Written public comments and letters.

(b) Contact reports of telephone conversations.

(c) Meeting summaries.

(3) Reports--published and unpublished factual materials including Chemical Testing Industry: Profile of Toxicological Testing (October, 1981).

B. References

(1) CMA's Isopropanol Program Panel. Comments on EPA's Proposed Test Rule for Isopropanol submitted to Public Information Office, USEPA (May 16, 1988).

(2) The Procter & Gamble Company. Comments on EPA's Proposed Test Rule for Isopropanol submitted to Public Information Office, USEPA (May 16, 1988).

(3) Natural Resources Defense Council. Comments on EPA's Proposed Test Rule for Isopropanol submitted to Public Information Office, USEPA (May 16, 1988).

(4) CMA's Isopropanol Program Panel. Letter from Geraldine V. Cox, Chemical Manufacturers Association, 2501 M Street NW, Washington, DC 20037, to Richard Troast, Test Rules Development Branch, Office of Toxic Substances, USEPA, Washington, DC (July 21, 1988).

(5) USEPA. "Worker exposure assessment for isopropanol (IPA)."

John D. Walker, Test Rules Development Branch, Office of Toxic Substances, USEPA, Washington, DC (November 20, 1985).

(6) Pellizzari, E.D., et al., "Purgeable organic compounds in mother's milk." Bulletin of Environmental Contamination and Toxicology, 28:222-238 (1982).

(7) McGregor, D.B. "Genotoxicity of glycol ethers." *Environmental Health Perspectives*, 57:97-103 (1984).

(8) Syracuse Research Corporation. "Response to public comments: Isopropanol." Contract No. 68-02-4209 (September 29, 1988).

(9) Nelson, B.K., et al., "Neurological, but not behavioral deviations in the offspring of rats following prenatal inhalation exposure to ethanol." *Neurotoxicology and Teratology*, 10:15-22 (1988).

(10) Nelson, B.K., et al., "Behavioral teratology investigation of 1-propanol administered by inhalation to rats." Paper presented at Teratology Society Meeting (1988).

(11) Eastman Kodak Company. Letter from John L. O'Donoghue, Eastman Kodak Company, 343 State Street, Rochester, NY 14650, to Carol Stack, Chemical Manufacturers Association, 2501 M Street NW, Washington, DC 20037 (July 9, 1987).

(12) USEPA. "Response to industry comments on the neuropathology portion of the glycol ether test rule." Intraagency memorandum from Robert C. MacPhail, Health Effects Research Laboratory, to Carol Glasgow, Test Rules Development Branch, Office of Toxic Substances, USEPA, Washington, DC (January 6, 1988).

(13) USEPA. "OTS-ORD comments on the proposed protocol for neurotoxicolo1gical testing of triethylene glycol 1monomethyl ether." Intraagency memorandum from David C. Rees, Health and Environmental Review Division, to Ralph Northrup, Test Rules Development Branch, Office of Toxic Substances, USEPA, Washington, DC (February 5, 1988).

(14) Mathtech, Inc. "Developmental neurotoxicity laboratory capability." Intraoffice memorandum from J.K. Orrell to Edmund Coe, Mathtech, Inc., 5111 Leesburg Pike, Falls Church, VA 22041 (September 19, 1988).

(15) Maizlish, N.A., et al. "Behavioral evaluation of workers exposed to mixture of organic solvents." *British Journal of Industrial Medicine*, 42:579-590 (1985).

(16) Boughton, L.I. "The relative toxicity of ethyl and isopropyl alcohols as determined by long term rat feeding and external application." Journal of *American Pharmacology Association*, 33:111-113 (1944).

(17) Thompson, E.D. "Comparison of *in vivo* and *in vitro* cytogenetic assay results." *Environmental Mutagenesis*, 8:753-767 (1986).

(18) Von der Hude, W. et al. "Genotoxicity of three-carbon compounds evaluated in the SCE test *in vitro*." *Environmental Mutagenesis*, 9:401-410 (1987).

(19) USEPA. Economic impact analysis of final test rule for isopropanol. Office of Toxic Substances, USEPA, Washington, DC (February 22, 1989).

(20) Mathtech, Inc. "Evaluation of TSCA guidelines for neurotoxicity testing: Impact of increased testing requirements." Prepared for Regulatory Impacts Branch, USEPA (April 14, 1987).

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection in the TSCA Public Docket Office, Rm. G-004, NE Mall, 401 M St., SW, Washington, DC 20460.

VII. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a rule is "major" and therefore subject to the requirement of a Regulatory Impact Analysis. EPA has determined that this test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order; i.e., it will not have an annual effect on the economy of at least $100 million, will not cause a major increase in prices, and will not have a significant adverse effect on competition or the ability of U.S. enterprises to compete with foreign enterprises.

This rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments from OMB to EPA, and any EPA responses to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule will not have a significant impact on a substantial number of small businesses because: (1) They are not likely to perform testing themselves, or to participate in the organization of the testing effort; (2) they will experience only very minor cost, if any, in securing exemption from testing requirements; and (3) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this final rule under the provisions of the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*, Pub. L. 96-511, December 11, 1980), and has assigned control number 2070-0033.

Public reporting burden for this collection of information is estimated to average 1,190 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to, Chief, Information Policy Branch (PM-223), U.S. EPA, 401 M St., SW, Washington, DC 20460 and to the Office of Information and Regulatory Affairs, OMB, Washington, DC 20503.

List of Subjects in 40 CFR Parts 795 and 799

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

Dated: September 22, 1989

Victor J. Kimm,

Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR chapter I, subchapter R, is amended as follows:

1. In part 795:

a. The authority citation for part 795 continues to read as follows:

Authority: 15 U.S.C. 2603.

b. By adding § 795.231 to read as follows:

§ 795.231 Pharmacokinetics of isopropanal.

(a) *Purpose.* The purposes of these studies are to:

(1) Ascertain whether the pharmacokinetics and metabolism of the "test substance" are similar after oral and inhalation administration.

(2) Determine bioavailability of the test substance after oral and inhalation administration.

(3) Examine the effects of repeated dosing on the pharmacokinetics and metabolism of the test substance.

(b) *Definitions.* (1) "*Bioavailability*" refers to the rate and relative amount of administered test substance which reaches the systemic circulation.

(2) "*Metabolism*" means the study of the sum of the processes by which a particular substance is handled in the body, and includes absorption, tissue distribution, biotransformation, and excretion.

(3) "*Pharmacokinetics*" means the study of the rates of absorption, tissue distribution, biotransformation, and excretion.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species.* The rat shall be used because it has been used extensively for metabolic and toxicological studies.

(ii) *Test animals.* For pharmacokinetics testing, adult male and female rats (Fischer 344 or strain used for major toxicity testing), 7 to 9 weeks of age, shall be used. The animals should be purchased from a reputable dealer and shall be identified upon arrival at the testing laboratory. The animals shall be selected at random for the testing groups and any animal showing signs of ill health shall not be used. In all studies, unless otherwise specified, each test group shall contain at least four animals of each sex for a total of at least eight animals.

(iii) *Animal care.* (A) Animal care and housing should be in accordance with DHEW Publication No. (NIH)-85-23, 1985, entitled "Guidelines for the Care and Use of Laboratory Animals."

(B) The animals should be housed in environmentally controlled rooms with at least 10 air changes per hour. The rooms shall be maintained at a temperature of 22±2 °C and humidity of 50±20 percent with a 12-hour light/dark cycle per day. The animals shall be kept in a quarantine facility for at least 7 days prior to use and shall be acclimated to the experimental environment for a minimum of 48 hours prior to treatment.

(C) During the acclimatization period, the animals should be housed in suitable cages. All animals shall be provided with certified feed and tap water *ad libitum.*

(2) *Administration of test substance*—(i) *Test substance.* The use of radioactive test substance is required for all materials balance and metabolite identification requirements of the study. Ideally, the purity of both radioactive and nonradioactive test substance should be greater than 99 percent. The radioactive and nonradioactive substances shall be chromatographed separately and together to establish purity and identity. If the purity is less than 99 percent or if the chromatograms differ significantly, EPA should be consulted.

(ii) *Dosage and treatment*—(A) *Intravenous.* The low dose of test substance, in an appropriate vehicle, shall be administered intravenously to four rats of each sex.

(B) *Oral.* Two doses of test substance shall be used in the oral portion of the study, a low dose and a high dose. The high dose should ideally induce some overt toxicity, such as weight loss. The low dose level should correspond to a no-observed effect level. The oral dosing shall be accomplished by gavage or by administering an encapsulated test substance. If feasible, the same high and low doses should be used for oral and dermal studies.

(C) *Inhalation.* Two concentrations of the test substance shall be used in this portion of the study, a low concentration and a high concentration. The high concentration should ideally induce some overt toxicity, while the low concentration should correspond to a no observed level. Inhalation treatment should be conducted using a "nose-cone" or "head only" apparatus to prevent ingestion of the test substance through "grooming".

(iii) *Dosing and sampling schedule.* After administration of the test substance, each rat shall be placed in a separate metabolic unit to facilitate collection of excreta. For the inhalation studies, excreta from the rats shall also be collected during the exposure periods. At the end of each collection period, the metabolic units shall be cleaned to recover any excreta that might adhere to the cages. All studies, except the repeated dose study, shall be terminated at 7 days, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(A) *Intravenous study.* Group A shall be dosed once intravenously at the low dose of test substance.

(B) *Oral studies.* (*1*) Group B shall be dosed once *per os* with the low dose of the test substance.

(*2*) Group C shall be dosed once *per os* with the high dose of the test substance.

(C) *Inhalation studies.* A single 6-hour exposure period shall be used for each group.

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(1) Group D shall be exposed to a mixture of the test substance in air at the low concentration.

(2) Group E shall be exposed to a mixture of test substance in air at the high concentration.

(D) *Repeated dosing study.* Group F shall receive a series of single daily oral low doses of nonradioactive test substance over a period of at least 7 consecutive days. Twenty four hours after the last nonradioactive dose, a single oral low dose of radioactive test substance shall be administered. Following dosing with radioactive substance, the rats shall be placed in individual metabolic units as described in paragraph (c)(2)(iii) of this section. The study shall be terminated 7 days after the last dose, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(3) *Types of studies*—(i) *Pharmacokinetics studies.* Groups A through F shall be used to determine the kinetics of absorption of the test substance. In groups administered the substance by intravenous or oral routes, (i.e., Groups A, B, C, F), the concentration of radioactivity in blood and excreta including expired air shall be measured following administration. In groups administered the substance by the inhalation route (i.e., Groups D and E), the concentration of radioactivity in blood shall be measured at selected time intervals during and following the exposure period. In the groups administered the substance by inhalation (i.e., Groups D and E), the concentration of radioactivity in excreta (including expired air) shall be measured at selected time intervals following the exposure period. In addition, in the groups administered the substance by inhalation, the concentration of test substance in inspired air shall be measured at selected time intervals during the exposure period.

(ii) *Metabolism studies.* Groups A through F shall be used to determine the metabolism of the test substance. Excreta (urine, feces, and expired air) shall be collected for identification and quantification of test substance and metabolites.

(4) *Measurements*—(i) *Pharmacokinetics.* Four animals from each group shall be used for these purposes.

(A) *Bioavailability.* The levels of radioactivity shall be determined in whole blood, blood plasma or blood serum at 15 minutes, 30 minutes, 1, 2, 3, 6, 9, and 18 hours after dosing; and at 30 minutes, 3, 6, 6.5, 7, 8, 9, 12, and 18 hours after initation of inhalation exposure.

(B) *Extent of absorption.* The total quantities of radioactivity shall be determined for excreta collected daily for 7 days, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(C) *Excretion.* The quantities of radioactivity eliminated in the urine, feces, and expired air shall be determined separately at appropriate time intervals. The collection of the intact test substance or its metabolites, including carbon dioxide, may be discontinued when less than 1 percent of the administered dose is found to be exhaled as radioactive carbon dioxide in 24 hours.

(D) *Tissue distribution.* At the termination of each study, the quantities of radioactivity in blood and in various tissues, including bone, brain, fat, gastrointestinal tract, gonads, heart, kidney, liver, lungs, muscle, skin, spleen, and residual carcass of each animal shall be determined.

(E) *Changes in pharmacokinetics.* Results of pharmacokinetics measurements (i.e., biotransformation, extent of absorption, tissue distribution, and excretion) obtained in rats receiving the single low oral dose of test substance (Group B) shall be compared to the corresponding results obtained in rats receiving repeated oral doses of test substance (Group F).

(F) *Biotransformation.* Appropriate qualitative and quantitative methods shall be used to assay urine, feces, and expired air collected from rats. Efforts shall be made to identify any metabolite which comprises 5 percent or more of the dose eliminated.

(G) *Changes in biotransformation.* Appropriate qualitative and quantitative assay methodology shall be used to compare the composition of radioactive substances in excreta from the rats receiving a single oral dose (Groups B and C) with those in the excreta from rats receiving repeated oral doses (Group F).

(ii) [Reserved]

(d) *Data and reporting.* The final test report shall include the following:

(1) *Presentation of results.* Numerical data shall be summarized in tabular form. Pharmacokinetics data shall also be presented in graphical form. Qualitative observations shall also be reported.

(2) *Evaluation of results.* All quantitative results shall be evaluated by an appropriate statistical method.

(3) *Reporting results.* In addition to the reporting requirements as specified in the EPA Good Laboratory Practice Standards (40 CFR 792.185), the following specific information shall be reported:

(i) Species and strains of laboratory animals.

(ii) Chemical characterization of the test substance, including:

(A) For the radioactive test substance, information on the site(s) and degree of radiolabeling, including type of label, specific activity, chemical purity, and radiochemical purity.

(B) For the nonradioactive substance, information on chemical purity.

(C) Results of chromatography.

(iii) A full description of the sensitivity, precision, and accuracy of all procedures used to generate the data.

(iv) Extent of absorption of the test substance as indicated by: percent absorption of the administered oral dose; and total body burden after inhalation exposure.

(v) Quantity and percent recovery of radioactivity in feces, urine, expired air, and blood.

(vi) Tissue distribution reported as quantity of radioactivity in blood and in various tissues, including bone, brain, fat, gastrointestinal tract, gonads, heart, kidney, liver, lung, muscle, skin, spleen and in residual carcass of each rat.

(vii) Biotransformation pathways and quantities of the test substance and metabolites in excreta collected after administering single high and low doses to rats.

(viii) Biotransformation pathways and quantities of the test substance and metabolites in excreta collected after administering repeated low doses to rats.

(ix) Pharmacokinetics model(s) developed from the experimental data.

2. In part 799:

a. The authority citation for part 799 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. By adding § 799.2325 to read as follows:

§ 799.2325 Isopropanol.

(a) *Identification of test substance.* (1) Isopropanol (CAS No. 67-63-0) shall be tested in accordance with this section.

(2) Isopropanol of at least 99.8 percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests, and submit data.* All persons who manufacture (including import or byproduct manufacture) or intend to manufacture or process isopropanol, from the effective date of this rule to the end of the reimbursement period, shall submit letters of intent to conduct testing, submit study plans, conduct tests, and submit data or submit exemption applications as specified in this section, subpart A of this part, and

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parts 790 and 792 of this chapter for single-phase rulemaking.

(c) *Health effects testing*—(1) *Subchronic inhalation toxicity*—(i) *Required testing.* A subchronic inhalation toxicity test shall be conducted with isopropanol in accordance with § 798.2450 of this chapter.

(ii) *Reporting requirements.* (A) The subchronic inhalation toxicity test shall be completed and the final report submitted to EPA within 15 months of the date specified in paragraph (d) of this section.

(B) Progress reports shall be submitted to EPA for the subchronic inhalation toxicity test at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the final report.

(2) *Reproduction and fertility effects*—(i) *Required testing.* A reproduction and fertility effects test shall be conducted by gavage with isopropanol in accordance with § 798.4700 of this chapter.

(ii) *Reporting requirements.* (A) The reproduction and fertility effects test shall be completed and the final report submitted to EPA within 29 months of the date specified in paragraph (d)(1) of this section.

(B) Progress reports shall be submitted at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the final report.

(3) *Developmental toxicity*—(i) *Required testing.* A developmental toxicity test shall be conducted in two mammalian species by gavage with isopropanol in accordance with § 798.4900 of this chapter.

(ii) *Reporting requirements.* (A) The developmental toxicity test shall be completed and the final report submitted to EPA within 12 months of the date specified in paragraph (d)(1) of this section.

(B) A progress report shall be submitted 6 months after the date specified in paragraph (d)(1) of this section.

(4) *Mutagenic effects—gene mutations*—(i) *Required testing.* (A) A gene mutation test in mammalian cells shall be conducted with isopropanol in accordance with § 798.5300 of this chapter.

(B)(*1*) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with isopropanol in accordance with § 798.5275 of this chapter, except for the provisions in paragraphs (d)(5)(ii) and (iii) of § 798.5275, unless the results of the mammalian cells in the culture gene mutation test conducted pursuant to paragraph (c)(5)(i)(A) of this section are negative.

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

(*i*) *Route of administration.* The route of administration shall be by exposure to isopropanol vapors or by injection of isopropanol.

(*ii*) [Reserved]

(C)(*1*) The mouse visible specific locus (MVSL) test shall be conducted with isopropanol by inhalation in accordance with § 798.5200, except for the provisions in paragraphs (d)(5)(ii) and (iii) of § 798.5200, if the results of the sex-linked recessive lethal test conducted pursuant to paragraph (c)(4)(i)(B) of this section are positive and if, after a public program review, EPA issues a **Federal Register** notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

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

(*i*) *Dose levels and duration of exposure.* A minimum of 2 dose levels shall be tested. The duration of exposure shall be for 6 hours per day. Duration of exposure shall be dependent upon accumulated total dose desired for each group.

(*ii*) *Route of administration.* Animals shall be exposed to isopropanol by inhalation.

(ii) *Reporting requirements.* (A) The gene mutation tests shall be completed and final report submitted to EPA as follows:

(*1*) The gene mutation in mammalian cells assay within 6 months of the date specified in paragraph (d)(1) of this section.

(*2*) The sex-linked recessive-lethal test in *Drosophila melanogaster* within 18 months of the date specified in paragraph (d)(1) of this section.

(*3*) The mouse visible specific-locus test within 51 months of the date of EPA's notification of the test sponsor by certified letter or **Federal Register** notice under paragraph (c)(4)(i)(C) of this section that testing shall be initiated.

(B) Progress reports shall be submitted to EPA for the *Drosophila* sex-linked recessive lethal test at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until the submission of the final report.

(C) Progress reports shall be submitted to EPA for the mouse visible specific locus test at 6-month intervals beginning 6 months after the date of EPA's notification of the test sponsor that testing shall be initiated until submission of the final report.

(5) *Mutagenic effects—chromosomal aberrations*—(i) *Required testing.* (A)(*1*) The micronucleus test shall be conducted with isopropanol in accordance with § 798.5395 of this chapter.

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

(*i*) *Route of administration.* Animals shall be exposed to isopropanol by either inhalation or oral gavage or inperitoneally (IP).

(*ii*) *Duration of exposure.* For inhalation, the duration of exposure shall be for 6 hours per day for 5 consecutive days with one sacrifice time or for 6 hours for 1 day with three sacrifice times.

(B)(*1*) A dominant lethal assay shall be conducted with isopropanol in accordance with § 798.5450 of this chapter, except for the provisions in paragraphs (d)(5)(ii) and (iii) of § 798.5450, unless the micronucleus test conducted pursuant to paragraphs (c)(5)(i)(A) of this section is negative.

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

(*i*) *Route of administration.* Animals shall be exposed to isopropanol by inhalation.

(*ii*) *Duration of exposure.* The duration of exposure shall be for 6 hours per day for 5 consecutive days.

(C)(*1*) A heritable translocation test shall be conducted with isopropanol in accordance with § 798.5460 of this chapter, except for the provisions in paragraphs (d)(5)(ii) and (iii) of § 798.5460, if the results of the dominant lethal assay conducted pursuant to paragraph (c)(5)(i)(B) of this section are positive and if, after a public program review, EPA issues a **Federal Register** notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

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

(*i*) *Route of administration.* Animals shall be exposed to isopropanol by inhalation.

(*ii*) [Reserved]

(ii) *Reporting requirements.* (A) The chromosomal aberration tests shall be completed and the final reports submitted to EPA as follows:

(*1*) The micronucleus test within 15 months of the date specified in paragraph (d)(1) of this section.

(*2*) The dominant lethal assay within 27 months of the date specified in paragraph (d)(1) of this section.

(*3*) The heritable translocation test within 24 months of the date of EPA's notification of the test sponsor by certified letter or **Federal Register** notice

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under paragraph (c)(5)(i)(C) of this section that testing shall be initiated.

(B) Progress reports shall be submitted to EPA for the the micronucleus and the dominant lethal assays at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the final report.

(C) Progress reports shall be submitted to EPA for the heritable translocation assay at 6-month intervals beginning 6 months after the date of EPA's notification of the test sponsor that testing shall be initiated until submission of the final report.

(6) *Neurotoxicity*—(i) *Required testing.* (A)(1) A functional observation battery shall be conducted with isopropanol in accordance with § 798.6050 of this chapter except for the provisions in paragraphs (d)(5) and (6) of § 798.6050.

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

(*i*) *Duration and frequency of exposure.* For subchronic study, animals shall be dosed for 6 hours per day, 5 days per week for 90 days. For acute study, animals shall be dosed for 4 to 6 hours once.

(*ii*) *Route of exposure.* Animals shall be exposed to isopropanol by inhalation.

(B)(1) A motor activity test shall be conducted with isopropanol in accordance with § 798.6200 of this chapter except for the provisions in paragraphs (d)(5) and (6) of § 798.6200.

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

(*i*) *Duration of exposure.* For subchronic study, animals shall be dosed for 6 hours per day, 5 days per week for 90 days. For acute study, animals shall be dosed for 4 to 6 hours once.

(*ii*) *Route of exposure.* Animals shall be exposed to isopropanol by inhalation.

(C)(1) A neuropathology test shall be conducted with isopropanol in accordance with § 798.6400 of this chapter except for the provisions in paragraphs (d)(5) and (6) of § 798.6400.

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

(*i*) *Duration of exposure.* Animals shall be dosed for 6 hours per day, 5 days per week for 90 days.

(*ii*) *Route of exposure.* Animals shall be exposed to isopropanol by inhalation.

(D) A developmental neurotoxicity test shall be conducted with isopropanol in accordance with § 795.250 of this chapter.

(ii) *Reporting requirements.* (A) The acute functional observation battery and motor activity tests shall be completed and the final report submitted to EPA within 15 months of the date specified in paragraph (d)(1) of this section. The subchronic functional observation battery, motor activity, and neuropathology tests shall be completed and the final reports submitted to EPA within 18 months of the date specified in paragraph (d)(1) of this section. The developmental neurotoxicity test shall be completed and the final report submitted to EPA within 21 months of the date specified in paragraph (d)(1) of this section.

(B) Progress reports shall be submitted to EPA for the functional observation battery, motor activity, neuropathology, and developmental neurotoxicity tests at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the applicable final report.

(7) *Pharmacokinetics studies*—(i) *Required testing.* An oral and inhalation pharmacokinetics test shall be conducted with isopropanol in accordance with § 795.231 of this chapter.

(ii) *Reporting requirements.* (A) The pharmacokinetic test shall be completed and the final report submitted to EPA within 15 months of the date specified in paragraph (d)(1) of this section.

(B) Progress reports shall be submitted to EPA for the pharmacokinetics test at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the final report.

(8) *Oncogenicity*—(i) *Required testing.* An oncogenicity test shall be conducted by inhalation with isopropanol in accordance with § 798.3300 of this chapter.

(ii) *Reporting requirements.* (A) The oncogenicity test shall be completed and the final report submitted to EPA within 53 months of the date specified in paragraph (d)(1) of this section.

(B) Progress reports shall be submitted at 6-month intervals beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the final report.

(d) *Effective dates.* (1) This test rule shall be effective on December 4, 1989.

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

(Information collection requirements have been approved by the Office of Management and Budget under control number 2070-7030).

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15 million pounds (Ref. 6). No imports of crotonaldehyde into the United States are currently reported; however, in 1985, 930,953 pounds of crotonaldehyde were imported into the United States from Mexico (Ref. 7).

Kodak reports that is converts approximately one-third of the crotonaldehyde that it produces into crotonic acid, using an enclosed process. Kodak believes that all of the crotonaldehyde that it sells is used as a chemical intermediate, and none is used to formulate products (Ref. 8).

Kodak estimates that up to 20 manufacturing workers might be exposed to crotonaldehyde. Worker exposure levels, determined by industrial monitoring, are generally less than 0.01 ppm (8-h Time-Weighted Average (TWA)); Kodak reported a single maximum exposure level of 1.13 ppm, which occurred under an upset condition (Ref. 8.).

Environmental exposures to crotonaldehyde can occur during its transportation, use, processing, and manufacture. EPA has estimated exposures to crotonaldehyde at Kingsport, TN, the site of Kodak's effluent discharge to the Holston River, to be 65 ppb during mean river flow conditions and 350 ppb during strictly natural 7Q10 low flow conditions (i.e., the lowest 7-day average river flow expected to occur once every 10 years). Monthly average concentrations are expected to range from 45 ppb to 87 ppb (Ref. 4). However, it should be noted in this context that the Holston River's flow is not as variable as it would be if it were a "wild" river, as its flow is controlled by contractural arrangements with the Tennessee Valley Authority (TVA) through several dams and holding ponds located on the River. EPA is examining what effects these contractual arrangements with TVA have on mitigating the Holston's natural flow variability and, hence, on the predicted concentrations of crotonaldehyde in the River.

Crotonaldehyde also occurs naturally, having been found in strawberries, algae-containing sedimentary deposits, and humans, apparently being produced as a metabolite of other substances (Refs. 5, 9, and 10). Crotonaldehyde is also a common combustion product of wood and hydrocarbon-based fuels (gasoline, jet fuel, etc.). Concentrations of crotonaldehyde in the exhaust/smoke from these sources have been measured, and range from 6 ppb to 116 ppm, with the highest values found in wood smoke (Refs. 5 and 11 through 13).

IV. Testing Program; Chemical Fate and Environmental Effects

The ITC recommended crotonaldehyde for chemical fate and environmental effects testing. The ITC did not recommend health effects testing, stating that crotonaldehyde has been extensively studied for health effects. EPA concurs with the ITC's recommendations.

Specifically, the ITC recommended aquatic biodegradation and volatility testing and acute aquatic toxicity testing.

A. Chemical Fate Testing

Volatilization of crotonaldehyde can be estimated using the calculated Henry's Law constant. The estimate thus obtained indicates that crotonaldehyde has a moderate volatilization half-life of 60 to 70 hours at 20 °C (Ref. 14). In air, crotonaldehyde photolyzes relatively quickly, with a half-life of only a few hours (Ref. 14). Information on crotonaldehyde's removal by acclimated sludge shows 37 percent removal of maximum theoretical oxygen demand, (ThOD) (Ref. 11). EPA estimates that, during wastewater treatment, 40 percent of crotonaldehyde will be removed, mostly by biodegradation (Ref. 4).

In view of this information, and information on crotonaldehyde's release to the environment, the ITC recommended additional studies on volatilization from water and aerobic biodegradation. Specific testing on these key removal processes would enable EPA to better predict crotonaldehyde's fate in the environment.

EPA intends that the chemical fate and environmental effects testing needed for crotonaldehyde be conducted under the sponsorship of Kodak under this Consent Order.

Although the ITC recommended both volatility and aerobic aquatic biodegradation testing, the chemical fate testing is limited in this Consent Order to the biodegradation testing for technical reasons. At the present time, EPA considers reliable tests for determining volatility to be available only for high- or low-volatility chemicals, but not for medium-volatility substances, such as crotonaldehyde. Therefore, EPA will continue to depend upon estimates of crotonaldehyde's volatility, as given in Unit III of this document. An indication of volatility will also be obtained during the algal bioassay, wherein the Consent Order requires that losses of test substance due to volatility be roughly estimated by measuring concentrations of crotonaldehyde in the test chambers and comparing these to the nominal, expected concentrations. The results of this volatility "measurement" are also relevant to the type of aerobic aquatic biodegradation test to be performed. If volatility, as observed in the algal assay, is greater than 15 percent over 96 hours, then a closed-bottle test (40 CFR 796.3200) shall be used; if volatility is less than or equal to 15 percent, then the modified Organization for Economic Cooperation and Development (OECD) test (40 CFR 796.3240) shall be used. Protocols and decision criteria as to which test will be used are specified in the Consent Order, and testing will be in accordance with the schedules and test protocols specified in the Order.

B. Environmental Effects Testing

Crotonaldehyde has been tested using a number of different aquatic organisms. The most relevant tests have been static 96-hour bioassays with bluegills, Lepomis macrochirus (96-hour LC_{50} of 3.5 mg/L), fathead minnows, Pimephales promelas (96-hour LC_{50} of 2.8 mg/L), and a saltwater fish, the tidewater silversides, Menidia beryllina (96-hour LC_{50} of 1.3 mg/L) (Refs. 15 and 16).

These acute toxicity values demonstrate that crotonaldehyde may have significant acute toxicity to marine and freshwater fish. Since the data were obtained using often less reliable static bioassay systems, the ITC recommended additional acute toxicity testing in flow-through or static-renewal tests. The ITC also recommended that additional environmental species be tested, to include algae.

Kodak has agreed to conduct or sponsor the conduct of acute toxicity tests on five species: -The algal species, Selanastrum capricornutum; two freshwater invertebrate species, the daphnid, Daphnia magna, and the gammarid, Gammarus fasciatus; and two freshwater fish species, the fathead minnow, Pimephales promelas, and the rainbow trout, Oncorhynchus mykiss (formerly Salmo gairdneri). All of these tests will be performed in accordance with the schedules and test protocols specified in the Order.

The Consent Order also requires daphnid chronic toxicity testing and fish early life stage (ELS) toxicity testing on the more sensitive fish (rainbow trout or fathead minnow). This aquatic chronic toxicity testing is required because EPA has calculated that the ratio of acute toxicity (48-hour or 96-hour EC_{50} or LC_{50} value) to the predicted environmental concentration (PEC) of crotonaldehyde in the Holston River is less than or equal to 100. If the fish acute toxicity data are equivocal regarding relative species sensitivity, EPA and Kodak will, if

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requested by Kodak, meet to discuss the interpretation of the acute toxicity data as to which fish species will be required to undergo early life stage (ELS) testing. If Kodak and EPA cannot come to agreement, EPA has the final authority in selecting the test species. EPA will provide Kodak in writing with its reasoning for requiring one test species over another.

Kodak believes EPA's PEC for the Holston River is too high, and has volunteered to measure effluent crotonaldehyde concentrations from their facility in Kingsport, Tennessee, that releases wastewater to the Holston River. Independent of the results of these effluent measurements, EPA will use two alternate criteria to require the chronic aquatic toxicity testing: (1) If any EC_{50} or LC_{50} value from conducting the five acute tests listed above is less than, or equal to, 1.0 mg/L, or (2) if any fish or aquatic invertebrate toxicity EC_{50} or LC_{50} value is less than, or equal to, 100 mg/L and there is also an indication of potential cumulative toxicity (the ratio of 24-hour to 48-hour or 24-hour to 96-hour toxicity values is greater than, or equal to, 2).

Daphnid chronic toxicity testing and fish ELS testing will not be required if all of the following conditions are met:

1. All five acute toxicity test values are greater than 1.0 mg/L.

2. All fish and aquatic invertebrate toxicity test values are less than or equal to 100 mg/L and there is no potential cumulative toxicity as defined in the Consent Order, or all fish and aquatic invertebrate toxicity test values are greater than 100 mg/L.

3. Aquatic concentration modelling by EPA using Kodak's measured effluent crotonaldehyde concentrations and best available flow data for the Holston River demonstrate that the ratio of the lowest acute toxicity value to the PEC (using the 7Q10 as the reference value) is greater than 100.

Neither the ITC nor EPA believes that bioconcentration will pose any environmental hazards, the low Log P of crotonaldehyde, estimated to be 0.55, strongly suggests that there is no significant potential for bioconcentration (Ref. 5).

C. Monitoring Study

EPA and Kodak have also included an optional monitoring study in the Consent Order. Wastewater effluent from Kodak's Kingsport plant, which ultimately empties into the Holston River, may be monitored for crotonaldehyde concentrations. Kodak may monitor its own wastewater effluent rather than the Holston River, itself, for reasons of ease (a less complicated experimental design) and expense (fewer samples needed for a comparably accurate measure of statistical variability). There is a trade-off, however, in that EPA will need to use the effluent monitoring data earlier in its environmental model calculations than would be the case with river sampling data. Nonetheless, the measured concentrations from the effluent should give more accurate estimates of crotonaldehyde concentrations in the river than do present estimates, which are based mainly on theoretical considerations. The effluent monitoring study will also address the question of the efficiency of removal of crotonaldehyde by Kodak's wastewater treatment system, which EPA has estimated to be 40 percent.

EPA's basic interest in this study lies in whether or not it will refute or verify the need for chronic toxicity testing of crotonaldehyde on aquatic species based on present PEC and acute toxicity data. Therefore, this study is not required, and Kodak has discretion as to whether or not it is conducted. If Kodak chooses not to conduct the monitoring study, EPA will rely on the currently existing exposure estimates, along with the results of the acute toxicity tests to determine whether chronic toxicity tests shall be conducted. Obviously, if the acute testing required under the Consent Order indicates a need for chronic testing (by an EC_{50} or LC_{50} value less than, or equal to, 1.0 mg/L or potential cumulative toxicity), as described in Unit IV.B of this notice, then Kodak would forego the monitoring study, because its results will have no effect on the chronic toxicity testing requirement. Kodak may also decide, for other reasons, to proceed with the chronic testing regardless of the acute toxicity testing results and without performing the monitoring study.

If Kodak decides to perform the monitoring study, then the study design and schedule that must be followed are those specified in the Consent Order. If Kodak decides not to perform the monitoring study, then it must notify EPA of its decision and proceed with chronic testing on the daphnid and the most sensitive fish species, as is also specified in the Consent Order.

D. Test Standards and Schedules

The tests, their standards, and schedules are those specifically contained in the Consent Order for crotonaldehyde. The basic test standards are as follows:

Standard	Guideline [illegible] 40 CFR
Fresh water algal acute	797.1050
Daphnid acute	797.1300
Gammarid acute	797.1310
Rainbow trout acute	797.1400
Fathead minnow acute	797.1400
Daphnid chronic	797.1330
Fish early life stage	797.1600
Aerobic biodegradation	796.3200 or 796.3240
Effluent monitoring	[illegible]

[1] Testing protocol/development by Kodak reviewed and approved by EPA, and specified in the Consent Order

All of the above test standards have undergone certain minor modifications these modified standards have been appended to the Consent Order.

Testing will be in accordance with the following schedule:

Test	Reporting requirement	Final report date
Freshwater algae acute	12 months	November 9, 1990
Daphnid acute	12 months	Do.
Gammarid acute	12 months	Do.
Rainbow trout acute	12 months	Do.
Fathead minnow acute	12 months	Do.
Aerobic biodegradation	12 months	Do.
Effluent monitoring	18 months	May 9, 1991.
Daphnid chronic	21 months [1]	August 9, 1991
Fish early life stage	21 months [1]	Do.
Daphnid chronic	27 months [2]	February 10, 1992.
Fish early life stage	27 months [2]	Do.

[1] This schedule applies if the effluent monitoring study is not performed, or if acute or potential cumulative toxicity data indicate a need for chronic testing.
[2] This schedule applies if the effluent monitoring study is performed and exposure data still indicate a need for chronic testing.

EPA has specified a longer time than normal for the toxicity and aerobic biodegradation tests, because of volatility questions and a need to develop some practical volatility data relevant to the conduct of these tests (i.e., use of open or closed systems, appropriate flow rate factors). Thus, EPA is allowing 12 months from the effective date to the final report due date for these tests for crotonaldehyde.

The final report for each test shall be submitted to EPA as soon as it becomes available, but no later than the date specified. For all except the five acute studies and the biodegradation study, interim progress reports shall also be submitted every 6 months, beginning 6 months after the effective date of this final rule.

V. Export Notification

The issuance of the Consent Order subjects any person who exports or intends to export crotonaldehyde, to the export notification requirements of section 12(b) of TSCA. The specific requirements are listed in 40 CFR part 707. In the Interim Rule of June 30, 1986 (51 FR 23706), establishing the Testing Consent Order process, EPA added subpart C of part 799 for listing of chemical substances or mixtures subject to testing consent orders issued by EPA. This listing serves as notification to persons who export or intend to export chemical substances or mixtures which are the subject of testing Consent Orders that 40 CFR part 707 applies.

VI. Rulemaking Record

EPA has established a record for this rule and the Consent Order (docket number OPTS-42108). This record contains the basic information considered by EPA in developing this rule and the testing Consent Order.

This record includes the following information:

A. Supporting Documentation

(1) Testing Consent Order between Kodak and EPA.

(2) Federal Register notices pertaining to this notice consisting of:

(a) Notice containing the ITC's recommendation of crotonaldehyde to the Priority List (53 FR 18196; May 20, 1988).

(b) Notice containing the ITC's designation of crotonaldehyde to the Priority List (53 FR 46262; November 16, 1988).

(c) Notice of the interim final rule on procedures for developing enforceable consent agreements (51 FR 23706; June 30, 1986).

(3) Communications consisting of:

(a) Written letters.

(b) Contact reports of telephone conversations.

(c) Meeting summaries.

(4) Reports—published and unpublished factual materials.

B. References

(1) Kirk-Othmer. *Kirk-Othmer Encyclopedia of Chemical Technology*. New York, N.Y. John Wiley & Sons, Inc. Vol. 7, pp. 207-218. (1979).

(2) Sax, N.I., and Lewis, R.J., Sr. *Hawley's Condensed Chemical Dictionary*. 11th rev. ed. New York. Van Nostrand Reinhold Co. p. 323. (1987).

(3) Merck. *The Merck Index*. 10th edition. Windholz, M., ed. Rahway, N.J. Merck & Co. p. 372. (1983).

(4) Nold, A. Memorandum on crotonaldehyde aquatic ecological assessment Annette Nold to John Walker. U.S. Environmental Protection Agency. (April 5, 1988).

(5) NRC. National Research Council. "Formaldehyde and other aldehydes". Washington, DC. National Academy Press. (1981).

(6) Tennessee Eastman Company. Kingsport, TN 37662. Letter to Dr. Robert H. Brink, Interagency Testing Committee. (June 19, 1987).

(7) USDOC. U.S. Department of Commerce. "U.S. Imports for Consumption and General Imports." Washington, DC. U.S. Bureau of the Census. Publication No. FT246. p. 1-580. (1985).

(8) Eastman Kodak Company. Kingsport, TN 37662. Letter to Mr. John Schaeffer, Office of Pesticides and Toxic Substances, EPA. (August 18, 1988).

(9) Gadel, F., and Bruchet, A. "Application of pyrolosis-gas chromatography-mass spectrometry to the characterization of humic substances resulting from decay of aquatic plants in sediments and water." *Water Research* 21:1195-1206. (1987).

(10) Krotoszynski, B.K., and O'Neill, H.J. "Involuntary bioaccumulation of environmental pollutants in nonsmoking heterogeneous human populations." *Journal of Environmental Science and Health*. A17:855-883. (1982).

(11) Verschueren, K. *Handbook of Environmental Data on Organic Chemicals*. 2nd ed. New York, N.Y. Van Nostrand Reinhold Co. pp. 410-431. (1983).

(12) Miyamoto, Y. "Eye and respiratory irritants in jet engine exhaust." *Aviation, Space and Environmental Medicine*. 57:1104-1108. (1986).

(13) Lipari, F., Dash, J.M., and Scruggs, W.F. "Aldehyde emissions from wood-burning fireplaces." *Environmental Science and Technology*. 18(5):326-330. (1984).

(14) Dynamac Corporation, Rockville, MD 20852. *Crotonaldehyde*. IR-497. EPA Contract No. 68-02-4251. (June 15, 1988).

(15) Dawson, G.W., Jennings, A.L., Drozdowski, D., and Rider, E. "the acute toxicity of 47 industrial chemicals to fresh and saltwater fishes." *Journal of Hazardous Materials*. 1:303-318. (1977).

(16) Union Carbide, Danbury, CT 06817. Letter to U.S. Environmental Protection Agency. (May 2, 1988). 8D-878216446.

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection in the TSCA Public Docket Office, Rm. NE-G004, 401 M St., SW., Washington, DC from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

VII. Other Regulatory Requirements

The Office of Management and Budget (OMB) has approved the information collection requirements contained in the Consent Order under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and has assigned OMB control number 2070-0033.

Public reporting burden for this collection of information is estimated to average 1.431 hours per response including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project (OMB Control No. 2070-0033), Washington, DC 20503.

List of Subjects in 40 CFR Part 799

Testing procedures, Environmental protection, Hazardous substances, Chemicals, Chemical export, Recordkeeping and reporting requirements.

Dated: October 2, 1989.

Linda J. Fisher,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR part 799 is amended as follows:

PART 799—[AMENDED]

1. The authority citation continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

2. Section 799.5000 is amended by adding crotonaldehyde to the Table in CAS Number Order to read as follows:

§ 799.5000 Testing consent orders.

* * * * *

CAS number	Substance or mixture name	Testing	FEDERAL REGISTER Citation
4170-30-3.....	Crotonaldehyde.	Environmental effects.	November 9, 1989.
		Chemical fate.	November 9, 1989.

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