40 CFR Part 799

[OPTS-42116; FRL 3800-7]

RIN 2070-AB94

Testing Consent Order for 4-vinylcyclohexene

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final Rule.

SUMMARY: This final rule announces that EPA has signed an enforceable Testing Consent Order for 4-vinylcyclohexene (4-VCH, butadiene dimer, CAS No. 100-40-3), with nine manufacturers, who have agreed to perform subchronic effects, mutagenicity, pharmacokinetics, and aqueous volatilization rate testing on 4-VCH. This rule adds 4-VCH to the list of Testing Consent Orders in 40 CFR 799.5000 for which the export notification requirements of 40 CFR part 707 apply. This rule constitutes EPA's response to the Interagency Testing Committee's (ITC) recommendation that EPA consider health effects and chemical fate testing of 4-VCH.

EFFECTIVE DATE: September 23, 1991.

FOR FURTHER INFORMATION CONTACT: David Kling, Acting Director, Environmental Assistance Division (TS-799), Office of Toxic Substances, rm. E-543B, 401 M St., SW., Washington, DC 20460, (202) 260-1404, TDD (202) 554-0551.

SUPPLEMENTARY INFORMATION: Under procedures described in 40 CFR part 790, nine manufacturers have entered into a Testing Consent Order with EPA in which they have agreed to perform subchronic effects, mutagenicity, pharmacokinetics (*in vitro* partition coefficient study and *in vitro* metabolism study), and aqueous volatilization rate testing for 4-VCH. This rule amends 40 CFR 799.5000 by adding 4-VCH to the list of chemical substances and mixtures subject to Testing Consent Orders.

I. ITC Recommendation

In its Twenty-Fifth Report to EPA, published in the **Federal Register** of December 12, 1989 (54 FR 51114), the ITC recommended 4-VCH for health effects and chemical fate testing. The health effects tests recommended were pharmacokinetics and oncogenicity by inhalation. The ITC recommended testing by inhalation because inhalation is likely to be the major route of exposure. The chemical fate test recommended was the aqueous volatilization rate test.

II. Testing Consent Order Negotiations

In the **Federal Register** of December 12, 1989 (54 FR 51114), and in accordance with the procedures established in 40 CFR 790.28, EPA requested persons interested in participating in or monitoring testing negotiations for 4-VCH to contact EPA. EPA held public meetings with interested parties (the nine manufacturers, the Synthetic Organic Chemical Manufacturers Association, and the International Institute of Synthetic Rubber Processors) on May 3, May 22, June 7, June 28, and October 23, 1990, to discuss the testing appropriate for 4-VCH. EPA and nine manufacturers signed a Testing Consent Order for 4-VCH. Under the Testing Consent Order, the nine manufacturers have agreed to conduct or to provide for the conduct of the following:

(1) An *in vivo* mammalian cytogenetics micronucleus assay in rats and mice.

(2) An *in vivo* testicular alkaline elution assay, if triggered.

(3) A pharmacokinetics study (*in vitro* partition coefficient and *in vitro* metabolism).

(4) Subchronic studies in rats in mice.

(5) An aqueous volatilization rate test.

EPA believes that on the basis of existing data and ongoing testing, EPA will be able to reasonably predict the potential oncogenicity of 4-VCH and is not recommending oncogenicity testing at this time. The specific test standards to be followed and the testing schedule for each test are included in the Testing Consent Order. Procedures for submitting study plans, modifying the Testing Consent Order, monitoring the testing, and other provisions are also included in the Testing Consent Order.

III. Production, Use, Exposure and Release

A. Physicochemical Properties

The substance 4-VCH is a colorless liquid with a water solubility of 5 ppm (Ref. 1). It has an estimated vapor pressure of 10.2 torr at 25° C and has a calculated log P of 3.38 (Ref. 1).

B. Production

Information submitted by the Butadiene Panel of the Chemical Manufacturers Association (the Panel) indicates that, in 1989, a total of approximately 8 million pounds of 4-VCH (butadiene dimer) was present in all streams leaving the crude or refined butadiene process. Approximately 350,000 pounds of 4-VCH was present in butadiene products leaving the production site (Ref. 2).

Approximately 4,630,000 pounds (58 percent) of the total 4-VCH in butadiene purge streams was destroyed. Approximately 3,300,000 pounds (42 percent) was blended into motor gasoline or fuel oil (Ref. 2).

Approximately 3 million to 4.5 million additional pounds of 4-VCH was generated in non-butadiene processes. Virtually all of that material was reacted or otherwise destroyed by the producer. The only exception was less than 500,000 pounds of 4-VCH which was sold as a product. This 4-VCH was then consumed by a small number of customers in industrial settings (Ref. 2).

In addition to being produced as a by-product in the butadiene and other processes, 4-VCH may be generated in processing butadiene into polymers and synthetic rubber and in processing synthetic rubber into other products such as tires.

C. Uses

4-VCH may be used as an intermediate in the manufacture of 4-vinylcyclohexene mono- and diepoxides, which are used to make epoxy resins, polyesters, coatings, and plastics; and may also be used in the manufacture of flame retardants, insecticides, plasticizers, and antioxidants (Refs. 3 and 4).

D. Occupational Exposure

Approximately 1,300 employees are potentially exposed to 4-VCH at 17 sites that produce crude or refined butadiene, or generate and isolate 4-VCH for use in other processes (Ref. 2). Because 4-VCH is almost always present with butadiene in crude or refined butadiene units, most of these employees are also exposed to butadiene. EPA believes that controls in place to protect workers from exposure to butadiene at butadiene manufacturing facilities will tend to limit worker exposure to 4-VCH at these facilities. At butadiene manufacturing facilities levels of 4-VCH in the workplace should be less than butadiene levels because 4-VCH's concentration of butadiene tends to be low, and in addition its vapor pressure is much lower than that of butadiene. Monitoring of personnel (short-term and time-weighted-average) has been conducted at one butadiene site and at two non-butadiene sites where 4-VCH is generated and isolated. Personnel samples for current plant operations averaged under 1 ppm (Ref. 2).

In addition, occupational exposure to 4-VCH may occur from its use as an intermediate, in the production of polymers made from butadiene, in the production of synthetic rubber, and in the use of synthetic rubber to make other products such as tires. The Panel has agreed to provide EPA with monitoring data from butadiene manufacturers, on-purpose producers of 4-VCH, and domestic 4-VCH customers. The International Institute of Synthetic Rubber Processors (IISRP) has agreed to provide EPA with monitoring data from the synthetic rubber processors and possibly from some downstream users of synthetic rubber, e.g., manufacturers of tires. However, the exposure monitoring program is voluntary and outside the framework of the Testing Consent Order.

E. Environmental Release and Exposure

Approximately 31,000 pounds per year of 4-VCH fugitive air emissions is released by 12 companies (17 sites), ranging from 0 to 15,000 pounds per year per site. Four of these companies (7 sites) reported a total of less than 100 pounds per year of air emissions from other sources. A total of approximately 6,000 pounds of 4-VCH at 13 sites (range: 0 to 3,500 pounds per site) is discharged each year into plant sewers and sent to plant waste treatment units (Ref. 2).

In a comprehensive survey sponsored by EPA's Office of Water, 4-VCH was detected in the following categories of waste water facilities (occurrence frequency; median and maximum concentrations in μg/L): organics and plastics (2; 227, 446.7), rubber processing (6; 78.8, 681.7), publicly owned treatment works (7; 4.9, 8.5) (Ref. 1).

F. Health Effects

1. *Metabolism and pharmacokinetics.* The metabolism of 4-VCH, studied *in vitro*, indicated that it is oxidized at either of its two double bonds to produce the corresponding diol compounds via intermediate epoxides (Refs. 5 and 6). Under the sponsorship of the National Toxicology Program (NTP), the chemical disposition of 4-VCH in rats has been studied by the oral route (Ref. 7).

2. *Acute and subchronic effects.* Acute effects have been reported by Striegel and Carpenter (Ref. 8), Bykov (Ref. 9) and Smyth et al. (Ref. 10). Prechronic (14-day) and subchronic (11-week) studies, sponsored by NTP on 4-VCH, were conducted in rats and mice by gavage (Ref. 11). There was a high incidence of mortality in both NTP studies.

In the 13-week NTP study, the major finding under histologic examination was a reduction in the number of primary follicles and mature graafian follicles of the ovaries of all 10 high-dose female mice, whether they died before or at the end of the study. (The ovaries of female mice receiving lower doses were not similarly examined.) Administration of 4-VCH by inhalation (1 g/m3 for 6 hours/day, over a period of 4 months) inhibited body weight increase and caused leucocytosis, leucopenia and impairment of hemodynamics in rats and mice (Ref. 9).

3. *Genotoxicity.* 4-VCH was non-mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 with or without metabolic activation (Ref. 12). 4-VCH gave a negative response in the cytogenetic (chromosomal aberration/sister chromatid exchange) assays and a positive response in the mouse lymphoma assay (Ref. 13).

4. *Oncogenicity.* NTP studied the carcinogenic effect of 4-VCH in rats and mice and found clear evidence of carcinogenicity in female mice, on the basis of a significant increase in the incidence of uncommon ovarian neoplasms. The results were inconclusive in male mice and both sexes of rats because of extensive early mortality (Refs. 13 and 14).

5. *Reproductive and developmental effects.* As discussed in Unit III.F.2. of this preamble in the 13-week subchronic study, 4-VCH caused a reduction in the number of primary follicles and mature graafian follicles in the ovary. 4-VCH was selected for a continuous breeding study by NTP. The exposure phase of this study has been completed; however, the final report is not yet available.

6. *Chronic (long-term) effects.* No information was found.

IV. Testing Program Under The Testing Consent Order

On May 29, 1990, the Panel presented a testing proposal for 4-VCH to EPA (Ref. 15). EPA believes that, with minor modifications, the testing outlined in that proposal along with existing data address EPA's data needs for 4-VCH and should also provide information on the relative potencies of butadiene and 4-VCH (butadiene dimer). Specifically, the nine signatory companies of the Testing Consent Order have agreed to conduct or sponsor, through the Panel, the health effects and chemical fate tests discussed in Units IV.A. and IV.B. of this preamble and summarized in the following Table 1:

TABLE 1.—TESTING PLAN FOR 4-VCH

Test	Report Date[1]
1. Aqueous Volatilization	10
2. Micronucleus, 2-day	12
3. Pharmacokinetics:	
(a) *In vitro* partition coefficient in rat and mouse tissue	18

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TABLE 1.—TESTING PLAN FOR 4-VCH—Continued

Test	Report Date[1]
(b) *In vitro* metabolism in rat and mouse tissue	18
4. Micronucleus, 13-week (to be conducted only if the 2-day micronucleus test is negative or equivocalin both rats and mice)	24
5. 90-day subchronic tests in rats and mice	30
6. In vivo testicular alkaline elution assay (to be conducted onlyif the 13-week micronucleus test is negative or equivocal in both rat and mouse)	42

[1] Number of months after the effective date of the Testing Consent Order when the final report must be submitted to EPA.

A. Health Effects Testing Under the Consent Order

1. *Subchronic study by the inhalation route.* This study will be carried out in both sexes of mice and rats using three groups exposed to 4-VCH, an unexposed group, and a group exposed to butadiene. The study will last for 90 days. The design of this study will provide a direct comparison between 4-VCH and butadiene in terms of systemic toxicity and target organs (e.g., lung).

2. *Cytogenetic study.* A micronucleus assay will be conducted in the bone marrow of both rats and mice. Rats and mice will be assessed for increased micronuclei formation following two 6-hour exposures. If the response is negative or equivocal following these exposures, the bone marrow of exposed and control animals will be examined following 13 weeks of exposure. The experimental design should allow for direct comparison of 4-VCH with butadiene, which does cause an increase in micronucleus induction and bone marrow toxicity in mice following two 6-hour exposures to 1,000 ppm butadiene in air. In the event the 13-week micronucleus test is negative or equivocal in both rats and mice, the Panel will conduct an *in vivo* testicular alkaline elution assay.

3. *Partition coefficient and in vitro* metabolism testing. To examine the pharmacokinetics and acquire data for development of a physiologically based pharmacokinetic (PBPK) model for 4-VCH, the Panel has agreed to:

(a) Determine the *in vitro* partition coefficients for 4-VCH, 4-VCH-1,2-epoxide, 4-VCH-7,8-epoxide, and 4-VCH-diepoxide in blood, lung, liver, and ovaries of rats and mice.

(b) Determine *in vitro* metabolic rate constants in the lung, liver, and ovaries of rats and mice for the conversion of 4-VCH to its monoepoxide metabolites, and for the monoepoxides to the diepoxide.

(c) Determine the rates of hydrolysis of the epoxides in the lung, liver and ovaries of rats and mice (Ref. 16).

B. Chemical Fate Testing Under the Testing Consent Order

Aqueous volatilization rate. The Panel has agreed to conduct the aqueous volatilization rate test recommended by the ITC. The results of this test will give EPA information on the persistence of 4-VCH in the environment.

C. Chemical Substance to be Tested

The substance 4-VCH will be tested and shall be as pure as can be reasonably attained but shall be at least 98 percent pure.

V. Standards and Methodologies for Conducting Testing

Testing shall be conducted in accordance with the protocols, guidelines, and methodologies set forth in the Appendices to the Testing Consent Order (collectively "Test Standards"). The Companies, through the Panel, and EPA will consult in a good faith effort to determine if test standard modifications are necessary. Modifications to this order shall be governed by 40 CFR 790.68.

VI. Reporting Requirements

All final Study reports must be submitted to EPA by the times specified in Table 1 (See Unit IV of this preamble), unless otherwise authorized by EPA. In addition, interim status reports for testing shall be submitted to EPA every 6 months beginning 6 months after the effective date of the Testing Consent Order until the last final report is submitted.

VII. Export Notification

The issuance of the Testing Consent Order subjects any person who exports or intends to export 4-VCH to the export notification requirements of section 12(b) of TSCA. The specific requirements are listed in 40 CFR part 707. A listing of Testing Consent Orders issued by EPA is published at 40 CFR 799.5000. 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.

VIII. Rulemaking Record

EPA has established a record for this Rule and the Testing Consent Order (docket number OPTS-42116). 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 for 4-Vinylcyclohexene.

(2) **Federal Register** notices pertaining to this final rule and the Testing Consent Order consisting of:

(a) Notice of Interim Final Rule on procedures governing Testing Consent Agreements and Test Rules and Exemption Procedures (51 FR 23706; June 30, 1986).

(b) Notice of Interim Final Rule on procedures governing Testing Consent Agreements and Test Rules (54 FR 36311, September 1, 1989).

(c) Toxic Substances Control Act Test Guidelines; Final Rules (50 FR 39252, September 27, 1985).

(d) Notice of Final Rule revising the Toxic Substances Control Act Test Guidelines (52 FR 19056, May 20, 1987).

(e) Notice of Final Rule requiring section 8(a) and 8(d) reports on 4-vinylcyclohexene (54 FR 51131, December 12, 1989).

(f) TSCA Section 8(a) Confidential Business Information (CBI) data submitted in response to final rule requiring TSCA section 8(a) reporting on 4-vinylcyclohexene (54 FR 51131, December 12, 1989).

(3) Communications consisting of:

(a) Written public comments and letters.

(b) Contact reports of telephone conversations.

B. References

(1) USEPA. Notice containing the ITC recommendation of 4-VCH to the Priority List and soliciting interested parties for developing a consent order for 4-VCH (54 FR 51114, December 12, 1989).

(2) CMA. Chemical Manufacturers Association. Report on the Survey of the Butadiene Panel of the Chemical Manufacturers Association. Submitted to the U. S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC (May 3, 1990).

(3) IARC. International Agency for Research on Cancer. "4-Vinylcyclohexene." IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. 11:277-81 (1976).

(4) IARC. International Agency for Research on Cancer. "4-Vinylcyclohexene." IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. 39:181-192 (1986).

(5) P.G. Gervasi, A. Abbondandolo, L. Citti and G. Turchi. "Microsomal 4-vinylcyclohexene mono oxygenase and mutagenic activity of metabolic intermediates." *Proceedings of the International Conference on Industrial and*

Environmental Xenobiotics, pp. 205–210 (1981).

(6) T. Watabe, A. Hiratsuka, N. Ozawa and M. Isobe. "A comparative study on the metabolism of Z-limonene and 4-vinylcyclohex-1-ene by hepatic microsomes." *Xenobiotica* 11:333–344 (1981).

(7) I.G. Sipes, D.E. Carter and B.J. Smith. "Chemical disposition in mammals: final report (investigations into the role of disposition and metabolism in 4-vinylcyclohexene (VCH) induced ovarian tumors) for the National Toxicology Program." (1989).

(8) J.A. Striegel and C.P. Carpenter. "Range finding tests on 4-vinyl-1- cyclohexene." Mellon Institute of Industrial Research Special Report. Report No. 24–78. Obtained from USEPA FYI-OTS–0785–0397 FLWP Sequence F. (August 28, 1961).

(9) L.A. Bykov. "Maximum permissible concentration of vinylcyclohexene in the air of industrial buildings." In: *Proceedings of a Conference on the Toxicology and Hygiene of Petrochemical Industrial Products*. Moscow, pp. 32–34 (1968).

(10) H.F. Smyth, Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J.A. Striegel and J.S. Nycum. "Range-finding toxicity data. VII." *American Industrial Hygiene Association Journal*. 30:470–476 (1969).

(11) J.J. Collins and A.G. Manus. "Toxicological evaluation of 4-vinylcyclohexene: I. Prechronic (14–day) and subchronic (13 week) gavage studies in Fischer 344 rats and B6C3F1 mice." *Journal of Toxicology and Environmental Health*. 21:493–506 (1987).

(12) E. Zeiger, B. Anderson, S. Haworth, T. Lawlor, K. Mortelmans and W. Speck. "Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals." *Environmental Mutagenesis*. 9(9):1–110 (1987).

(13) NTP. National Toxicology program. "NTP CHEMTRACK. [data base]." Research Triangle Park, NC: National Toxicology Program/National Institute of Environmental Health Sciences. U.S. Department of Health and Human Services. Results report as of 10–30–89 (1989).

(14) NTP. National Toxicology Program. "Toxicology and carcinogenesis studies of 4-vinylcyclohexene (CAS No. 100–40–3) in F344/N rats and B6C3F1 mice (gavage studies)." NTP Technical Report Series No. 303, NIH PB No. 86–2559, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health (1986).

(15) CMA. Chemical Manufacturers Association, Washington, DC. Proposed Framework for Addressing the ITC's Testing Recommendations for 4-VCH with Addendum. Submitted to the U. S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC (May 29, 1990; June 22, 1990).

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 12 noon, and from 1 p.m. to 4 p.m., Monday through Friday, except legal holidays.

IX. Paperwork Reduction Act

The information collection requirements contained in this rule have been approved by the Office of Management and Budget (OMB) under the provisions of the Paperwork Reduction Act, 44 U.S.C. 3501 et seq. and have been assigned OMB control number 2070–0033.

Public reporting burden for this collection of information is estimated to average 445 hours per response. This estimate includes 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. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project, (2070–0033) Washington, DC 20503.

List of Subjects In 40 CFR Part 799

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

Dated: September 13, 1991.

Victor J. Kimm,

Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR part 799 is amended as follows:

PART 799—[AMENDED]

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

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

2. Section 799.5000 is amended by adding the following chemical substance in Chemical Abstract Service (CAS) Registry Number order to the table, to read as follows:

§ 799.5000 Testing consent orders for substances and mixtures with Chemical Abstract Service numbers.

* * * * *

CAS Number	Substance or mixture name	Testing	FR Citation
*	*	*	*
100–40–3	4-vinylcyclohexene	Health effects Chemical fate	[Insert FR date] [Insert FR date]
*	*	*	*

[FR Doc. 91–22872 Filed 9–20–91; 8:45 am]

BILLING CODE 6560–50–F

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