CMA

CHEMICAL MANUFACTURERS ASSOCIATION

MEMORANDUM

TO: VDC Program Panel

FROM: Robert R. Romano RRR/ekg

SUBJECT: VDC Program Panel Update - EPA's Hearing on Proposed TSCA 4a Test Rule

DATE: April 27, 1987

EPA's hearing (public meeting) on VDC was held on February 12, 1987. The Panel had requested the meeting, and in addition to Panel testimony, NRDC also provided a statement. Attached for your information is all the material obtained to date on the hearing. Within three weeks a full transcript of the hearing will be available. I will attempt to send you a copy.

The Panel will continue to work with EPA and answer all possible questions that arose from the hearing. Your participation on the Panel is important; please plan to attend the next meeting. A notice will be forthcoming.

Please do not hesitate to call me at (202) 887-1198 if I can be of further assistance.

SL 061566

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 799

[OPTS-42082 (FRL-3031-2)]

Toxic Substances, 1,1-Dichloroethylene; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing that manufacturers and processors of 1,1-dichloroethylene [CAS No. 75-35-4] be required, under section 4 of the Toxic Substances Control Act (TSCA), to conduct distribution, excretion and metabolism (DEM) studies and a two-year inhalation oncogenicity bioassay in mice. The Agency proposes to delay the initiation of the oncogenicity testing until after the DEM data have been completed and evaluated.

DATES: Submit written comments on or before October 14, 1986. If persons request an opportunity to submit oral comment by September 26, 1986, EPA will hold a public meeting on this rule in Washington, DC. For further information on arranging to speak at the meeting see Unit VIII of this preamble.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42082), in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. NE-G004, 401 M St., SW., Washington, DC 20460.

A public version of the administrative record supporting this action (with any confidential business information deleted) is available for inspection at the above address from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460, Toll free: (800-424-9065), In Washington, DC:

(554–1404), Outside the USA: (Operator—202–554–1404).

SUPPLEMENTARY INFORMATION:

I. Introduction

A. Chemical Recommendation

1,1-Dichloroethylene (vinylidene chloride) was recommended for testing by EPA's Office of Air Quality Planning and Standards. The chemical had been considered for regulation as a potentially toxic air pollutant under the Clean Air Act, but the decision was made not to regulate at that time (50 FR 32632; August 13, 1985). This decision was made because the available information was insufficient to support a decision to regulate, although some data suggest that this chemical may be an oncogen. The Agency proposes to use the testing authority of section 4 of TSCA to obtain data needed to better assess the oncogenic potential of 1,1-dichloroethylene.

B. Test Rule Development Under TSCA

Under section 4(a) of TSCA, EPA shall by rule require testing of a chemical substance or mixture to develop appropriate test data if the Agency finds that:

(A)(i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.

(ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or

(B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture.

(ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

EPA uses a weight-of-evidence approach in making a section 4(a)(1)(A)(i) finding; both exposure and toxicity information are considered in determining whether available data support a finding that the chemical may present an unreasonable risk. For the findings under section 4(a)(1)(A)(ii), EPA examines toxicity and fate studies to determine whether existing information is adequate to reasonably determine or predict the effects of human exposure to the chemical. In making the finding under section 4(a)(1)(A)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's approach to determining when these findings apply is described in detail in its first and second proposed test rules, published in the Federal Register of July 18, 1980 (45 FR 48524) and June 5, 1981 (46 FR 30300).

In evaluating the testing recommendations for 1,1-dichloroethylene, EPA considered all available relevant information, including published and unpublished data available to the Agency. From its evaluation, EPA is proposing health effects testing requirements for 1,1-dichloroethylene under section 4(a)(1)(A).

II. Review of Relevant Data

Most of the following material has been reviewed by the Environmental Protection Agency in a published Health Assessment Document (Ref. 1).

1,1-Dichloroethylene production capacity in the United States is approximately 150 million pounds per year (Economic Analysis Support Document). Virtually all of the chemical produced is used in the production of polymers. About 4 percent of 1,1-dichloroethylene is used as a chemical intermediate for non-polymer products.

Because of its high volatility, 1,1-dichloroethylene is lost to the atmosphere during manufacture of the monomer and polymer. The estimated total emission to all media from manufacturing and processing facilities is 1.3 million pounds per year. The estimated median ambient air level in urban/suburban areas of the U.S. is 0.005 parts per billion (ppb). However, for ambient air in the vicinity of point sources of emission the measured median concentration value is substantially higher (2.2 ppb). The estimated population residing within 5 miles of plants producing or processing 1,1-dichloroethylene totals 3.8 million (Ref. 1).

EPA has evaluated 18 chronic studies in animals for evidence of oncogenicity. Positive results were seen in one inhalation study (Ref. 2). "Swiss" mice were exposed to 10 or 25 parts per million (ppm) 1,1-dichloroethylene 4 hours per day, 4 to 5 days per week for 52 weeks. The experiment was terminated at 128 weeks. A significant increase in kidney adenocarcinomas was observed in male mice at 25 ppm, but not at 10 ppm or in controls. Mice were also exposed at higher dose levels, 200, 100 and 50 ppm, but exposure was discontinued because of toxicity after 2 days at the two highest doses, and after 1 week at 50 ppm. These animals were held for the remainder of the 128-week experiment. No renal adenocarcinomas were seen in the animals at 200 or 100 ppm exposure, but two were seen at the 50 ppm level. This study by Maltoni et al. was considered by EPA to provide limited evidence of animal oncogenicity (Ref. 1).

The remaining 17 animal bioassays provide no evidence of oncogenicity. All but one of these studies had significant flaws in design. These included studies in three species (mouse, rat, hamster) by five routes of administration (gavage, ingestion, inhalation, skin-painting, subcutaneous (sc) injection). The Chinese hamster study was by inhalation at the same doses and under the same conditions seen in the mouse study discussed earlier (Ref. 2). The five mouse studies which showed no oncogenic effect used four different strains of mice ($B6C3F_1$, CD, CD–1, Ha-ICR) by four routes of administration (gavage, inhalation, skin-painting, sc injection). The 11 rat studies utilized four different strains of rat (Fischer 344, Sprague-Dawley, CD, Wistar) by three different routes of administration (gavage, ingestion, inhalation).

Exposure to the chemical in these studies ranged from a minimum of one month in two inhalation studies in rats and mice, with 13 months observation, to a maximum of lifetime exposure in the skin-painting and sc injection studies in mice. However, the skin-painting study only included three applications per week and the sc injection study only treated the animals once a week.

The negative findings in these studies may be partially explained by study characteristics such as: dosing regimens of less than 2 years duration; less than a maximally tolerated dose; differences in routes of administration; and testing at a single dose level. These limitations individually or in combination reduce the sensitivity of detecting a positive response (Ref. 1).

The only study considered by EPA to have an adequate protocol to demonstrate a chemical's lack of oncogenic potential was the National Toxicology Program's (NTP) two-year gavage study of 1,1-dichloroethylene in F344 rats and $B6C3F_1$ mice (Ref. 3).

However, this study may not have achieved a sufficiently high dose. Although chronic renal inflammation was seen in high-dose (5 mg/kg) rats of both sexes and increased necrosis of the liver appeared in high-dose (10 mg/kg) male mice and low-dose (2 mg/kg) female mice, no effects on weight or survival on either sex of either species were observed. While the cumulative dose of the NTP high-dose mouse gavage study (130 mg) and the Maltoni 25 ppm mouse inhalation group (112.5 mg) are roughly equivalent, there is a possibility that the route of administration and the strain of mouse used made a difference in the results because of differences in distribution and metabolism in the tissue or if normal metabolic routes are overcome. Further discussion of these areas is detailed in Unit IV.

The authors of an epidemiologic study of 1,1-dichloroethylene (Ref. 4) concluded that it showed no oncogenic effect attributable to the chemical. EPA has reviewed the study (Ref. 1) and has determined that the population examined in this study may be too small to evaluate oncogenic potential for a weak oncogen.

EPA has reviewed several other studies that provide suggestive evidence of 1,1-dichloroethylene's oncogenic potential (Ref. 1). These include several positive responses in bacterial and yeast mutagenicity studies, one positive plant mutagenicity study, binding of 1,1-dichloroethylene to mammalian DNA, and an increase in unscheduled DNA synthesis in mammalian cells. 1,1-Dichloroethylene also acted as an initiator in a mouse skin-painting study, although it did not act as a complete oncogen. Finally 1,1-dichloroethylene is structurally related to a known human oncogen, chloroethylene (vinyl chloride).

III. Findings

EPA finds under TSCA section 4(a)(1)(A) that the manufacture and processing of 1,1-dichloroethylene and its subsequent inhalation by the population living near manufacturing and processing plants may present an unreasonable risk of oncogenicity. These findings are based on: (1) The positive evidence of oncogenicity for 1,1-dichloroethylene in the Maltoni study; (2) its mutagenicity in several test systems; (3) its interaction with DNA; (4) its activity as a tumor initiator; and (5) its structural relationship to chloroethylene. The Agency also finds that available data, as described in Unit II, are not sufficient to reasonably determine or predict the effects to human health of exposure to 1,1-dichloroethylene and that testing is necessary to develop such data.

IV. Proposed Rule

A. Proposed Testing and Test Standards

The Agency is proposing that comparative DEM studies be done as specified in 40 CFR 798.7475 as published in the **Federal Register** of November 6, 1985 (50 FR 46116). These studies shall be done in two mouse strains, the "Swiss" strain used by Maltoni (Ref. 2) and the B6C3F$_1$ strain used by the NTP (Ref. 3). The DEM tests are being proposed because of the differences in protocol and outcome between the negative in the gavage NTP and the positive in the Maltoni inhalation studies. The Maltoni study (Ref. 2) showed renal adenocarcinomas, as well as liver and kidney toxicity in mice. In the mice used for the NTP study only hepatotoxicity was seen (Ref. 3). It may be that the "Swiss" mice used by Maltoni are more sensitive than other strains of mice. It may also be that the maximum tolerated dose was not attained in the NTP study. Furthermore, it is known that differential toxicity may occur as a result of different routes of administration. With dichloromethane, for example, lung oncogenicity was seen in animals exposed by inhalation, but not in those treated orally. Some evidence suggests that differences in the route of administration may be significant for 1,1-dichloroethylene as well. Oral and inhalation exposures are associated with greater distribution of 1,1-dichloroethylene to the liver and kidney, respectively. The influence of these differences in distribution upon potential oncogenic responses are unknown. For 1,1-dichloroethylene, the one gavage study in mice (Ref. 3) may or may not have been adequate, but all three of the known mouse inhalation studies are known to be inadequate, in part because of insufficient periods of exposure and/or observation. However, one of these studies, the Maltoni bioassay (Ref. 2), did give a positive oncogenicity response.

The proposed DEM tests should determine if metabolic and disposition differences due to the strain of mouse or the route of administration may account for the differences in the results of the existing bioassays. The results will be used in decision-making and to aid in the design of the oncogenicity bioassay.

EPA is also proposing that an oncogenicity test be conducted on 1,1-dichloroethylene in accordance with the TSCA test guidelines for oncogenicity specified in 40 CFR 798.3300, published in the **Federal Register** of September 27, 1985 (50 FR 39252) and modified as proposed in the **Federal Register** of January 14, 1986 (51 FR 1522). This testing shall be performed with the "Swiss" mouse, because of its demonstrated sensitivity, and the route of exposure shall be by inhalation.

B. Test Substance

The proposed test substance is 1,1-dichloroethylene (CAS No. 75-35-4), of at least 99.8 percent purity, which is a commercially available grade.

C. Persons Required To Test

Section 4(b)(3)(B) of TSCA specifies that the activities for which the Agency makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "import"). Processors are required to test if the findings are based on processing. Both manufacturers and processors are required to test if the exposures giving rise to the potential risk occur during use, distribution, or disposal.

Because EPA has found that existing data and experience are insufficient to reasonably determine or predict the effects of the manufacture or processing of 1,1-dichloroethylene on the potential for oncogenicity, the Agency is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process 1,1-dichloroethylene 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 proposed rule. The end of the reimbursement period will be 5 years after the last final report is submitted or an amount of time after the submission of the last final report required under the test rule equal to that which was required to develop data, if more than 5 years.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate on such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to EPA for an exemption from the requirement. EPA promulgated procedures for applying for TSCA section 4(c) exemptions in 40 CFR Part 790.

Manufacturers (including importers) subject to this rule are required to submit either a letter of intent to perform testing or an exemption application within 30 days after the effective date of the final test rule. The required procedures for submitting such letters and applications are described in 40 CFR Part 790.

Processors subject to this rule, unless they are also manufacturers, will not be required to submit letters of intent or exemption applications, or to conduct testing unless manufacturers fail to submit notices of intent to test or later fail to sponsor the required tests. The Agency expects that the manufacturers will pass an appropriate portion of the costs of testing on to processors through the pricing of their products or reimbursement mechanisms. If manufacturers perform all the required tests, processors will be granted exemptions automatically. If manufacturers fail to submit notices of intent to test or fail to sponsor all the required tests, the Agency will publish a separate notice in the **Federal Register** to notify processors to respond: this procedure is described in 40 CFR Part 790.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for 1,1-dichloroethylene. The EPA is interested in evaluating the effects attributable to 1,1-dichloroethylene itself and has specified a nearly pure substance for testing.

Manufacturers and processors who are subject to this test rule must comply with the test rule development and exemption procedures in 40 CFR Part 790 for single-phase rulemaking.

D. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its TSCA Good Laboratory Practice (GLP) standards 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 no later than 45 days before the start 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. The Agency is proposing that the DEM testing be completed and the final report submitted to EPA within 15 months of the effective date of this test rule. The oncogenicity testing shall be completed and the final report submitted to EPA within 68 months of the effective date of this test rule. Progress reports for each proposed test are required at 6-month intervals starting 6 months from the effective date of the final test rule.

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, the Agency will publish a notice of receipt in the **Federal Register** as required by section 4(d).

Persons who export a chemical substance or mixture which is subject to a section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final regulations interpreting the requirements of section 12(b) appear in 40 CFR Part 707. In brief, as of the effective date of this test rule, an exporter of 1,1-dichloroethylene must report to EPA the first annual export or intended export of 1,1-dichloroethylene to any one country. EPA will notify the foreign country about the test rule for the chemical.

E. Enforcement Provisions

The Agency 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 the Act or any regulation or rule issued under TSCA.

Additionally, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by 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 * * *." The Agency 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 EPA representatives to determine compliance with any final rule for 1,1-dichloroethylene. These inspections are conducted for purposes which include verification that testing has been at schedules are being met, and reports accurately reflect the underlying raw data and interpretations and evaluations to determine compliance with TSCA GLP standards 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 such other requirements as are necessary to provide such assurance. The Agency 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 provision of section 16 of TSCA, any person who violates section 15 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 that fail to submit a letter of intent or an exemption request and that continue manufacturing after the deadlines for such submissions. This provision would also apply to processors that fail to submit a letter of intent or an exemption application and continue processing after the Agency has notified them of their obligation to submit such documents (see 40 CFR 790.28(b)). Intentional violations could lead to the imposition of criminal penalties of up to $25,000 for each day of violation and imprisonment for up to 1 year. 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 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 various 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.

V. Issues for Comment

1. Are the existing studies of 1,1-dichloroethylene's oncogenic potential adequate to assess the risks of exposure to this substance?

2. The Agency is proposing both the DEM studies and the inhalation bioassay at this time. EPA is requiring the DEM work to be completed before the bioassay is initiated, and the results of the earlier tests to be used to help design the bioassay. Are the DEM studies appropriate for this purpose? Should be bioassay be finalized only after review by the Agency of the DEM results, to allow EPA to include necessary modifications? Will the DEM studies be useful in helping address the need for the bioassay?

3. The Agency is basing the need for a further oncogenicity bioassay in mice on the differential response that can be seen in animal bioassays depending on the route of exposure. EPA solicits comments on this justification.

4. Should EPA require an epidemiology study for 1,1-dichloroethylene in lieu of a 2-year animal bioassay, and can appropriate cohorts be identified? While EPA considers the Ott study (Ref. 4) to be inadequate to determine that 1,1-dichloroethylene is not a human oncogen, it is possible that a well-designed study with a sufficient number of workers followed for a long enough time may be a better choice for evaluating the possible oncogenicity of the compound.

5. Because of the narrow range of toxicity of 1,1-dichloroethylene (Ref. 2) and the lack of positive results seen in most of these bioassays, some modifications to these studies have been considered. Among the possible changes are an increase in the size of the groups to increase the power of the bioassay, particularly at lower doses. The compound is known to have a shorter half-life in the body than some of the other chlorinated ethylenes (e.g., tetrachloroethylene), and using a lower dose while increasing the daily time of exposure to a greater proportion of a 24-hour day would more realistically represent the type of human exposure upon which this proposed rule is based (persons living in the vicinity of the manufacturing or processing plants). The third possible alteration also deals with this exposure problem. Should EPA consider exposing the animals in utero and beyond through exposure of the dams, and/or exposing them to the chemical directly at a younger age? The Agency requests comments on these possible modifications to the proposed testing.

6. Should EPA require that two species be tested in the oncogenicity study in conformance with the Agency's normal test guidelines or are adequate data now available to indicate that the mouse is the most sensitive species and that testing should be limited to that species? In addition, is the "Swiss" mouse the most appropriate strain in which to perform the inhalation bioassay?

VI. Economic Analysis of Proposed Rule

To evaluate the potential economic impact of test rules, EPA has adopted a two-stage approach. All candidates for test rules go through a Level I analysis. This consists of evaluating each chemical or chemical group on four principal market characteristics: (1) Demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The results of the Level I analysis, along with the consideration of the costs of the required tests, indicate whether the possibility of a significant adverse economic impact exists. Where the indication is negative, no further economic analysis is done for the chemical substance or group. However, for those chemical substances or groups where the Level I analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted. This Level II analysis attempts to predict more precisely the magnitude of the expected impact.

Total testing costs for the proposed rule for 1,1-dichloroethylene are estimated to range from $734,990 to $959,306. The estimated costs for the comparative oral and inhalation DEM studies for this test rule range from $144,613 to $191,573, while the costs for the other proposed testing, the mouse inhalation bioassay, range from $590,376 to $767,634. The annualized test costs (using a cost of capital of 25 percent over a period of 15 years) range from $190,448 to $248,573. Based on the estimated 1984 production of 150 million pounds, the unit test cost is 0.17 cent per pound. In relation to the current list price of 30 to 37 cents per pound for 1,1-dichloroethylene, this cost is equivalent to 0.45 to 0.55 percent of unit value.

The Level I economic analysis indicates that the potential for adverse economic effects due to the estimated test cost is low. This condition is based on the following observations: (1) Demand for 1,1-dichloroethylene appears relatively inelastic owing to its dominant use as a captive intermediate; (2) the market expectations for 1,1-dichloroethylene are optimistic; and (3) the estimated unit test costs are very low. A Level II analysis is not necessary.

VII. 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 NTIS (PB 82-140773). On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing in this proposed rule.

VIII. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting subsequent to the close of the public comment period in Washington, D.C. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll Free: (800-424-9065); In Washington, D.C.: (554-1404); Outside the U.S.A. (Operator—202-554-1404), by September 26, 1986. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

Should a meeting be held, the Agency will transcribe the meeting and include the written transcript in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will become part of EPA's record for this rulemaking.

IX. Public Record

EPA has established a record for this rulemaking, (docket number OPTS-42062). This record contains the basic information considered by the Agency in developing this proposal and appropriate Federal Register notices.

This record includes the following information:

A. Supporting Documentationn

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

(a) Air Pollution Control: Decision Not To Require Vinylidene Chloride and Solicitation of Information (50 FR 32632: August 13, 1985).

(b) Notice of final rule on EPA's TSCA good laboratory practice standards (48 FR 53922: November 29, 1983).

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

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

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

(f) Revisions to the Toxic Substances Control Act Test Guidelnes Proposed Rule (51 FR 1522: January 14, 1986).

(2) Support document consisting of 1,1-dichloroethylene's economic analysis.

(3) Communications before proposal: contact report of telephone coversation.

B. References

(1) U.S. Environmental Protection Agency. "Heath Assessment Document for Vinylidene Chloride". Washington, DC: Office of Health and Environmental Assessment. EPA Report No. 600/8-83-031F (1985).

(2) Maltoni, C., Lefemine, G., Chieco, P., Cotti, G., and Patella, v. *Experimental Research on Vinylidene Chloride Carcinogenesis*. Princeton, N.J.: Princeton Scientific Publishers, Inc. (1985).

(3) National Toxicology Program. "NTP Technical Report on the Carcinogenesis Bioassay of Vinylidene Chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F$_1$/N Mice (Gavage Study)". Washington, DC: National Toxicology Program. NIH Publication No. 82-1784 (1982).

(4) Ott, M.G., Fishbeck, M.D., Townsend, J.C. and Schneider, E.J. "A Health Study of Employees Exposed to Vinylidene Chloride". *Journal of Occupational Medicine* 18: 735-738 (1976).

X. Other Regulatory Requirements

A Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation 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 proposed regulation 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 response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (15 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses because: (1) They are not expected to perform testing themselves, or to participate in the organization of the testing effort; (2) they will experience only very minor costs in securing exemption from testing requirements; and (3) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The Office of Management and Budget (OMB) has approved the information collection requirements contained in this proposed rule 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. Submit comments on these requirements to the Office of Information and Regulatory Affairs: OMB; 726 Jackson Place, NW., Washington, DC 20503, marked "Attention: Desk Officer for EPA." The final rule will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Part 799

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

Dated: August 4, 1986.

Victor J. Kimm,

Acting Assistant Administrator, for Pesticides, and Toxic Substances.

PART 799—[AMENDED]

Therefore it is proposed that 40 CFR Part 799 be amended as follows:

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

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

2. By adding § 799.1545 to read as follows:

§ 799.1545 1,1-Dichloroethylene.

(a) *Identification of test substance.* (1) 1,1-Dichloroethylene (CAS No. 75-35-4) shall be tested in accordance with this section.

(2) 1,1-Dichloroethylene of at least 99.8-percent purity shall be used as the test substance.

(b) *Person required to submit study plans, conduct tests, and submit data.* (1) All persons who manufacture or process 1,1-dihloroethylene, other than as an impurity, from the effective date of this section (44 days after the publication date of the final rule in the **Federal Register**) to the end of the reimbursement period shall submit letters of intent to conduct testing or exemption applications, submit study plans, conduct tests in accordance with Part 792 of this chapter, and submit data as specified in this section, Subpart A of this Part, and Part 790 of this chapter.

(c) *Health effects*—(1) *Distribution, excretion and metabolism—Required testing.* (A) Distribution, excretion and metabolism tests shall be conducted with 1,1-dichloroethylene in accordance with § 798.7475 of this chapter.

(B) Modifications. The following modifications to § 798.7475 of this chapter are required.

(*1*) *Species.* The requirement under § 798.7475(c)(1)(i) shall be modified so that 1,1-dichloroethylene shall be tested in two strains of mice, the "Swiss" mouse used by Maltoni et al. (1985) as cited under paragraph (d) of this section and the B6C3F$_1$ strain of mouse.

(*2*) *Age.* The requirement under § 798.7475(c)(1)(ii) is modified so that 1,1-dichloroethylene shall be tested in mice 6 to 8 weeks old.

(*3*) *Animal care.* The requirement under § 798.7475(c)(1)(iii) is modified so that food and water are provided *ad libitum*, except during the exposure period in the inhalation studies.

(*4*) *Kinetic studies.* The requirements under § 798.7475(c)(2)(iii) (B) (*1*), (*2*), and (*3*) are modified so that they are no longer required. This modification will also cancel the requirement under § 798.7475(c)(2)(iii)(D).

(*5*) *Repeated dosing study.* The requirement under § 798.7475(c)(2)(iii)(E) is modified so that the test species shall undergo repeated dosing by inhalation as well as by oral administration. Mice of both strains (4 animals from each sex) shall receive daily 6-hour exposure to non-radioactive test substance in air for 7 days, followed the next day by a 6-hour exposure to the radioactively by labeled test substance in air. Both high and low-dose levels shall be tested under each route of administration in each strain for each sex. Exposure to

non-radioactive test substance shall be re-instituted following exposure to the label. and shall be continued until sacrifice.

(8) *Blood levels.* The requirement under § 798.7475(c)(3)(i) (A) is modified so that blod levels need by taken only at sacrifice.

(7) *Expired air, urinary and fecal excretion.* The requirement under § 798.7475(c)(3)(i)(B) is modified so that animals in the oral and inhalation repeated dosing studies shall be included. When collection of excreta is ended. the animals shall be sacrificed to determine tissue distribution of the label.

(8) *Tissue distribution.* The requirement under § 798.7475(c)(3)(i)(C) is modified to reduce the number of tissues and organs to be examined for ^{14}C-labeled compounds. Only the liver and kidney need to be checked. However. these tissues shall be analyzed to determine the ^{14}C-label's distribution within the cell. *e.g.*, protein-bound. DNA-bound, or free in the cytoplasm.

(9) *Biotransformation.* The requirement under § 798.7475(c)(3)(ii) is modified to include all repeated dosing groups

(10) *Biotransformation changes.* The requirement under § 798.7475(c)(3)(iii) is modified to add the comparison of the ^{14}C-labeled components of urine collected at 24 and 48 hours after dosing group F. with that collected at similar times in the repeated inhalation dosing studies.

(11) *Test report.* The requirement under § 798.7475(d)(3)(v) is modified so that only the kidney and liver distribution and analysis shall be reported.

(ii) *Reporting requirements.* (A) The distribution. excretion and metabolism testing shall be completed and final results submitted to the Agency with 15 months of the effective date of the final rule.

(B) Progress reports shall be submitted at 6-month intervals beginning 6 months after the effective date of the final rule.

(2) *Oncogenic effects*—(i) *Required testing.* Oncogenicity tests shall be conducted in "Swiss" mice by inhalation with 1.1-dichloroethylene. in accordance with § 798.3300 of this chapter.

(ii) *Reporting requirements.* (A) The oncogenicity testing shall be completed and final results submitted to the Agency within 68 months of the effective date of the final rule.

(B) Progress reports shall be submitted at 6-month intervals beginning 6 months after the effective date of the final rule.

(d) *Reference.* Maltoni. C., Lefemine. G., Chieco. P., Cotti. G., Patella. V. *Experimental Research on Vinylidene Chloride Carcinogenesis.* Princetion, N.J.: Princetion Scientific Publishers. Inc. (1985).

(Approved by the Office of Management and Budget under control number 2070–0033)

[FR Doc. 86–18129 Filed 8–11–86; 8:45 am]

BILLING CODE 6560–50–M

SL 061573

February 12, 1987

AGENDA

Public Meeting on Proposed Test Rule
for 1,1-Dichloroethylene (Vinylidene Chloride)
OPTS-42082

I. Welcome and Introduction - Dr. Ralph Northrop, EPA

II. History and Basis of EPA proposal -
Dr. Nancy Pate, EPA-PAB/OAQPS

III. Statements by Non-industry Participants

IV. Industry Presentations

A. Brief Summary of VDC Program Panel Position - Dr. Robert Romano; Bruce Dickson, Esq.

B. New Emissions/Potential Exposure Data - Dr. Romano

C. Existing Toxicity Database - Dr. Jesse Norris

D. Utility of Metabolism and Pharmacokinetic Data in Carcinogenicity Risk Assessment for VDC - Dr. Rory Connelly

E. Summary and Conclusions - Bruce Dickson

V. Discussion

SL 061574

SECTION 4 - PROPOSED TEST RULE FOR
VINYLIDENE CHLORIDE

MAR 3

Environmental Protection Agency
Northeast Mall, Room 103
Thursday, February 12, 1987

List of Attendees

Dr. Ralph Northrop
EPA

Carol Glasgow
EPA

John Harris
EPA

Dr. Nancy Pate
EPA

Dr. Robin Whyatt
Natural Resources Defense Council

Bruce Dickson, Esq.
Paul, Hastings, Janofsky and Walker

Charles Abernathy
EPA

Jim Barter
PPG

Dr. Rory Conolly
CMA

Mark Greenberg
Office of Health and Environmental Assessment

Susan Hearn
Dow Chemical Company

Jessie Norris
Dow Chemical Company

Dr. Robert Romano
CMA

John Schaffer
EPA

Cheryl Siegel-Scott
EPA

Purnima K. Shah
EPA

Letetia Tohan
EPA

Lorenz Rhomberg
EPA

Gary Timm
EPA

ORAL COMMENTS TO EPA-OPTS ON PROPOSED TEST RULE FOR, 1,1-DICHLOROETHLENE (VINYLIDENE CHLORIDE) OPTS-42082

FEBRUARY 12, 1987

REVIEW OF EXISTING TOXICOLOGICAL DATA IN BEHALF OF THE CMA-VINYLDENE CHLORIDE PANEL

BY: J. M. NORRIS
THE DOW CHEMICAL COMPANY
MIDLAND, MICHIGAN 48674

I have been asked to speak on the existing toxicological data base on VDC and specifically to the interpretation of the animal data regarding oncogenicity for man. There have been 18 investigations of the toxicity and/or oncogenicity of VDC in several strains of rats and mice, as well as in the hamster and the dog. VDC has been administered to animals by inhalation, gavage, in drinking water, by subcutaneous injection and dermal application. The findings in all these studies contribute to our understanding of the effect of VDC on animal species. For the purposes of conducting risk assessment relative to possible carcinogenicity for man, the totality of the data on VDC must be used. This includes the long-term toxicity and oncogenicity drinking water and inhalation studies conducted under CMA sponsorship and the gavage oncogenicity studies conducted by NTP plus an understanding of the comparative pharmacokinetics/metabolism and mechanism of toxic (and oncogenic) action. The drinking water study was conducted for 2 years and the inhalation study for 18 months of exposure with sacrifice at 2 years in Sprague Dawley rats, male and female. The dosages selected in these studies are in the range of 14,000 to 17,000 fold greater than what one might be exposed to in the ambient air environment, assuming the ambient air concentration was 2.2 ppb 24 hours a day and 6,000,000 fold greater than the concentration of 0.2 ppb in water cited by NRDC in their written comments. (Overheads 1-4).

The exposure duration in the CMA inhalation study, 18 months, has been cited as a reason for not using the data in the development of a risk assessment estimate. However, the experience in the laboratory in which these studies were conducted is that the normal life span of the Sprague-Dawley rat is considerable shorter than the Fischer rat used by NTP. And in fact, the exposure period of the Sprague-Dawley rat in the CMA inhalation study, 18 months, covered a portion of the animals' life-span that is comparable to the portion of the Fischer rat life span covered by the 2-year exposure. Most importantly, the Sprague-Dawley rat has been shown in numerous studies in this laboratory to respond to carcinogenic agents within the time span of the VDC study. Life-span survival data for both rat strains are given in Overhead 5.

The dose levels used in the CMA inhalation study (25 and 75 ppm) were below those causing hepatocellular necrosis after 30 days of exposure, namely, 125 and 200 ppm in a study conducted in the same laboratory. Long-term exposure at 75 ppm was not anticipated to compromise the interpretation of the study outcome. At 75 ppm toxic effects, vacuolization and fatty infiltration of hepatocytes were observed demonstrating that a MTD was achieved under criteria set forth in an EPA draft position paper on Maximum Tolerated Dose in Oncogenicity Studies (Harris, et al., 1986). Additional evidence for the appropriateness of the high dose in the CMA study comes from

the Maltoni bioassay with Sprague-Dawley rats. After only 2 exposures to VDC at 200 ppm for 4 hours, the high toxicity observed compelled him to lower the top dose to 150 ppm for the remainder of the bioassay.

(Overhead 6). The CMA studies in addition to the assessment of target organ toxicity provided for the evaluation of effects of VDC exposure on clinical chemistry, hematology and urinalysis parameters at 6, 12 and 18 and/or 24 months and cytogenetic analyses of bone marrow cells at 6 months. No treatment-related effects were observed in any of these parameters. It is important to note that in neither study was there any indication of a leukemic response in animals exposed from weanling through a major portion of their lifetime. With regard to the aggregate finding in the Maltoni study, several observations are important. As noted at the EPA Workshop, there is a question among experts as to the diagnosis and the appropriateness of aggregating dissimilar findings under the general term leukemia. In addition a review of other Maltoni bioassay data in Sprague-Dawley rats used as controls reveal a range of leukemia incidence as high as 19%. The reported findings in the in utero study are within the range of historical control data in that laboratory. Thus, there is no evidence that VDC causes any oncogenic effect in rats. The NRDC proposal for a rat study is unwarranted.

The NTP studies conducted in the Fischer rat and the $B_6C_3F_1$, mouse were conducted at appropriately high gavage doses based on the findings in the subchronic studies. The results of the NTP Fischer rat study were not inconsistent with those of the CMA studies.

The results of the 18 long-term studies on VDC have shown that the mouse (all strains) is more sensitive to the toxic effects of VDC than is the rat or the hamster. Of the 18 long-term studies, only following exposure of the Swiss mouse to vapor concentrations that were markedly toxic and near the acutely lethal level was a tumorigenic response observed.

Metabolism, pharmacokinetic and mechanistic data provide a framework to evaluate the significance of mouse data for possible relevance for man. To follow the advice of the Environmental Health Committee of the Science Advisory Board, the pharmacokinetic and metabolism data on VDC should be integrated into the development of a quantitative risk estimate.

The differences between the mouse and the rat in regard to the pharmacokinetics and metabolism of VDC has been studied in various strains of both rodent species. A comparison of the overall fate of inhaled or ingested VDC in rats and mice shows that the major differences were quantitative rather than qualitative. (Overhead 7). Evidence of the species differences include:

(1) Evidence of a correlation between toxicity, including mortality, with the capacity to metabolize the chemical to toxic metabolites. There is scientific consensus on the role of metabolism in the expression of the toxicity of VDC. This understanding has been reached by IARC, the EPA in the Drinking Water Criteria Document, and Maltoni among others. It has been shown that a quantitative relationship exists between the acute toxicity of VDC in the rat and the amount of VDC metabolized in the range between 200 and 1000 ppm. In this range there was a direct correlation between exposure duration which was required to kill rats and the time calculated to produce a constant amount of metabolite. Mortality was observed after formation of 25-30 mg of metabolite/Kg.

Mortality and target organ toxicity occurs at significantly lower levels in the mouse than in the rat. Mortality in several strains of mice exposed acutely to VDC has been observed in the range of 50 to 100 ppm. Mice metabolize VDC to the same reactive metabolites but more rapidly than do rats and toxicity, including mortality, seen in mice correlate with this greater capacity to metabolize the chemical.

(2) The quantitative differences in the metabolism of VDC between the species are attributed to a combination of physiological and biochemical factors. (Overhead 8). The metabolism of VDC is a saturable process. At low doses, below the metabolic saturation point, VDC is biotransformed to water soluble products, thiodiglyoxylic acid and N-acetyl-S-cysteinyl acetyl derivative, which are excreted in the urine. As the dose increases and metabolic saturation is reached, increasingly larger percentages of unchanged VDC are excreted via the pulmonary system. Species differences relative to the percentage of an orally administered dose excreted by way of the lungs is an indication of species metabolic differences. For example, following oral administration of 50 mg

VDC/Kg Wistar rats excreted twenty-eight percent (28%) of the administered dose via the pulmonary system compared to 6% excreted by Alderley Park mice. Sprague-Dawley rats administered the same oral dose, 50 mg/Kg, excreted 19% of the administered dose as unchanged VDC.

(Overhead 9) The quantitative differences in pulmonary uptake between rats and mice exposed to VDC via inhalation relate to the rate of metabolite formation. At low concentrations the rate of metabolite formation is limited by the blood flow to the liver. Since the rate at which the inhaled VDC is presented to the liver is related to pulmonary uptake, the species having the smaller breathing volume (liters/min/Kg) would produce smaller amounts of toxic metabolites. The mouse breathing volume (1.24 l/min/Kg) is greater than the rat (0.65 l/min/Kg) and the rat breathing volume is greater than man's (0.13 l/min/hr).

The initial step in the metabolism of VDC has been proposed to be the epoxidation of VDC (1,1-dichloroethylene oxide) catalyzed by microsomal monooxygenases with further biotransformation, via two pathways:

(1) reaction with glutathione to produce a water soluble conjugate which is excreted in the urine; and

(2) rearrangement of the 1,1-dichloroethylene oxide to chloroacetyl chloride and monochloracetic acid, reactive metabolites which react with glutathione to form a

series of water soluble conjugates which are also excreted in the urine.

Results of experiments with rats suggested-that the conjugation with glutathione serves to detoxify the reactive metabolites of VDC. When, however, glutathione is depleted, the reactive metabolites are available to react with the cellular macromolecules to cause various toxic endpoints.

The greater sensitivity of the mouse than the rat to the toxic effects of VDC can be attributed in part to the fact that the mouse possesses high monooxygenase activity relative to the rat. A greater portion of VDC administered to the mouse is metabolized to the reactive metabolite, 1,1-dichloroethylene oxide. Since the availability of 1,1-dichloroethylene oxide is greater in the mouse than in the rat, the potential of the reactive metabolites to react with cellular macromolecules resulting in toxicity is likewise greater.

The mechanism of action for the vinylidene chloride-induced tumors in the mouse is nongenetic. The potential of VDC to cause DNA alkylation, DNA repair, and/or DNA replication with associated tissue damage in the rodent target organs has been researched in male Sprague-Dawley rats and male CD-1 mice. Overall alkylation of DNA by VDC was low in both kidney and liver of the rat and mice following exposure to 50 ppm or 10 ppm. DNA repair, measured directly in the mice, showed a

very small but significant increase only in the kidneys of mice exposed to 50 ppm VDC. The tissue damage in the kidneys of the CD-1 mice exposed to 50 ppm VDC for 6 hours was determined directly after cessation of exposure at various times up to 192 hours. The results showed toxic nephrosis immediately after exposure and progressive nephrosis at 8 and 24 hours. If one considers the greater strain sensitivity of the Swiss mouse, the fact that there was a significant degree of nephrosis in the Swiss mice would indicate that the MTD was exceeded in the Maltoni study. This issue was raised by the Science Advisory Board. At the 10 ppm concentration slight dilation and swelling were observed immediately after exposure with nephrosis evident after 96 hours post-exposure.

Failure to demonstrate significant genetic effects at the tumorigenic doses of VDC in mice and the reported dose-related tissue damage and increased DNA replication in the kidneys of mice suggests that the tumors in the kidneys of the mice did, in fact, arise via a non-genetic mechanism, namely, recurrent cytotoxicity.

In-vitro comparison mutagenicity tests conducted on VDC using tissue extracts from rats and mice have given results consistent with species differences observed in in-vivo studies.

In summary, the pharmacokinetic/metabolism and mechanistic data on VDC exposed rats and mice clearly indicate

that inherent species differences contributed to the observed differences in target organ toxicity and in the tumorigenic response in the kidney of the mice following exposure to concentrations in excess of a maximum tolerated dose. The capacity to metabolize VDC to the reactive metabolites correlated with the sensitivity to the toxic effects of VDC observed in these species. The mouse which has a greater capacity to metabolize VDC than does the rat, is more sensitive to VDC-caused tissue injury and tumorigenicity.

For many xenobiotics, including the halogenated hydrocarbons, the rate of oxidative metabolism appears to be roughly related to the body surface area. Thus in man, the total amount of reactive metabolites formed by the metabolism of VDC would be less than that formed by the laboratory rodents. This observation is consistent with the findings that the rat metabolizes less VDC than the mouse and reported significant metabolic dissimilarities which exist between man and the mouse relative to the monooxygenases which catalyze the metabolism of VDC to the reactive species.

All the information presented to this point should provide the Agency with a basis, under TSCA, for making a reasonable prediction of human health effects resulting from manufacturer and/or processing of VDC.

The extensive pharmacokinetic and metabolism data base that exists on VDC provide a basis for developing a

quantitative risk estimate for man. Furthermore, in using a pharmacokinetic approach, the significant degree of uncertainty that is associated with the use of the mouse tumorigenicity data for calculating a risk estimate following the methodology used by CAG, would be apparent. The calculation of unit risk estimate using the CAG methodology is an extrapolation below the dose range of experimental data. There is no scientific basis for using mathematical extrapolation models to relate exposure to cancer risk at the extremely low concentrations as found for VDC in the ambient environment. In the absence of the scientific data that would permit interpretation of animal bioassay findings such calculations may be of value to give a hypothetical upper bound. However, such is surely not the case with vinylidene chloride.

The next few comments will address the risk assessment scenarios which are relevant to the issue raised by NRDC. (Overhead 10). The q* reported by CAG in the table of relative carcinogenic potencies which is included in recent health assessment documents is 0.15 $(mg/Kg/day)^{-1}$ not 1.16 $(mg/Kg/day)^{-1}$, the value found in the Health Assessment Document for Vinylidene Chloride dated August 1985 and used by NRDC in calculating the risk associated with the possible ingestion of water containing trace quantities of VDC. The q* value of 0.15 $(mg/Kg/day)^{-1}$ has been confirmed by CMA. The upper-bound incremental risk from intake of water is calcu-

lated to be 4.4×10^{-6} and at the MCL of 7 ug/l, the risk would be 31×10^{-6}. The water concentration corresponding to a risk of 1 x 10-6 is 0.2 ug/l, the virtual safe dose. The incorporation of pharmacokinetic and metabolic information into the criterion for risk determination has been done for other chemicals. The calculations show that an acceptable level typically would be about two orders of magnitude higher than the virtual safe dose calculated by the CAG methodology.

Estimated Dosage to VDC in the Ambient Environment
Relative to Dosages Administered to Rats in the
Various Long-Term Studies

Ambient Environment: Human Dosage

Assumptions:

- 2.2 ppb ambient concentration, 24 hours/day
- $25m^3$ air intake of a 60Kg individual during 24-hour period
- 100% VDC inhaled at 2.2 ppb retained
- 75% of air inhaled reaches pulmonary air spaces

Exposure = Conc. VDC ($\mu g/m^3$) x air intake (m^3) x % retained x % reaching pulmonary air spaces

= 2.2 ppb (4 $\mu g/m^3$) x $25m^3$/60 Kg/day x 100% x 75%

= 2.75 μg/Kg/day

1 ppm = 4 mg/m^3

JMN:2/87

SL 061588

Estimated Dosage to VDC in the Ambient Environment
Relative to Dosages Administered to Rats in the
Various Long-Term Studies

Experimental Dosage: Rat

Conditions:

- Exposure conc. - 75 ppm (0.004 mg/l)
- Rat inhales - 0.225 l/minute
- Rat weight - 0.5 kg
- Exposure duration - 360 minutes/day

$$\text{Exposure} = \frac{\text{Conc. VDC mg/l x air intake l/min x exposure min/day}}{\text{Weight of Rat}}$$

$$= \frac{75\ (0.004\ \text{mg/l}) \times 0.225\ \text{l/min} \times 360\ \text{min/day}}{0.5\ \text{Kg}}$$

$$= 48.6\ \text{mg/Kg/day}$$

JMN:2/87

SL 061589

Estimated Dosage to VDC in the Ambient Environment
Relative to Dosages Administered to Rats in the
Various Long-Term Studies

Difference Between Rat and Human "Dosages"

$$\frac{\text{Rat: } 48.6 \text{ mg/Kg/day}}{\text{Human: } 2.75 \text{ } \mu\text{g/Kg/day}} = 17{,}000$$

JMN:2/87

SL 061590

Difference Between Ingested Dose to Rats on VDC Drinking Water Study and Possible Human Intake via Drinking Water

Assumptions:

- Human adult (60 Kg) water consumption 2 liters/day

Condition:

- Detected concentration in water 0.2 ppb

Calculation:

$$\frac{0.2 \text{ ppb } (\mu g/l) \text{ VDC} \times 2 \text{ liters/day}}{60 \text{ Kg}} = 0.0067 \ \mu g/Kg/day$$

Difference in dose administered to rats and possibly ingested by man:

$$\frac{\text{Rat: } 40 \text{ mg/Kg/day}}{\text{Human: } 0.0067 \ \mu g/Kg/day} = 6{,}000{,}000$$

JMN:2/87

SL 061591

Survival of Sprague-Dawley Rats and Fischer 344 Rats in Facility Conducting the CMA-VDC Long-Term Studies

Sprague-Dawley Rat (Males):

40 - 81% at 18 months

6 - 24% at 24 months

Fischer Rat (Males):

75% at 24 months

JMN:2/87

SL 061592

Parameters Monitored in the 2-Year Studies on Inhaled and Ingested Vinylidene Chloride

Parameter	Days on Test			
	180	365	540	730
Hematology	X	X	X	X
Urinalysis	X	X	X	X
Clinical Chemistry	X	X	X	X
Necropsy*	X	X		X
Ophthalmologic Exam*	X	X		X
Organ Weights*	X	X		X
Histopathology*	X	X		X
Cytogenic Analysis*	X			X

*Inhalation study only at 180 and/or 365 days.

JMN:2/87

SL 061593

Evidence of Rodent Species Differences
in the Response to Exposure to VDC

- Correlation between toxicity, including mortality, with the capacity to metabolize VDC

  - Mortality and target organ toxicity occurs at significantly lower levels in the mouse

  - Metabolism more rapid in mice than rats

JMN:2/87

SL 061594

Evidence of Rodent Species Differences
in the Response to Exposure to VDC

Attributed to a Combination of
Physiological and Biochemical Factors

- Metabolism is a saturable process

  - Below metabolic saturation, VDC biotransformed and excreted via urine

  - At and above metabolic saturation, unchanged VDC excreted via lungs

  - At 50 mg/Kg, mice excrete less % of administered dose than do rats, indicating more VDC metabolized

JMN:2/87

SL 061595

Evidence of Rodent Species Differences
in the Response to Exposure to VDC

Attributed to a Combination of
Physiological and Biochemical Factors

. Rate of metabolism

.. Limited by blood flow to liver

.. Related to breathing volume

mouse > rat > man

1.24 l/min/Kg > 0.65 l/min/Kg > 0.13 l/min/Kg

JMN:2/87

SL 061596

Risk Assessment Estimates

Conditions:

Based on Maltoni mouse data

Global 82

Calculations

- $q^* = 0.147$ mg/Kg/day^{-1}
- upper-bound incremental risk

  1 µg VDC/liter of water = 4.4×10^{-6}

  7 µg VDC/liter of water = 31×10^{-6}
- water consumption corresponding to a risk of 1×10^{-6} = 0.2 µg/liter (VSD)

Physiologically-Based Computer Modeling

and

Carcinogenicity Risk Assessment for VDC

Rory B. Conolly, Sc.D.

Purpose of this presentation:

1. To illustrate how physiologically-based computer modeling can be used to incorporate pharmacokinetic and metabolic information into risk assessment.

2. To explain why this will lead to better risk assessment.

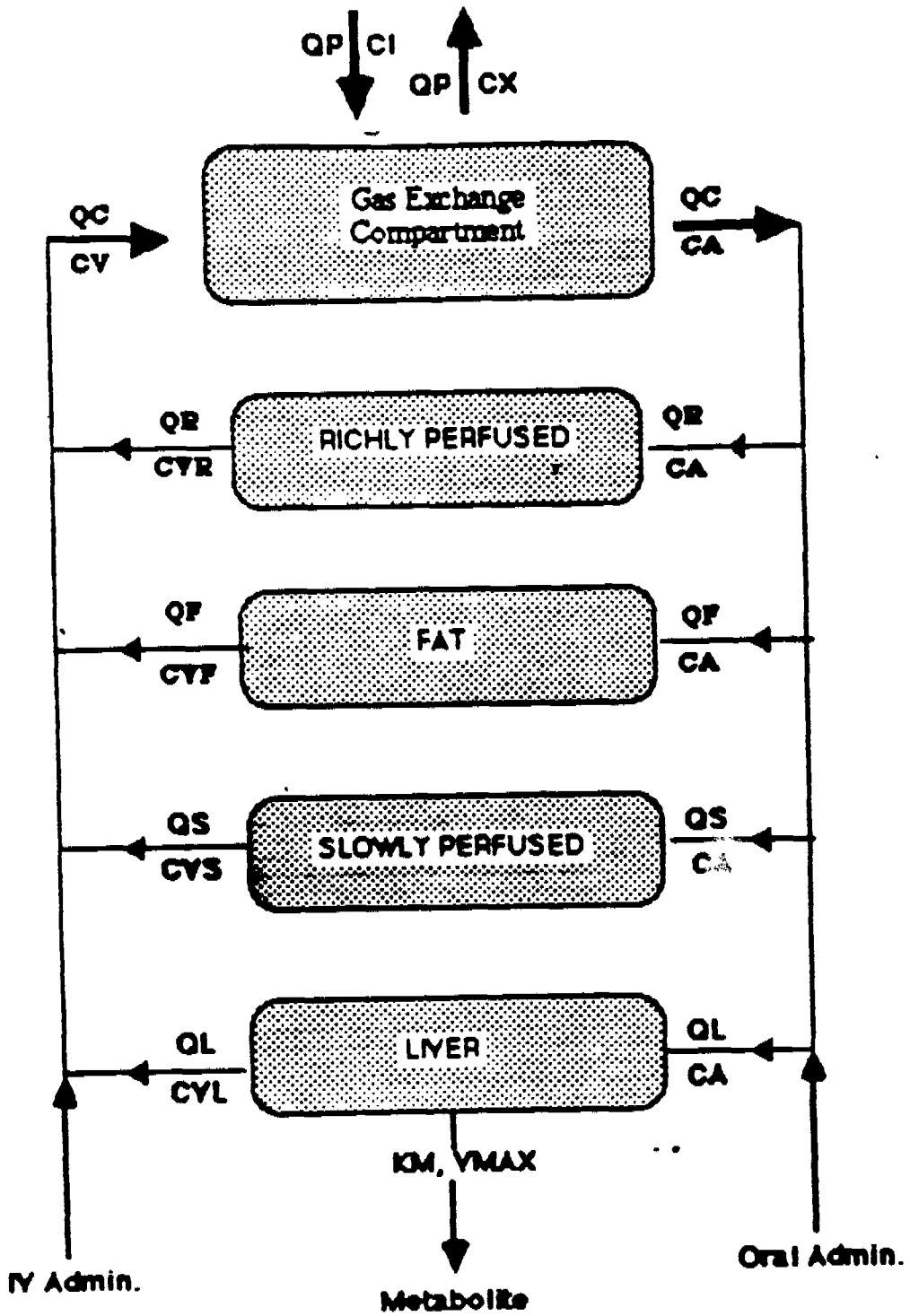
3. To indcate what types of data are needed in order to use physiologically-based computer modleing.

Brief Introduction to Physiologically-Based Computer Modeling

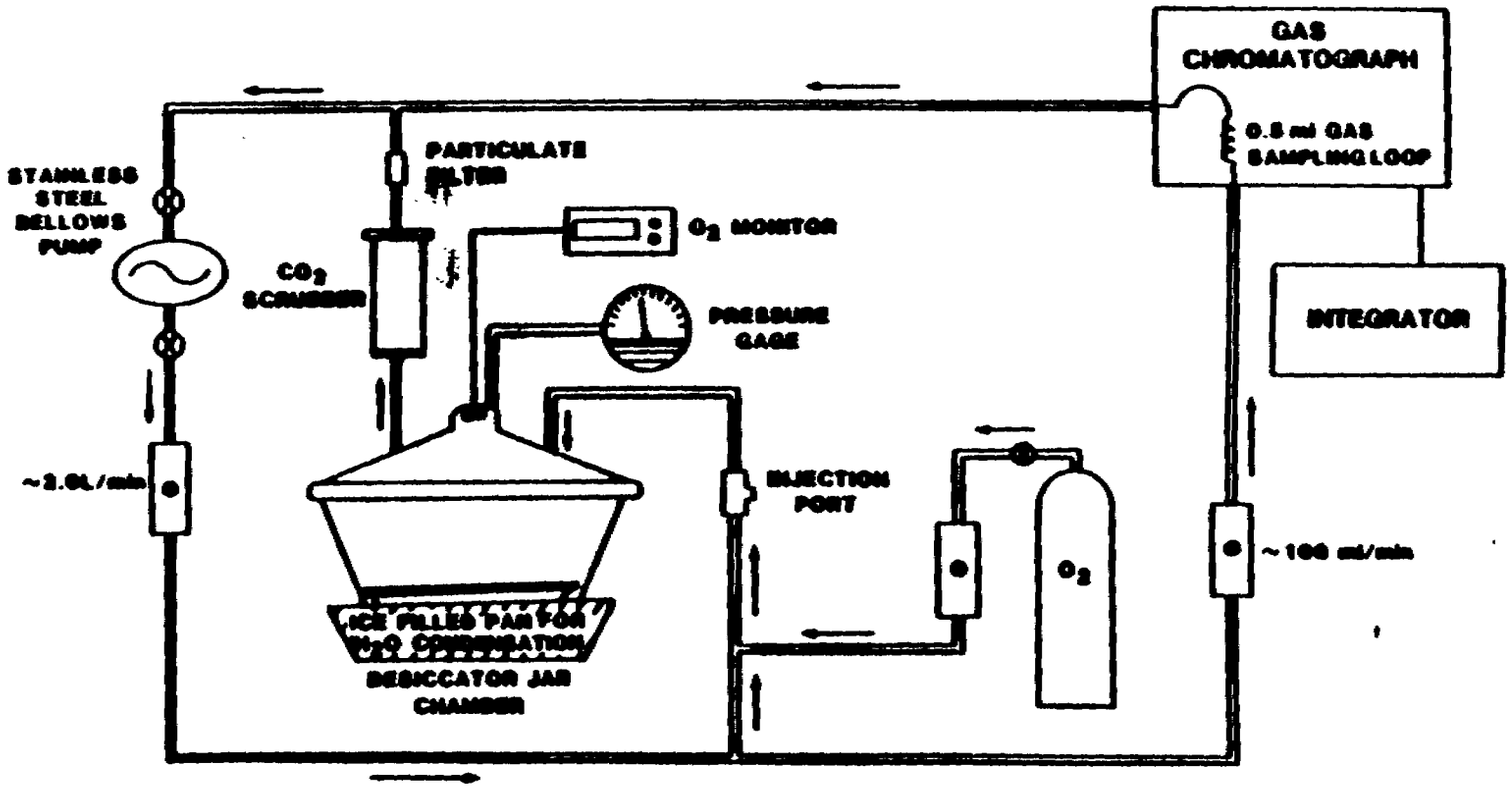
-A compartmental model in which the compartments correspond to physiological entities

SL 061600

Physiologically-Based Pharmacokinetic Model used for Modeling Dose Delivery of Active Metabolites.

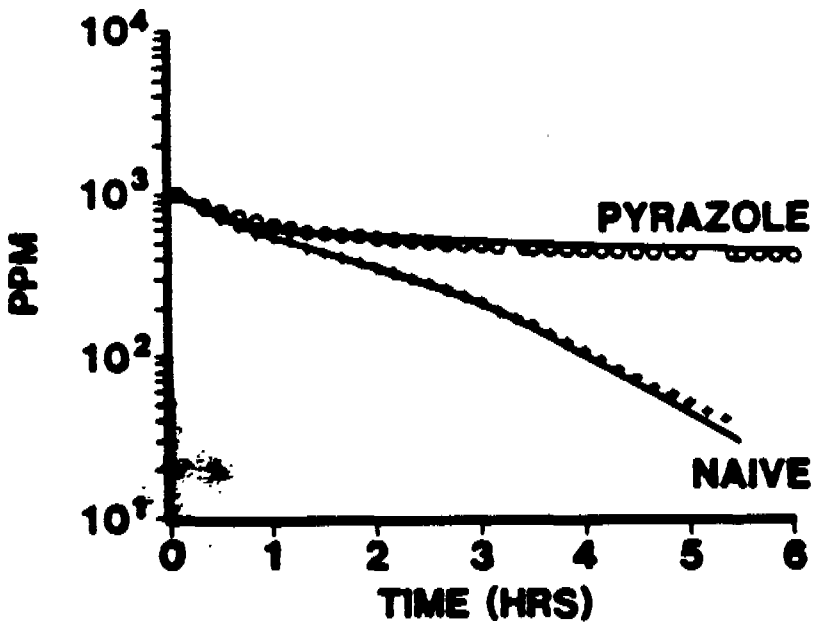


SL 061601


GAS CHROMATOGRAPH
0.5 ml GAS SAMPLING LOOP
INTEGRATOR
STAINLESS STEEL BELLOWS PUMP
PARTICULATE FILTER
CO_2 SCRUBBER
O_2 MONITOR
PRESSURE GAGE
~2.0L/min
INJECTION PORT
O_2
~100 ml/min
ICE FILLED PAN FOR H_2O CONDENSATION
DESICCATOR JAR CHAMBER

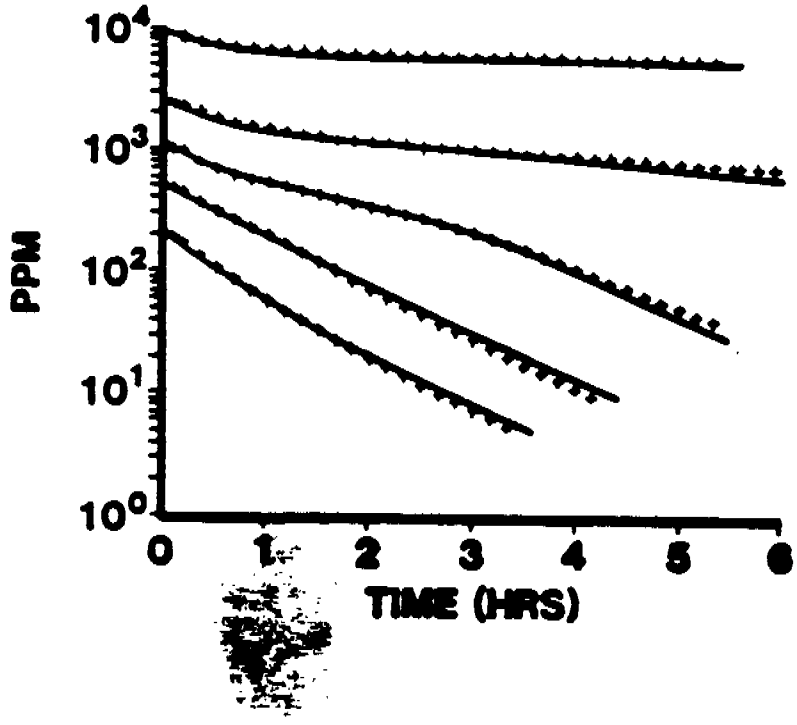
SL 061602

1,1-DICHLOROETHYLENE



SL 061603

1,1-DICHLOROETHYLENE



SL 061604

Fed/Fasted Hepatic GSH in Sprague-Dawley Rats

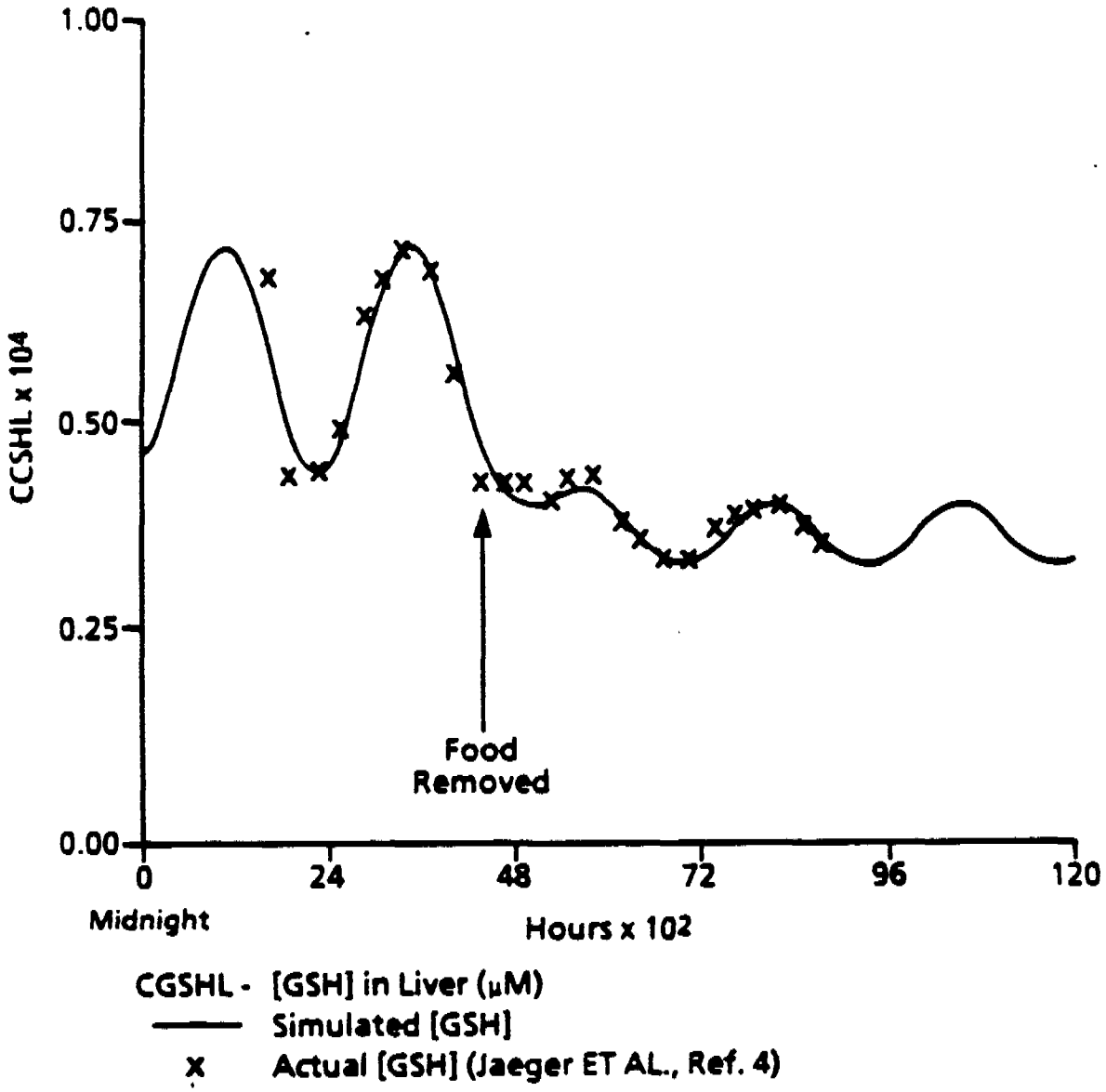


Figure 3. Diurnal variation in hepatic GSH concentration in male, Sprague-Dawley rats. In the simulation (——), rats were normally fed through 0-43 hr and fasted thereafter. Data (x x x) from Jaeger ET Al. (4) are plotted over the simulation.

SL 061605

Fed/Fasted Hepatic GSH in Fisher-344 Rats

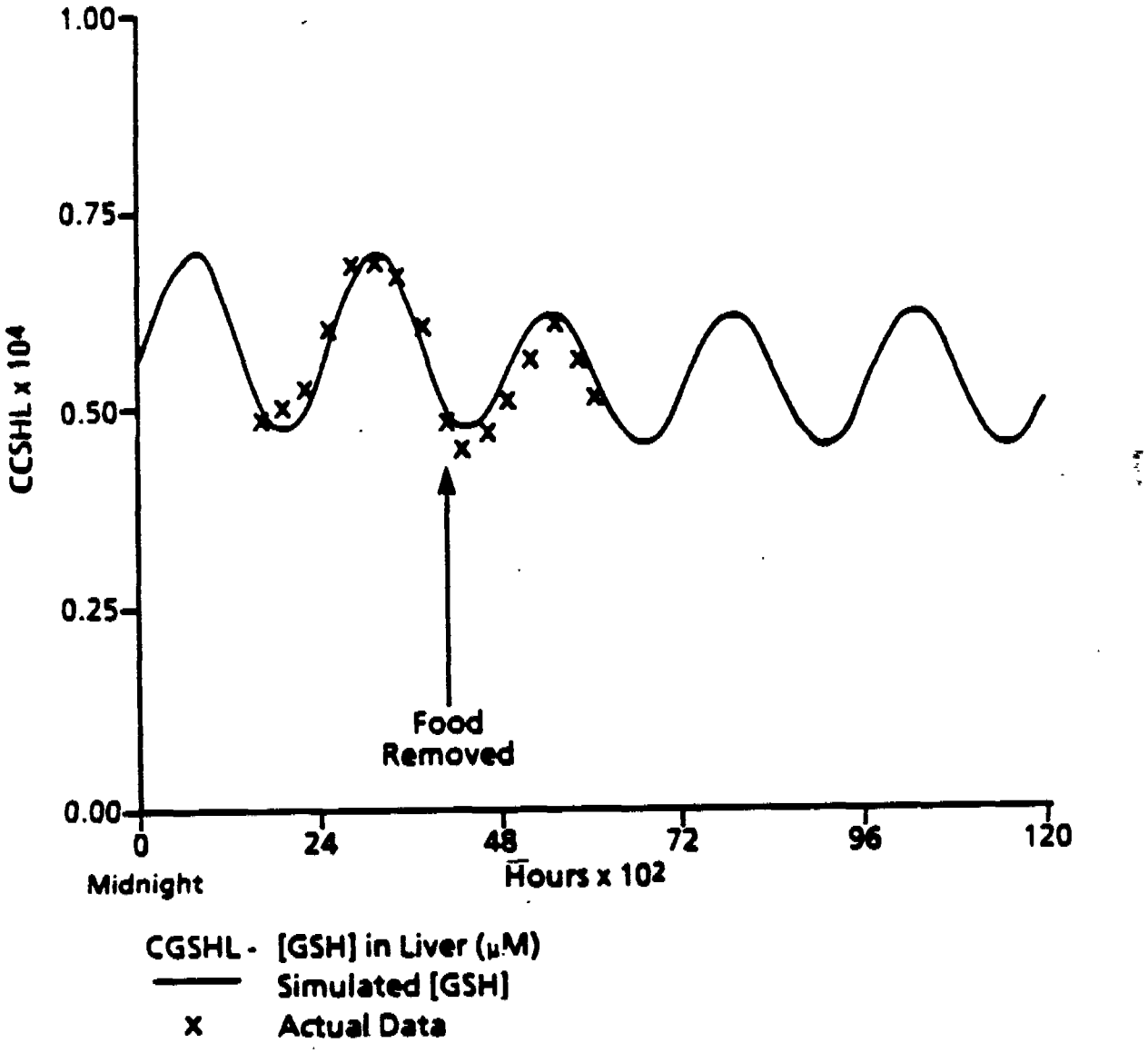
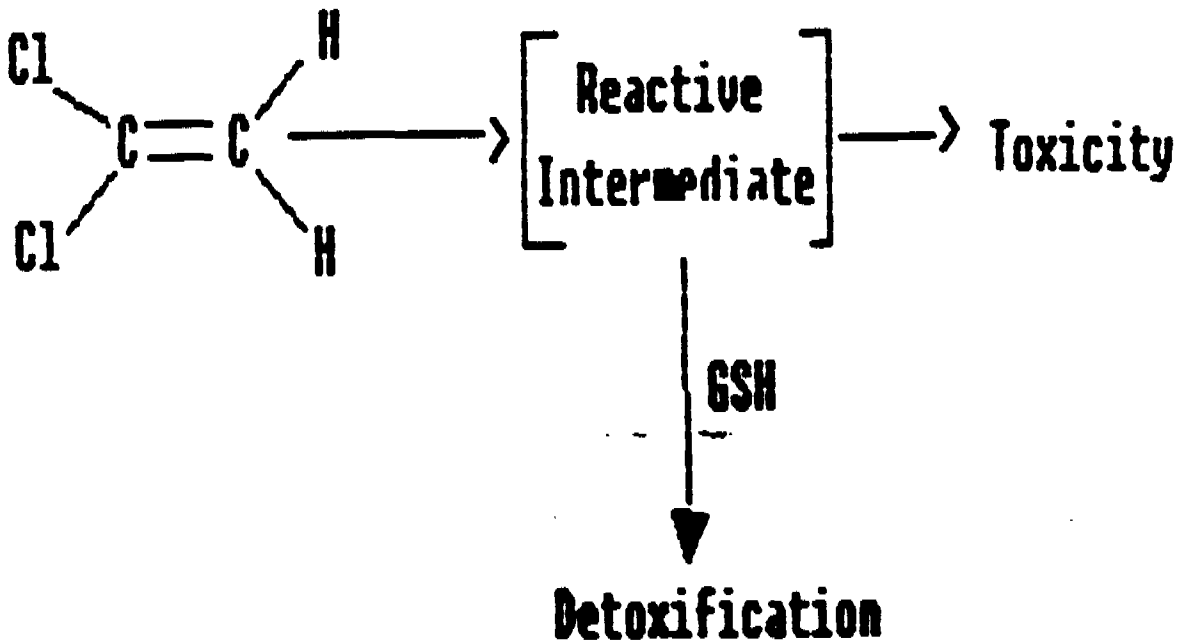


Figure 4. Diurnal variation in hepatic GSH concentration in male, Fisher-344 rats. In the simulation (——), rats were normally fed through 0-43 hr and fasted thereafter. Data obtained by RBC and JC are plotted over the simulation.

SL 061606

1,1-Dichloroethylene (VDC) Toxicity



-Cytochrome P-450 activation

-Glutathione (GSH) detoxification

--Toxicity due to a metabolite that escapes GSH conjugation

VDC cytotoxicity depends on:

-tissue dose of VDC

-rate and amount of metabolism

-initial GSH in target tissue and rate of GSH resynthesis

-amount of reactive VDC metabolite that escapes detoxification

SL 061608

VDC Tumorigenicity

-VDC is a potent acute cytotoxicant.

-Little or no capacity to directly damage DNA in vivo.

-Cytotoxicity is itself a genotoxic process.

-VDC tumorigenicity is probably secondary to its cytotoxicity.

Questions a model can help answer:

-At what rate must VDC be activated and how much activated metabolite must escape GSH detoxification in order for cytotoxicity to occur?

-What VDC exposure levels result in tissue doses sufficient to cause cytotoxicity?

-How do strain and species differences in pharmacokinetic behavior, bioactivation capacity, GSH level, and GSH conjugating capacity influence strain and species sensitivity to VDC?

SL 061610

The information obtained in answering these questions will help us to address to more:

-Do any of the strains or species which have been used in VDC bioassays have unusual sensitivity or unusual resistance to VDC toxicity?

- Which of the animal models used for VDC bioassays handles VDC in the manner most similar to man?

Answers to these questions would allow VDC bioassay data to be evaluated in light of its physiological relevance to man. It is anticipated that some data sets would be found to be more relevant than others.

SL 061611

A physiologically-based computer model, incorporating the appropriate kinetic and biochemical data, could integrate all of this information and produce simulations of actual exposure scenarios. Allometric scaling would allow the model to be used for different species.

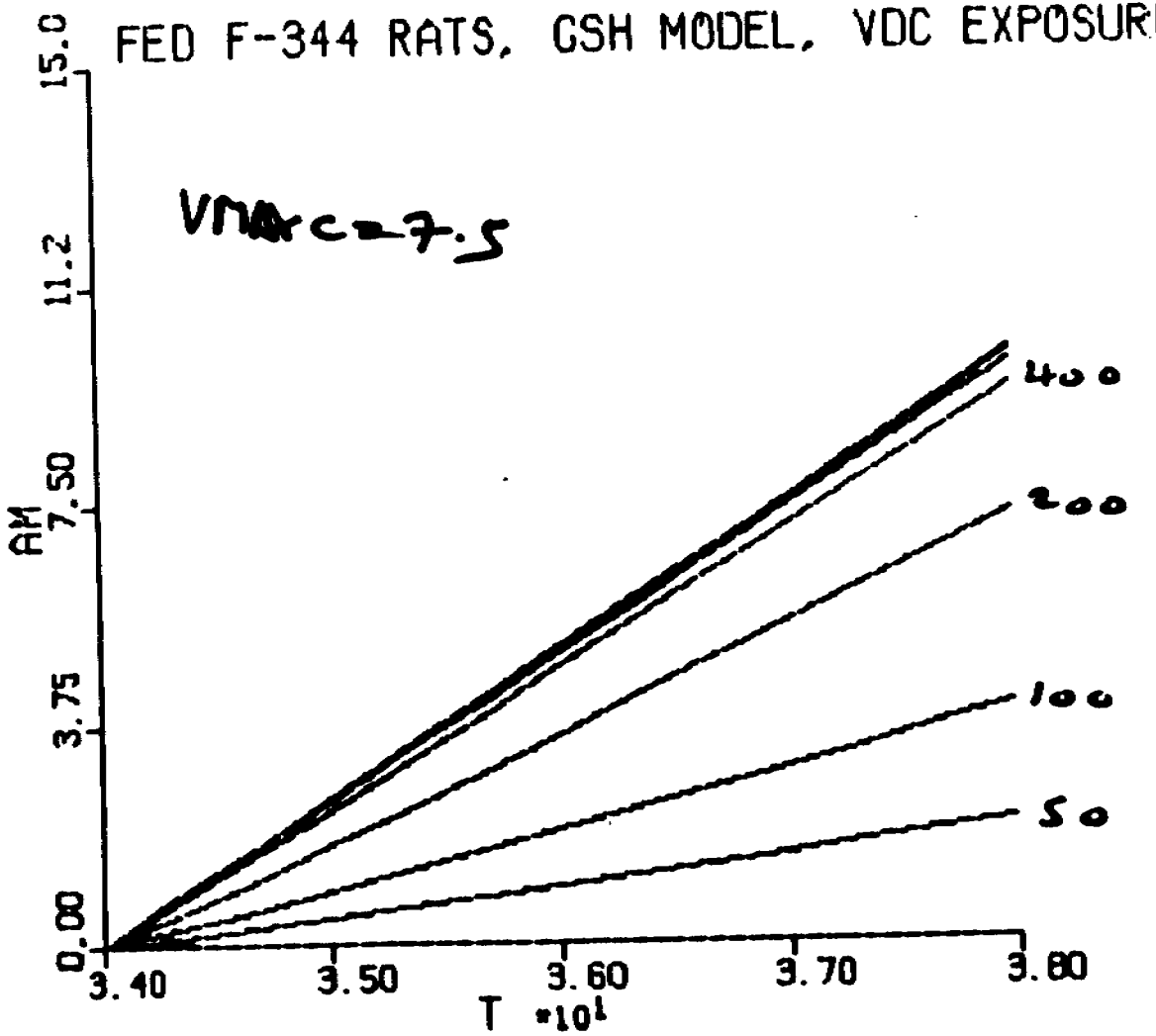
Data set needed for a physiologically-based computer model for VDC

For each animal species and strain the following data should be collected:

Uptake pharmacokinetics
GSH levels during and after exposure
Expired CO_2
Partition coefficients

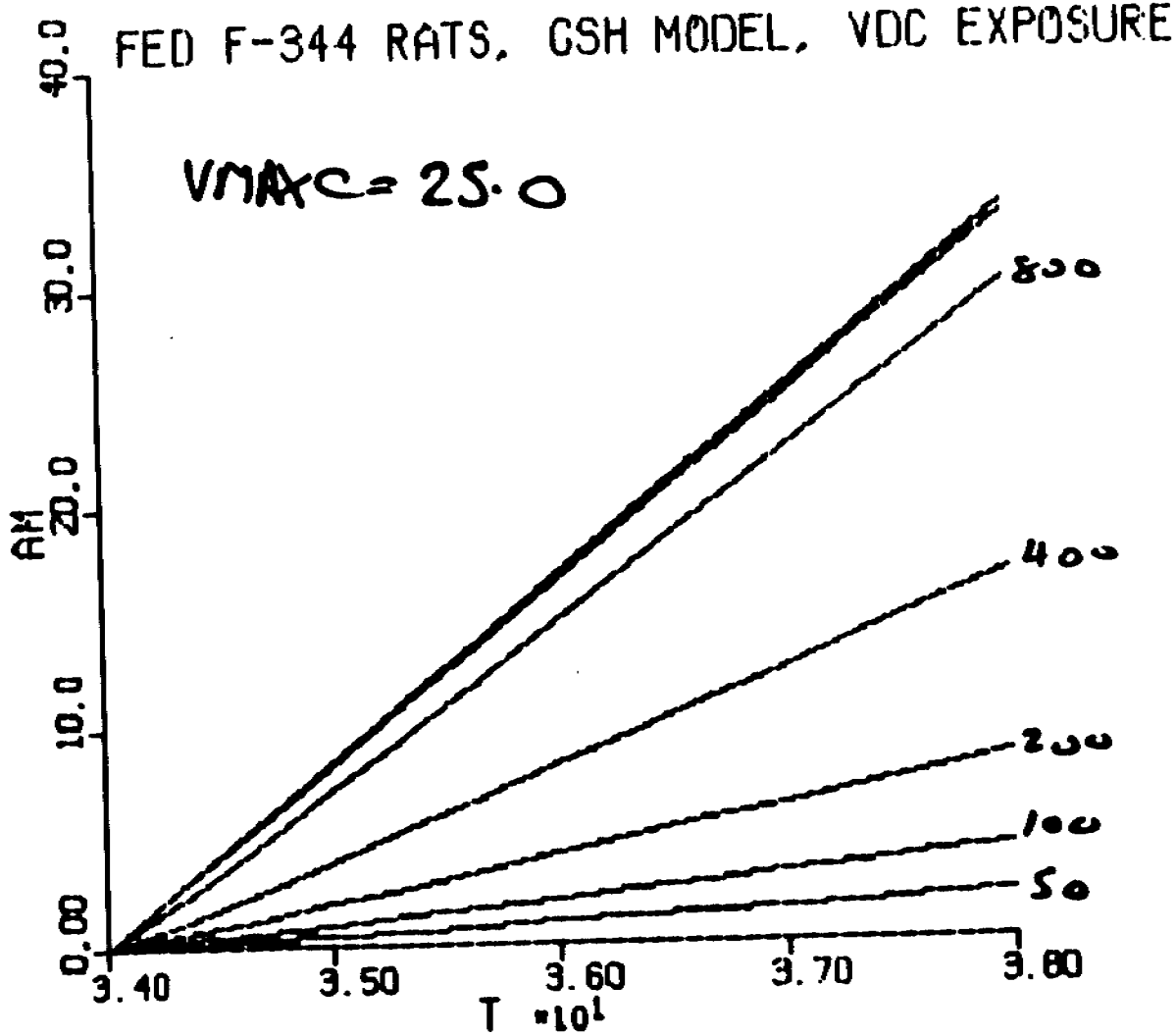
SL 061613

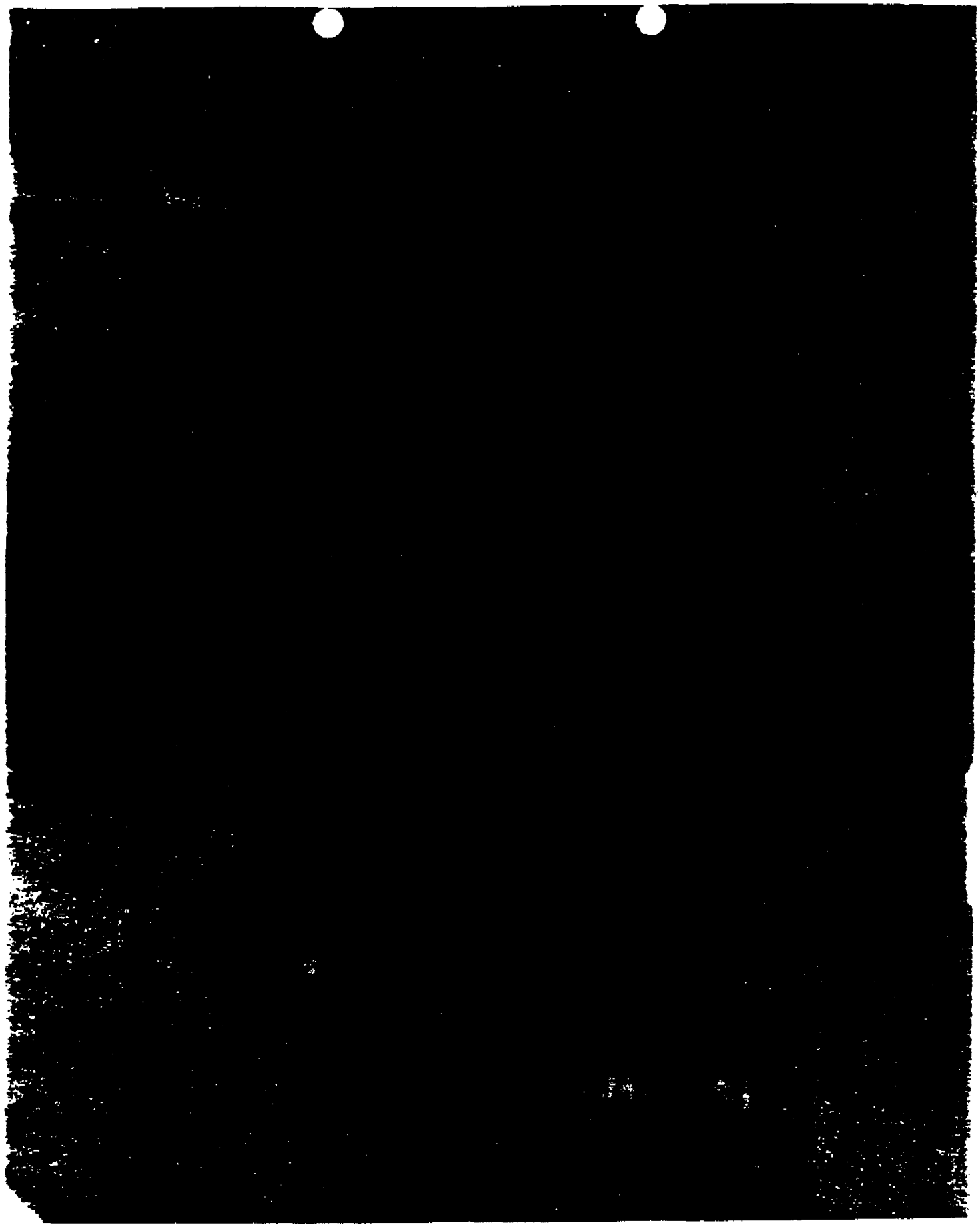
FED F-344 RATS, GSH MODEL, VDC EXPOSURE

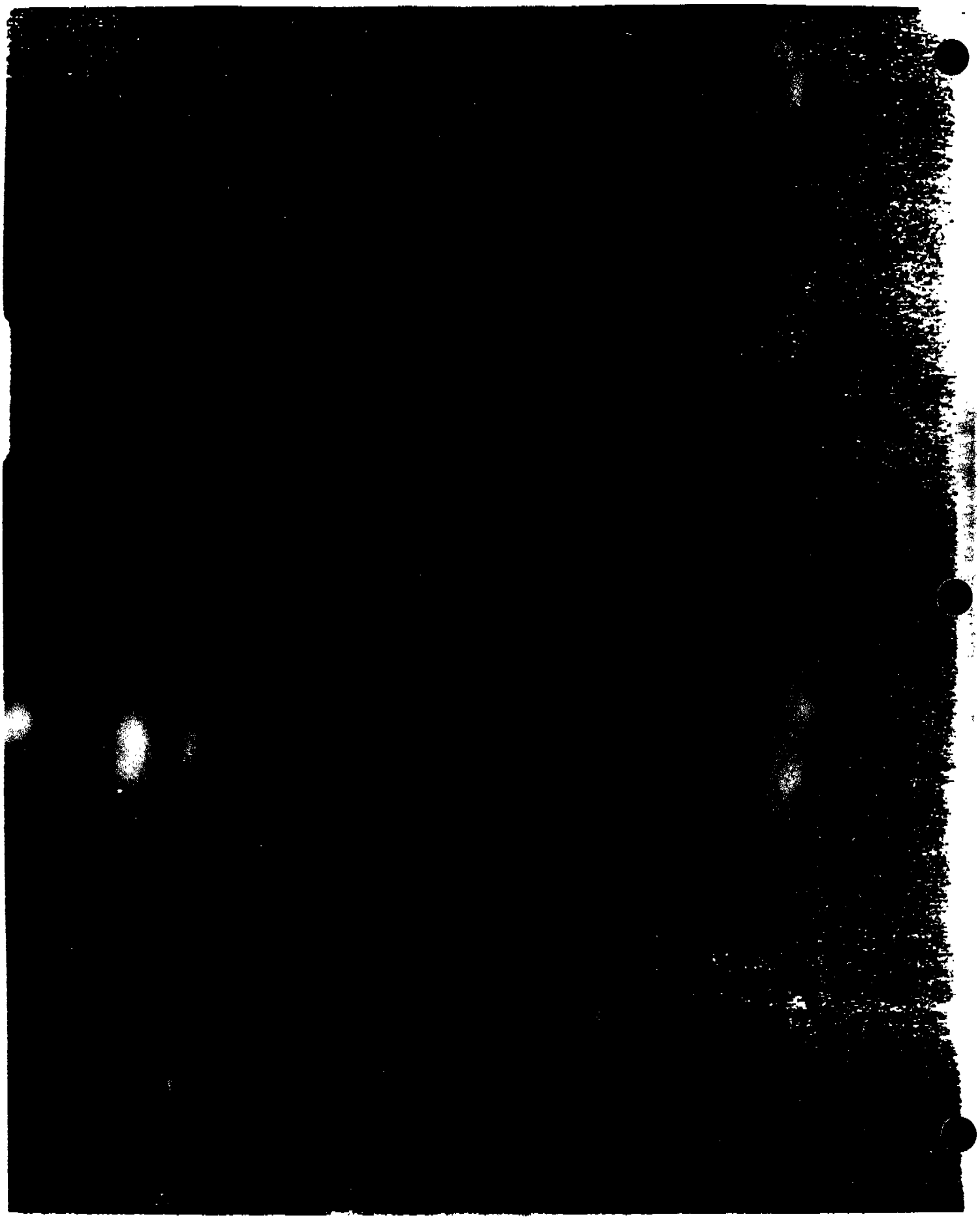


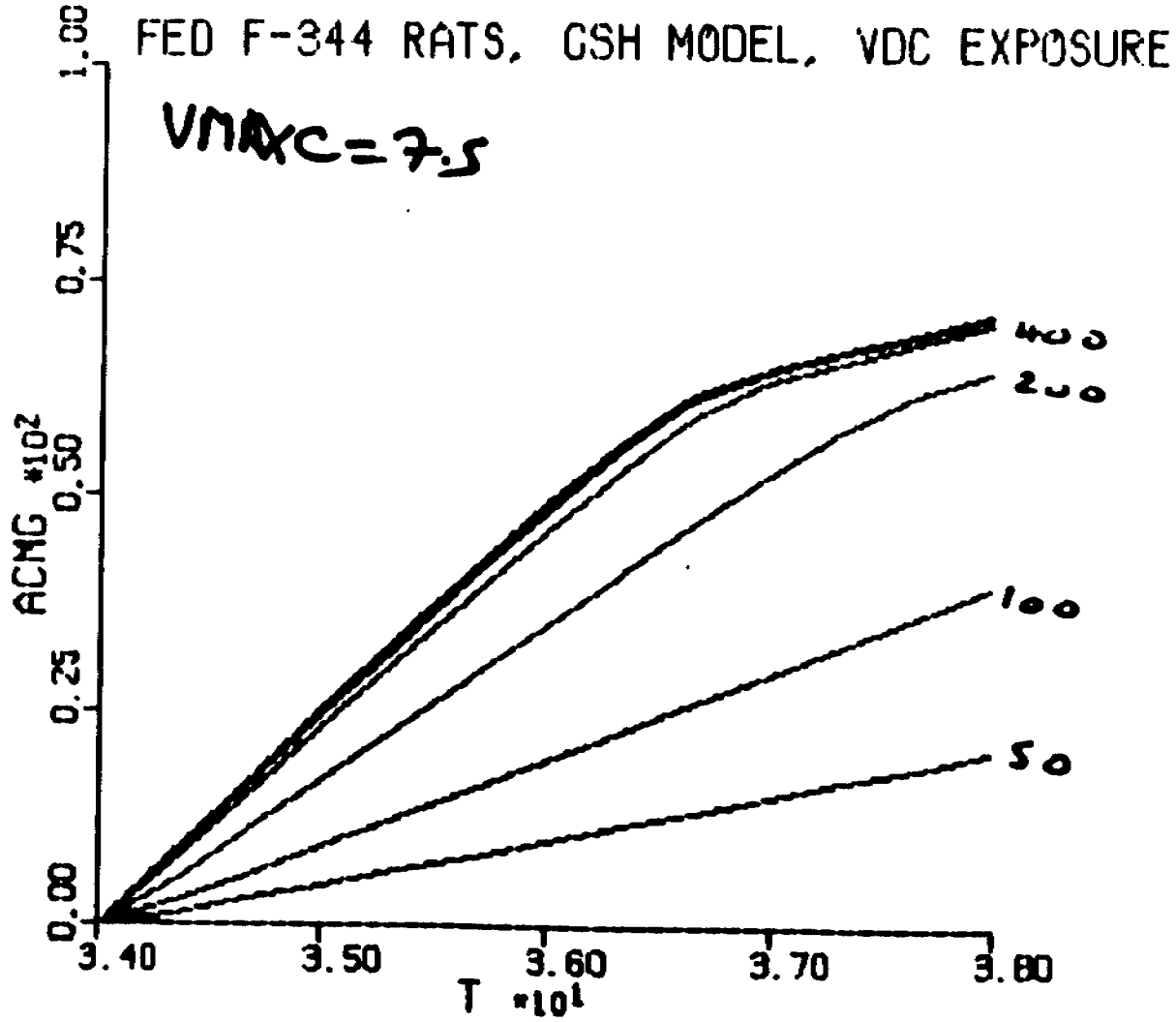
SL 061614

SL 061615


FED F-344 RATS. CSH MODEL. VDC EXPOSURE
VMAXC= 25.0
800
400
200
100
50
AM
40.0
30.0
20.0
10.0
0.00
3.40
3.50
3.60
3.70
3.80
T *10^1

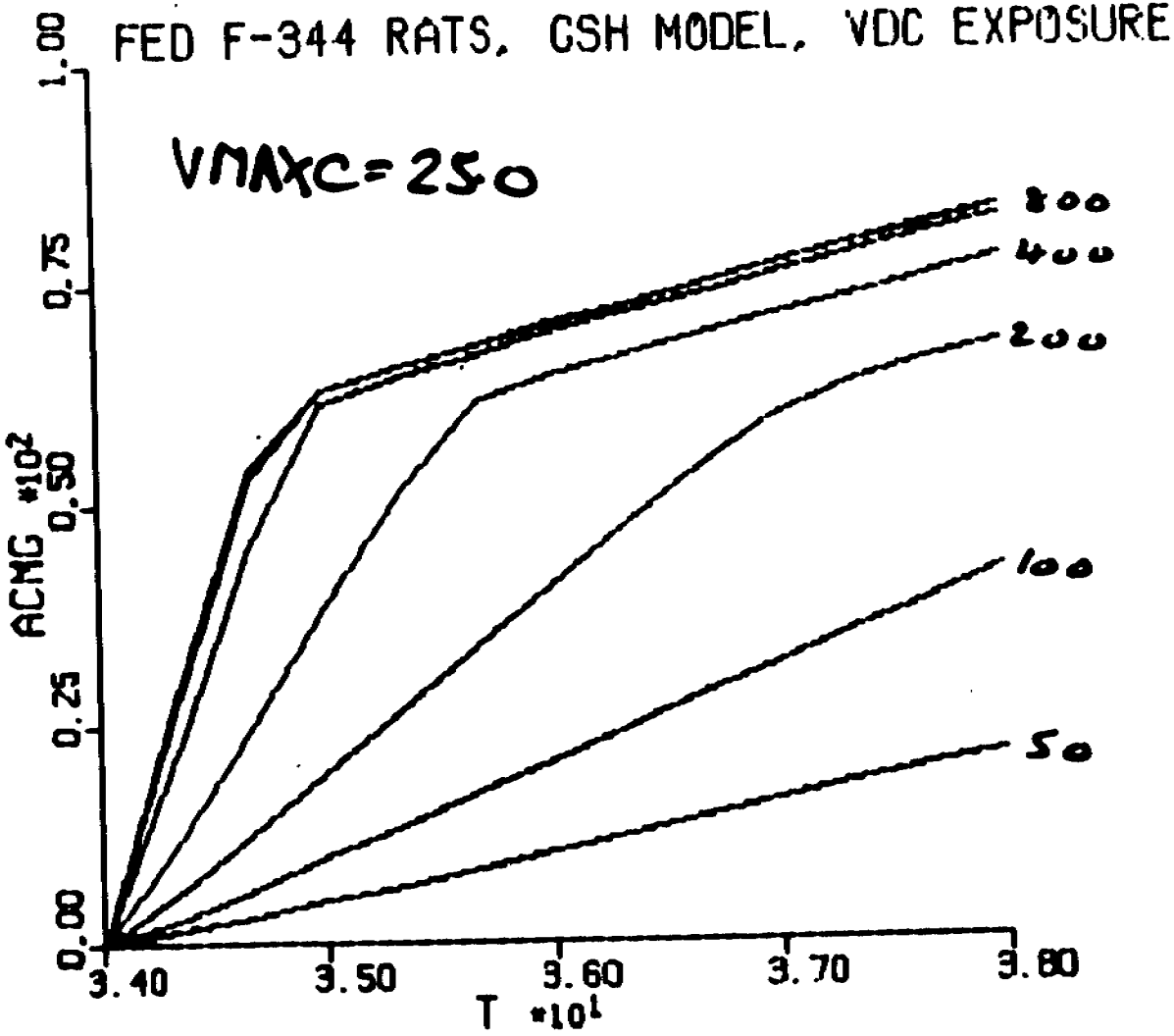


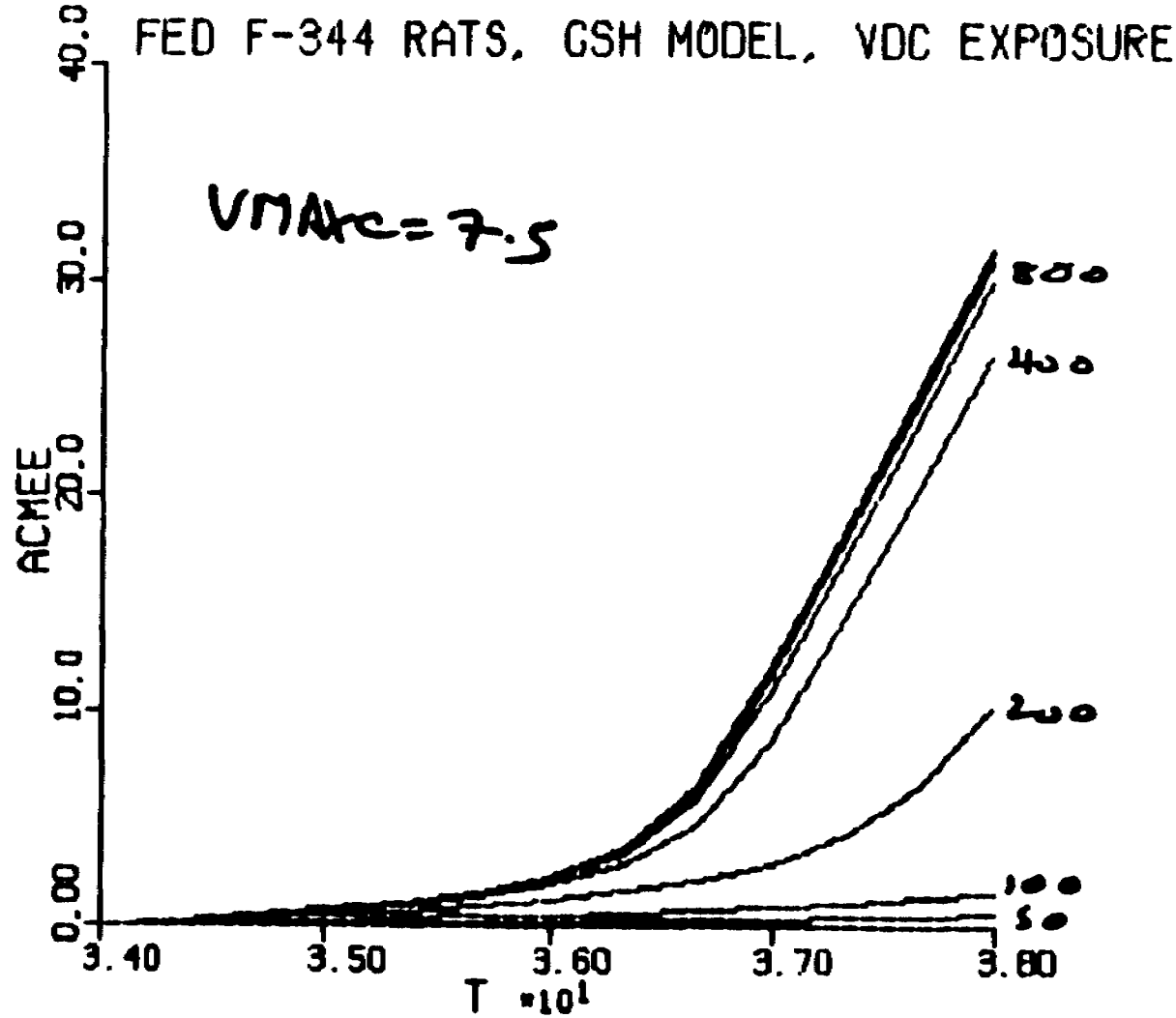



FED F-344 RATS, CSH MODEL, VDC EXPOSURE
VMAXC=7.5
1.00
0.75
0.50
0.25
0.00
ACMG *10²
400
200
100
50
3.40
3.50
3.60
3.70
3.80
T *10¹

SL 061616

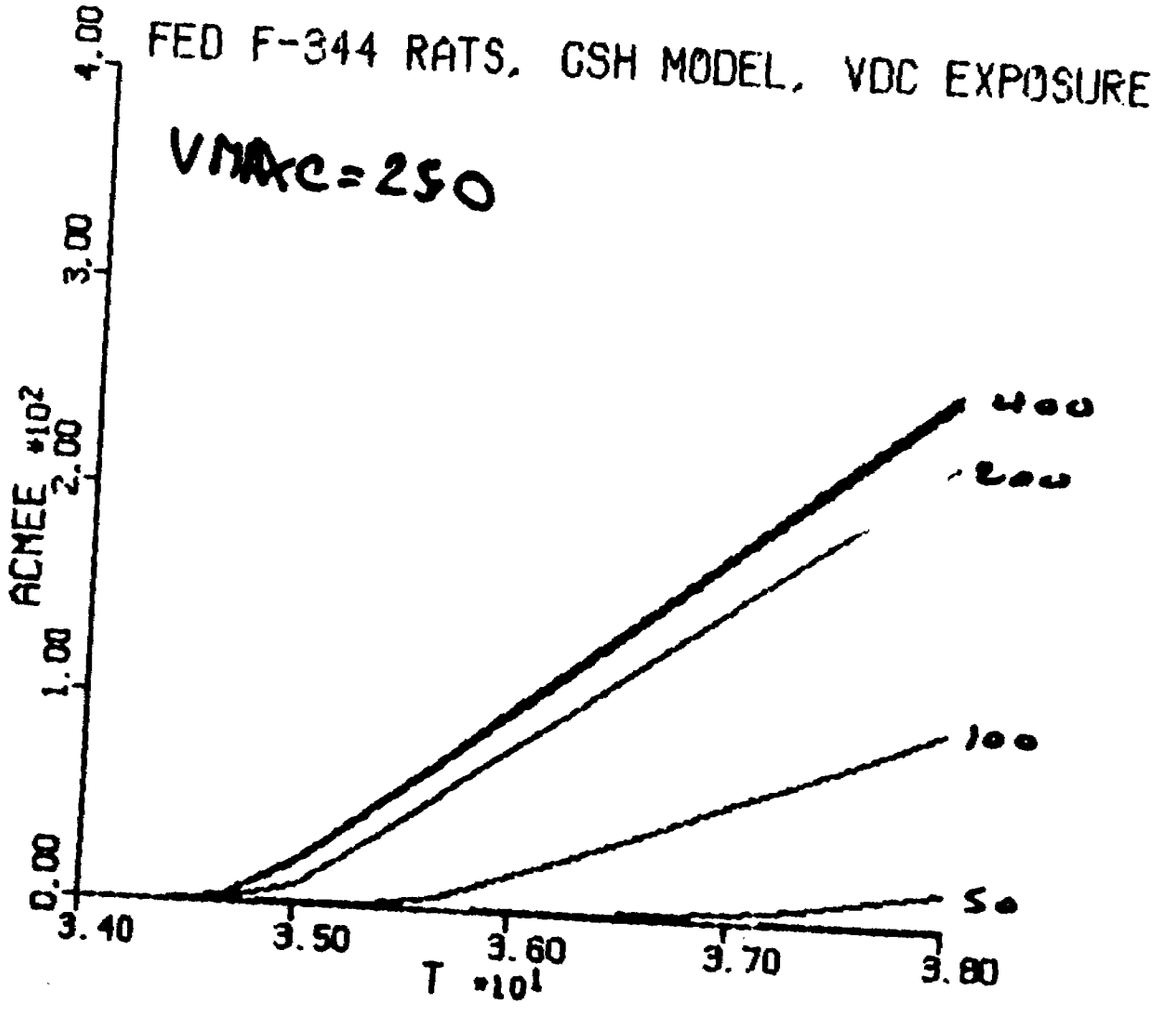
SL 061617


FED F-344 RATS. CSH MODEL. VDC EXPOSURE
VMAXC=250
800
400
200
100
50
ACMG *10²
1.00
0.75
0.50
0.25
0.00
3.40
3.50
3.60
3.70
3.80
T *10¹


FED F-344 RATS, GSH MODEL, VDC EXPOSURE
VMAxc=7.5
ACMEE
40.0
30.0
20.0
10.0
0.00
800
400
200
100
50
3.40
3.50
3.60
3.70
3.80
T *10¹

SL 061618

SL 061619


FED F-344 RATS. CSH MODEL. VDC EXPOSURE
VMAC=250
4.00
3.00
2.00
1.00
0.00
ACMEE *10²
400
200
100
50
3.40
3.50
3.60
3.70
3.80
T *10¹

40-8730024

Natural Resources Defense Council

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COMMENTS OF THE

NATURAL RESOURCES DEFENSE COUNCIL, INC.

ON THE

U.S. ENVIRONMENTAL PROTECTION AGENCY'S

PROPOSED TEST RULE FOR 1,1-DICHLOROETHYLENE

UNDER SECTION 4(a) OF THE TOXIC SUBSTANCES CONTROL ACT

51 FEDERAL REGISTER 48840-48846

JANUARY 15, 1987

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These comments are submitted by the Natural Resources Defense Council (NRDC) in support of the U.S. Environmental Protection Agency's (EPA) proposed test rule for 1,1-dichloroethylene under §4(a) of the Toxic Substances Control Act (TSCA).[1] If promulgated, this rule would require manufacturers and processors of the chemical to conduct distribution, excretion and metabolism studies as well as a two-year inhalation oncogenicity bioassay. NRDC, a national, nonprofit, environmental organization supported by over 60,000 members and contributors, has closely monitored the implementation of TSCA, and especially the testing provisions of the statute, since its passage in 1976. We have submitted extensive comments on many of EPA's proposed rules under the Act, and we applaud the use of TSCA to support other EPA programs in carrying out their mandates. As set forth below, we believe that the available evidence warrants promulgation of a test rule under §4(a) for 1,1-dichloroethylene.

I. Evidence on 1,1-dichloroethylene clearly meets the TSCA section 4(a) requirements for requiring testing of a chemical substance

Under 4(a) of TSCA, EPA is required to issue a test rule if the Administrator finds that manufacturing, processing,

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1 Toxic Substances, 1,1-Dichloroethylene; Proposed Test Rule, 51 Fed. Reg. at 28940 (August 12, 1986).

distribution, use or disposal of a chemical may present an unreasonable risk of injury to health or the environment.[2] EPA has compelling reason to conclude that 1,1-dichloroethylene may present an unreasonable health risk to humans. Although not conclusive, experimental data strongly suggest that 1,1-dichloroethylene is a carcinogen. Further, human exposure to this chemical via both ambient air and drinking water is widespread. If 1,1-dichloroethylene is in fact a carcinogen, current evidence indicates, this exposure may present a substantial carcinogenic risk to the population. For this reason, EPA is clearly justified in its desire to obtain additional evidence on the chemical's oncogenicity.

II. Experimental data provide a strong indication that 1,1-dichloroethylene is a carcinogen.

The evidence that 1,1-dichloroethylene is carcinogenic comes from positive experimental bioassays, sufficient evidence of mutagenicity in short term assays, and the structural similarity of 1,1-dichloroethylene to vinyl chloride, a known human carcinogen. The most compelling evidence comes from a series of experimental bioassays conducted by Maltoni, et al., from 1975 through 1983.[3] The latter concluded that the bioassays demonstrate that 1,1-dichloroethylene is carcinogenic in

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2 TSCA §4(a), 15 U.S.C. §2603(a).

3 Maltoni, C., et al., Experimental research on vinylidene chloride carcinogenesis. In: Maltoni, C. and Mehlman, M.A., eds. Archives of Research on Industrial Carcinogenesis, Vol. III, Princeton, N.J.: Princeton Scientific Publishers Inc., 1985.

rodents.[4] Most noteworthy, the Maltoni, et al. study found a significant increase in kidney adenocarcinomas in male Swiss mic exposed via inhalation.[5]

Two additional findings by Maltoni, not reviewed by EPA in the instant proposal[6] are also noteworthy. These include a statistically significant increase in mammary adenocarcinomas in female Swiss mice, and a statistically significant increase in pulmonary adenomas in both sexes of Swiss mice. These findings do not provide as strong evidence of carcinogenicity as the kidney adenocarcinomas because in neither case was the increase dose-related, and the increase in pulmonary tumors was in benign tumors only. Nonetheless, both provide a further indication of the possible carcinogenic potential of 1,1-dichloroethylene. In the first place, the absence of a clear-cut dose response does not necessarily indicate a lack of carcinogenicity, although the presence of such a relationship strengthens the evidence that the agent is a carcinogen.[7] According to the Interagency Regulatory Liason Group, the absence of a dose-response may be attributable to testing in a portion of the dose-response curve with a shallow slope or even with a declining slope due to competing risks.

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4 Id.

5 Swiss mice were exposed to 10 or 25 ppm 1,1-dichloroethylene 4 hr/d, 4-5 d/wk for 52 weeks with the experiment terminated after 126 weeks. No kidney tumors were seen in the 10 ppm exposure group. However, 25 out of 120 (20.8%) of males in the 25 ppm group evidenced kidney adenocarcinomas versus zero in controls.

6 51 Fed. Reg. at 28841 (August 12, 1986).

7 Guidelines for Carcinogen Risk Assessment, 51 Fed. Reg. at 33994 (September 24, 1986).

Therefore, a positive dose-response relationship is not necessary to reach a conclusion of carcinogenicity.[8] Moreover, the fact that the increase in pulmonary tumors in the Maltoni bioassay were benign tumors only does not negate the significance of this finding since chemica that induce benign tumors frequently also induce malignant tumors, and benign tumors often progress to their malignant counterpart.[9] For this reason, the EPA Cancer Risk Assessment Guidelines provide that when an increased incidence of benign tumors is observed in the absence of malignant tumors, as is the case here, the evidence will be considered to be limited evidence of carcinogenicity.[10]

In addition to the Maltoni, et al. experiments, several findings indicate that 1,1-dichloroethylene is capable of interacting with DNA and initiating the carcinogenic process. This is important since it is widely accepted that cancer is a multi-stage disease with the first stage the interaction of the chemical with genetic material.[11] The Van Duuren et al. findings that 1,1-dichloroethylene acts as a tumor initiator in a two-stage mouse skin-painting bioassay[12] indicates that 1,1-

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8 Scientific Bases for Indentification of Potential Carcinogens and Estimation of Risks; Request for Comments on Report, 44 Fed. Reg. at 39866, July 6, 1979.

9 51 Fed. Reg. at 33994 (September 24, 1986).

10 Id.

11 National Academy of Sciences, Drinking Water and Health, Vol. 6, p. 164, 1986. See also, 50 Fed. Reg. at 10376 (March 14, 1985).

12 Van Duuren, B.L., et al., Carcinogenicity of Halogenated Olefinic and Alliphatic Hydrocarbons in Mice, JNCI, 63:1433-1439, 1979.

dichloroethyl ne is active in this initial stage of carcinogenesis.

Additional confirmation of the ability of 1,1-dichloroethylene to interact with genetic material comes from positive mutagenicity data. The chemical has been found to be mutagenic in a number of different short-term assay systems. Experiments have consistently shown it to be mutagenic to bacterial systems.[13,14] It has also been shown to produce positive results in gene reversion and conversion in yeast.[15] 1,1-dichloroethylene has also been shown to alkylate DNA in the liver and kidney of mice in an in vivo inhalation bioassay.[16] More recently, 1,1-dichloroethylene has been shown to cause unscheduled DNA synthesis in rat hepatocytes.[17] In 1982, IARC concluded that there was sufficient evidence of mutagenicity in short term tests.[18] Sufficient evidence of mutagenicity is germane to the evaluation of a chemical's potential ability to

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13 International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4, 1982.

14 U.S. Environmental Protection Agency, Office of Drinking Water, Final Draft Criteria Document for the Dichloroethylenes, 1985.

15 Id.

16 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

17 Costa, A.K. and Ivanetich, K.M., Chlorinated ethylenes: their metabolism and effect on DNA repair in rat hepatocytes, Carcinogenesis, 5:1629-1635, 1984.

18 International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4, 1982.

cause cancer. The consensus of available information suggests that short term tests, when properly used and validated, can provide strong indications of potential carcinogenicity.[19]

Finally, the structural similarity of 1,1-dichloroethylene to vinyl chloride, an established human carcinogen, also provides a strong indication of the potential carcinogenicity of 1,1-dichloroethylene. In general, the structural similarity of a chemical to a known carcinogen is recognized as an important predicter of the potential carcinogenicity of the chemical.[20] For example, the cancer policy of the Occupational Safety and Health Administration (OSHA) points out that "there is substantial and documented evidence that for substances that clearly fall into certain classes, strong evidence of potential carcinogenicity can be drawn on the basis of structural similarity alone."[21]

Subsequent to the demonstration of the carcinogenicity of vinyl chloride in experimental animals and epidemiological studies in the 1970s, concern has increased over the potential carcinogenicity of the structural analogs of vinyl chloride. To date, all the compounds in this series that have been adequately tested have yielded positive results in chronic

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19 Chemical Carcinogens; A Review of the Science and Its Associated Principles, 50 Fed. Reg. at 10408 (March 14, 1985).

20 National Academy of Sciences, Drinking Water and Health, Vol. 6, p.167, 1986.

21 Identification, Classification and Regulation of Potential Occupational Carcinogens, 45 Fed. Reg. at 5177 (January 22, 1980).

bioassays for carcinogenicity.[22,23,24,25]

Based on the positive experimental evidence, the positive mutagenicty data and the structural similarity of vinyl chloride, EPA has classified 1,1-dichloroethylene as a possible human carcinogen.[26] NRDC concurs with this classification.

III. The existence of negative bioassays do not detract from the significance of the positive experimental data on 1,1-dichloroethylene.

In addition to the positive experimental data discussed above, a number of additional bioassays have been conducted to evaluate the carcinogenic potential of 1,1-dichloroethylene. In

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22 1,1-dichloroethylene belongs to a series of six compounds known as chlorinated ethylenes. This series also includes vinyl chloride, trichloroethylene, tetrachloroethylene, and cis and trans-1,2-dichloroethylene. Vinyl chloride is an established human and animal carcinogen. Trichloroethylene has been shown to cause significant increases in liver tumors in mice and has been classified by EPA as a Group B2 carcinogen, i.e., sufficient evidence of carcinogenicity. Tetrachloroethylene has been shown to induce a number of different malignant neoplasms in both sexes of rats and mice in a recently completed NTP bioassay. EPA is currently reevaluating its classification of tetrachloroethylene as a result of this bioassay. 1,1-dichloroethylene as discussed herein has induced significant increases in several different tumors in mice. Neither cis- nor trans-1,2-dichloroethylene has been assessed for carcinogenicity in long-term bioassays.

23 National Primary Drinking Water Regulations; Volatile Synthetic Organic Chemicals, 50 Fed. Reg. at 46887 (November 13, 1985).

24 Costa, A.K. and Ivanetich, K.M., Chlorinated ethylenes: their metabolism and effect on DNA repair in rat hepatocytes, Carcinogenesis, 5:1629-1635, 1984.

25 U.S. Environmental Protection Agency. Office of Drinking Water, Final Draft Criteria Document for the Dichloroethylenes, 1985.

26 50 Fed. Reg. at 46888 (November 13, 1985).

general, thes bassays provide no vidence of oncogenicity.[27] However, these negative studies do not detract from the positive evidence discussed previously. First, it is a general consensus of federal cancer risk assessment policies that positive results should outweigh negative findings.[28] EPA's own cancer guidelines state that positive carcinogenic responses in one species/strain/sex are not generally negated by negative results in other species/strains/sex.[29] These guidelines make clear that negative studies give rise to questions about the validity of positive ones only where "[r]eplicate negative studies...are ssentially identical in all other respects to a positive study."[30] In the instance case, none of the negative studies replicate the one positive Maltoni bioassay. According to EPA analysis, the only other inhalation studies in mice used either a shorter exposure period or a shorter observation period.[31]

More significantly, in various reviews by EPA, the National Academy of Sciences (NAS) and the International Agency for Research on Cancer (IARC), all of the negative studies were found to have design limitations that compromise the significance of the negative findings. A number of studies hav been criticiz d

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27 51 Fed. Reg. at 28841 (August 12, 1986).

28 See for example the OSHA Cancer Policy, 45 Fed. Reg. at 5079 (January 22, 1980).

29 51 Fed. Reg. at 33995 (September 24, 1986).

30 Id.

31 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride, Final Report (EPA/600/18-83/031F), 1985.

by EPA and NAS because the exposure levels were too low for an adequate evaluation. These include the Dow Chemical inhalation and drinking water studies in Sprague Dawley rats as reported by Rampy, et al. (1977),[32] McKenna, et al. (1982)[33] Quast, et al. (1983),[34] and Humiston, et al. (1978).[35,36,37]

The Ponomakov and Tomatis bioassay (1980) in rats[38] and the Maltoni, et al., (1985), inhalation study in hampsters and gavage study in rats,[39] have similarly been criticized because the doses used appeared to be below the maximum tolerated

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32 Rampy, L.W. et al., Interim results of two-year toxicological studies in rats on vinylidene chloride incorporated in the drinking water or administered by repeated inhalation. Environ. Health Perspect. 21:33-34, 1977.

33 McKenna, M.J., et al., Vinylidene Chloride: a chronic inhalation toxicity and oncogenicity study in rats. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical USA, Midland, MI, 1982.

34 Quast, J.F., et al., A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fundam. Appl. Toxicol. 3(1):55-62.

35 Humiston, C.G., et al., Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. MCA Report No. VCD 1.3 - Tox-Orl-Dow. Toxicological Research Laboratory Health and Env ro mental Research, Dow Chemical U.S.A., Midland, MI, 1978.

36 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

37 U.S. Environmental Protection Agency, The Carcinogen Assessment Group, Preliminary Risk Assessment on Vinylidene Chloride, 1978.

38 Ponomarkov, V. and Tomatis, L., Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats, Oncology 37:136-141, 1980.

39 Maltoni, C., et al., Experimental research on vinylidene chloride carcinogenesis. In: Maltoni, C. and Mehlmen, M.A., eds. Archives of Research on Industrial Carcinogenesis, Vol. III, Princeton, N.J., Princeton Scientific Publishers, Inc., 1985.

dose.[40,41] The Lee, et al., 1978, inhalation study in rats and mice[42] has been criticized by EPA and IARC because its short duration, only twelve months, precluded observing tumors with long latencies.[43,44,45] The Viola and Caputo, 1977 inhalation study in rats[46] has been criticized by EPA because of the lack of microscopic examination of the tissues as well as the short duration of exposure.[47,48]

Finally, EPA has reasoned that the small number of animals

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40 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

41 National Academy of Sciences, Drinking Water and Health, Vol. 5, 1983.

42 Lee, C.C., et al., Carcinogenicity of vinyl chlroide and vinylidene chloride, J. Toxicol. Environ. Health. 4(1):15-30.

43 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

44 International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 19, 1979.

45 U.S. Environmental Protection Agency. The Carcinogen Assessment Group, Preliminary Risk Assessment in Vinylidene Chloride, 1978.

46 Viola, P.L. and Caputo, A., Carcinogenicity studies on vinylidene chloride. Environ. Health Perspect., 21:45-47, 1977.

47 U.S. Environmental Protection Agency, The Carcinogen Assessment Group, Preliminary Risk Assessment on Vinylidene Chloride, 1978.

48 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

in each exposure group in the Hong, et al., 1981 study[49] in rats and mice weakened the ability of this study to detect a tumorigenic response, and further that the exposure period was considerably shorter than potential lifetime of the animals.[50] Results of the NTP gavage bioassay[51] in rats and mice, the only negative study on 1,1-dichloroethylene considered by EPA to have an adequate design protocol[52] has nonetheless been questioned by both the Agency and by the NAS because of doubts as to whether the maximum tolerated dose had been used in the study.[53,54] Because of design limitations in all of the negative studies, none of them can be relied on to demonstrate the lack of oncogenic potential of 1,1-dichloroethylene. Thus, "there are insufficient data...upon which the effects [of vinylidene chloride] on health or the environment can reasonably be

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49 Hong, C.B., et al., Follow-up study on the carcinogencity of vinylchloride and vinyldidene chloride in rats and mice; tumor incidence and mortality subsequent toi exposure, J. of Toxicol. and Environ. Health, 7:909-924, 1981.

50 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

51 National Cancer Institute/National Toxicology Program, NTP Technical Report on the Carcinogenesis Bioassay on Vinylidene Chloride in F344/N Rats and B6C3F1/Mice (Gavage Study). NTP No. 80-82 NIH Pub. No. 82-1784. NTP Research Triangle Park, N.C. and Bethesda, Md. U.S. Dept. of Health and Human Services, Public Health Services, National Institute of Health, 1982.

52 51 Fed. Reg. at 28840 (August 12, 1986).

53 National Academy of Sciences, Drinking Water and Health, Vol. 5, 1983.

54 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride (EPA/600/8-83/031F), 1985.

predicted," and "testing..is necessary to develop such data." TSCA §4(a)(1)(A)(ii) and (iii).

IV. Human exposure to 1,1-dichloroethylene from both ambient air around manufacturing plants and from drinking water is widespread and poses a potentially substantial carcinogenic risk.

In the instant proposal, EPA discusses only exposure to 1,1-dichloroethylene in ambient air in the vicinity of manufacturing plants. However, exposure via drinking water may also present an unreasonable cancer risk. The presence of 1,1-dichloroethylene in drinking water is widespread. Over 2% of the population is exposed to levels at or above 0.2 ug/l, according to EPA estimates.[55] Approximately 0.1% or 52,000 individuals are xposed to levels above 5 ug/l.[56] Preliminary lifetime cancer risk estimates associated with these exposures range from 6.6×10^{-6} to greater than 1.6×10^{-4} based on EPA's q^*_1 value for 1,1-dichloroethylene of 1.16 $(mg/kg/d)^{-1}$.[57] This value was derived from the Maltoni, et al., finding of increased kidney adenocarcinomas in male mice exposed by inhalation.[58] If the risk estimates are based on the q^*_1 value of 0.58 $(mg/kg/d)^{-1}$ derived from the negative NTP oral bioassay, they range from

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55 U.S. Environmental Protection Agency, Office of Drinking Water, Draft Criteria Document for the Dichloroethylenes, September, 1985.

56 Id.

57 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride, (EPA/600/8-83/031F), 1985.

58 Id.

$3.3x10^{-6}$ to greater than $8.3x10^{-5}$.[59]

EPA has recently proposed a primary drinking water standard for 1,1-dichloroethylene of 7 ug/l.[60] This proposed standard was based on chronic toxicity data, primarily liver effects, with an additional margin of safety to account for the limited evidence of carcinogenicity.[61] Lifetime cancer risk associated with this standard range from $2.3x10^{-4}$ to $1.2x10^{-4}$, based on the Maltoni _et al._ and NTP derived q^*_1 values respectively. While these estimates are preliminary, they do indicate that if 1,1-dichloroethylene is in fact a carcinogen, as experimental evidence indicates, current drinking water exposures may carry substantial carcinogenic risks for many people and the proposed drinking water standard may well be set at an extremely high cancer risk level.

Exposure to 1,1-dichloroethylene in ambient air in the vicinity of manufacturing plants may also present a substantial carcinogenic risk. EPA has estimated that the median and mean concentrations respectively, within the vicinity of 1,1-dichloroethylene monomer and polymer plants are 2.2 and 3.8 ppb.[62] There are approximately 38 such plants in the United States, with an estimated population totally 3.6 million residing

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59 _Id._

60 National Primary Drinking Water Regulations; Volatile Synthetic Organic Chemicals. 50 Fed. Reg. at 46902 (November 13, 1985).

61 50 Fed. Reg. at 46880 (November 13, 1985).

62 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride, (EPA/600/8-83/031F), 1985.

within five miles of the plants.[63] Continuous xposure to 2.2 and 3.8 ppb of 1,1-dichloroethylene in air carries lifetime cancer risks of 4.4×10^{-4} to 7.6×10^{-4}, based on EPA's q^*_1 value of 1.16 $(mg/kg/d)^{-1}$.

Because of the potential for substantial carcinogenic risks associated with exposure to 1,1-dichloroethylene in both drinking water and air, EPA is clearly justified in its desire to obtain additional data to better assess the oncogenic potential of 1,1-dichloroethylene. For these reasons, NRDC strongly supports the proposed test rule for 1,1-dichloroethylene.

V EPA should require that two species be tested in the oncogenicity study in conformance with the Agency's normal testing guidelines.

The proposed test rule is somewhat unusual in that EPA is requiring oncogenicity testing in only one species, the mouse, because of its demonstrated sensitivity to 1,1-dichloroethylene.[64] The chemical has already been tested in several species of rats by inhalation in a number of bioassays with generally negative results.[65] However, in one of the Maltoni et al. bioassays of Sprague Dawley rats, there was an increase in the incidence of an aggregate of hemopoietic and

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63 Id.

64 51 Fed. Reg. at 8842 (August 12, 1986).

65 U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Health Assessment Document for Vinylidene Chloride, (EPA/600/8-83/031F), 1985.

lymphatic diseases classified as leukemia.[66] This increase occurred in rats exposed to 100 ppm when the exposure began in utero.[67] In a recent workshop of representatives of EPA's Carcinogen Assessment Group and other scientist called by EPA to assess the Maltoni, et al. study, a doubling and quadrupling in leukemias in rats were noted when exposure began at conception and continued for 52 weeks or a full two years after birth.[68] Although there was some question whether all the tumors in rats classified as leukemia had been accurately classified,[69] this vidence raises a serious question about whether 1,1-dichloroethylene is a leukemogen in rats.

Because of the possibility that 1,1-dichloroethylene causes an increase in leukemia in rats as indicated by the Maltoni, et al. bioassay, NRDC recommends that EPA include in the final rule a requirement that 1,1-dichloroethylene be tested in two species, mice and rats, in conformance with the Agency's normal testing guidelines. We further recommend that Sprague Dawley rats be used in light of the Maltoni, et al. findings and that exposures begin in utero in order to adequately assess the possibility of an increase in leukemia.

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66 Maltoni, C., et al., Experimental research on vinylidene chloride carcinogenisis. In: Maltoni, C. and Mehlman, M.A. eds. Archives of Research on Industrial Carcinogenesis. Vol. III, Princeton, N.J., Princeton Scientific Publishers, Inc. 1985.

67 Id.

68 Workshop Report of Vinylidene Chloride and Trichloroethylene Carcinogenicity Studies at the Benivoglio Laboratories, November 21, 1985.

69 Id.

VI. Conclusion

For the reasons stated above, NRDC believes that issuance of a test rule under §4(a) is necessary and appropriate to determine whether 1,1-dichloroethylene is carcinogenic. Serious flaws in the design and/or methodology of much of the existing body of data as well as strongly suggestive short-term test results and structure-activity analysis all support the Agency's determination to issue such a rule. NRDC strongly concurs with this determination, and urges that a final rule incorporating additional requirements for testing rats as well as mice be promulgated as expeditiously as possible.

February 12, 1987

CMA's VDC EMISSIONS AND EXPOSURE SURVEY RESULTS

by Robert R. Romano

Good afternoon. On behalf of CMA's VDC Panel I am pleased to be here.

In an effort to generate data which would provide a more reliable basis upon which to estimate exposure, CMA conducted a survey of manufacturers and processors of VDC. A confidential questionnaire was sent to each company identified in the HAD, as well as to customers of the manufacturers. The survey was seeking information regarding emissions from process vents, storage tanks, and fugitives. Estimates of populations residing within five miles of plants and distances from VDC process facilities to property boundaries and to the nearest residents were also obtained. Finally, the questionnaires asked about the availability of meteorologic data and of occupational monitoring data.

1. Number of VDC Manufacturers and Processors

The survey revealed that many of the companies listed in the 1985 HAD no longer use VDC. Of a total of 42 companies reported by EPA to be producing or using VDC 31 companies responded to the survey. Of these, 15 companies indicated that they no longer used or produced VDC leaving only 16 companies using or producing VDC. All major processors did submit responses, and the manufacturers of VDC believe that the 11 companies that did not respond do not presently use the chemical.

2. Quantity of VDC Released

The HAD estimated that emissions of VDC from these facilities amounted to 1,300,400 pounds per year, HAD at 5-12. If the CMA survey data are combined, less than 162,500 pounds per year were reported emitted through process vents, fugitive emissions, storage tanks and loading/unloading areas. While it is possible that this figure would be larger if the survey had received a 100% response rate, as opposed to 74% received to date, actual emissions are probably quite close to this figure. Because all of the major processors of VDC have responded, additional emissions are likely to be slight.

In any event, the total emissions are about 8 times lower than than the 1,300,400 pounds per year estimated in the Agency's HAD.

3. Population

EPA had estimated that a total of 3,573,395 people lived within five miles of producing or processing plants, HAD at 7-7. The CMA survey revealed a total of only 1,515,383 living within five miles of facilities responding. This figure is less than half that estimated by EPA.

4. Air Transport

Th HAD noted that dispersion modeling could theoretically provide an estimate of VDC concentrations at certain distances from the plant sites, but that such data were not presently available. The CMA

survey a mpted to generate realistic data that could be used in such modeling.

The distance from the source of release to the property boundary reported in the survey ranged from 100 feet to 5,900 feet with an average of about 1,000 feet. The distance from the source of release to the nearest resident ranged from 260 feet to 6,000 feet with an average of over 2,421 feet or about one half mile. The survey also revealed that meteorologic data and occupational monitoring data are available for nearly all sites surveyed.

Based on the previously available emission estimates, the Agency concluded in their Federal Register notice of 1985 not to regulate VDC as a Hazardous Air Pollutant because public exposure to VDC levels were low (50 Fed. Reg. at 32634). These survey results support that conclusion, suggesting emissions nearly an order of magnitude lower than that estimated by EPA. These survey results certainly will improve the Agency's exposure assessment, and conclude that public exposures to VDC are lower than those estimated by EPA. In addition, this lower exposure will more th likely reduce the presently existing small risk of VDC to th ublic even more.

Thank you for your attention, I will be pleased to answer any questions.

VINYLIDINE CHLORIDE
(1,1-Dichloroethylene)

	EPA's HAD	CMA's '86 SURVEY
-- Estimated Emission (lbs/yr)	1,300,400	162,500
-- Estimated Population	3,573,395	1,515,383

2/12/87

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CHEMICAL MANUFACTURERS ASSOCIATION

February 3, 1987

Mr. Ralph Northrop
Test Rules Development Branch
Office of Toxic Substances
Environmental Protection Agency
Room 101, Northeast Mall
401 M Street, S.W.
Washington, D.C. 20460

Re: Proposed Test Rule for 1,1-Dichloroethylene (Vinylidene Chloride)
OPTS-42081

Dear Mr. Northrop:

On January 15, 1987, the Chemical Manufacturers Association ("CMA") Vinylidene Chloride Program Panel ("VDC Panel") submitted comments on EPA's proposed test rule for 1,1-dichloroethylene (vinylidene chloride). The comments point out that EPA's proposal raises significant scientific issues regarding interpretation of the extensive existing data regarding vinylidene chloride. The comments also present additional pharmacokinetic and metabolism data and suggest that these data should be used by EPA in carcinogenicity risk assessment.

The VDC Panel looks forward to discussing these significant scientific issues with EPA scientists at the February 12, 1987 public hearing on EPA's proposed test rule. In that connection, I am enclosing a suggested agenda for the public hearing which is intended to foster and accommodate a scientific dialogue on these issues among scientists from EPA and from industry. The VDC Panel believes that the public hearing will be most productive if it can serve as a forum in which to commence such a discussion among the appropriate scientists.

The VDC Panel will identify those scientists who could best contribute to a discussion of the issues raised in our comments. We request that EPA furnish by February 9 a list of scientific personnel from offices within the Agency, such as OAQPS and OTS, as well as from other relevant federal agencies, such as NTP, who plan to attend and participate in

the public hearing. The Panel will then attempt to bring scientists who can most appropriately engage in a scientific discussion with the government experts.

The VDC Panel would welcome any suggestions you might have on how best to achieve the objective of conducting a meaningful and productive scientific dialogue on the issues raised in our comments. We look forward to seeing you on February 12, 1987.

Sincerely yours,

Robert R. Romano

Robert R. Romano, Ph.D.
Manager
Vinylidene Chloride Program Panel
Chemical Manufacturers Association

Enclosure

cc: Carol Glasgow

PROPOSED AGENDA
FOR FEBRUARY 12, 1987 PUBLIC HEARING
ON PROPOSED TEST RULE
FOR 1,1-DICHLOROETHYLENE (VINYLIDENE CHLORIDE)
OPTS-42082

I. Introduction -- History and Basis of EPA Proposal

II. Brief Summary of VDC Program Panel Position

III. New Emissions/Potential Exposure Data

IV. Existing Toxicity Database

V. Utility of Metabolism and Pharmacokinetic Data in Carcinogenicity Risk Assessment for VDC

VI. Summary and Conclusions

CHEMICAL MANUFACTURERS ASSOCIATION

March 20, 1987

Ralph Northrup, Ph.D.
Test Rules Development Branch
U.S. Environmental Protection Agency
401 M Street, S.W.
Room NE100
Washington, D.C. 20460

Re: Proposed Test Rule for 1,1-Dichloroethylene
51 Fed. Reg. 28840 (August 12, 1986)

Dear Dr. Northrup:

On behalf of the Chemical Manufacturer Association's Vinylidene Chloride Panel, I commend you on the scientific nature of the February 12, 1987 VDC hearing. I sincerely appreciate the meaningful dialogue between industry scientists and Agency scientists on the issues raised by the proposed test rule for VDC. I would also like to provide additional information promised at the hearing.

First, as I noted during the hearing, CMA has received additional VDC emissions survey responses from a number of companies since the Panel's written comments were filed. The new information was included in my oral remarks at the hearing. I am enclosing for your use a copy of my remarks.

Second, you asked whether the uses of VDC were likely to vary over time in such a way that the emissions data could change. We have discussed this question with members of the industry, including importers of VDC based copolymers, and have learned that it is unlikely that the use of VDC will expand. A review of the past few years demonstrates that the user industry is shrinking. If you compare the number of sites at which VDC was used a number of years ago as reflected in the HAD, with the number of sites reporting current use in the CMA survey, you will see that the number of sites reporting VDC use has significantly declined. Thus, if there is any change in the industry over the next few years that is likely to affect emissions, it will be reflected in a decrease in sources of emissions and total amount of emissions.

Third, we are looking into the questions raised by Dr. Greenberg at the hearing. Certain of those questions would require additional review of the literature to determine what further data exist. These data might be useful in refining the Agency's risk assessment through pharmacokinetic modeling. We hope to have further information and suggestions for Dr. Greenberg in the very near future.

As we explained at the hearing, the Panel believes that the extensive data base for VDC -- and the fact that EPA has conducted a carcinogenicity risk assessment for VDC -- makes it inappropriate for the Agency now to conclude that there are insufficient data to enable EPA reasonably to predict carcinogenic effects. Therefore, a test rule is inappropriate.

If you have any further questions, please do not hesitate to contact me at (202) 887-1198.

Sincerely,

Robert R. Romano

Robert R. Romano, Ph.D.
Associate Director, Special Programs
& Program Manager, VDC Panel

cc: G. Timm
C. Glasgow
N. Pate
M. Greenberg

SL 061644

CHEMICAL MANUFACTURERS ASSOCIATION

March 20, 1987

Dr. Nancy B. Pate
U.S. Environmental Protection Agency
Office of Air Quality Planning and
Standards
Mail Drop 12
Research Triangle Park, NC 27711

Re: Proposed Test Rule for 1,1-Dichloroethylene
51 Fed. Reg. 28840 (August 12, 1986)

Dear Dr. Pate:

I would like to thank you for your help in making the February 12, 1987 hearing the successful technical dialogue that we had hoped it would become. Your participation in the meeting and your more recent explanation of the use to which an oncogenicity test would be put by the Air Office help us understand the role of this test rule in the possible future activities of the Air Office and the EPA State Initiative Program. I was particularly interested to learn that a test rule for VDC is seen as potentially helpful to EPA, not in improving risk assessment, but rather in enrolling VDC in the State Initiative Program.

As you know from our hearing statements, the Panel believes that the proposed test rule is inappropriate because the present data base for VDC is sufficient to enable the Agency reasonably to predict carcinogenic effects without the need for another oncogenicity study. We do feel that it is inappropriate to seek oncogenicity data through the test rule mechanism when the Agency can already assess risk. The ability of states to act under the State Initiative Program should not be a motivating factor in issuing a test rule.

I would like to give you additional information as a follow-up to the hearing. Of particular interest to your office is the information that I provided regarding CMA's emissions survey. As I noted at the hearing, CMA has received additional survey responses from a number of companies that had not responded by the time the Panel's written comments were filed. This new information was detailed in my oral remarks, a copy of which is enclosed.

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Dr. Northrup asked an important question regarding the significance of the survey results. He inquired whether the uses of VDC were likely to vary over time in such a way that the emissions data could change. We have discussed this issue with members of the industry, including importers of VDC based copolymers and have learned that it is unlikely that the use of VDC will expand. A review of the past few years demonstrates that the user industry is shrinking. If you compare the number of sites at which VDC was used a number of years ago as reflected in the Health Assessment Document, with the number of sites reporting current use in the CMA survey, you will see that the number of sites reporting VDC use has significantly declined. Thus, if there is any change in the industry over the next few years that is likely to affect emissions, it will be reflected in a decrease in sources of emissions.

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Sincerely yours,

Robert R. Romano

Robert R. Romano, Ph.D.
Associate Director, Special Programs
& Manager, VDC Panel

Enclosure

cc: C. Glasgow

SL 061646

February 12, 1987

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(1,1-Dichloroethylene)

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2/12/87

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