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May 9, 1980

Docket Officer
Docket H-034
Room S6212
U.S. Department of Labor
200 Constitution Avenue, N. W.
Washington, D. C. 20210

Re: Docket H-034, Occupational Safety and Health Administration Request for Information on Vinyl Chloride and Polyvinyl Chloride - 44 Fed. Reg. 74928, December 18, 1979; 45 Fed. Reg. 668, January 29, 1980.

Dear Sir:

Pursuant to Section 4 of the Administrative Procedure Act, as amended, 5 U.S.C. Section 553(c), and the above-referenced U.S. Department of Labor - Occupational Safety and Health Administration (OSHA) Request for Information on Vinyl Chloride and Polyvinyl Chloride and the subsequent Notice extending the time during which interested persons are invited to submit written data, views, and comments with regard to the issues described in the original Notice, The Society of the Plastics Industry, Inc. (hereinafter referred to as "SPI" and/or "The Society"), by its attorneys, hereby submits in quadruplicate certain information which is intended to be responsive to the Agency's Request.

I.

INTRODUCTION AND SUMMARY OF INFORMATION PRESENTED

SPI is a corporation organized under the Not-for-Profit Corporation law of the State of New York. Its 1500 member companies and individuals and 67 operating divisions include those who supply raw materials; process or manufacture plastics or plastics products; engineer or construct molds or similar accessory equipment for the plastics industry; and engage in the manufacture of machinery used to make plastics products and materials of all types. SPI is the major national trade association of the plastics industry. The majority of its members are the processors and converters of the plastics resins and end products which represent 75% of the dollar volume of sales of plastics in this country; SPI's membership also represents 95% of all plastics materials and machinery manufactured in the U.S.A.

The Society's concern with vinyl chloride and polyvinyl chloride begins with the manufacture of the ethylene dichloride (used to manufacture the monomer) and the manufacture of vinyl chloride monomer (VCM), carries forth through its polymerization into polyvinyl chloride (PVC), continues with the various processes which convert the PVC resin into its multitude of end uses, and includes, ultimately, the recycling or disposal of PVC products. In the United States there are 17 ethylene dichloride plants, 13 plants which produce vinyl chloride monomer and 42 polymerization plants.

Twenty-two companies representing over 95% of the domestic VCM and PVC capacity are active members of SPI's PVC Safety Group.

SPI's PVC Safety Group has prepared the information, data and views contained in what follows, and it is presented in a form which corresponds in large part to the explicit requests for information contained in the Agency's Notice.

In summary, The Society's responses to the questions asked are as follows:

1. OSHA is aware of the studies on vinyl chloride sponsored by Imperial Chemicals Industries, Limited; Montedison; Rhone-Poulenc Industries; and Solvay et Cie. in Dr. Maltoni's laboratory in Bologna, Italy.

   These most recent data of Maltoni indicate possible effects in rats exposed to 10 ppm of vinyl chloride but no increase in tumors was found in experimental rats exposed below 10 ppm. It is clearly evident that rodents are more susceptible than humans and that human experience should be given higher importance than animal studies. Animal data have predicted an angiosarcoma incidence rate over 500 times higher than that observed in man.

2. It has been reported in the literature that VCM can exert a carcinogenic effect transplacentally;

however, this phenomenon has only been demonstrated in pregnant rats exposed to very high concentrations. Additional work in this area needs to be done using lower, more realistic doses since available data indicate that the rates of metabolism in the rat shift as exposure concentrations of vinyl chloride change. Vinyl chloride did not cause significant embryonal or fetal toxicity and was not teratogenic in studies in rats, mice or rabbits. We know of no valid scientific paper associating vinyl chloride with human birth defects at any level of exposure.

3. While no carcinogenic effect of inhaled PVC has been demonstrated in animals or man, recent data indicate that like most nuisance dusts slight effects may occur in the lungs following exposure to high concentrations of the dust.

4. Although there are no new epidemiological data on health effects associated with vinyl chloride exposure which would appear to change the conclusions from those considered in the current standard, The Society has contracted for a complete, independent analysis of all available, relevant epidemiologic data. This is particularly important since it is not always made clear in subsequent papers reviewing them that many of

the studies which have been reported represent repeated investigations of the same population or subsets thereof. Considering the magnitude of this project, it will not be finished by the May 9, 1980 deadline associated with the Request but these materials will be submitted to the Agency when they have been completed.

5. The Society is not aware of any new, unpublished case reports on cancer associated with vinyl chloride or polyvinyl chloride but is submitting to the Agency the most recent, world-wide compilation of all liver angiosarcoma cases associated with VCM.

6. It has been demonstrated that if mutagenic effects occur as monitored by chromosomal analysis of circulating lymphocytes, they were the results of high exposures; the changes have not been permanent since they have been reversible. The changes did not occur at lower levels of exposure. The clinical significance of the reversible changes is not known.

7. Being a poorly soluble gas, vinyl chloride does not accumulate from chronic exposure, but, rather, is rapidly exhaled after exposure ceases. Hence, there can be no body burden in the usual meaning of the term.

8 and 9. An overview of PVC manufacturing operations, types of resin, residual monomer levels, and PVC dust experience is presented with information on monitoring results, control technology and personal protective devices. Variability in resin type and the resin type relationship to differing residual monomer content in the resin, varying VCM exposure potential from both resin and dust, and the type of PVC dust and other conditions which might be expected in both the polymerization and fabricating industries are explained.

10. SPI is unaware of any change in the types of occupations, jobs and industries which present a potential for exposure to VCM or PVC. The Society has no data on the numbers or breakdown by sex of employees exposed.

11. The VCM/PVC industry is engaging in the use of appropriate engineering controls, work practices and personal protective equipment and is trying to stay in compliance with the existing standard; the industry knows of no additional, feasible measures to reduce exposure below the present level. PVC dust is adequately regulated by OSHA's nuisance dust permissible exposure level (29 C.F.R. §1910.1000) and has not been shown to be hazardous at that level of exposure.

II.

SPECIFIC INDUSTRY RESPONSES TO INFORMATION REQUESTED

(1) Experimental Test Results for Carcinogenicity of Vinyl Chloride At Atmospheric Exposures Less Than 50 ppm

The current studies on vinyl chloride are those conducted in Dr. Maltoni's laboratory in Bologna, Italy. As OSHA is aware, these investigations are sponsored by Imperial Chemicals Industries, Limited; Montedison; Rhone-Poulenc Industries; and Solvay et Cie.

These most recent data of Maltoni indicate probable effects in rats exposed to 10 ppm of vinyl chloride but no increase in tumors was found in experimental rats exposed below 10 ppm. As to the mammary tumors Maltoni noted at lower levels, the data are not convincing because the experimental animals used are known to have a high incidence of spontaneous mammary tumors. As will be discussed below rodents are more susceptible than humans and human experience should be given higher importance than animal studies.

Dr. Maltoni's data were reported in detail at a recent OSHA/NIOSH/NIEHS sponsored Symposium, March 20 and 21, 1980 in Bethesda, Maryland. An unedited stenographic transcript of the entire Symposium and photographic copies of most of the slides are attached as Appendix A.

In Maltoni's studies, rats, mice and/or hamsters were exposed to concentrations ranging from 30,000 ppm to

1 ppm. The attached summary statement by the European sponsors quotes Dr. Maltoni and indicates that extensive statistical evaulations of Dr. Maltoni's data have been completed. Appendix B.

In that summary, Dr. Maltoni summarized his animal studies as follows:

> ...the following tumours should be given proper attention viz, extra-hepatic angiosarcomas, hepatomas, Zymbal gland carcinomas, liver angiosarcomas, neuroblastomas, nephroblastomas, forestomach papillomas and mammary carcinomas.
>
> In oncological terms, the meaning of the results at the lowest doses may be better evaluated by considering, not separately, but together, the tumours found to be VCM dependent. Thus the following results should be considered: -
>
> at 25 ppm - In 120 animals, 5 liver angiosarcomas, 4 Zymbal gland carcinomas and 1 nephroblastoma.
>
> at 10 ppm - In 120 animals, 1 liver angiosarcoma, 2 extra-hepatic angiosarcomas and 2 Zymbal gland carcinomas.
>
> at 1mg/kg - In 150 animals, 3 liver angiosarcomas, 1 extra-hepatic angiosarcoma, 1 hepatoma and 5 Zymbal gland carcinomas....

These data add to that previously published by Dr. Maltoni since tumors occurred in rats exposed to 25 or 10 ppm of vinyl chloride gas. Maltoni's European sponsors state,

> In addition, it is worthwhile emphasising that none of the previously cited tumours have been observed at 5 ppm by inhalation and 0.03 mg/kg by ingestion.

These data will be published as part of the proceedings of Club de Cancerogenese Chemique held at the Curie

Foundation in Paris, France, November 10, 1979. These proceedings, which will be supplied to OSHA as soon as available, will contain an even more complete report of Maltoni's studies than was presented in Bethesda on March 20, 1980.

In regard to the response of laboratory animals to vinyl chloride gas, the attached paper by Gehring, Watanabe and Park is extremely pertinent. Appendix C. This paper indicates the necessity of considering the rate of metabolism and body size of different species when comparing the response of different species to vinyl chloride.

Many factors, such as those considered by Gehring, Watanabe and Park, no doubt are involved in the wide difference between the high incidence of angiosarcoma in small rodents and the much lower incidence in man.

It is clearly evident that rodents are more susceptible than humans and that human experience should be given higher importance than animal studies. Dr. David Rall, Director of NIEHS, has commented on the wide difference between the susceptibility of man and rodents. Appendicies D and E. He stated that in regard to angiosarcoma the available data

> ...project a cancer incidence rate 500 times higher than has so far been reported in man by epidemiological studies for vinyl chloride. (Rall, 1977, Appendix D, p. 2.)

(2) Studies of Transplacental Carcinogenic and Teratogenic Effects in Humans or Animals at Any Level of Exposure to Vinyl Chloride

It has been reported that VCM can exert a carcinogenic effect transplacentally[1/2/]; however, the phenomenon has only been demonstrated in pregnant rats exposed to very high (10,000 or 6,000 ppm) concentrations of the material. Additional work needs to be done using lower, realistic doses since available data indicate that rates of metabolism in rats shift as exposure concentrations of vinyl chloride change and that some mechanisms of metabolism are saturable.[3/] Vinyl chloride did not cause significant embryonal or fetal toxicity and was not teratogenic in studies in rats, mice or rabbits[4/] even at levels which resulted in maternal toxicity. We know of no valid scientific paper associating vinyl

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1/ Maltoni, C., Vinyl Chloride Carcinogenecity: An Experimental Model for Carcinogenesis Studies. In "Origins of Human Cancer. Book A: Incidence of Cancer in Humans." H.H. Hiatt, J.D. Watson and J.A. Winsten, Cold Spring Harbor, Cold Spring University, 1977.

2/ Maltoni, C., Carcinogenicity Bioassays of Vinyl Chloride Monomer: A Model of Risk Assessment on Experimental Basis. Symposium Paper No. 1 (1980).

3/ Watanabe, P.G. and Gehring, P.J., Dose Dependent Fate of Vinyl Chloride and Its Possible Relationship to Oncogenicity In Rats. Environmental Health Perspectives 17:145-152 (1976).

4/ John, J.A., Smith, F.A., Leong, B.K.J., and Schwetz, B.A., The Effects of Maternally Inhaled Vinyl Chloride on Embryonal and Fetal Development in Mice, Rats, and Rabbits. Toxicol. and Appl. Pharmacol. 39:497-513 (1977).

chloride with human birth defects at any level of exposure.

1. TRANSPLACENTAL CARCINOGENESIS

Maltoni has reported that exposure of female rats to 10,000 and 6,000 ppm of vinyl chloride has resulted in transplacental effects in their offspring. No data have been found in which pregnant animals have been exposed to lower concentrations. Rice[5/], although not having actually studied vinyl chloride in his laboratory, reviewed the subject of transplacental carcinogenesis. In discussing the above-mentioned work of Maltoni, Rice refers to the important role of biotransformation of VC to the probable carcinogenic metabolite. This metabolic transformation in the pregnant female, the possibility of a similar transformation in the fetus, the kinetics of placental transfer (which processes can be bidirectional), and the metabolic degradation in both the gravid female and the fetus all illustrate the complexity of transplacental carcinogenesis.

Rice also rightly points out that in the case of VCM the probable carcinogenic metabolite has a relatively short half-life. This would limit the times for transfer across the placenta to the fetus and for distribution to the fetus. Although the data of Maltoni indicate that the metabolite either crosses the placental barrier or is formed in the fetus in sufficient concentration to elicit a carcinogenic

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5/ Rice, J., Transplacental Carcinogenic Effects. Symposium Paper No. 27 (1980).

response, the short half-life suggests that the effect would be minimized at lower levels of maternal exposure. Unfortunately, sufficient data are lacking on much of the foregoing, and, therefore, definitive conclusions cannot be reached.

Another complicating factor, even over and above those usually recognized in extrapolating from Maltoni's transplacental carcinogenic data to rats to a possible human situation, is the knowledge that rats are far more sensitive to VCM than humans. (See response to Request no. 1.) In addition, there are marked differences in placental structure between humans and rodents.

The following discussion of the possible effects of these differences in placentation with regard to teratogenesis is equally germane to the consideration of transplacental carcinogenesis:

> ...Both man and the test animals commonly used possess chorioallantoic placentae, but that of man is the hemochorial one consisting essentially of fetal villi hanging in a pool of maternal blood. The chorioallantoic placenta of rodents and lagomorphs (rabbits) is the complex hemoendothelial type which consists of closely juxtaposed and highly modified fetal and maternal cells, permeated by a labyrinth of blood sinuses. An even more significant difference between the two types is that man has only the chorioallantoic placenta, whereas the rodents and the lagomorphs have a yolk-sac placenta as well. In man, once the chorioallantoic placenta has formed, most if not all, drugs reach the fetus by this route. In the rodents, often used as test animals, the presence of two types of placentae in the same animal means that the drugs might reach the embryo in two different ways, and it seems probable that in the earliest most vulnerable stage, the drugs that enter

> the embryo do so predominantly via the yolk-sac placenta6/....

The marked difference in the structure of the placenta between rats and humans, the alteration in metabolism at lower dosages, and the recognized higher susceptibility of the rat to angiosarcoma must all be taken into account in interpreting Maltoni's results at extremely high concentrations. The highly idealized scheme (Figure 1) may serve to highlight some of the complexities of these factors.

2. TERATOGENIC EFFECTS

The landmark study of the teratogenic potential of VCM remains the industry-supported study of three species by John et al., first reported in part at the 14th Annual Meeting of the Society of Toxicology in 1975. John and her co-workers subsequently published a detailed report of the work[7/], and again reiterated the findings at this most recent Symposium. The authors' published summary of this important study is as follows:

> ...Groups of pregnant CF-1 mice, Sprague-Dawley rats and New Zealand white rabbits were exposed to 500 ppm of vinyl chloride 7 hr. daily during the period of major organogenesis. Subsequently, other groups of mice were similarly exposed to 50 ppm of vinyl

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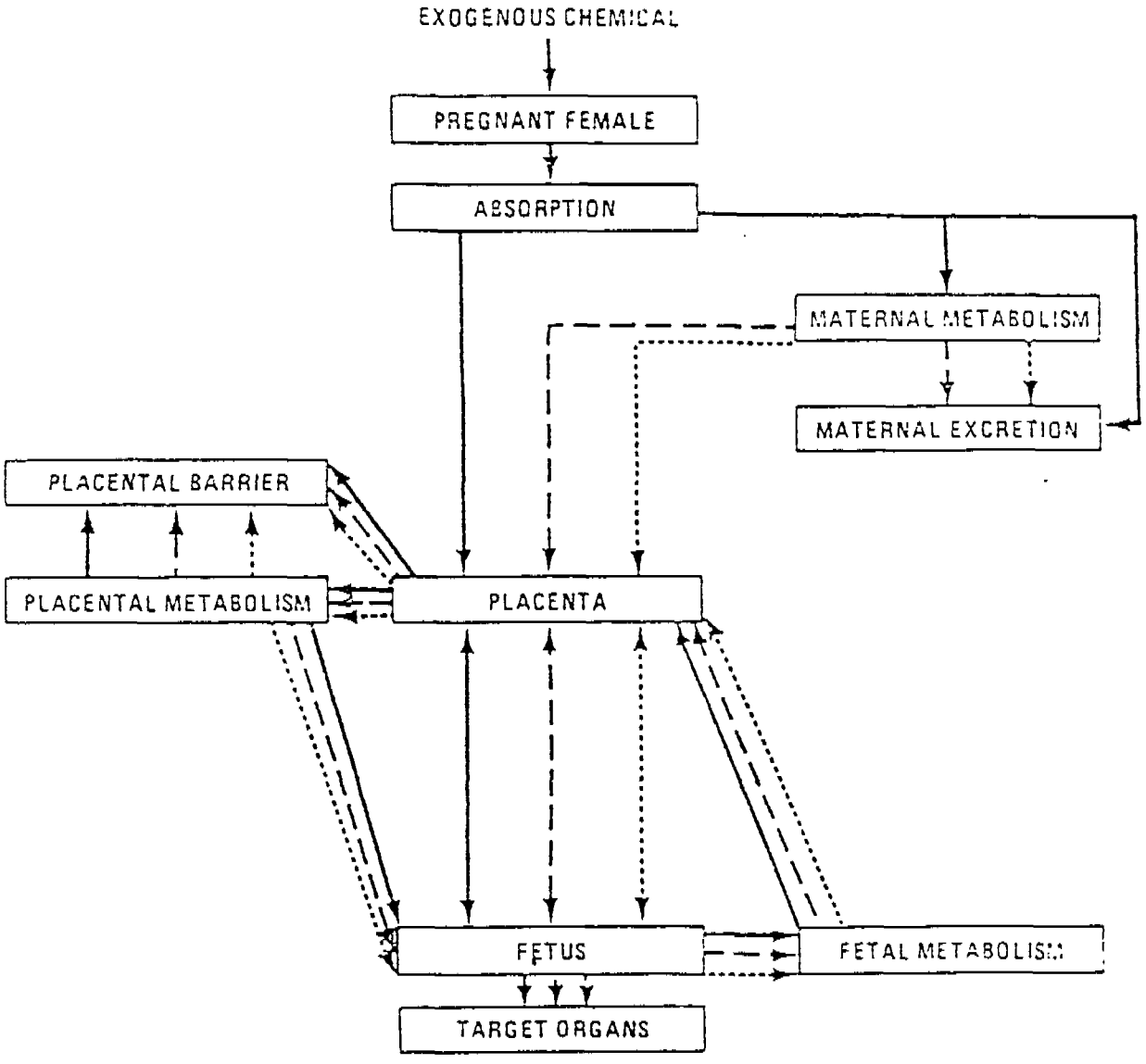
6/ "The Testing of Chemicals for Carcinogenicity, Mutagenicity and Teratogenicity," Minister of Health and Welfare, Canada, 1973.

7/ John, J.A., Smith, F.A., Leong, B.K.J. and Schwetz, B.A., The Effects of Maternally Inhaled Vinyl Chloride on Embryonal and Fetal Development in Mice, Rats, and Rabbits. Toxicol. and Appl. Pharmacol. 39:497-513 (1977).



LEGEND

——— CHEMICAL

– – – TOXIC (CARCINOGENIC) METABOLITE

····· NON-TOXIC (NON-CARCINOGENIC) METABOLITE

FIGURE 1. HIGHLY CONCEPTUALIZED SCHEME OF THE PATHWAYS FROM MATERNAL EXPOSURE TO A CHEMICAL TO THE EXPOSURE OF FETAL TARGET ORGANS. THE INFLUENCE OF THE PHYSICOCHEMICAL PROPERTIES OF THE SPECIFIC CHEMICAL, AS WELL AS MANY BIOLOGICAL CAPABILITIES OF THE ORGANISM, ON THESE PATHWAYS ARE NOT CONSIDERED IN THE DRAWING.

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> chloride and rats and rabbits were exposed to 2500 ppm of vinyl chloride. While maternal toxicity was observed, vinyl choride alone did not cause significant embryonal or fetal toxicity and was not teratogenic in any of the species at the concentrations tested. Maternal toxicity was more prominent among mice than among rats and rabbits. Simultaneous exposure of some of the pregnant animals to vinyl chloride by inhalation plus 15 percent ethanol in the drinking water resulted in toxic effects greater than those associated with exposure to vinyl chloride alone in the three species. The maternal toxicity was enhanced to an extent greater than the embryotoxicity. (Emphasis added.)

It should be noted that, to our knowledge, the conclusions reached by John et al. with regard to the teratogenic potential of VCM have not been seriously questioned and, in fact, have been confirmed.

Dr. John, in her presentation at the Symposium, discussed briefly the results of two additional studies of the teratogenic potential of VCM which have appeared in the recent literature. The first was a report of work carried out in Hungary,[8/] the findings of which were consistent with those reported by John et al. The second report, originating with the Institute of Hygiene and Occupational Health in Bulgaria, is still available only in abstract form. Although sufficient detail is not presented in the abstract to permit a critical evaluation of the study, the report alleges a teratogenic response at much lower levels of VCM exposure than those shown to have no effect by either Ungvary

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8/ Ungvary, G., The Teratogenic Effect of Vinyl Chloride. MUNKAVEDELEM (Work Safety) 25:29-33 (1979).

or John et al. A complete assessment of this Bulgarian study is essential before it can be given any credence.

Dr. John also mentioned the Symposium presentation of Hehir[9/]. As far as can be determined from the transcription of Dr. Hehir's talk, as well as what can be gleaned from a prepublication copy of the CPSC report[10/], the study did not address teratogenesis. All F_0 animals were exposed before mating but progeny were not. Thus, although effects on reproductive capacity or genetic changes in the germ cells (e.g., dominant lethal effects) could possibly be manifest, true teratogenic events dependent upon exposure of the fetus could not be revealed. It should be noted, however, that the F_0 exposure did not result in any alterations in the various parameters monitored in the F_1, F_2, and F_3 generations.

In summary, the most completely documented study of the teratogenic potential of VCM, viz., the study of John et al., reveals that under the high exposure conditions of that study inhalation of VCM by pregnant rats, mice or rabbits was neither embryo nor fetotoxic, nor was it teratogenic

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9/ Hehir, R., Cancer Induction Following Single and Multiple Exposures to a Constant Amount of Vinyl Chloride Monomer. Symposium Paper No. 5 (1980).

10/ Hehir, R.M., Bierbower, G., Williqan, D.A., Kolaja, G., Marrs, G.E., Hinton, D.E., Dimmick, R.L. and Wiles, J.S., Toxicology, Carcinogeniity and Reproductive Effects of Single and Multiple Exposures to Vinyl Chloride in Rats and Mice. CPSC Prepublication Release, April 1, 1979.

even at concentrations sufficient to cause maternal toxicity. While an additional published report basically confirms the latter conclusions, results available only in abstract form from the Bulgarian literature purport to reveal a teratogenic effect for VCM at lower levels. Although this latter information is contradictory of the study by John and her coworkers, as well as that of the Hungarian study, its full significance must await evaluation of the complete report when it becomes available.

Further, it should be noted that the maximum dose levels tested in the study of John et al., 2500 ppm in rats and rabbits and 500 ppm in mice, provide ample margin for safety extrapolation from these test species to the human situation.

Finally, to our knowledge, there are no reports which clearly relate birth defects in humans to maternal, or for that matter, paternal exposure to VCM. Two relevant studies which have been published[11/][12/] indicate no relationship between population exposure to VCM in the area surrounding PVC formulation plants and birth defects. Infante et al.,[13/]

11/ Edmonds, L.D., Anderson, C.D., Flynt, J.W. Jr., and Heath, C.W. Jr., Congenital Cental Nervous System Malformations, Kanawah County, West Virginia. U.S. Public Health Service, CDC, Atlanta, EPA-76-60-2 (1976).

12/ Edmonds, L.D., Falk, H. and Nissim, J.E., Congenital Malformations and Vinyl Chloride. Lancet ii:1098 (1975).

13/ Infante, P., Wagoner, J.K., McMichael, A.J., Waxweiler, R.J. and Falk, H., Genetic Risks of Vinyl Chloride. Lancet 11:734-35 (1976).

have suggested a causal relationship between paternal exposure to VCM in the industrial setting and pregnancy outcome. The adequacy of the data supplied by Infante et al. was almost immediately questioned[14/]. More recently, Haas and Schottenfeld[15/] have leveled severe criticisms at the Infante study, and the following is extracted from their paper:

> ...Analysis of questionnaire responses suggested that the number of fetal deaths per 100 conceptions was higher in the VCM-exposed group than in the comparison group. This difference was reported only for the period following vinyl chloride exposure. Adjustments removing women who were chronic aborters eliminated statistically significant differences. While the authors felt that these observations were likely to reflect a real difference in pregnancy outcome not attributable to either interviewer or patient recall bias, the conclusions were based on indirect sources of information and could not take into account the multiplicity of maternal factors known to affect pregnancy outcome. The study design precluded documenting in even the crudest manner the validity of pregnancy histories. Without such adjustments and validation, the inferences made cannot be sustained and little light is shed on the possible association of abnormal pregnancy outcome with paternal occupational exposure to VCM. (Emphasis added.)

Likewise, others have raised serious doubts regarding the validity of the conclusions drawn by the authors of the Infante et al. study. For example, Downs et al.[16/] so com-

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14/ Paddle, G.M., Genetic Risks of Vinyl Chloride Lancet 1:1079 (1976). Appendix F.

15/ Haas, J.F. and Schottenfeld, D., Risks to the Offspring from Parental Occupational Exposures. J. Occup. Med. 21:607-13 (1979). Appendix G.

16/ Downs, T.D., Stallones, R.A., Frankowski, R.F. and Labarthe, D.R., Vinyl Chloride, Birth Defects, and Fetal Wastage: A Critical Review. Private Communication. Appendix H.

pletely discredited the study that their ultimate conclusion was as follows:

> ...It does not seem possible to salvage anything from this study....
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> Among the more specific criticisms are the following:
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> The authors gave no information on the distribution of workers' reported recall of time intervals since pregnancies. Such information would be useful in assessing the validity of this study, since it is well known that the reliability of recall of past events decreases with time elapsed since the events.
>
> The authors' analytical methods are invalid since the ...test requires that the two rates being compared be independent, and this is not the case....
>
> ...The methods used by the authors to test significance are inappropriate since pregnancies are clustered....
>
> ...The misleading conclusions drawn by the authors were brought about through the selection and use of their control group.
>
> ...The purpose of adjusting rates is to make them comparable. Adjusting a rate r to a population A and another rate to a population B, and then comparing the adjusted rates r and s is contrary to the purpose of adjusting rates, and the resulting comparison does not make any sense. But this is precisely what the authors do when they adjust the prior exposed rate to the prior control group, then adjust the subsequent exposed rate to the subsequent control group, and then compare the adjusted rates. When adjusted rates are to be compared the rates should be adjusted to the same population.
>
> ...The comparisons of rates made by the authors are irrelevant to the hypotheses tested by them and to their corresponding conclusions. (Emphasis added.)

Similarly, McMahon[17/] opens his review of the Infante paper with the following comment:

> ...It is disappointing to see an article of such poor quality as this published in the Lancet. The data are subject to serious criticism on several counts.

and, after detailed point-by-point analysis of the study, presents the following conclusory statement:

> In short, this paper deserves ...no consideration whatsoever in weighing the question of whether there is or is not a genetic risk associated with exposure to VCM. (Emphasis added.)

The foregoing reviews, two of which were available in 1977, completely rebut the scientific validity of the paper by Infante et al. in this matter. Absent a scientifically sound defense of this paper by the authors or their scientific peers, continued citation of this paper is inappropriate.

17/ MacMahon, B. (Professor of Epidemiology, Harvard School of Public Health) Vinyl Chloride and Human Reproduction. Private Communication, 1977. Appendix I.

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(3) Experimental Studies of Carcinogenicity and Other Toxic Manifestations For Any Level of Polyvinyl Chloride Exposure. These Effects Should Include, But Are Not Limited to, Mutagenicity, Teratogenicity, Embryo Toxicity, and Other Transplacental Effects As Well As Cytotoxic and Cytogenic Effects on Sperm Cells. To the Greatest Extent Possible, Complete Information Concerning the Industrial Source of the Polyvinyl Chloride, the Size and Characteristics of the Particles, and Exposure Levels or Concentrations of PVC and Residual VC Should Be Included for Each Study

While no carcinogenic or other toxic effect of inhaled PVC has been demonstrated in animals or man, recent data indicate that, like most nuisance dusts, slight effects may occur in the lungs following high exposures to PVC dust.[18/]

Two reports on PVC dust were presented during the

18/ The American Conference of Governmental Industrial Hygienists in the preface to the 1979 List of Threshold Limit Values for Chemical Substances in the Work Air makes the following statement concerning nuisance particles:

> Nuisance particulates. In contrast to fibrogenic dusts which cause scar tissue to be formed in lungs when inhaled in excessive amounts, so-called "nuisance" dusts have a long history of little adverse effect on lungs and do not produce significant organic disease or toxic effect when exposures are kept under reasonable control. The nuisance dusts have been called (biologically) "inert" dusts, but the latter term is inappropriate to the extent that there is no dust which does not evoke some cellular response in the lung when inhaled in sufficient amount. However, the lung-tissue reaction caused by inhalation of nuisance dusts has the following characteristics: (1) The architecture of the air spaces remains intact. (2) Collagen (scar tissue) is not formed to a significant extent. (3) The tissue reaction is potentially reversible.

course of the Symposium, that is, the papers by Groth and Wagner. The paper by Frongia, et. al., cited as reference no. 3 in the December 18, 1979 Notice, is one of many publications which deal with experimental exposure of test animals to vinyl chloride. In addition, SPI is aware of feeding studies conducted either with polyvinyl chloride resin, polyvinyl chloride copolymer resins, or low molecular weight fractions extracted from commercial PVC resins and/or copolymers. Two of these reports, one done at Harvard and one by Smith et al., are attached as Appendices J and K. Other reports are in the files of the Food and Drug Administration (FDA) and efforts are being made to obtain copies. As soon as they have been released to us, copies will be sent to the Docket Officer.

With regard to the papers presented by both Groth and Wagner, the specific nature and particle sizes of the samples used are not completely clear. It is essential that when written versions of their papers become available for study, these deficiencies be eliminated. For the present, we can only assume that fine particles (dispersion resins) were used. As noted by Wagner, these may contain surfactants or other suspending agents. Hence, their use may result in effects which were misattributed. As stated by Dr. Wagner, he has not been able to reproduce the positive results of his early work despite repeated attempts.

Nevertheless, taking the reports at face value, both studies appear to be consistent in demonstrating that exposure

of experimental animals to respirable PVC dust results only in a low level of toxic response and in the retention of dust particles in the lungs with the development of macrophage aggregates, a normal clearance mechanism used by the lung. It is significant to note that these experimental exposures (at least in the work of Groth with monkeys) did not result in impairment of pulmonary function. Although both authors considered that the dust induced a low-level pneumoconiosis[19/] in the exposed animals, their reports did not indicate the presence of fibrotic tissue which is observed in acute pneumoconiosis resulting from exposure to other substances such as silica.

The observations of Groth and Wagner appear to be quite consistent with the experimental work and observations reported by Frongia and his co-workers. Thus, it appears that in the experimental animals studied, exposure to respirable PVC dust particles results in retention of such dust particles for long periods of time, perhaps for the entire lifetime, and the development of macrophagic responses to these particles.

A major deficiency in all these studies is the ab-

19/ Pneumoconiosis, which literally means dust in the lung, can range from benign effects such as mere storage of particles in the lung to very severe effects such as fibrotic changes and death. It must be emphasized that as used in this response and by the speakers at the March 20-21 Symposium only lung storage and very minimal tissue response were seen. Fibrotic changes were not observed.

sence of a control using another inert "nuisance" dust. Thus, the observations made as a result of exposure to PVC dust may be a characteristic response of many dusts rather than a phenomenon unique to PVC.

As to the ingestion studies undertaken for the purpose of assuring the safety of PVC packaging materials, feeding either the whole resin or the low molecular weight (extractable) fractions showed no observed chronic effects up to the maximum quantities used, i.e. in the range of 5%-10% of the animals' diets. In this connection, one other study should be mentioned, i.e., that conducted by CIVO/TNO in Holland, a copy of which is attached as Appendix L. It is mentioned here only because a porous PVC powder was incorporated into the animals' diets as the vehicle to carry vinyl chloride monomer in a feeding study intended to measure the carcinogenic response of rats to vinyl chloride monomer. In that study, while it was not one directed at PVC, there was no observed effect attributed to exposure to PVC.

Summarizing, except for the feeding studies utilizing PVC and its copolymers, studies which showed no toxic effect attributable to PVC, and those studies discussed above, SPI is not aware of other experimental studies dealing with the toxicity of PVC.

Perhaps comment should be made on the speculative remarks made at the Bethesda Symposium concerning the impact of PVC dust on occupational exposure to vinyl chloride.

The hypothesis is that the dust is carried into the lung and thereby distributed throughout the body. Even were the hypothesis correct, and we think it is not, the quantity of monomer currently contained in PVC is so small that it would make this speculative exposure of no practical significance.

(4) Epidemiologic Studies of Either Vinyl Chloride or of Polyvinyl Chloride (i.e., cohort, cross-sectional, or case-control)

Because of the importance of this area of information, The Society postponed preparing responsive commentary until the recent Conference to Reevaluate the Toxicity of Vinyl Chloride, Polyvinyl Chloride and Structural Analogs had been held. Prior to this Symposium it had been speculated that, perhaps, some new epidemiologic data or information might be presented concurrently with the industry-sponsored presentation of Dr. W. Clark Cooper. This, of course, did not happen. In fact, it is The Society's view that nothing new in this area was presented at all.

However, because of the Agency's interest in the subject area, SPI concluded that a detailed review of the existing epidemiology would be in order and appropriate for filing with this OSHA Docket in response to the request for this information. Accordingly, The Society has contracted for a complete, independent analysis of all the relevant epidemiologic data. Considering the magnitude of this project, it is obvious that it will not be finished by the May 9, 1980 deadline associated with the Request; hence these materials will be submitted when completed. It should be pointed out that, as is apparent from papers presented at the Bethesda Symposium, a factor complicating the preparation of this analysis involves the fact that it is not always

made clear in subsequent papers reviewing them that many of the studies which have been reported represent repeated investigations of the same population or subsets thereof.

(5) Case Reports and Case Series of Brain, Lympho-hematopoietic, Lung, and Liver Cancers By Facility and Relevant Demographic Variables, Such As Age, Sex, Race, Date of Diagnosis, Date of Death, Date of First Exposure, and Length of Exposure For Either Vinyl Chloride or Polyvinyl Chloride

At present, The Society is unaware of any information responsive to request §5 which is not already contained in the published literature.

However, since the papers prepared by Dr. John Stafford of Imperial Chemical Industries, Ltd. were not considered appropriate for presentation at the above-referenced Symposium, it has occurred to SPI that the Agency might care now to have a copy of the most recent compilation of data on the world-wide incidence of angiosarcoma of the liver. Dr. Stafford's tables, copies of which have already been supplied (and, indeed, have been supplied on an ongoing basis) to the Director of the National Institute for Occupational Safety and Health, are a complete compilation of all liver angiosarcoma deaths due to exposure to vinyl chloride monomer through January, 1980. Appendix M. As can be seen from a review of these data, there have been only 42 cases of liver angiosarcoma reported in the last five years and a total of 84 cases reported to date.

For background information on how Dr. Stafford came to be interested in keeping a register of the liver angiosarcoma cases refer to the attached correspondence between Dr. Stafford and Dr. Robbins of NIOSH. Appendix. N.

(6) Mutagenicity Study Results of Vinyl Chloride or Polyvinyl Chloride As Measured By Analysis of Human Body Fluids, e.g., Direct Mutagenic Testing With Peripheral Blood Lymphocytes, Non-Disjunction In Humans With YFF Sperm Test And *In Vivo* Cytogenetics

It has been demonstrated that if mutagenic effects occur, as measured by circulating lymphocytes, they were the results of high exposures; the measured effects have not been permanent changes since they were reversible. The effects did not occur at lower levels of exposure. The clinical significance is not known.

The attached report by Hansteen, Hillestad, Thiis-Evensen and Heldaas is extremely important. Appendix O. The mean chromosome-breakage frequency, which was significantly higher than controls when analyzed in 39 workers in 1974, was found on subsequent reexamination 2-2.5 years later to be no higher than the controls. Hence, whatever "effects" may have been measured or whether they were related to high exposure to vinyl chloride or not, the "effects" reverted to normal when exposures to vinyl chloride (and possibly other materials) were reduced. It is our understanding that similar results on a similar study are being prepared for publication by ICI in England and that they will supply a copy of the manuscript when it is available.

Picciano *et al.* found no effect in a study of men producing vinyl chloride monomer and those workers probably had lower levels of exposure than those above. Appendix P.

They summarized their data as follows:

> This report presents cytogenetic findings from a group of 209 workers employed for up to 28 years in the manufacture of vinyl chloride monomer at the Texas Division of Dow Chemical U.S.A. Cytogenetic evaluation results from this group were compared to results found in examination of individuals being considered for employment. Statistical analyses were performed on a group basis for chromatid aberrations, chromosome aberrations and proportion of abnormal cells; no statistical difference of significance was found between the two groups. Comparison of these results with reported studies suggests that the level of cytogenetic aberrations in vinyl chloride workers is probably related to the length and level of exposure, and that risk of adverse genetic effect can be avoided in controlled, minimal-exposure environments.

Fabricant attempted to summarize the mutagenic studies on vinyl chloride at the Symposium. This report merely reviewed the collected, previously-published information; nothing new was presented.

The Fabricant report pointed out that in the U.S. genetic anomalies resulting in infant mortality increased from 5% in 1915 to 15% in 1965. She alleged that 33% of pediatric hospital admissions are due to genetic defects and that 80% of all clinical mental retardation in the U.S. arises from genetic causes. She speculates that these observations are due to "an environmental component" creating birth defects. No mention is made of higher incidence as a result of the use of improved diagnostic tools or longer survivership of affected infants.

This author also relied on the discredited paper

by Infante et al. This publication (reference 12 in the December 18 Notice in the Federal Recister) alleging reproductive effects in wives as a result of mutagenic changes in husbands who were exposed to vinyl chloride has been discredited because of faulty methodology. See Appendicies G, H, and I. The faulty nature of this study has been repeatedly called to OSHA's attention and, therefore, absent a sound scientific defense of this study by the authors or their scientific peers, Fabricant should not have cited it.

(7) Body Burden Measurments
of Vinyl Chloride In Humans

The meaning of this specific request for information is not clear. Being a poorly soluble gas, vinyl chloride does not accumulate from chronic exposure but, rather, is rapidly exhaled after exposure ceases. Hence, there can be no body burden of vinyl chloride as the term is usually applied to the accumulation of heavy metals, large organic compounds or radio nuclides.

Baretta, Stewart and Mutchler studied this subject and reported on "Monitoring Exposures to Vinyl Chloride Vapor: Breath Analysis and Continuous Air Sampling." American Industrial Hygiene Association Journal, Vol. 30, November-December 1969. The data in this study clearly shows a rapid decay in the expired air in industrially exposed employees and laboratory subjects when exposure to VCM ceases.

Published metabolic studies on laboratory animals[20/] and human subjects also indicate rapid excretion of vinyl chloride in expired air. This, again, is consistent with the high volatility and low solubility of vinyl chloride gas.

20/ Watanabe, P.G., McGowan, G.R. and Gehring, P.G., Toxicol. and Appli. Pharmacol. 36:339-352 (1976).

(8) For Operations Involving Polyvinyl Chloride, the Types of Resin in Use, the Concentration of Vinyl Chloride Trapped in the Resin, and the Concentration of VC and PVC Dust in the Atmosphere Where Individuals Are Working. This Information Should Include Estimates of the Particles Sizes and Concentrations of Particles That Fall Within the Respirable Range

and

(9) In PVC Bagging and Milling Operations, Atmospheric Levels of PVC and VC, Monitoring Devices Used to Detect VC, and the Type of Respirator Protection Program for Individuals Working in These Operations. This Should Include the Sensitivity and Validity of the Analytic Techniques in Use

Information supplied to answer the inquiries cited above is likely to create confusion if used out of context. Past regulatory effort on the part of OSHA has resulted in the promulgation of regulations that covered resins containing any amount of contained vinyl chloride and materials that contained little or no vinyl chloride monomer; therefore it appears necessary to call OSHA's attention to all aspects of the industry.

Operations involving polyvinyl chloride are broken down into the following sections:

1. Manufacture of PVC
2. Distribution
3. Compounding
4. Fabrication into semi-finished materials
5. Conversion of semi-finished materials to finished products

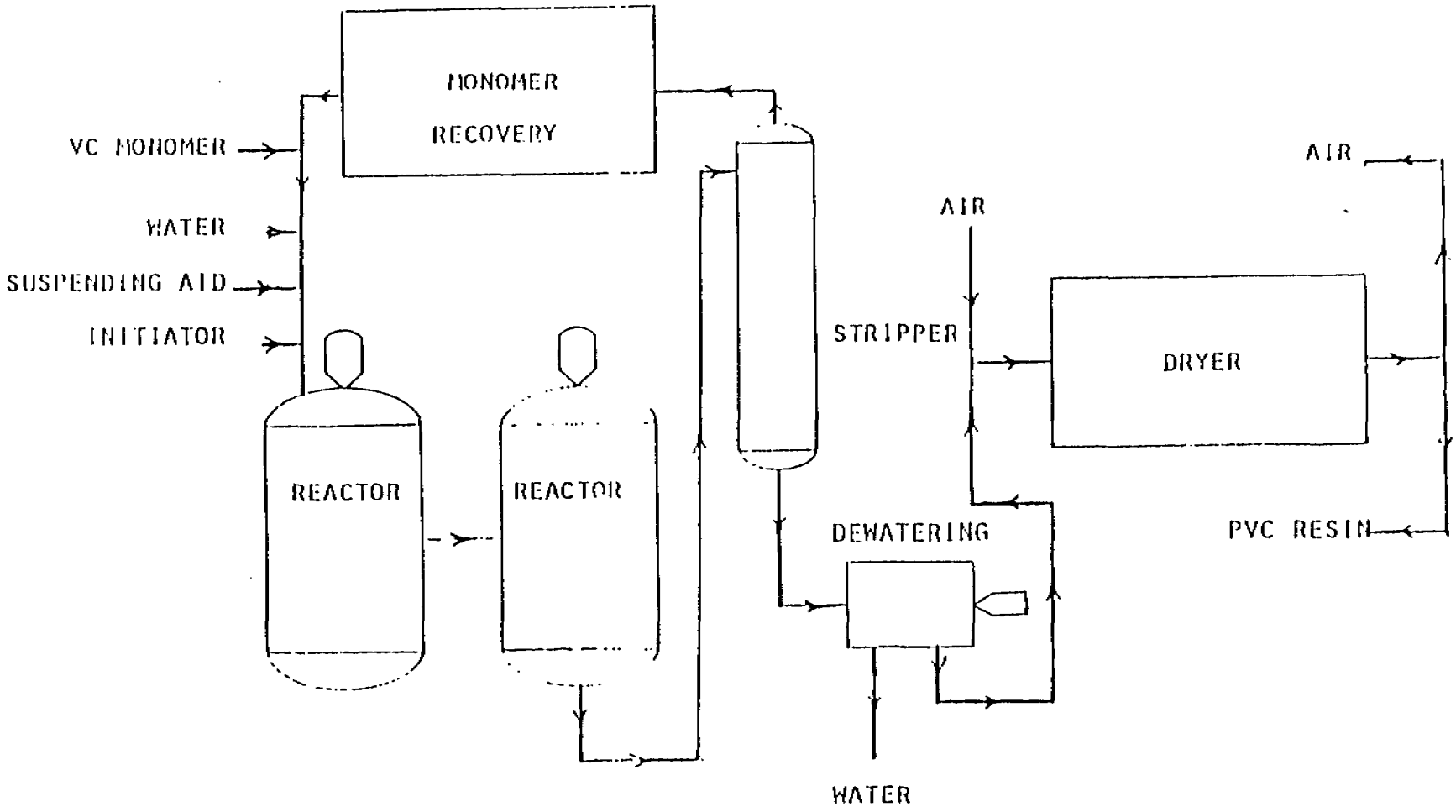
The manufacture of synthetic resins (PVC) from vinyl chloride and other monomers involves reacting these monomers in agitated pressure vessels in the presence of catalysts in such a way that these liquids and/or gases are converted to solid resins. A considerable amount of heat is generated by the reaction. This is removed by cooling the vessel. As the monomer is converted to polymer during the reaction, the rate of reaction slows down. The unconverted monomers are removed from the reacting mass by heat and vacuum, and the resin (PVC) is recovered as a dried powder or as a latex or solution. The polymerization reaction may take place in pure monomer, in a solution, in a water-monomer emulsion or in a water-suspension of monomer. The nature of the polymerization process determines the nature of the subsequent recovery process and the nature of the resin particles produced.

Currently there are four basic vinyl chloride polymerization techniques;

1. Suspension
2. Emulsion/Dispersion
3. Bulk
4. Solution

Suspension polymerization is the major process used for the manufacture of PVC resins and is used for about 82-85% of U.S. production. (Figure 1). It involves the charging of one or two parts water and one part vinyl chloride

OCC 6403



SUSPENSION POLYMERIZATION PROCESS

FIGURE 1

monomer or co-monomer mixture to an agitated reactor along with initiator and suspending agents. The mass is reacted at 50 to 65°C until about 85-90% of the monomer is converted to resin. The resin-water mixture is then heated, sometimes under vacuum, until the unconverted monomer is substantially removed. The resin is then removed from the water and dried in rotary, flash or fluid bed dryers by exposure to heated air. The dried resin is transferred to storage silos prior to shipment in bulk containers or in paper bags. If only vinyl chloride monomer is reacted, the product is homopolymer PVC. If a monomer such as vinyl acetate is mixed with the vinyl chloride, then a co-polymer PVC is produced.

Resin products of the suspension resin process are many and varied in terms of molecular weight, composition, particle size, monomer retention, heat stability and ultimate use. A general description of the various grades of resins follows:

(a) General purpose homopolymer for flexible materials such as shower curtains and wire insulation are porous, large particle (~100 microns or more diameter) size, high molecular weight resins with good heat stability and low monomer retention characteristics. These resins contain essentially no particles less than 10 microns in diameter and the residual monomer content is in the range of non-detectable (N.D.) to 25 ppmw.21/ Particle porosity is a critical property.

21/ Particles 10 microns or larger in diameter are considered non-respirable.

(b) Homopolymer resins for pipe manufacture are dense, large particle size (~100 microns in diameter), high molecular weight resins with good heat stability. Monomer retention characteristics are medium to low. These resins contain essentially no particles less than 10 microns in diameter and residual monomer content is in the range of N.D. to 30 ppmw. Generally the lower the molecular weight the higher the monomer retention. Particle density is a critical property.

(c) Homopolymer resins for rigid extruder shapes and calendered rigid sheeting are dense, medium particle size (~80 microns in diameter), medium molecular weight resins with reasonable heat stability and medium monomer retention characteristics. These resins contain essentially no particles less than 10 microns in diameter and the residual monomer content ranges from N.D. to 50 ppmw. Particle density is desirable and porous particles are difficult to produce.

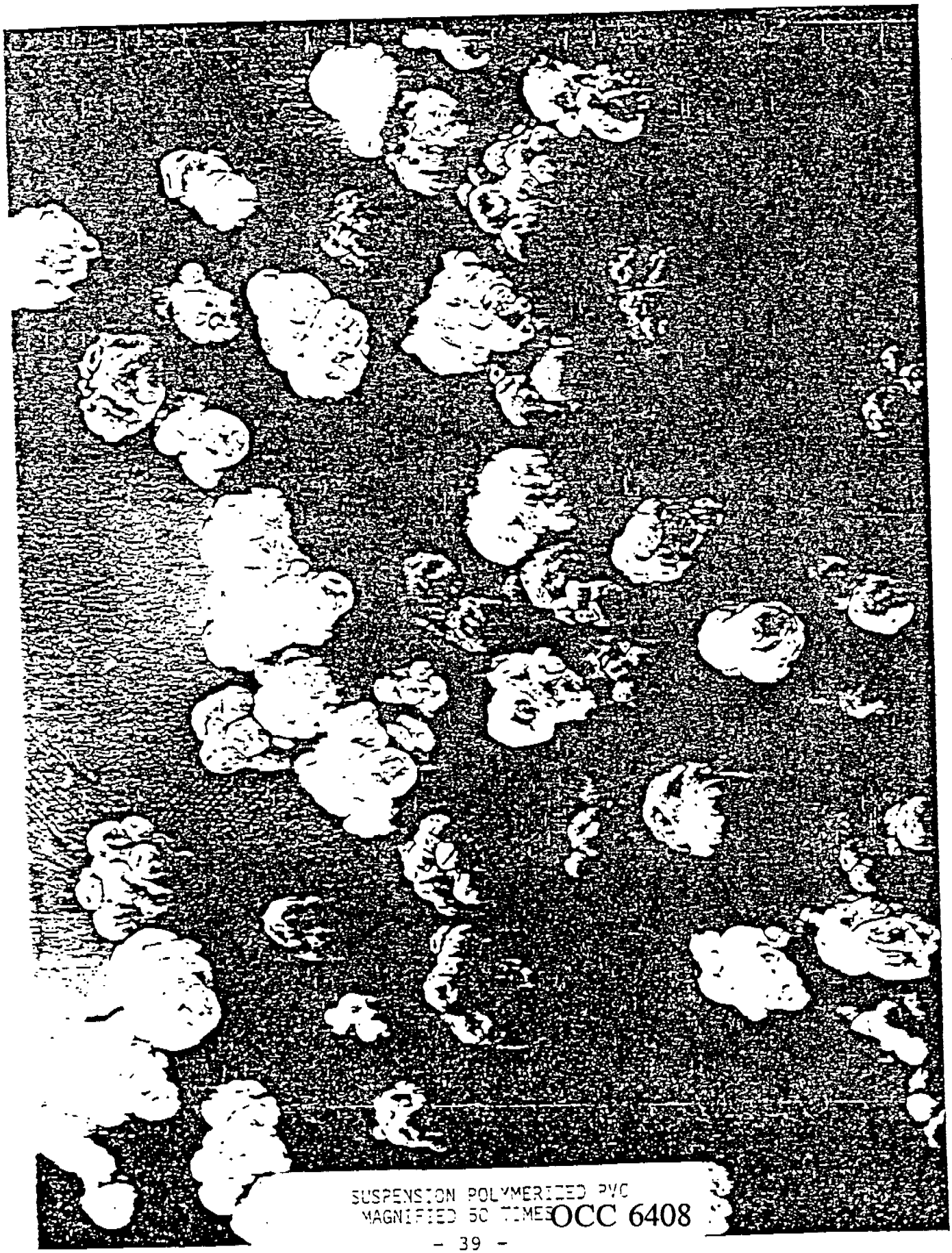
(d) General purpose copolymer resins for rigid sheeting, molding and flooring are medium particle size (~80 microns in diameter), glassy to low porosity, low to medium molecular weight, and high in monomer retention with poor heat stability. Comonomer content ranges up to 20%. The monomers most often used are vinyl acetate and vinylidene chloride. These resins contain essentially no particles less than 10 microns in diameter and residual monomer in the range of 100 to 300 ppmw. The poor heat stability coupled with the glassy particles make vinyl chloride monomer removal difficult. Copolymer resins offer ease of fabrication and have the ability to take up high loadings of fillers and pigments.

(e) Copolymer resins for coating applications are low molecular weight, medium particle size (~75 microns in diameter), glassy non-porous particles, poor in heat stability and high in monomer retention. Co-monomer content ranges up to 40%. These resins contain few particles less than 10 microns and residual vinyl chloride monomer contents of 25 to 100 ppmw.

(f) Plastisol additive resins for dispersion resin fabrication are medium molecular weight, small particle size (~25 microns in diameter), low in particle porosity, and medium in heat stability materials. The addition of these resins to a dispersion resin plastisol reduces the plastisol viscosity and reduces the product cost. The ability to perform uniformly in a plastisol is critical. These resins contain appreciable quantities of particles smaller than 10 microns in diameter and contain N.D. to 25 ppmw of residual vinyl chloride monomer.

Suspension process plants are generally meeting the permissible personal exposure limit of 1 ppmv TWA_8 imposed by the OSHA Standard but are having difficulty meeting the 5 ppmv ceiling value without the use of respirators. Certain tasks, such as maintenance, cleaning and correcting process upsets, involve personnel exposure to brief periods of high vinyl chloride concentrations. These personnel are protected by continuus air-supplied respirators. Elimination of all use of respirators cannot be considered a realistic requirement.

Suspension PVC, except for plastisol additive resins, presents no hazard from exposure to respirable dusts since these resins contain essentially no particles less than 10 microns in diameter. Indeed, except for the plastisol additive resins, the use of cyclone collectors on resin dryers and resin transfer systems obviates the presence of such particles in suspension resins, i.e., such particles are lost in the dryer exhaust.



SUSPENSION POLYMERIZED PVC
MAGNIFIED 50 TIMES

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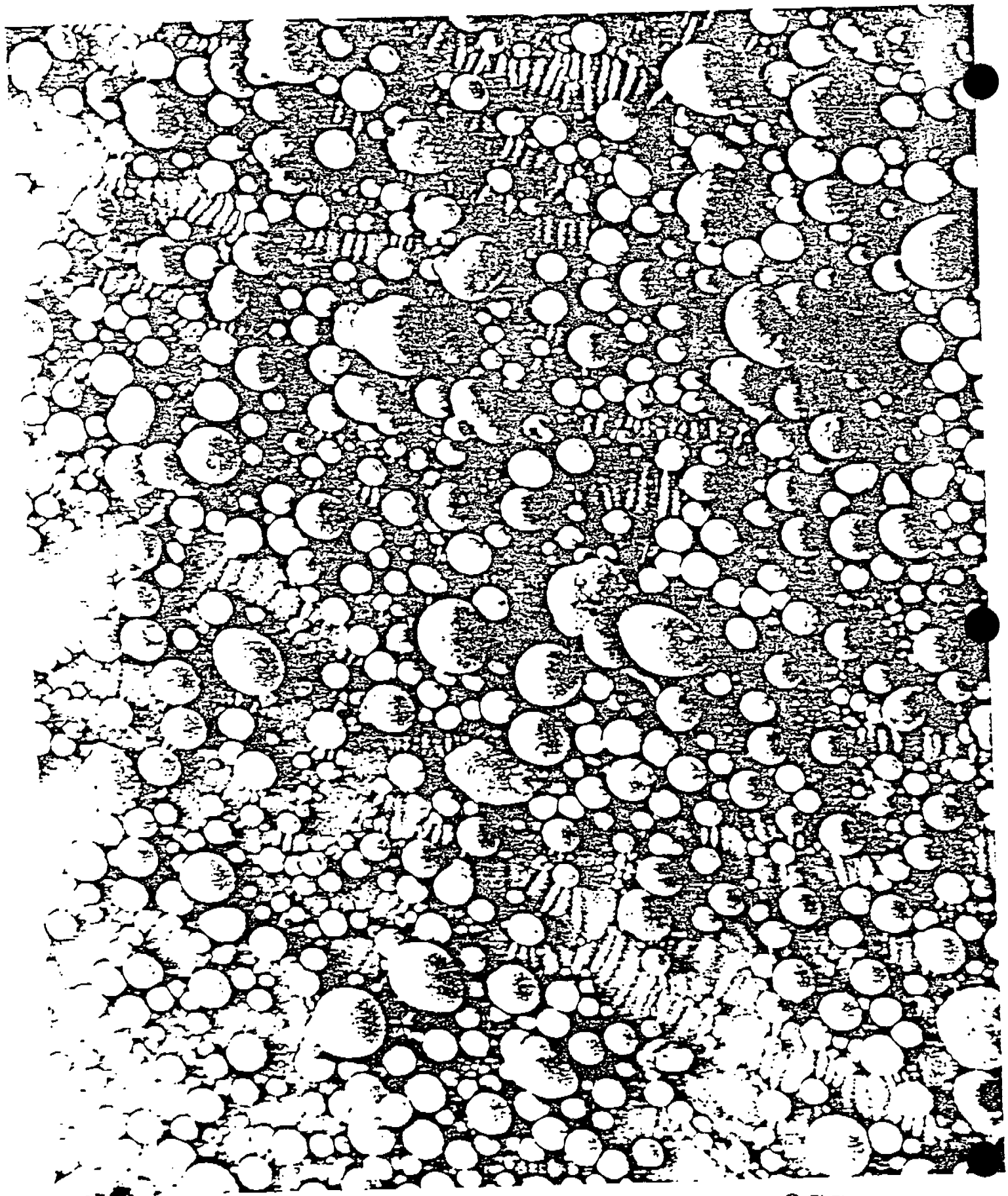

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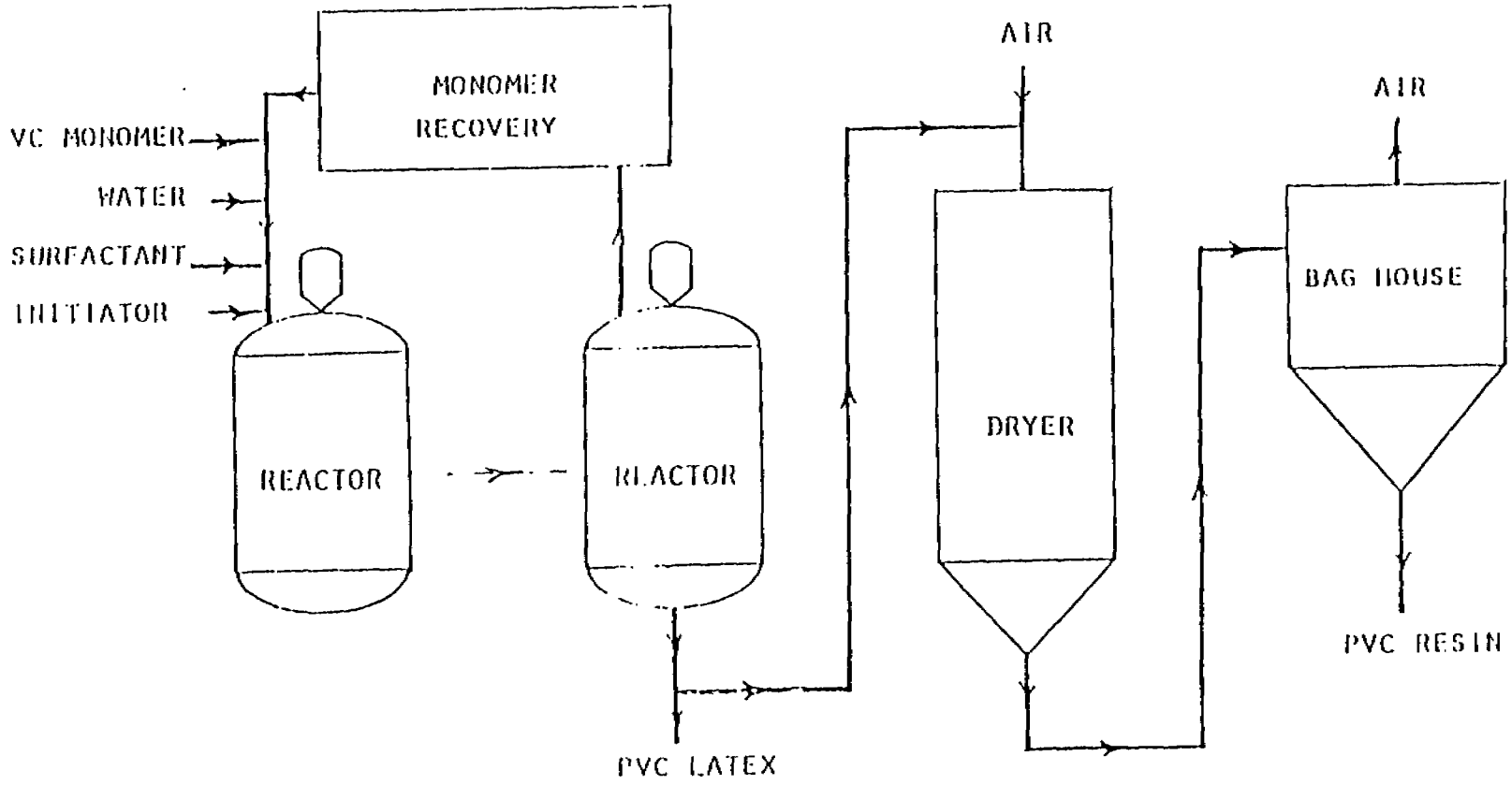
SUSPENSION POLYVINYL COPOLYMER
PVC RESIN MAGNIFIED 80 TIMES

Emulsion/dispersion polymerization is the second most widely used process for the manufacture of PVC resins and amounts to 10-12% of total U.S. production. One of the important things to understand about emulsion polymerization is that it is not a single process but a family of processes, each producing specialized products that are defined or specified in terms of performance in a particular application. In the interest of brevity only the two major process families, the water soluble initiator system and the oil-soluble initiator system, will be discussed. (Figure 2).

In the water soluble initiator system one to two parts water, one part monomer, 0.01 to 0.03 parts surfactant and water-soluble initiator (a redox system or a persulfate salt) are charged or fed to an agitated reactor and reacted at 30 to 60°C to form a latex emulsion. The reactor agitation must be sufficiently vigorous to emulsify the monomer-water mixture but not so vigorous that the latex is destabilized. When 80 to 95% of the monomer is converted to polymer the latex may be gently stripped of the unconverted monomer with heat and vaccum or it may be subjected to a second initiator treatment and reacted to essentially 100% monomer conversion. The product of this polymerization may be simply filtered and shipped to consumers as a latex for use in the manufacture of coatings, mastics, laminations, and the like, or the polymer may be recovered as a dry resin. Recovery techniques vary. The most commonly used is to spray-dry



EMULSION POLYMERIZATION PROCESS

FIGURE 2

the latex, though some resins are recovered by coagulating the latex and dewatering with subsequent drying of the coagulum (resin).

In the oil soluble initiator system one part monomer containing an organic peroxide is emulsified in one to two parts water containing 0.01 to 0.03 parts surfactant. The resulting emulsion is reacted at 30 to 60°C to form a latex. From this point onward the oil soluble initiator system is similar to the water soluble initiator system.

The choice of process depends to a great extent on the ultimate use of the resin. If resin particle size is critical the oil soluble initiator system is preferred. The resin particles formed during emulsion polymerization range in size from 0.05 to 2 microns. In the course of recovery and drying these may be agglomerated to particles as large as 30 microns. For some uses the agglomerates may be ground to a median particle size of about two microns. The small particle size results in rapid loss of residual vinyl chloride so that the resin contains only about 1 ppm free monomer. Because of handling problems nearly all the resin is bagged. In this process, the small amount of monomer retained easily escapes before the resin arrives at a fabricating plant. Some proprietary dispersion resins, however, have material handling properties comparable to larger particle size suspension resins. These can be shipped, stored, conveyed and processed in bulk instead of in bags.

Resin products of the emulsion process are more difficult to list because most products are sold on a performance basis as opposed to suspension products which are sold largely on specification and price. A rough classification is as follows:

(a) Plastisol resins are the major emulsion process products. These are very small particle size (2 to 3 micron diameter), non-porous, very high molecular weight, 100% vinyl chloride resins with good heat stability and low monomer retention characteristics. These resins consist of particles less than 10 microns in diameter, contain significant amounts of surfactants and about 1 ppmw of residual vinyl chloride monomer. When stirred into approximately 60 parts of plasticizer per hundred parts resin, these resins yield a viscous liquid plastisol which, when baked, fuses to a flexible vinyl plastic.

(b) Foam resins are substantially the same as the plastisol resins except that they are medium molecular weight instead of high. The lower molecular weight yields a plastisol which fuses near the temperature at which a blowing agent yields up its gas. This is how a stable plastic foam is formed.

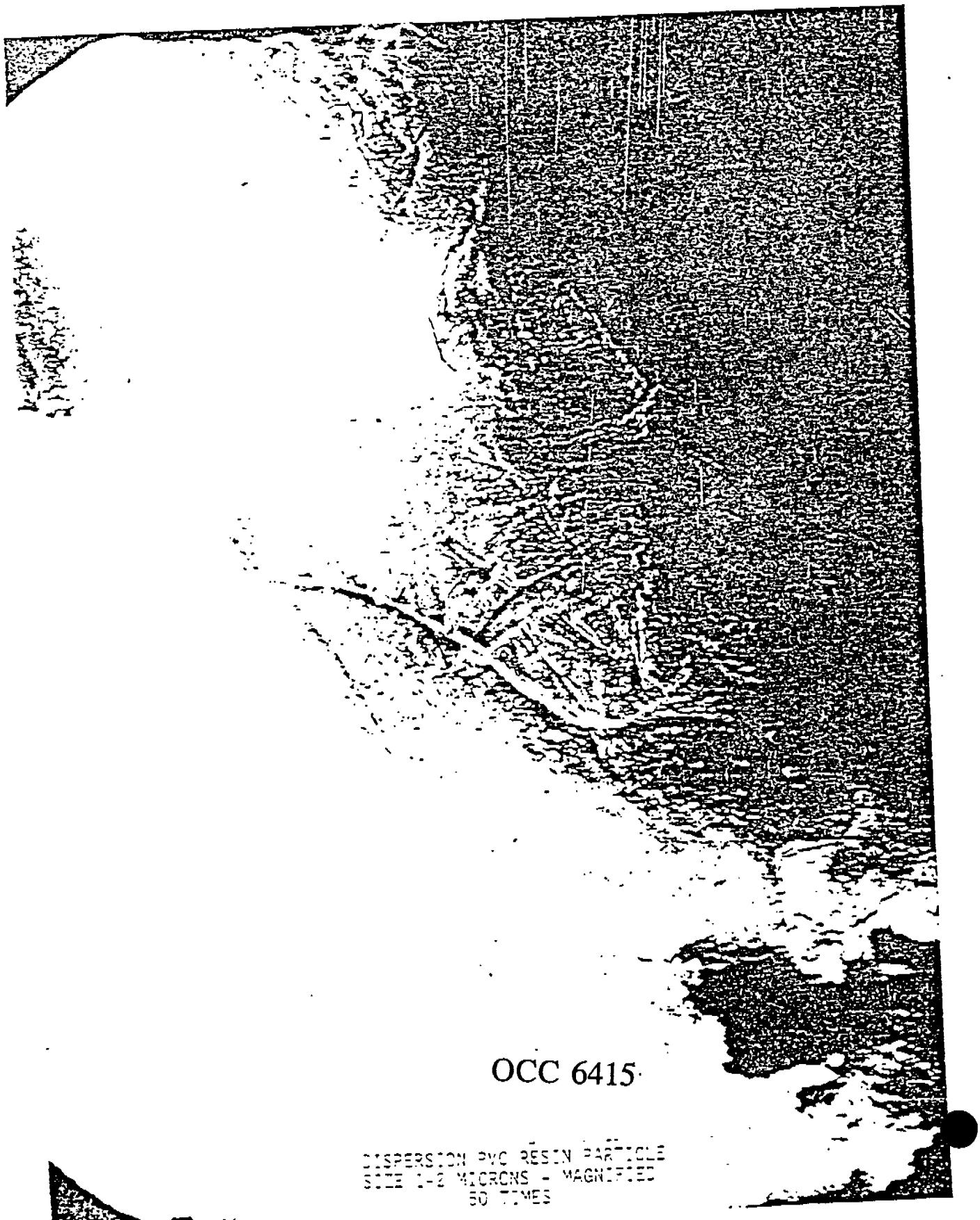
(c) Organosol resins are a special variety of plastisol resin primarily used for metal coating. If a high molecular weight PVC homopolymer dispersion resin is very finely ground and the remaining agglomerates are loosely bound together, it can be blended further with ketone, naphtha, pigments, stabilizers and adhesion promoters to yield a liquid coating material. This organosol is coated on metal and baked to provide a tough, abrasion resistant coating.

(d) Specialty resins are an assortment of materials that make use of the flexibility of the emulsion process for their manufacture. These are made from vinyl chloride in combination with other monomers. The resins are recovered from the latex by coagulation and subsequent drying. Uses of these materials range from film for food packaging to modifiers for other resin fabrication. Further characterization of these

materials is not possible, and they are mentioned here only to call attention to the fact that these important resins are impacted by vinyl chloride and polyvinyl chloride regulations.

(e) Latexes, too, are an assortment of materials generated by the flexibilty of the emulsion process. These are liquid materials containing 40 to 50% resin solids emulsified in water. Latexes containing resin solids high in vinyl chloride content are usually formulated with plasticizers and solvents and applied to a substrate. The substrate is heated or baked to yield a resin film. Latexes containing resin solids low in vinyl chloride content will yield a resin film when the latex coating is simply air dried. These latexes find major use in latex paints, impregnants, mastics and adhesives. Since both types of latexes are used as liquids, there is obviously no possibility of PVC dusts. Depending on the latex produced, most PVC latexes contain less than 10 ppmw of residual vinyl chloride monomer. This monomer is released slowly, and employee exposures in subsequent formulating and use is rarely over 0.5 ppmv.

As is the case with suspension PVC process plants, emulsion process PVC plants are generally meeting the OSHA permissible exposure limit of 1 ppmv TWA_8 for employees. However, these plants, too, are experiencing difficulty meeting the ceiling limit without reasonable use of respirators. The manufacture of dispersion PVC resins represents a source of respirable PVC dusts, and dust respirator use is usually required in dusty locations such as bagging. Certain proprietary dispersion resins do, however, have low dusting properties which greatly simplify control of the workplace dust normally associated with handling dispersion resins.



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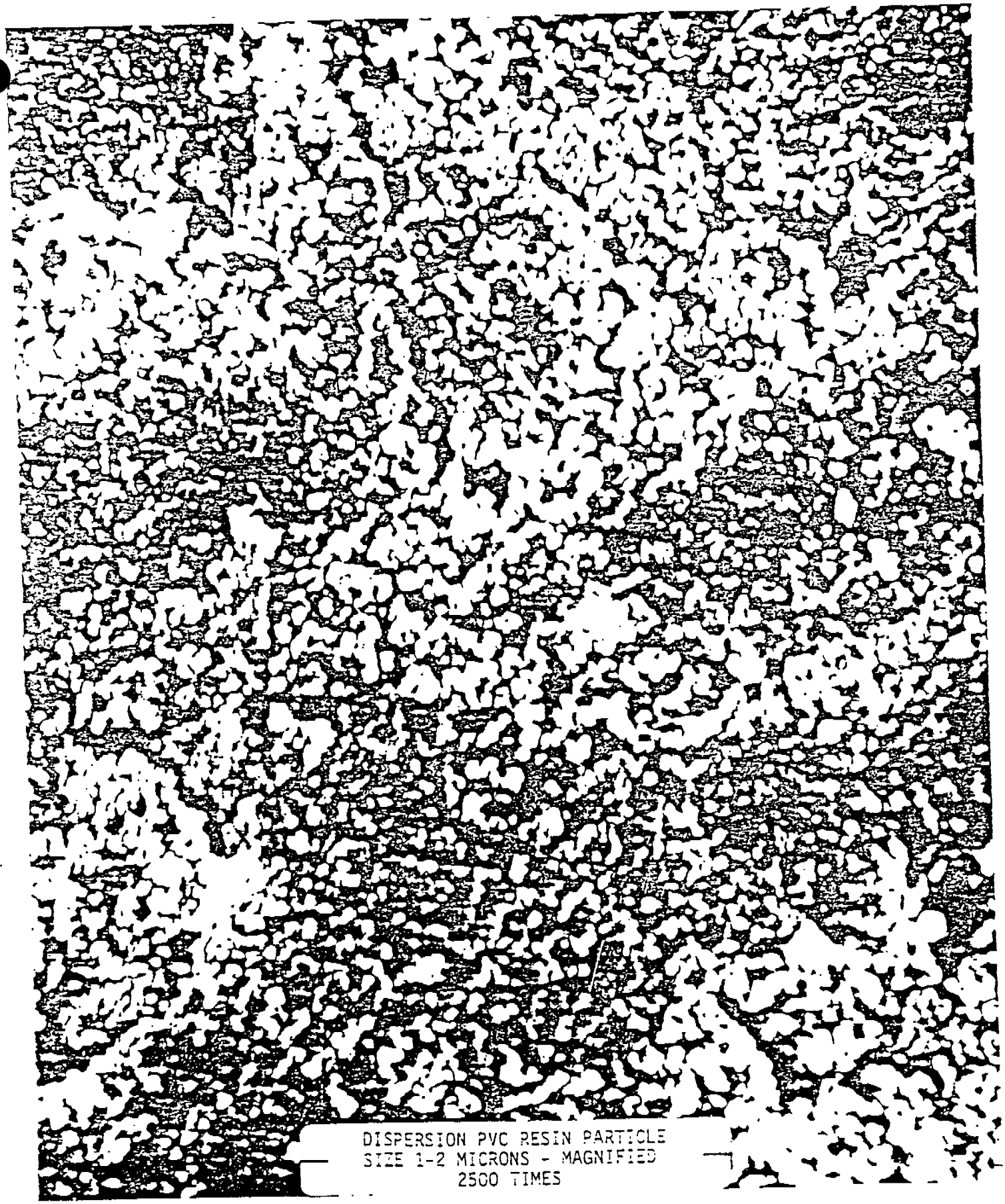
DISPERSION PVC RESIN PARTICLE
SIZE 1-2 MICRONS - MAGNIFIED
50 TIMES

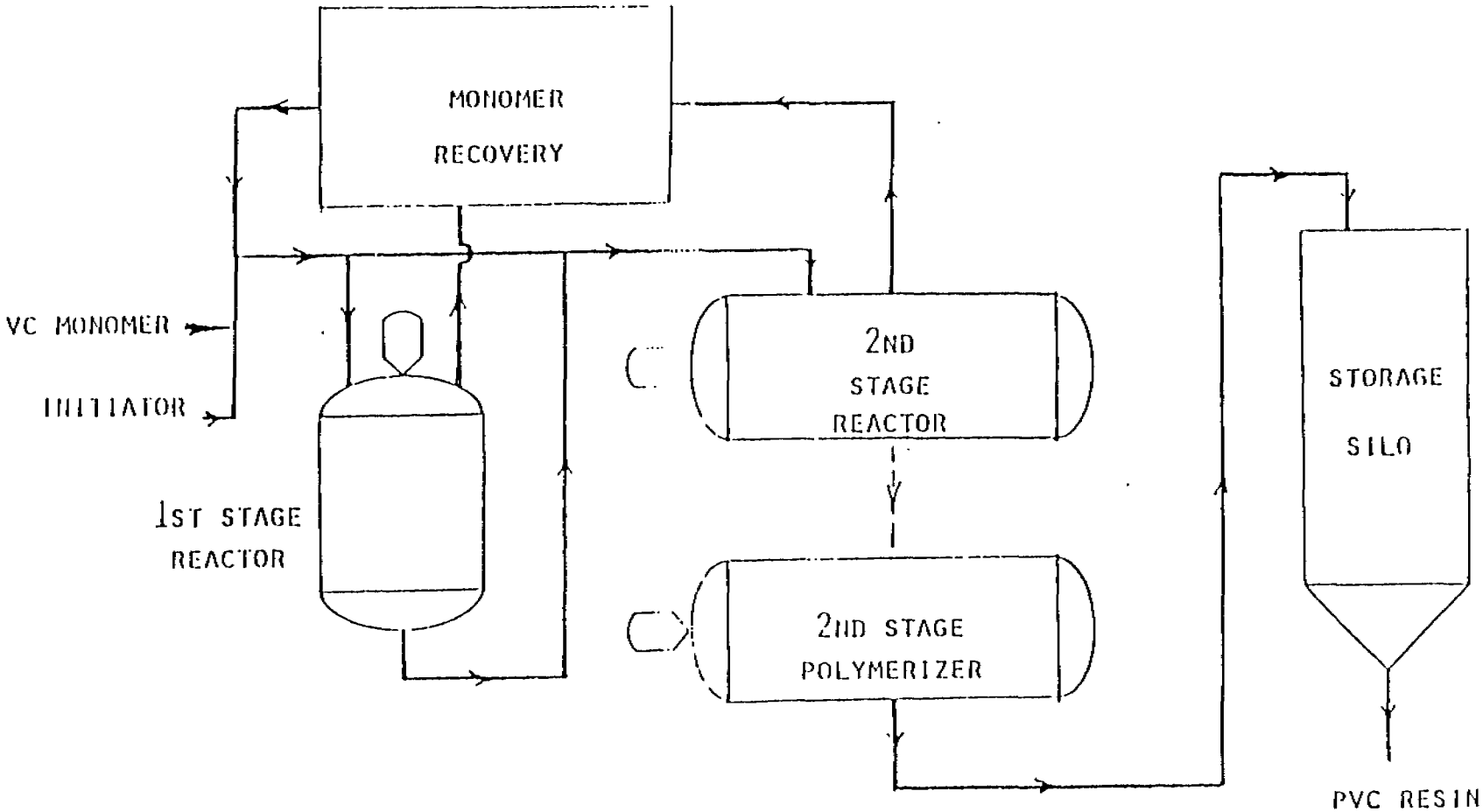


DISPERSION PVC RESIN PARTICLE
SIZE 1-2 MICRONS - MAGNIFIED
2500 TIMES

Bulk polymerization is the third major process in terms of volume for the manufacture of PVC resins but accounts for only about 5% of U.S. production. (Figure 3). The process involves the charging of vinyl chloride monomer and initiator to a first stage polymerizer where about 10% of the monomer is converted to polymer. This batch is then transferred to a second stage polymerizer where additional monomer and sometimes initiator are added. The polymerization is continued until about 80-85% of the monomer is converted to polymer. The unreacted vinyl chloride is removed by heat and vacuum and the finished resin product transferred to storage bins for later shipment to fabricating plants. The absence of water in the polymerization stage eliminates the need for the drying step.

The advantages of the bulk process are its simplicity, the uniformity of the resin particle size, the high porosity of the resin particles, the purity of the polymer (no soaps or suspending aids) and the granular, low dustiness of the product. The disadvantages are less flexibility in product mix (homopolymers only) than the suspension process and poorer removal of residual monomer. These bulk process resins are competitive with suspension process PVC homopolymers.

Bulk process PVC resins are used in applications where clarity of the finished plastic, uniform resin particle size and high resin particle porosity are desired. A simple classification of their uses is as follows:



BULK POLYMERIZATION PROCESS

FIGURE 3

(a) Rigid and flexible plastic materials produced by extrusion and calendering requires resins with large porous particles (100 microns in diameter), good heat stability and low monomer retention. These medium molecular weight homopolymer resins contain essentially no particles less than 10 microns and the residual VC monomer content is less than 50 ppmw.

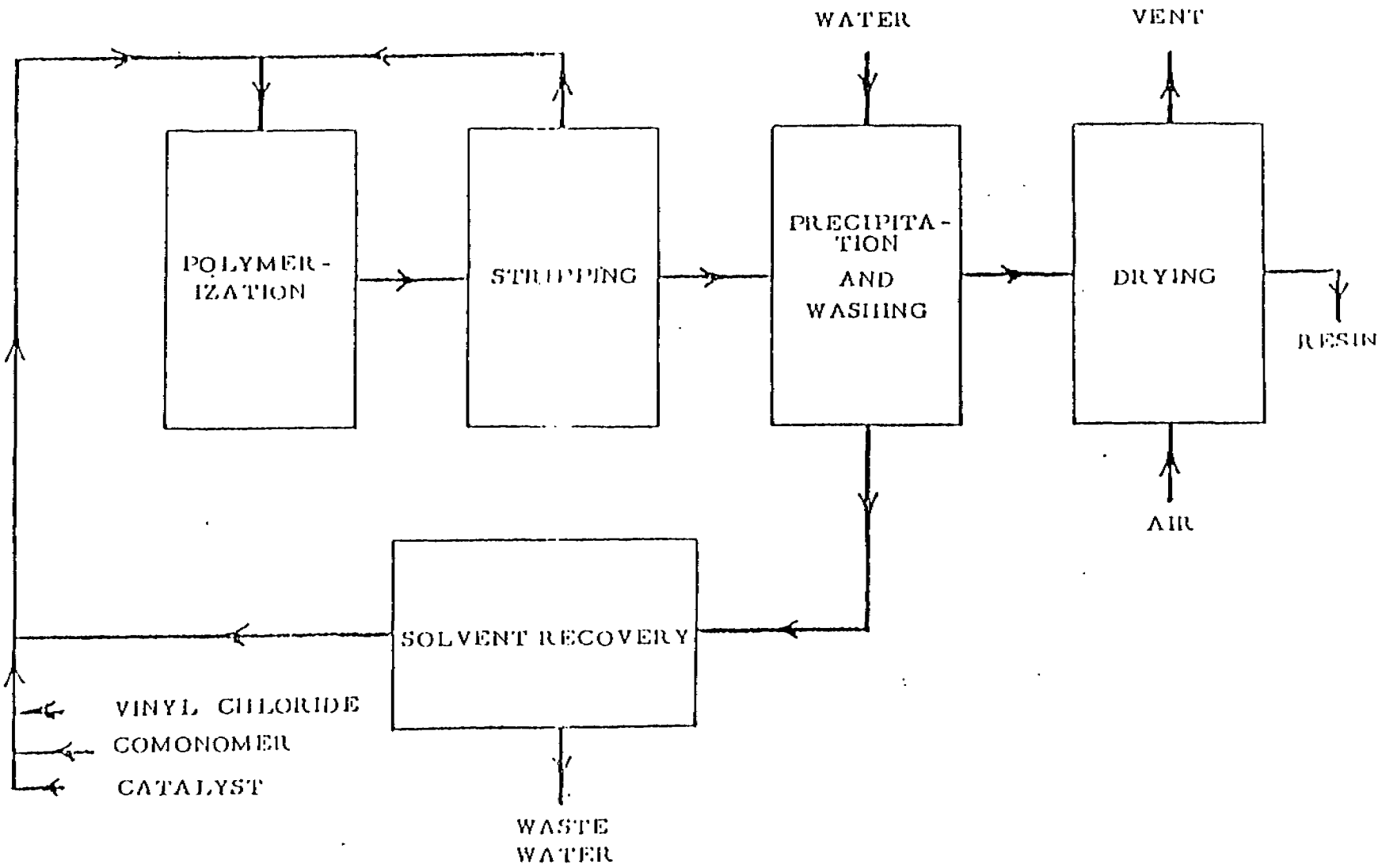
(b) Rigid plastic moldings, plastisol additive resins and powder coatings are made from low molecular weight homopolymers with a particle size of 75 microns. Particle porosity is good and monomer retention is low. There are few particles less than 10 microns in diameter and residual vinyl chloride content is less than 50 ppmw.

Bulk process plants have the same general types of personnel exposures to vinyl chloride noted for suspension process plants.

Solution polymerization is a process unique to one company and accounts for about two percent of the total resin produced. (Figure 4). Vinyl chloride monomer, co-monomer, solvent and initiator are fed to a continuous reactor system. The polymer formed is soluble in the reacting mass so that the reactor product is a viscous resin solution. This solution is distilled to remove the unconverted monomers and the resin is recovered by treating the resin solution with water and drying the product. The resin particle is very porous, is always a copolymer, is free of soaps and suspending agents, has a median particle size of 75 microns and contains less than 0.2 ppm residual vinyl chloride. Solution process PVC resins are very often confused with suspension process resins for solution application. Molecular weight

FIGURE 4

SOLVENT VINYL RESIN PROCESS



of these resins ranges from low to very low to achieve solubility in solvents. Essentially all these materials are used for coatings in combination with other resinous materials.

The solution PVC resin process, because of its nature, exposes personnel to vinyl chloride concentrations below 0.5 ppm. The resin contains essentially no particles less than 10 microns in diameter.

In addition to the resins produced by the four basic processes there are resins which are chemically modified in a second operation after the resin has been produced. The major product in this area is chlorinated PVC. In the coatings area copolymer resins are often modified through reactive sites in the co-monomer. These materials are mentioned only to note their existence and to point out that the very nature of chemical modification and subsequent processing removes all possibility of their release of vinyl chloride in subsequent applications.

Distribution of PVC resins poses some potential for personnel exposure to vinyl chloride monomer and to polyvinyl chloride. The structure and the economics of the distribution system have acted to cause such exposures to be minimal except for certain special situations.

Suspension and bulk process PVC resins, except for plastisol addition powder coating, solution coating and ex-

port sales move from the producing plant to the user via bulk carriers such as rail cars (containing approximately 150,000 pounds) or hopper trucks (containing approximately 35,000 pounds). These carriers are loaded via gravity from overhead bins or by pneumatic conveyor. The carrier is sealed during transit. On arrival at the delivery site, the carrier is unloaded by pneumatic conveyor to a storage silo. There is some vinyl chloride monomer emitted during the loading and unloading process, but personnel exposure is well below the OSHA Standard "action level". Monitoring of this operation when the resin contained 800 ppmw of residual vinyl chloride monomer showed personnel VCM exposures of approximately 1 ppmv TWA_8. Although there is no recent data, with current residual VCM levels of approximately 50 ppm, one would expect personnel exposures to be down around 0.1 ppm TWA_8. There is some resin dusting and spillage in the loading and unloading process, but the relatively large particle sizes and remote contact by personnel obviate any potential hazard.

The bagging of the 5 to 10% of suspension and bulk process resins that are handled in this fashion is highly automated and messy, but personnel exposure to dusts or VCM are negligible. Resin is delivered to the packaging machine via gravity or pneumatic conveyor. The packaging machine operator inserts the filling tube into a filling valve-type kraft paper bag and actuates the machine to fill the bag. The filled bag drops off the filling tube to a conveyor and

the operator repeats the operation with another bag. Filled bags are automatically or manually stacked on pallets which may be stored in a warehouse awaiting shipment or may be loaded on a truck or railcar immediately.

When the filled bag drops off the packing machine a small puff of resin and air is emitted from the bag valve as it closes. Subsequent handling of the bag causes some shifting of resin out of the valve. There are also faulty bags which may break on filling. Thus, the resin bagging area is usually messy. However, monitoring conducted in these areas indicates personnel vinyl chloride exposures are less than the OSHA Standard "action level." Dust measurements for suspension and bulk resin bagging show less than 1 mg/m^3 respirable dust.

Bagging and storage of suspension and bulk process resins causes a significant reduction in the residual vinyl chloride content of the resin. Tests of moderately porous medium molecular weight resins show a reduction of over 50% in free monomer after one week. Handling and transport of suspension and bulk PVC resin in bags via truck or rail car appears to present no unusual hazards if normal work space ventilation standards are met in storage, loading and unloading resins.

Except for some special situations where bulk transport or fiber drums are used, essentially all emulsion process PVC resins are packaged in kraft paper multi-wall bags. The bagging operation is essentially the same as that de-

scribed for suspension and bulk process resins. Vinyl chloride exposure is less than the OSHA Standard "action level." The NIOSH study by Mr. J.H. Jones in 1974 indicated that exposure is not likely unless it comes from emissions in adjacent operations.22/ Dust exposure is potentially a problem due to the resin's small particle size but local ventilation can control this readily. Current dust monitoring shows respirable dust less than 5 mg/m^3.

The storage and truck shipment of emulsion PVC resins offer minimal vinyl chloride exposure opportunities for personnel.

Warehouse and closed truck vinyl chloride monitoring show levels well below 0.5 ppmv vinyl chloride in the air.

Solution process PVC resins are also packaged primarily in kraft paper multi-wall bags. Bagging is essentially the same as described for suspension resins. The NIOSH study in 1974 indicated vinyl chloride exposure to baggers of N.D. to 0.7 ppmv and total dust of less than 2 mg/m^3. Vinyl chloride exposure currently is about 0.1 ppmv with no change in total dust exposure. Respirable dust is about 0.1 mg/m^3.

Monitoring of storage and truck shipment of solution process PVC resins usually shows undetectable amounts of

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22/ Jones, J.H., Worker Exposure to Vinyl Chloride During Production and Fabrication of Vinyl Chloride and Polyvinyl Chloride. Study conducted with the Bendix Corporation under NIOSH Contract CDC-99-74-50. Draft of this Report is at Appendix Q. See p. 36.

vinyl chloride monomer.

Polyvinyl chloride latexes are most often handled and shipped in tank cars or trucks and in fifty-five gallon drums. There is some emission of vinyl chloride during loading and unloading operations but, if the latex contains 10 ppmw residual vinyl chloride or less, the personnel exposures are less than 0.5 ppmv. Dust is not a problem with latex shipments.

Compounding a PVC resin or latex means the mixing of that material with pigments, stabilizers, plasticizers, fillers and other additives to yield an intermediate material for subsequent conversion into finished or semi-finished products. In major plastics operations this is simply a single process step in a large integrated factory, but in the specialty resin area, as well as with small plant operations, a compound is produced by one plant and is subsequently shipped in a container to the user. Thus, in terms of regulation, these materials are classified as polyvinyl chloride. Often, however, the properties of the material are completely dissimilar to the PVC resin raw material, i.e., the vinyl chloride monomer content is diluted or reduced by heating and dustiness is reduced sharply or eliminated completely. Some examples are pelletized PVC compounds, powder blends, organosols, plastisols, lacquers, dry blends, and latex paints.

The purpose of compounding is to combine the resin and additives into a homogeneous state suitable for further

processing. The level of compounding ingredients employed for PVC is substantially higher than for most plastics. Resin content of a compound may vary from 99% for rigid sheeting to 15% for floor tile. Some compounding ingredients introduced in PVC fabrication are as follows:

(a) Plasticizers are high boiling temperature esters of phthalic acid, adipic acid, azelaic acid, phosphoric acid and so on. Epoxidized oils, epoxy resins, and polyester resins are also used.

(b) Heat stabilizers are compounds of lead, barium, cadmium, tin and zinc. Epoxies and phosphites are also used.

(c) Fillers consist of clay, talc, mica, asbestos, calcium carbonate, titanium dioxide, diatomaceous earth and barytes.

(d) Pigments may be inorganic compounds, such as titanium dioxide, chromium oxide, ultramarine blue or molybdate orange, or they may be organic compounds, such as phthalocyanine, quinacridone and benzidine salts.

(e) Modifying resins improve processing characteristics and impact resistance. These are acrylate, ABS, and chlorinated polyethylene resins.

(f) Lubricants make subsequent processing easier. Some of these are waxes, stearic acid and metal stearates.

(g) Light stabilizers provide ultra-violet light resistance. Examples are benzotriazoles or benzophenones.

(h) Fungicides give resistance to fungal attack. Materials commonly used are amines, arsenates and organotins.

(i) Flame retardants, such as antimony oxide and the boranes, are used where plasticizer content is high.

(j) Anti-static agents reduce dust and dust pickup. These are often amine compounds.

(k) Brighteners yield a whiter, clearer film.

(l) Anti-oxidants, such as bisphenol A, are sometimes used.

Additionally, particularly in the coatings area, there are specialized additives such as surfactants, pigment wetting aids, solvents, and diluents.

These compounding ingredients and additives are mentioned in some detail to show the difficulty of isolating causative agents if an employee health problem is believed to exist in the PVC fabricating area. It is certainly a mistake to attribute dust problems solely to PVC dust and toxic vapor problems solely to vinyl chloride monomer.

Compounding PVC resins for subsequent fabricating via calendering, extrusion or molding involves two basic steps; dry or powder blending followed by melt compounding. The choice of equipment is important because variations in the homogeneity of the resin compound may cause serious deficiencies in processing and in the finished product. The calendering, extrusion and molding operations involve large scale operations with suspension and bulk process PVC resins which are almost always handled in bulk. Resin is charged from a bulk silo to a weigh hopper and dumped into the mixer. Plasticizers are metered into the charge. Other additives are charged by similar techniques though small volume additives may be first mixed into a portion of the plasticizer.

also appear as part of the total dust measurement. (See attached Tables 30 and 32 from the NIOSH report along with flow sheets for calendering, pipe extrusion and flexible film extrusion).

Plastisol techniques for compounding and fabricating PVC involve the use of dispersion process PVC resins along with plastisol additive resins from the suspension and bulk PVC processes. The principal advantages to this fabrication technique are low investment in fabricating equipment and flexibility in changing from one product to another. A basic plastisol might consist of 100 parts dispersion process PVC resin, 55 parts dioctyl phthalate plasticizer, 5 parts epoxy plasticizer and 3 parts barium, cadium, or zinc liquid stabilizer. Heating the plastisol to 350-375°F fuses it into a flexible homogeneous plastic. In practice, however, the only time this simple formulation is used is to test resins. Additive resins are used to reduce cost, to alter the plastisol viscosity and to increase the hardness. Reactive resins, such as epoxies and acrylates, are added for hardness. Pigments are added for color and opacity. Anti-foamers reduce foaming during deaeration and fusion.

Plastisol preparation is carried out in a slow speed, unheated mixing vessel. Plasticizer is weighed or metered into the vat and followed by the requisite number of bags of various resins, fillers and so forth. When the mixture is homogeneous, it is either transferred to a deaerator or

Table 30

Polyvinyl Chloride Dust Sampling Data
Plant L

Location	Dust Concentration mg/m³
Near Blender	12.5
"	7.22
"	6.67
"	8.75
"	11.67
Near Mixer	10.0
"	6.06
Near Calender	11.67
"	8.33

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The mixer is closed and heat is applied externally or generated by the shear action of the mixer itself. The charge is subjected to mixing and heat (approximately 200-250°F) for some predetermined time or until the mass is a dry powder. Gases from the charge are vented outside the work area. On completion of the dry or powder blending, the mix may be cooled and stored for subsequent use or charged directly to a high intensity mixer or to an extruder.

The mixers and/or the extruder melt the dry or powder compound blend to secure a hot plastic mass. For calendering, the mixer or extruder charge is transferred to the calender where it is formed into flexible film or into rigid sheets as semi-finished products. For extruded products, the extruder may simply be fitted with a die, as in the manufacture of pipe, to form the finished product. The industrial hygiene survey carried out by NIOSH in 1974 and 1975 indicated that vinyl chloride monomer exposures for this type of operation in the range of N.D. to 0.6 ppm. (See attached Table 33 from the NIOSH report). With the current low levels of residual vinyl chloride monomer in suspension and bulk process PVC resins, vinyl chloride monomer exposure is negligible.

Dust is a problem in calendering, molding and extrusion processing but as Mr. Jones points out in his NIOSH report the dust is probably not all PVC since fillers and other additives are used. Mr. Jones does not mention, however, that plasticizer aerosols formed during processing

Table 33

Summary of Vinyl Chloride Sampling Data by Job
—All Fabrication Plants Sampled

Job	n	$\bar{x}^*$ (ppm)	$\tilde{x}$ (ppm)	Range (ppm)
Calender Personnel	28	0.57	0.24	ND–2.44
Compounding Personnel	78	0.11	0.05	ND–0.69
Extrusion Personnel	58	0.09	0.04	ND–0.76
Lab Personnel	18	0.08	0.05	ND–0.68
Maintenance Personnel	10	0.01	<0.01	ND–0.02
Molding Personnel	16	<0.01	<0.01	ND–0.03
Plastisol Dipping Personnel	40	0.01	<0.01	ND–0.06
Miscellaneous Personnel	20	<0.01	<0.01	ND–0.01
Total of Personal Samples	268	0.14	0.03	ND–2.44
Composite of All Area Samples	32	0.04	0.05	ND–0.68

* $\bar{x}$ = TWA

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Table 31

Polyvinyl Chloride Dust Sampling Data
Plant V

Location	Dust Concentration mg/m³
Mixing Area	6.67
Blender Area	1.67
Mill Area	6.67
Banbury Mixer Area	13.33
Calender Area	6.67
Plastisol Mixing Room	7.9
Cast Film Line	7.27

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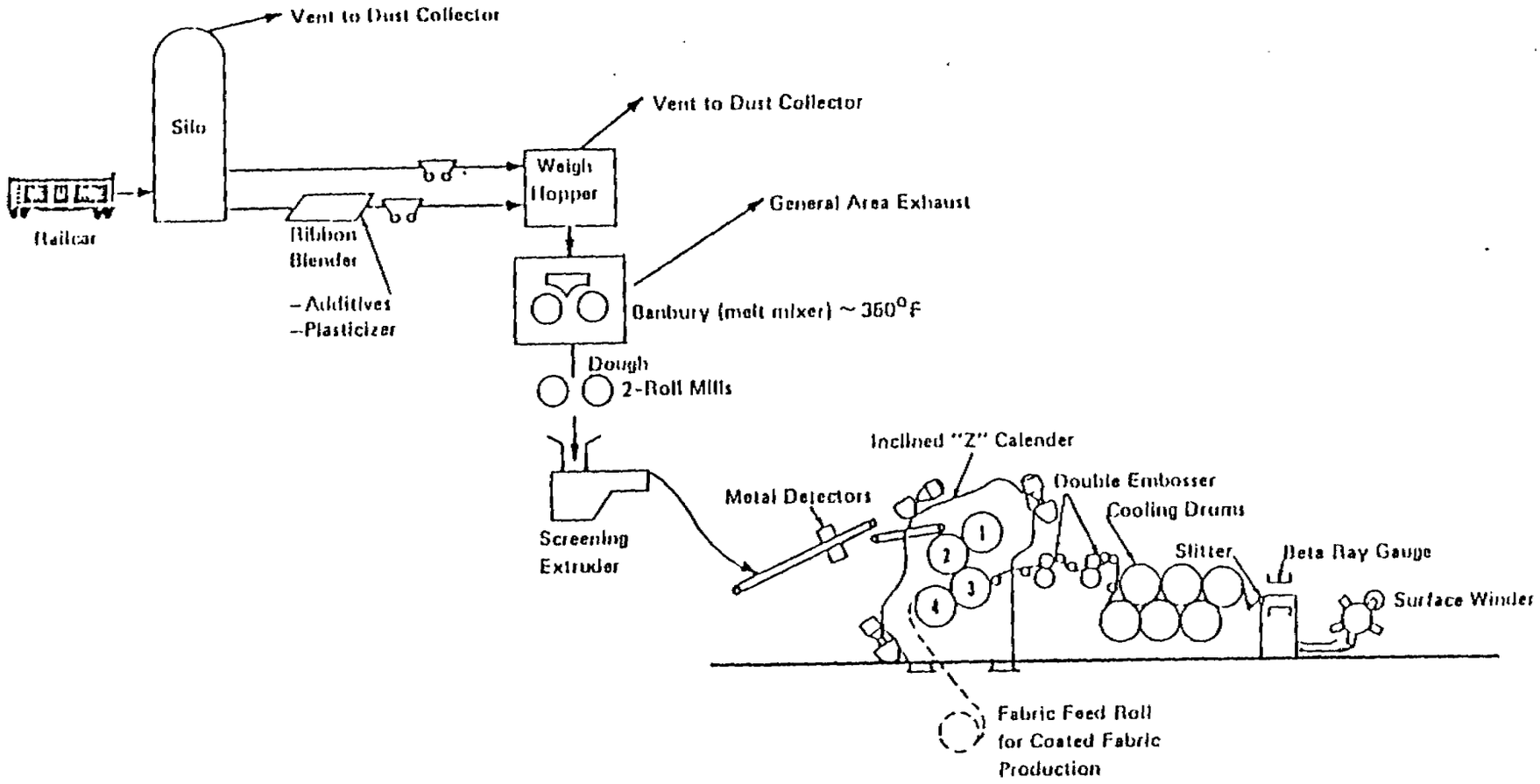

FIGURE IV–11 TYPICAL CALENDERING OPERATION

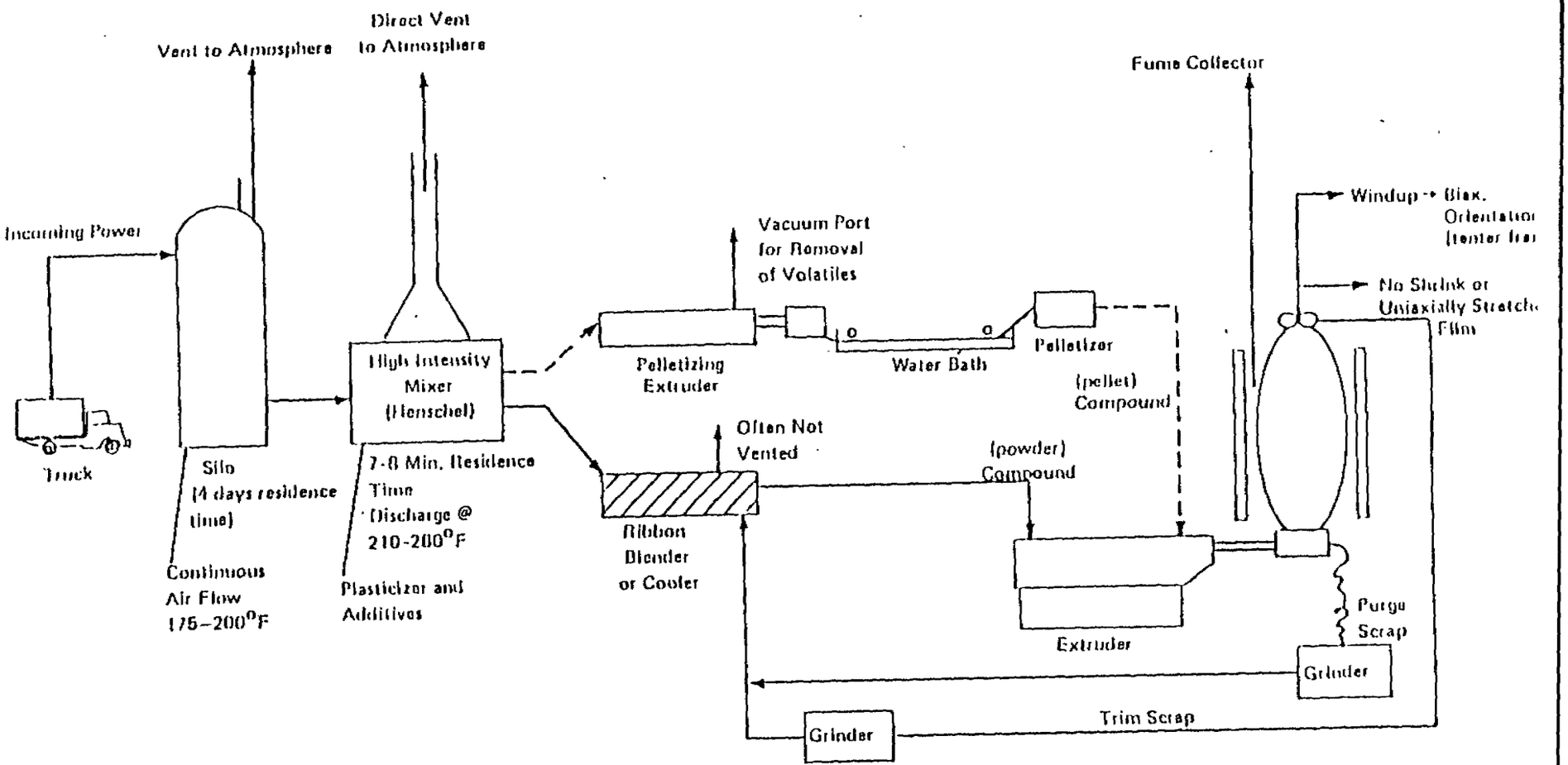

FIGURE IV-8 FLEXIBLE PVC FILM EXTRUSION WITH IN-PLANT COMPOUNDING

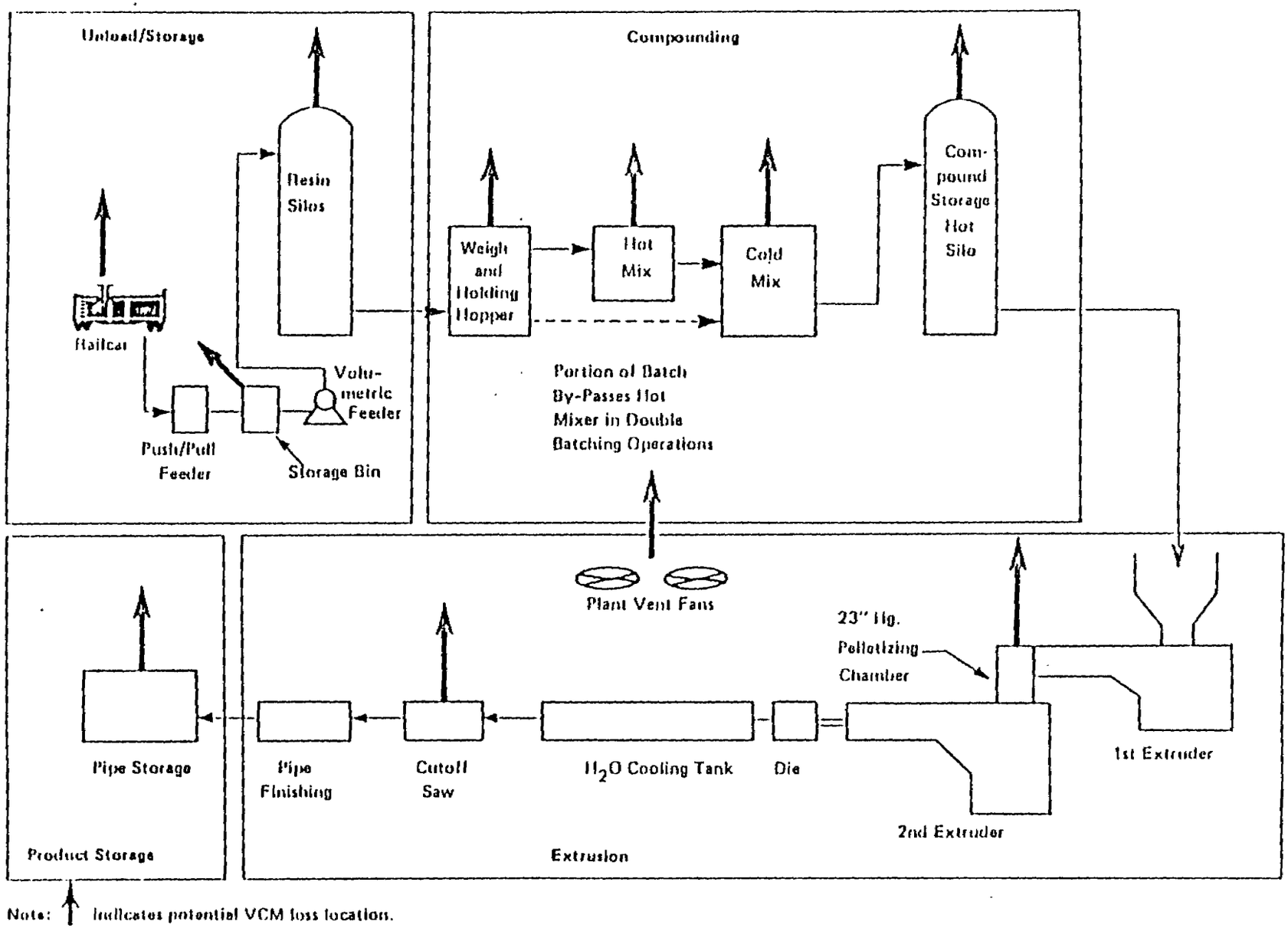

FIGURE IV–9 TYPICAL PVC PIPE EXTRUSION OPERATION

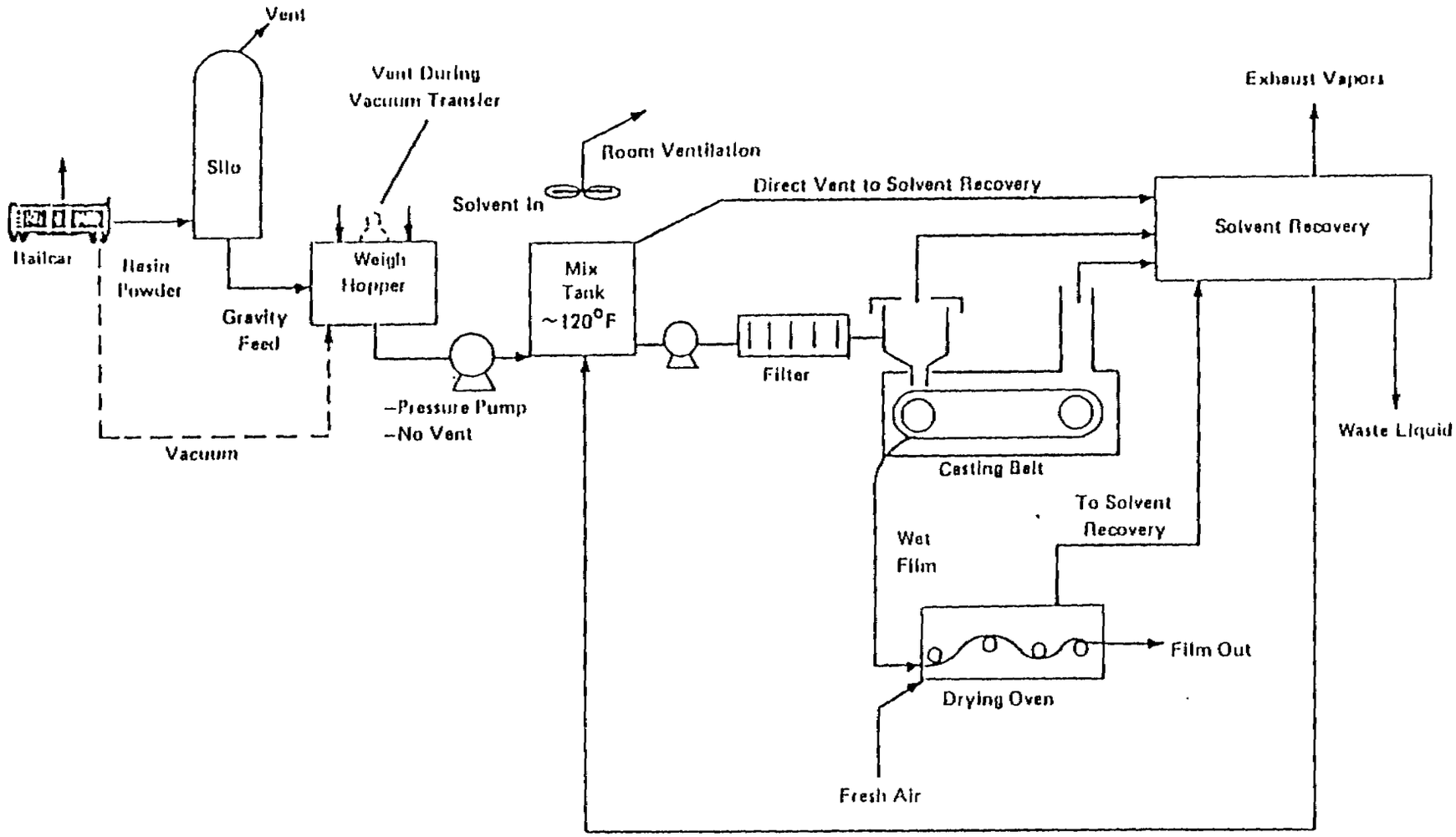

FIGURE IV–12 SOLVENT CAST PVC FILM PRODUCTION

the mixing vessel may be closed and a vacuum applied to remove entrained air carried in by the solid components. After deaeration the plastisol is ready for fabrication. It may be coated on a release paper, on a metal substrate or on a fabric. These items pass into an oven where the plastisol is fused to yield a plastic film which may be stripped from the release paper or a coated metal sheet or fabric. The plastisol may be poured into metal molds which are subsequently heated. This fuses the plastic for later removal from the mold. To produce foamed plastic, the plastisol may be mechanically frothed or a blowing agent such as an azide can be added. The blowing agent releases gas during the fusion step and the result is a sponge-like plastic.

Plastisol fabrication is likely to be less sophisticated, involve smaller plants and be more labor intensive than conventional PVC fabrication. In such operations, the potential for exposure to PVC dust and vinyl chloride monomer is usually greater. Dispersion PVC and PVC plastisol additive resins are low in residual monomer content when manufactured and are usually shipped and used in paper bags after a considerable time lag for analysis and warehousing. Accordingly, vinyl chloride monomer exposure in this type of operation is minimal. The attached table from the NIOSH survey in 1974-1975 could be said to be representative of the VCM exposures in plastisol operations.

Exposure to dust may be considerable in these operations due to the small particle size of dispersion and additive PVC resins as well as the small particle size of the fillers and pigments. During the fusion step plastisols also give off plasticizer aerosols which appear as a part of total dust. Because dust control is largely an individual matter for each installation to resolve based on plant configuration and the like, no generalized statement can be made for the industry except to point out that the dust is not wholly PVC.

Organosols are a specialized version of a plastisol. Ketones, esters and hydrocarbons are added to the plastisol to yield a low viscosity liquid composition which is sprayed, roller-coated or brushed onto a substrate. The resulting coated substrate is baked to drive off the diluents and fuse the coating.

Solution coating is a small, specialized area of PVC resin fabrication. PVC resins dissolved in organic solvents and applied to a suitably prepared substrate yield coatings with excellent resistance to water, alkalis, acids and weather. The resins used are copolymers produced by solution polymerization or by special suspension resin processes. These resins must be exceptionally free of electrolytes and insoluble materials. The resin typically is dissolved in a mixture of toluene, methyl ethyl ketone and methyl isobutyl ketone. Pigments and stabilizer are added

Table 24

Summary of Vinyl Chloride Sampling Data by Job
in Fabrication Plant I

Job	n	$\bar{x}^*$ (ppm)	$\tilde{x}$ (ppm)	Range (ppm)
Lab Personnel	4	ND	ND	ND
Plastisol Dipping Personnel	40	0.01	0.01	ND–0.06
Total of Personal Samples	44	<0.01	<0.01	ND–0.06
Composite of All Area Samples	4	ND	ND	ND

* $\bar{x}$ = TWA

and the mixture "ground" in a colloid mill or similar device. The resulting coating is sprayed on the substrate and either oven or air-dried. Each coating is formulated for performance in certain areas and coating formulations are closely guarded by individual formulators.

Formulation of coatings is a small scale operation generally dealing with resins in paper bags and solvents in bulk. There is little or no exposure to residual vinyl chloride monomer from most solution resins since VCM is virtually non-detectable in the resin. Dust exposure from resin and pigments is low because only small volumes are handled. Most formulators have fume control systems for control of solvent vapors and these also remove dusts from the work area. Monitoring for vinyl chloride monomer at coating formulators generally shows non-detectable to 0.05 ppmv.

Solvent cast PVC film is a small fabrication operation which is based on solution coating with solvent recovery. Higher molecular weight resins are often used to achieve higher film strength. A high solids vinyl resin solution is cast on a stainless steel belt. Heat drives off the solvent until a very thin transparent film can be stripped off and dried further on heated rolls. The solvent is collected and reused. More expensive solvents, such as tetrahydrofuran, are often used to reduce solution viscosity. Exposures to dust and vinyl chloride monomer are similar to that of a coating formulator.

PVC and PVC copolymer dispersions are produced for

use in latex form for coating, binder and saturant applications. These latexes fall into two categories. One is a PVC homopolymer or copolymer, high in vinyl chloride content, for industrial use. The second is a copolymer latex containing less than 50% vinyl chloride in the polymer. This type of process forms films drying the latex at ambient temperature.

Latexes are formulated with the additives listed earlier for vinyl resins plus thickeners, surface active agents, colloids, solvents and anti-foamers. Open or semi-open vessels equipped with low speed, low shear agitators are used for formulation. Oils such as plasticizers are often emulsified with water prior to addition to the mix.

Depending on the latex the finished compound may be applied to a substrate by dipping, roller coating or spraying and the coated substrate baked to fuse the resin and drive off the water or it may simply be applied and air dried as a latex paint.

When pigments and fillers are used, dust is a potential problem during the charging of the formula mix. There is, of course, no PVC dust. Residual vinyl chloride monomer in the latex is controlled by the latex producer. Latexes containing 10 ppmw or less RVCM do not emit enough vinyl chloride monomer during formulation or application to cause employee exposures in excess of the OSHA standard "action level". Latexes containing more than 10 ppmw RVCM are usually processed under controlled conditions where employee exposure

is within the prescribed limits.

The PVC resin industry is very large, and the versatility of the products is such that all uses and modes of application cannot be covered in this brief overview. Others include powder coating, blending resin for polyethylene wire compounds, and rug fiber flame proofing. Health hazards in these applications are negligible.

Conversion of semi-finished PVC plastics to finished products involves drilling, cutting, welding, and heating of the material. Considerable concern has been expressed by many persons that heated PVC will breakdown to its monomer or that enough residual VCM is contained in the product to be emitted during heating or welding. There are a number of studies by NIOSH, EPA and others that conclusively show that this is not the case although there can be evolution of plasticizer fumes, acetic acid, hydrogen chloride and, ultimately, oxides of carbon when PVC is heated. Trace amounts of vinyl chloride have been detected in some cases but only after considerable production of irritating gases which would preclude employee inhalation.

As regards vinyl chloride monitoring devices where there is potential massive exposure to vinyl chloride via leaks, vessel rupture or emergency discharge, the most effective monitors are those automatic systems based on organic vapor detection, chromatographic analysis, and infrared absorption spectroscopy. These give prompt warning of such VCM emissions and permit prompt protective action by the

employee. Portable units such as the HNu unit or the Century Systems Corp. OVA-98 are extremely useful for leak control and on the spot monitoring.

Respirators in use for vinyl chloride protection are those prescribed by NIOSH. Most vinyl chloride and polyvinyl chloride producers rely heavily on self-contained breathing air units or hose-fed breathing air masks.

(10) Types of Occupations, Job Classifications, and Industries Where Where Exposure to Either VC or PVC At Any Level May Occur, and The Numbers of Employees Involved in Each Vinyl Chloride and Polyvinyl Chloride Exposure Situation, Separated By Sex and Race

As to the types of occupations, jobs and industries presenting a potential for exposure to either vinyl chloride or polyvinyl chloride, SPI is unaware of any change in these areas whatsoever since the time of the initial OSHA rule making on vinyl chloride. As the industry trade association, SPI neither has nor collects data on the numbers of employees involved in each exposure situation, separated by sex and race.

(11) Appropriate Engineering Controls, Work Practices, and Personal Protective Equipment Available to Reduce Levels of Exposure to VC or PVC Below the Current Standards Or To the Lowest Levels Feasible

The Society is informed that the individual company members of the PVC Safety Group are presently engaging in the use of appropriate engineering controls, work practices and personal protective equipment to reduce levels of exposure to vinyl chloride and polyvinyl chloride to the currently permitted levels.

As to vinyl chloride, the current standard for controlling occupational exposure to VCM is sufficiently stringent that great difficulty has been encountered by industry in coming into compliance with the standard that is currently in effect. Because of its stringency, not all work places are at all times in compliance with the current standard. In short, there are no feasible, additional engineering controls, work practices and/or personal protective equipment available to reduce levels of vinyl chloride scientifically below the present exposure level. Therefore, it would seem that the current standard is the lowest level attainable and that techniques to reduce the current exposure levels are not known. Furthermore, SPI submits that the present permitted exposure level is adequate to safeguard employee health. No new evidence has been presented to refute this conclusion.

As to PVC generally, we know of no reason to control exposure to the polymer because polyvinyl chloride in any form is not a health hazard. In fact, PVC is so stable and inert that it finds use in such demanding applications as surgical implants, medical tubing and high voltage electrical wire.

As to respirable dust which may be associated with certain operations involving PVC production, these dusts are currently governed by OSHA's nuisance dust regulations. 29 C.F.R. §1910.1000. Controls are utilized to comply with these regulations and to protect workers from any hazard which would be associated with exposure to the dust. Consequently, extensive investigation into appropriate engineering controls, work practices and personal protective equipment available to reduce the levels of exposure to PVC dust further are not areas known to us to have been investigated in any great detail.

As a final comment it should be noted that inasmuch as PVC dust has not been shown to be a health hazard at levels below those to which it is currently controlled (or at any other level, for that matter), we know of no purpose which would be served by speculating on methods to reduce levels of exposure.

III.

CONCLUSION

As to VCM, OSHA is aware of Maltoni's experiments which indicate possible effects in animals exposed to 10 ppm VCM. The Agency must also be aware that no increase of neoplasms was found in animals exposed to less than 10 ppm. Based on these and previous experiments, it is clearly evident that rodents are more susceptible to VCM than are humans. Accordingly, that cancer can be induced in animals at levels lower than previously reported seems to be of scientific interest only. The fact is that human experience should be given higher importance than animal studies, the animal data having predicted a cancer incidence rate over 500 times greater than that observed in man.

The Agency also appears to be interested in another report from Maltoni to the effect that VCM can exert a carcinogenic effect transplacentally. This phenomenon, however, has only been demonstrated in pregnant rats exposed to very high concentrations of vinyl chloride. Additional work in this area needs to be conducted using lower, more realistic doses since available data indicate that the rates of metabolism in the rat shift as exposure concentrations of vinyl chloride change.

Of further interest to OSHA should be the fact that vinyl chloride did not cause significant embryonal or fetal

toxicity and was not teratogenic in studies in rats, mice or rabbits. In fact, SPI knows of no valid scientific paper associating vinyl chloride with human birth defects at any level of exposure.

Regarding effects in humans caused by exposure to vinyl chloride, there is no new epidemiologic data on vinyl chloride exposed populations. The Society has, however, contracted for a complete, independent analysis of all available, relevant epidemiologic data. This is particularly important since it is not always made clear in subsequent papers reviewing them that many of the studies which have been reported represent investigations of the same population or subsets thereof. The next epidemiologic data on VCM exposure is expected to be the five year update on the original Tabershaw and Gaffey study. The Society is informed that this study will soon begin under the direction of the Chemical Manufacturers Association and will be a straight forward epidemiology update with special emphasis on neoplasms of the brain.

In the meantime, SPI is submitting to the Agency with these Comments the most recent compilation of all liver angiosarcoma cases associated with VCM.

If mutagenic effects occur as monitored by chromosomal analysis of circulating lympocytes, it has been demonstrated that they were the results of high exposures; the changes have not been permanent since they have been reversible. The changes did not occur at lower levels of exposure.

The clinical significance of the reversible changes observed is not known.

Being a poorly soluble gas, vinyl chloride does not accumulate from chronic exposure but, rather, is rapidly exhaled after exposure ceases. Hence, there can be no body burden in the usual meaning of the term.

Responsive to the Agency's questions about personnel exposure to VCM and appropriate engineering controls, work practices and personal protective equipment available to reduce levels of exposure to VCM below the current standards or to the lowest levels feasible, the VCM/PVC industry is presently using appropriate engineering controls, work practices and personal protective equipment aimed at achieving compliance with the existing standard. It must be recognized by OSHA, however, that the Vinyl Chloride Standard is very stringent and industry is still encountering significant difficulties relative to achieving full time compliance with it. Although the industry has made tremendous strides in controlling VCM exposure, the variability in resin type and the resin type relationship to differing VCM exposure potential has the industry in a position where the use of work practices and respiratory protective equipment to achieve day-to-day compliance with the standard is still wide-spread. Because of process variability no additional, feasible measures to reduce exposure levels significantly below the present level are known by the industry to exist. It would appear that they are all in use and that the present

permitted exposure level is adequate to safeguard employee health.

As to PVC, experimental studies show no carcinogenic or other toxic manifestations related to polyvinyl chloride exposure. Solid PVC has long been known to be inert and the effects resulting from experimental exposure to PVC dust appear to be characteristic of nuisance dusts in general. The effects appear to be similar in man, that is, they are limited to deposition of dust in the lungs in a manner which can cause slight effects to occur but no carcinogenic or other toxic effects have been observed.

Regarding epidemiology or case reports of cancer associated with exposure to PVC, the only new information that SPI knows to be available is that presented by Dr. Seaton at the Bethesda Symposium. As to that study and the others referenced in the Request for Information, it is The Society's position that PVC dust is adequately regulated by OSHA's general dust control standards and has not been shown to present any hazard at these low levels.

As to the hypothesis that PVC dust carried into the lung can result in its being distributed throughout the body, SPI believes that, even were this hypothesis correct -- and it is not thought to be correct, the minute quantity of monomer in PVC dust particles is so small that it would make this speculative exposure of no practical significance.

In PVC manufacturing operations, both the quantity and size of dust particles vary depending on the resin

being handled. The same variability is inherent in the residual vinyl chloride in dust particles and other conditions which might be expected in manufacturing and fabricating different resins. In light of these conditions, appropriate control technology, work practices and personal protective equipment are employed as required.

In addition to the information and views presented above, the Agency should be advised as noted in the body of this document that SPI has additional comments and information to submit for the Record. These materials will be assembled and supplied to the Docket Officer when they are available.

The foregoing considered, SPI's PVC Safety Group most strongly asserts that, based on the information being considered by the Agency in its reassessment of VCM, no data are available to suggest any new or greater hazard associated with occupational exposure to vinyl chloride. The Society is also steadfastly of the opinion that PVC dust is merely a nuisance dust and that no adverse health hazard information has been presented to change this position. Accordingly, SPI suggests that the available data indicate that both vinyl chloride and polyvinyl chloride are adequately regulated to protect worker health.

Respectfully submitted,

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Mortality Study of Workers in the Manufacture of Vinyl Chloride and its Polymers*

Irving R. Tabershaw, M.D. and William R. Gaffey, Ph.D.

Animal studies have shown that inhalation of vinyl chloride produces in rats angiosarcoma of the liver as well as cancers of the lung, kidney, skin and other sites. Although workers in occupations involving exposure to vinyl chloride have been found to have an increased risk of hemangiosarcoma, no excess of other cancers has so far been reported.

This historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride before December 31, 1972, demonstrated that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population, with the exception of cancers of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to estimated exposure. The explanation for the latter finding is not apparent.

The other major findings of the study are: (1) The overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U.S. males; (2) No cause of death showed a statistically significant excess over what would be expected in a comparable U.S. male population; and, (3) No deaths identified as angiosarcoma of the liver were found other than those previously identified.

This is the first epidemiological study which suggests that in humans vinyl chloride may also be associated with cancer of multiple sites.

Drs. Tabershaw and Gaffey are from Tabershaw-Cooper Associates, Inc., Suite 308, 6000 Executive Blvd., Rockville, MD 20852.

*The research on which this report is based was supported by a group of companies engaged in the synthesis and/or the polymerization of vinyl chloride, and administered in their behalf by the Manufacturing Chemists Association.

Vinyl chloride in its manufacture and polymerization has been identified as a narcotizing agent,[1] as a liver toxin,[2,3] and as a vasospastic agent producing a specific occupational disease, acroosteolysis.[4] Recently, vinyl chloride has been incriminated as a carcinogen producing in a group of workers engaged in the manufacture of polyvinyl chloride a rare fatal liver tumor, hemangiosarcoma.[5] Large doses of the chemical in rats reportedly produced cancer of the skin, lung and other organs.[6] Unpublished but public information[7] indicates that inhalation experiments with rats in doses easily reached in manufacturing operations produces in addition to angiosarcoma of the liver, skin, kidney and other malignant lesions.

The present study, however, was not restricted to the conditions and sites suggested by the above investigations, but concerned itself with the entire spectrum of causes of death, to the extent permitted by the size of the study group. The objectives of the study were: (1) To compare the mortality of individuals who have worked in vinyl chloride plants with that of the general population; (2) To compare mortality patterns within the population of vinyl chloride workers, based upon estimated occupational exposure; and (3) To compare mortality among vinyl chloride workers with the mortality of other occupational groups.

The study population consisted of individuals from 33 plants who had worked for at least one year in a job involving exposure to vinyl chloride before December 31, 1972, and included retired and terminated as well as active workers. For each such worker the date of birth and an employment history were obtained, and the vital status of the worker as of December 31, 1972, was ascertained. For those found to have died, those death certificates that were available were obtained and the cause of death determined. The observed mortality was compared with that of the United States male population.

Data Collection

In each plant, data were collected for each worker stated by the plant management to have been employed for at least one year in a job involving exposure to vinyl chloride. In some plants, particularly those producing the monomer, this determination could be made on the basis of job titles. Usually, however, exposure was a function of both job title and the location of the job in the plant, so that the assessment of exposure had to be made on a case-by-case basis by plant officials.

Data were collected for as far back in time as complete records were kept. In most cases this covered the entire history of the plant. In others, records were kept for a fixed period such as a decade. In a few, records were kept for different periods, depending on whether the worker had died on the job or had left employment.

In most plants it was impossible to quantify exposure. However, industrial hygiene and safety personnel in each plant were able to identify certain jobs and locations as involving the highest exposures in the plant, and to classify other exposures as medium or low relative to the "high" represented by the jobs with the greatest exposure. Consequently, each exposed job in a worker's history was scored 1, 2, or 3 to indicate low, medium or high estimated exposure.

This gross classification has two major failings, as a result of the subjective nature of the estimates. The first is that the scores represent estimated relative exposure within a *given* plant. It is therefore possible that, in objective terms, a "high" score in one plant corresponds to a "medium" or even "low" score in another. The second is that the scores usually do not take into account changes in exposure over time. A worker with long service may therefore have had jobs in the remote past which involved "low" exposure relative to other jobs at that time, but which might be "high" in comparison with current exposures in the same job. This subjective classification is therefore of questionable validity in characterizing the exposure of a given worker. For epidemiological purposes, however, those who have high scores can reasonably be expected, on the average, to have had the greatest exposure; those with low scores will have had the least, even though the true exposure in each group may vary considerably from person to person.

The estimated exposure history of each worker was summarized by calculating an Exposure Index (EI). This was done by multiplying the number of months on each job by the exposure score, totaling these overall exposed jobs, and dividing by the total number of months of exposure.

Follow-up of Study Population

A follow-up procedure was instituted for those who had left employment and whose vital status could not be determined at the local plant, using company mail follow-up and retail credit bureau investigations. Table 1 shows the vital status of the population as of December 31, 1972. Follow-up is 85% complete. Those who were not found were lost (and began their exposure) about 10 years before the group on which follow-up was complete, and had about half the duration of employment in exposed jobs with a slightly higher EI. Although there appears to be nothing very unusual about this group in terms of work history and exposure, it is nevertheless true that their exposures took place further back in time than that of the group successfully traced. It is therefore possible that their mortality, after a substantial latent period, might show a somewhat different pattern from that of the traced group.

All of the subsequent analysis is concerned with the 7128 workers on whom follow-up was complete. Table 2 shows their distribution by duration of exposed employment and the year in which employment began. Although almost half the study group first entered exposed employment in 1960 or later, there are nevertheless 854 workers with 20 years or more exposure, and 1961 with 15 years or more. Table 3 shows the relationship between duration of exposure and EI. There does not appear to be a close relationship between the

Table 1. — Follow-up Status of 8384 Vinyl Chloride Workers.

	Total	Alive	Dead	Unknown	Death Certificate Rec'd.	Death Certificate Not Rec'd.
Number	8384	6776	352	1256	328	24
Percent	100.0	80.8	4.2	15.0	92.7	7.3

...the duration of exposure, that is ... with a higher EI do not differ ...ntially in duration of exposure ... those with a lower EI. One im... is that in assessing the relation... between mortality and exposure, ... duration and level of exposure can ... examined separately, as well as in ...bination.

Calculation of Risk of Death

The risk of death is expressed as a ...ndardized Mortality Ratio (SMR), ...ch is the ratio of the number of ...rved deaths in the study population ... number of deaths to be expected ... a comparable population of U.S. ... SMR's were calculated for overall ...ality and for 33 major cause groups.

Table 4 shows observed and expected ...aths, and the SMR, for each of these ...ups for the total study group. In ...culating the SMR's for specific causes, ... 24 deaths for which no certificates ...re found were assumed to have the ...me cause distribution as those for ...ich certificates were available.

In the standard population, each SMR ...uld be equal to 100. Therefore, the ...tistical significance of the deviation of ...ch SMR in the study population from ... expected value of 100 was tested.[8] A ...gle dagger indicates those SMR's ...hich differed significantly from 100 at ... 5% level, that is, which had a ...obability of .05 or less of occurring by ...ance. A double dagger indicates those ...hich were significant at the 1% level. ...MR's based on fewer than five ob...rved cases were not tested for ...nificance.

Table 5 shows the same SMR's for ...orkers with an Exposure Index below ...5 versus those at 1.5 or above. The ...ding point of 1.5 represents a level ...tway between "low" and "medium."

Table 6 shows similar results for ...orkers with less than five years ex...posure versus those with five years or more.

In order to examine the possible interaction between duration and level of exposure, the study population was divided into four groups on the basis of both EI (low vs high) and duration of exposure (short vs long) using the same dichotomization as Tables 5 and 6.

Table 7 shows the results for short versus long exposure in the low EI group, and Table 8 shows the same comparison in the high EI group.

In each of the above tables, deaths for which certificates had not been received were assumed to be distributed as a uniform percentage of all causes. The cause specific SMR's were therefore adjusted upward by a percentage which varied in each subgroup.

Results of Analysis

The overall mortality of the study population is statistically significantly lower than that of the U.S. male population. There were 352 observed deaths compared with 467 expected, for an SMR of 75.

Table 4 shows that no specific cause of death was statistically significantly greater than expected. Several, particularly heart disease, accidents and "other diseases" not detailed in the tables, were significantly below their expected values.

When the study population is divided according to intensity and duration of exposure (Tables 5 and 6) and combinations of these measurements (Tables 7 and 8) three major patterns emerge.

For malignant neoplasms as a whole, the SMR increases with increasing exposure, whether measured by level, duration, or both. In the high exposure group with 5 years or more exposure (Table 8) there are 36 observed cases and 26.11 expected.

For cardiovascular — renal diseases as a group, there are also increases in the SMR with increasing exposure, but the numbers of observed cases remain less than expected, the differences being statistically significant in all groups except the high exposure, long duration group in Table 8.

For all other causes, there are no consistent relationships with exposure.

Within the malignant neoplasms, the largest (although not statistically) significant SMR is in cancers of the buccal cavity and pharynx, with five observed, 2.84 expected, and an SMR of 189. However, Tables 5 to 8 show that all these cases have Exposure Indexes below 1.5 and four out of the five have less than five years exposure. Table 10 is a listing of these deaths with age at death, duration of exposure, and cause as stated on the death certificate.

Cancer of the digestive system shows

Table 2. — Distribution of Months in Exposed Employment by Year in Which Exposure Began, for 7128 Vinyl Chloride Workers with Completed Follow-up.

Year Exp. Started	Total	Months of Exposure							
		< 60	60-119	120-179	180-239	240-299	300-359	360-419	Unknown
1930-39	35	2	4	1	4	6	13	5	
1940-49	1048	135	93	119	151	277	237	34	2
1950-59	1962	389	257	383	631	282			20
1960-69	3368	1714	1442	195					17
1970-71	715	715							
Total	7128	2955	1796	698	786	565	250	39	39

Table 3. — No. and % of 7128 Vinyl Chloride Workers by Months of Exposed Employment and Exposure Index.

Exposure Index	Total	Months of Exposure							
		< 60	60-119	120-179	180-123	240-299	300-359	360-419	Unknown
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	
1.0-1.4	4032 (100)	1715 (43)	1125 (28)	402 (10)	406 (10)	247 (7)	92 (2)	18 (0)	
1.5+	3057 (100)	1240 (41)	671 (22)	295 (10)	380 (12)	291 (10)	159 (5)	21 (1)	
Unknown	39								39
Total	7128 (100)	2955 (41)	1796 (25)	697 (10)	786 (11)	565 (8)	251 (4)	39 (1)	39 (1)

Table 4.— Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers.

Cause of Death with I.C.D. Number	Obs/Exp	SMR*
All causes	352/467.28	75 *
Tuberculosis (001-019)	1/5.71	19
Tuberculosis of respiratory system (001-008)	1/5.34	20
Malignant neoplasms (140-205)	79/77.16	110
Malignant neoplasms, buccal cavity and pharynx (140-148)	5/2.84	189
Malignant neoplasms, digestive organs and peritoneum (150-159)	19/21.67	94
Malignant neoplasms, respiratory system (160-164)	25/23.93	112
Malignant neoplasms, genital organs (170-179)	3/3.55	91
Malignant neoplasms, urinary organs (180-181)	1/3.60	36
Malignant neoplasms, other and unspecified sites (190-199)	17/11.75	155
Leukemia and aleukemia (204)	3/3.77	85
Lymphomas (200-203, 205)	6/6.06	106
Diabetes mellitus (260)	7/6.31	120
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	155/207.46	78 *
Vascular lesions affecting CNS (330-334)	13/24.48	57 *
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	5/6.87	78
Arteriosclerotic heart disease (420)	121/137.33	95
Nonrheumatic endocarditis (421, 422)	1/6.58	16
Hypertensive heart disease (440-443)	3/9.33	35
Other hypertensive disease (444-447)	3/2.60	124
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/4.27	0
Influenza and pneumonia (480-493)	5/9.96	54 *
Ulcer of stomach and duodenum (540, 541)	2/3.83	56
Appendicitis (550-553)	0/0.66	0
Hernia and intestinal obstruction (560, 561, 570)	1/1.51	71
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	1/1.31	82
Cirrhosis of liver (581)	3/15.60	21
Hyperplasia of prostate (610)	0/0.39	0
Symptoms, senility and ill-defined conditions (780-795)	1/7.34	15
All other diseases (residual)	21/45.78	49 *
Motor vehicle accidents (810-835)	17/32.70	56 *
Other accidents (800-802, 840-962)	18/30.64	63 *
Suicide (963, 970-979)	16/16.83	107
Homicide (964, 980-985)	1/11.98	9
No. of workers	7128	
Person-years	77846	

*SMR's adjusted for deaths with cause unknown.
†Significant at 5% level.
‡Significant at 1% level.

no excess in the study population as a whole. However, in those workers with an EI of 1.5 or higher, there are 12 observed cases where 9.14 are expected (Table 5). In the subgroup of the above workers with five years or more exposure, there are 11 observed cases and 7.47 expected.

Respiratory cancer shows a slight excess in the total group, and a similar pattern for different exposure categories, with 13 observed versus 10.28 expected when the Exposure Index is 1.5 or higher, and 12 observed versus 8.50 expected when, in addition, the duration of exposure is five years or more.

Malignant neoplasms of other and unspecified sites show an excess in the total group, and an increase with both level and duration of exposure (Tables 5 and 6). The relationship with exposure is more pronounced, since those with exposures of less than five years have fewer cases than expected.

The lymphomas, although occurring at about the expected rate when the whole group is considered, are concentrated almost entirely in the high exposure, long duration group. In that category there are four cases observed and 1.84 expected.

Cancers of the genital and urinary organs, and leukemia, have fewer cases than expected. The number of cases too small to examine any trends.

Discussion

The favorable overall mortality of the study population is a phenomenon commonly observed in working populations. Standardized Mortality Ratios in the low 80's and below have been found.[1,2] Even in occupations with well defined hazards which cause an increased risk from a specific cause, the overall mortality may still be favorable because of the low risk from other major causes of death, frequently in the cardiovascular — renal category.[11]

Table 5. — Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers, by Estimated Level of Exposure.

Cause of Death with I.C.D. No.	D < 1.5		D ≥ 1.5	
	Obs/Exp	SMR*	Obs/Exp	SMR*
All Causes	188/270.33	70 **	157/195.68	80 **
Tuberculosis (001-019)	0/3.38	0	0/2.33	0
Tuberculosis of respiratory system (001-008)	0/3.16	0	0/2.18	0
Malignant neoplasms (140-205)	37/44.28	90	41/32.67	134
Malignant neoplasms, buccal cavity and pharynx (140-148)	5/1.62	330	0/1.21	0
Malignant neoplasms, digestive organs and peritoneum (150-159)	7/12.50	60 *	12/9.14	141
Malignant neoplasms, respiratory system (160-164)	11/13.56	86	13/10.28	135
Malignant neoplasms, genital organs (170-179)	2/2.30	93	1/1.43	75
Malignant neoplasms, urinary organs (180-181)	1/2.07	51	0/1.52	0
Malignant neoplasms, other and unspecified sites (190-199)	9/6.57	146	8/4.52	190
Leukemia and aleukemia (204)	1/2.18	49	2/1.57	136
Lymphomas (200-203, 205)	1/3.48	31	5/2.54	212
Diabetes mellitus (260)	5/3.65	146	2/2.65	81
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	84/120.11	75 **	69/86.99	85 *
Vascular lesions affecting CNS (330-334)	7/14.42	52 **	6/10.06	64
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	3/3.98	80	2/2.85	75
Arteriosclerotic heart disease (420)	68/78.94	92	51/58.05	95
Nonrheumatic endocarditis (421, 422)	0/4.20	0	1/2.89	38
Hypertensive heart disease (440-443)	1/5.48	19	2/3.86	56
Other hypertensive disease (444-447)	1/1.52	70	2/1.07	201
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/2.50	0	0/1.77	0
Influenza and pneumonia (480-493)	5/5.80	92	0/4.13	0
Ulcer of stomach and duodenum (540, 541)	1/2.21	48	1/1.60	68
Appendicitis (550-553)	0/0.39	0	0/0.27	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.88	0	1/0.63	171
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	0/0.76	0	1/0.55	196
Cirrhosis of liver (581)	2/8.90	23	1/6.64	16
Hyperplasia of prostate (610)	0/0.25	0	0/0.14	0
Symptoms, senility and ill-defined conditions (780-795)	0/4.22	0	1/3.09	34
All other diseases (residual)	14/21.90	68 *	6/15.89	41 **
Motor vehicle accidents (810-835)	8/19.08	45 **	9/13.46	72
Other accidents (800-802, 840-962)	11/17.83	66 *	6/12.67	50 **
Suicide (963, 970-979)	9/9.73	98	7/7.02	107
Homicide (964, 980-985)	0/5.98	0	1/4.94	21
No. of workers	4032		3057	
Person-years	45354		32108	

*SMR's adjusted for deaths with cause unknown
**Significant at 5% level.
***Significant at 1% level.

In view of these facts, SMR's which are higher than expected may be worthy of attention even if they are not statistically significant. This is especially true in the present study since the number of deaths from many causes is quite small, and even a relatively high SMR may not reach statistical significance.

If, in addition, a particular cause shows a consistent pattern of increase with exposure or estimated exposure, the findings are particularly interesting.

By these criteria, mortality from digestive cancer, respiratory cancer, cancer of other and unspecified sites, and lymphomas, appear to be related to exposure as defined in this study.

In view of the association between vinyl chloride exposure and angiosarcoma of the liver, the digestive cancers were examined further to see what contribution angiosarcoma made to the observed mortality pattern.

Of the 19 digestive cancers, seven were liver cancers, of which two were angiosarcomas according to the death certificate. However, among angiosarcoma deaths in vinyl chloride workers identified by other investigators, there were six which occurred in the present study population during the study period. They were all found in the course of the study. Table 11 shows these cases with the cause of death as given on the death certificate. Note that one case was certified as cirrhosis, and was so considered throughout this study, since the validity of comparisons with population data required that cause of death be determined only from information on the death certificate. The other five were correctly classified as

Table 6. — Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers by Duration of Exposed Employment

Cause of Death with I.C.D. No.	< 60 months		≥ 60 months	
	Obs/Exp	SMR*	Obs/Exp	SMR*
All causes	94/140.53	67 ‡	251/329.30	76 ‡
Tuberculosis (001-019)	0/2.23	0	0/3.55	0
Tuberculosis of respiratory system (001-008)	0/2.07	0	0/3.33	0
Malignant neoplasms (140-205)	13/19.96	78	65/57.61	116
Malignant neoplasms, buccal cavity and pharynx (140-148)	4/0.70	688	1/2.16	47
Malignant neoplasms, digestive organs and peritoneum (150-159)	2/5.26	46	17/16.56	106
Malignant neoplasms, respiratory system (160-164)	3/5.52	65	21/18.51	116
Malignant neoplasms, genital organs (170-179)	0/0.99	0	3/2.76	112
Malignant neoplasms, urinary organs (180-181)	0/0.83	0	1/2.79	37
Malignant neoplasms, other and unspecified sites (190-199)	2/3.40	71	15/8.23	187
Leukemia and aleukemia (204)	1/1.25	96	2/2.53	81
Lymphomas (200-203, 205)	1/2.01	60	5/4.07	126
Diabetes mellitus (260)	2/1.80	134	5/4.54	113
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	28/51.45	65 ‡	125/157.39	81 ‡
Vascular lesions affecting CNS (330-334)	4/5.97	81	9/18.71	49 ‡
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	2/2.39	101	3/4.53	68
Arteriosclerotic heart disease (420)	21/32.54	78 ‡	98/105.39	95
Nonrheumatic endocarditis (421, 422)	0/1.79	0	1/5.35	20
Hypertensive heart disease (440-443)	1/2.42	49	2/7.01	30
Other hypertensive disease (444-447)	0/0.79	0	3/1.82	170
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/1.55	0	0/2.76	0
Influenza and pneumonia (480-493)	3/2.93	123	2/7.09	29 ‡
Ulcer of stomach and duodenum (540, 541)	1/1.07	112	1/2.78	37
Appendicitis (550-553)	0/0.24	0	0/0.43	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.42	0	1/1.10	93
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	1/0.40	301	0/0.92	0
Cirrhosis of liver (581)	1/4.49	26	2/11.18	18
Hyperplasia of prostate (610)	0/0.07	0	0/0.33	0
Symptoms, senility and ill-defined conditions (780-795)	1/2.28	53	0/5.09	0
All other diseases (residual)	4/11.97	40	16/26.34	63 ‡
Motor vehicle accidents (810-835)	10/16.14	75	7/16.65	43 ‡
Other accidents (800-802, 840-962)	7/12.94	65 †	10/17.82	58 †
Suicide (963, 970-979)	6/6.34	114	10/10.28	100
Homicide (964, 980-985)	1/5.80	20	0/6.20	0
No. of Workers	2955		4134	
Person-years	34201		43240	

*SMR's adjusted for deaths with cause unknown.
†Significant at 5% level.
‡Significant at 1% level.

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Table 7. — Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers with Exposure Indices Below 1.5, by Duration of Exposed Employment.

Cause of Death with I.C.D. No.	< 60 Months Exposure		≥ 60 Months Exposure	
	Obs/Exp	SMR*	Obs/Exp	SMR*
All Causes	56/89.23	63†	132/181.28	73†
Tuberculosis (001-019)	0/1.41	0	0/1.97	0
Tuberculosis of respiratory system (001-008)	0/1.31	0	0/1.85	0
Malignant neoplasms (140-205)	8/12.86	73	29/31.46	95
Malignant neoplasms, buccal cavity and pharynx (140-148)	4/0.45	1036	1/1.17	88
Malignant neoplasms, digestive organs and peritoneum (150-159)	1/3.43	34	6/9.08	68
Malignant neoplasms, respiratory system (160-164)	2/3.58	65	9/10.00	93
Malignant neoplasms, genital organs (170-179)	0/0.68	0	2/1.62	127
Malignant neoplasms, urinary organs (180-181)	0/0.55	0	1/1.53	67
Malignant neoplasms, other and unspecified sites (190-199)	1/0.97	120	8/4.43	187
Leukemia and aleukemia (204)	0/0.79	0	1/1.40	73
Lymphomas (200-203, 205)	0/1.26	0	1/2.23	46
Diabetes mellitus (260)	2/1.15	203	3/2.50	124
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	21/33.38	73†	63/86.82	75†
Vascular lesions affecting CNS (330-334)	2/3.93	59	5/10.51	49†
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	2/1.50	155	1/2.49	41
Arteriosclerotic heart disease (420)	16/21.14	88	52/57.87	93
Nonrheumatic endocarditis (421,422)	0/1.18	0	0/3.02	0
Hypertensive heart disease (440-443)	1/1.58	74	0/3.90	0
Other hypertensive disease (444-447)	0/0.50	0	1/1.02	101
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/0.97	0	0/1.53	0
Influenza and pneumonia (480-493)	3/1.86	188	2/3.95	53
Ulcer of stomach and duodenum (540, 541)	0/0.68	0	1/1.53	67
Appendicitis (550-553)	0/0.15	0	0/0.24	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.27	0	0/0.61	0
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	0/0.26	0	0/0.51	0
Cirrhosis of liver (581)	1/2.80	42	1/6.09	16
Hyperplasia of prostate (610)	0/0.05	0	0/0.20	0
Symptoms, senility and ill-defined conditions (780-795)	0/1.43	0	0/2.79	0
All other diseases (residual)	4/7.45	63	10/12.92	79
Motor vehicle accidents (810-835)	3/9.87	35	5/9.22	56
Other accidents (800-802, 840-962)	3/7.98	44	8/9.85	83
Suicide (963, 970-979)	3/4.08	86	6/5.66	109
Homicide (964, 980-985)	0/3.55	0	0/3.43	0
No. of Workers	1715		2317	
Person-years	21418		23920	

*SMR's adjusted for deaths with cause unknown.
†Significant at 5% level.
‡Significant at 1% level.

Table 8. — Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers with Exposure Indices of 1.5 or Greater, by Duration of Exposed Employment.

Cause of Death with I.C.D. No.	< 60 Months Exposure		≥ 60 Months Exposure	
	Obs/Exp	SMR*	Obs/Exp	SMR*
All Causes	34/47.93	79	119/147.81	81
Tuberculosis (001-019)	0/0.76	0	0/1.57	0
Tuberculosis of respiratory system (001-008)	0/0.71	0	0/1.48	0
Malignant neoplasms (140-205)	5/6.57	96	36/26.11	141
Malignant neoplasms, buccal cavity and pharynx (140-148)	0/0.23	0	0/0.99	0
Malignant neoplasms, digestive organs and peritoneum (150-159)	1/1.67	76	11/7.47	151
Malignant neoplasms, respiratory system (160-164)	1/1.79	71	12/8.50	144
Malignant neoplasms, genital organs (170-179)	0/0.29	0	1/1.41	73
Malignant neoplasms, urinary organs (180-181)	0/0.26	0	0/1.26	0
Malignant neoplasms, other and unspecified sites (190-199)	1/1.18	107	7/3.51	204
Leukemia and aleukemia (204)	1/0.44	288	1/1.13	90
Lymphomas (200-203, 205)	1/0.71	178	4/1.84	222
Diabetes mellitus (260)	0/0.61	0	2/2.04	100
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	7/16.54	54	62/70.46	90
Vascular lesions affecting CNS (330-334)	2/1.87	135	4/8.19	50
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	0/0.82	0	2/2.04	100
Arteriosclerotic heart disease (420)	5/10.41	61†	46/47.65	98
Nonrheumatic endocarditis (421, 422)	0/0.57	0	1/2.32	44
Hypertensive heart disease (440-443)	0/0.76	0	2/3.10	66
Other hypertensive disease (444-447)	0/0.27	0	2/0.81	253
Chronic & unspecified nephritis & renal sclerosis (552-594)	0/0.54	0	0/1.23	0
Influenza and pneumonia (480-493)	0/0.99	0	0/3.13	0
Ulcer of stomach and duodenum (540, 541)	1/0.35	362	0/1.25	0
Appendicitis (550-553)	0/0.08	0	0/0.19	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.14	0	1/0.49	209
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	1/0.14	904	0/0.41	0
Cirrhosis of liver (581)	0/1.56	0	1/5.08	20
Hyperplasia of prostate (610)	0/0.01	0	0/0.13	0
Symptoms, senility and ill-defined conditions (780-795)	1/0.80	158	0/2.30	0
All other diseases (residual)	0/4.02	0	6/11.88	51
Motor vehicle accidents (810-835)	7/6.05	146	2/7.43	28
Other accidents (800-802, 840-962)	4/4.73	107	2/7.96	26
Suicide (963, 970-979)	3/2.40	158	4/4.62	88
Homicide (964, 980-985)	1/2.18	58	0/2.76	0
No. of Workers	1240		1817	
Person-Years	17822		19305	

*SMR's adjusted for deaths with cause unknown.
†Significant at 5% level.
‡Significant at 1% level.

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Table 9. — Other Malignancies (190-199, I.C.D.) in VDM Epidemiology Study Population.

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
2744	38	186	Widespread metastatic melanoma (1 yr.) Malignant melanoma of back	yes
3700	48	50	Malignant melanoma with widespread metastases	no
2096	67	69	Brain tumor (carcinoma) (8 mos.)	
3946	43	64	Meningitis and pneumonitis (5 wks.) Ependymoma, fourth ventricle-brain (2 mos. post-op craniotomy)	no
4433	54	81	Astrocytoma, malignant-left cerebral hemisphere (1 yr.)	yes
4800	61	51	Carcinoma of the brain Arteriosclerosis Pneumonia due to static congestion	no
7279	57	271	Brain tumor, glioblastoma multiforme (18 mos.)	
7300	44	211	Brain tumor, malignant (2 mos.)	
7371	58	249	Brain tumor, malignant	no
7306	53	216	Thyroid carcinoma with metastases	no
5769	52	239	Carcinomatosis Carcinoma vertebral body	yes
5246	67	201	Liposarcoma with metastasis (3 mos.)	yes
2850	64	193	Carcinomatosis, primary region not known (Past history, rheumatoid arthritis, myocardial infarction)	no
4778	54	300	Cardiac arrest (1 hr.) Respiratory arrest and cerebral hypoxia (2 days) Widespread metastatic carcinoma (2 mos.)	
4786	61	318	Generalized metastasis undifferentiated (7 mos.) Squamous cell carcinoma, primary site undetermined	yes
5783	69	166	Metastatic carcinoma of abdomen Critical site undetermined (Pulmonary emphysema)	
7301	55	133	Carcinomatosis (4 mos.) Primary site undetermined	no

liver cancer, but only two were specified as angiosarcoma.

If there had been no angiosarcomas, the number of deaths classified as cirrhosis in this study would have decreased by one, and the number classified as digestive cancer would have decreased by five. The pattern of duration and intensity of exposure in these five cases was such that if they had not been present there would have been no relationship between exposure and digestive cancer. The mortality pattern in this cause group is therefore attributable to angiosarcomas of the liver.

The other cause group worth further investigation is cancer of other and unspecified sites, both because it is a heterogeneous category and because it seems, unlike the other cancers, to be more related to duration than to level of exposures.

Table 9 shows a list of the specific causes included in this category, which is essentially brain cancer and generalized cancer with primary site unknown. About 40% of the observed deaths were due to brain cancer. In the general male population, about 22% of this category is due to brain cancer, so that not only is the mortality from cancer of other and unspecified sites excessive, but brain cancer is overrepresented within the category.

The possibility exists based on the lack of specificity of some of the listed causes that some of the brain cancers were not primary, but metastases from another unidentified site such as the lung.

The cancers of the buccal cavity and pharynx are difficult to explain because of their occurrence in the low exposure, short exposure group. It is possible that this is a chance occurrence, that exposures to other substances were involved, or that the mouth and pharynx may be peculiarly susceptible because of the gaseous nature of the chemical.

Possible Biases in the Calculation of Risk

There are two major potential sources of bias in the study. The first is that the follow-up rate is lower than is desirable. The second is that observations of workers with long exposures followed by a long latent period are not adequately represented, so that the power of the study to detect causes of death associated with long exposure and long latency is impaired. Populations with such characteristics exist and should be investigated.

Table 10. — Malignant Neoplasms of Buccal Cavity and Pharynx (140-148, I.C.D.) in VCM Epidemiology Study Population.

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
3003	31	49	Carcinoma of lip with metastasis to lung and neck (5 yrs.)	no
3431	56	30	Pulmonary edema (50 min.) Pulmonary metastases (Carcinoma, epidermoid, tongue and mandible)	no
3001	57	71	Metastatic squamous cell ca. primary lesion palate	yes
7365	54	40	Atelectasis due to metastasis to mediastinum (4 mos.) Multiple malignant metastases to brain, liver & mediastinum (1 yr.) Adeno-carcinoma of nasal pharynx (2 yrs.)	yes
3354	63	26	Massive hemorrhage into tracheo-tree Status post laryngo-pharyngectomy, left radial neck dissection Well-differentiated keratinizing squamous cell carcinoma of left pyriform sinus (mos.)	yes

Table 11. — Angiosarcoma Deaths in VCM Epidemiology Study Population.

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
4250	54	203	Cirrhosis of liver (sev. weeks)	yes
4255	60	281	Bleeding from hepatoma (3 days) (Laennecs cirrhosis)	yes
5765	45	167	Angiosarcoma rt. lobe of liver (10 mos.)	yes
7303	38	174	Liver failure (1 mo.) Cancer of liver, primary (15 mos.)	
7376	52	238	Cardiac tampanade and massive left hemothorax (mins.) Widely metastatic angiosarcoma of liver (4 mos.)	
7385	43	214	Hepatic failure Primary carcinoma liver	yes

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E-5

TOXICOLOGY AND APPLIED PHARMACOLOGY 49, 15–21 (1979)

Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats

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Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats. GEHRING, P. J., WATANABE, P. G., AND PARK, C. N. (1979). *Toxicol. Appl. Pharmacol.* 49, 15–21. Dose–response data for the induction of angiosarcoma in rats exposed to various levels of vinyl chloride (VC) together with attendant biotransformation data were used to estimate the risk of developing angiosarcoma in persons exposed to VC. Since a biotransformation product of VC, not VC *per se*, is responsible for the induction of angiosarcoma, the body surface area of people relative to rats was used to estimate the dose of the carcinogen biotransformed from VC by the former. Four models were used to extrapolate the data. Using a probit model, 10 hepatic angiosarcomas were predicted to occur in a recently reported epidemiological cohort of 9677 workers whereas five have occurred. Linear models and that based on the equation, Risk $= 1-e^{-\beta x}$, where x = dose, do not appear as reliable. For an 8-hr day, 5 days/week, 35-year time-weighted-average exposure of 1 ppm, the predicted incidence of hepatic angiosarcoma using the probit model is 1.5×10^{-4}.

Exposure of rats (Maltoni and Lefemine, 1975) and humans (Creech and Johnson, 1974; Tabershaw and Gaffey, 1974; Makk *et al.*, 1976; Fox and Collier, 1977) to vinyl chloride (VC) has been associated with the development of hepatic angiosarcoma. Numerous studies in rats indicate that it is not VC *per se* which is responsible for production of angiosarcoma but rather a reactive metabolite formed from it in the body (Bartsch *et al.*, 1975; Barbin *et al.*, 1975; Kappus *et al.*, 1976; Malavielle *et al.*, 1975; Bolt *et al.*, 1975; Watanabe *et al.*, 1978). Biotransformation of VC in rats is a nonlinear process occurring in accordance with Michaelis–Menten kinetics:

$$v = V_m S/(K_m + S) \qquad (1)$$

(Watanabe *et al.*, 1976a,b,c; Bolt *et al.*, 1976). In this equation, v and V_m are velocity and maximum velocity, respectively, for the biotransformation of VC expressed as microgram equivalents VC metabolized daily. S and K_m are the concentration of VC being inhaled and the Michaelis constant expressed as micrograms of VC per liter of air, respectively.

Utilizing the foregoing information, Gehring *et al.* (1978) revealed a good correlation between the probit percentage incidence of angiosarcoma in rats exposed to varying concentrations of VC, 4 hr daily, and the amount of vinyl chloride biotransformed, v, microgram equivalents VC metabolized per day. The probit equation is:

$$\text{Probit percentage incidence} = -1.625 + 1.543 \text{ Log } v. \qquad (2)$$

Hypothesizing that the biotransformation of VC is related directly to body surface area,

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Gehring *et al.* (1978) determined that the amount of VC transformed to a reactive form by man on a mass equivalent basis to rat is:

$$V\ \mu g/8\ hr = \frac{1675\ \mu g/hr \cdot S\ \mu g/liter}{860\ \mu g/liter + S\ \mu g/liter}. \quad (3)$$

Utilizing this relationship together with the foregoing probit equation, it was determined that incidence of hepatic angiosarcoma in workers exposed to 200 ppm should be approximately 1%. This incidence is 50-fold higher than that experienced (Fox and Collier, 1977). Various plausible explanations were put forth to explain this difference including greater sensitivity of rats and increasing latency for development as v decreases.

One plausible explanation not mentioned was that in worker populations studied to-date, many were exposed for only fractions of their working life. Furthermore, for some, the duration since initial exposure was likely insufficient for development of clinically detectable disease.

Recently available is a comprehensive epidemiological study[1] entitled, "Epidemiological Study of Vinyl Chloride Workers, Final Report." In this study, reasonably detailed information on 10,173 workers has been obtained for duration of exposure and lapsed time since first exposure.

Thus, much better information is available now to assess the reliability of the model proposed by Gehring *et al.* (1978) for predicting the incidence of hepatic angiosarcoma in humans utilizing data collected in rats. This assessment is reported here. In addition, three other models for estimating the incidence have been used for comparison of their reliability for predicting the incidence being experienced by workers exposed to vinyl chloride.

[1] Prepared for Manufacturing Chemists Association, 1825 Connecticut Avenue, N.W., Washington, D.C. 20009; prepared by Equitable Environmental Health, Inc., 6000 Executive Blvd, Suite 308, Rockville, Md. 20852, January, 1978.

METHODS

Four mathematical models were selected to analyze their reliability for calculating the incidence of hepatic angiosarcoma in rats as function of microgram equivalents of VC metabolized daily by rats exposed 4 hr/day, 5 days/week for 1 year. These models were as follows:

(A) Probit %

$$\text{Probit } \% = a + b(\text{Log } v)$$
$$= -1.625 + 1.543(\text{Log } v).$$

(B) Linear

$$\% = a + b(v)$$
$$= -1.48 + 0.389 \times 10^{-2}(v).$$

(C) Linear forced through origin

$$\% = bv$$
$$= 0.3565 \times 10^{-2}(v).$$

(D) One-hit model (Cancer Assessment Group, National Cancer Institute)

$$\% = 1 - e^{-\beta(v)}$$
$$= [1 - \exp(-0.38 \times 10^{-4} \times v)]100.$$

The constants given for the preceding models were determined by linear regression analysis and represent the best fit of the data for the incidence of hepatic angiosarcoma versus the amount of VC metabolized daily in rats exposed to different concentrations of VC (Gehring *et al.*, 1978).

The data used to derive the constants are given in Table 1. Using the equations derived for the models, the predicted incidence of angiosarcoma for the groups of rats exposed to different concentrations of VC were calculated. These results are shown also in Table 1.

All four models overpredict the incidence of hepatic angiosarcoma in rats exposed to 10,000 ppm VC. This is as expected because this exposure resulted in excessive mortality unrelated to development of angiosarcoma.

With respect to the predicted versus experimental incidence of hepatic angiosarcoma experienced by groups of rats exposed to the remaining concentrations of VC, none of the four models is unequivocally more reliable than any other. Thus, any one of the four models represents adequately the experimental data. Since no clear preference is discernible, all four models will be used to predict the incidence of hepatic angiosarcoma experienced or to be experienced by workers exposed to VC.

TABLE 1

PREDICTED INCIDENCE OF ANGIOSARCOMA IN RATS EXPOSED TO VINYL CHLORIDE USING VARIOUS MODELS VERSUS DOSE (v, μg VC METABOLIZED PER DAY) COMPARED TO EXPERIMENTAL RESULTS

Exposure[a] (ppm)	Dose[b] (v, μg/day)	Experimental[a] (%)	Predicted percentage (Models)[c]			
			A	B	C	D
10,000	5521	14.8 (9/61)	19.8	20.0	19.7	18.9
6,000	5403	21.7 (13/60)	19.3	20.5	19.3	18.6
2,500	5030	22.0 (13/59)	17.9	18.1	17.9	17.4
500	3413	11.9 (7/59)	12.1	11.8	12.2	12.2
250	2435	6.8 (4/59)	8.1	8.0	8.7	8.8
50	739	1.7 (1/59)	1.4	1.4	2.6	2.8

[a] From Maltoni and Lefemine (1975).

[b] Calculated from $v = [5706\ (\mu g\ VC/4\ hr) \cdot S(\mu g/liter)]/[860\ (\mu g/liter) + S(\mu g/liter)]$, where $S = 2.56\ (\mu g/ppm/liter) \times$ exposure (ppm) (Gehring *et al.*, 1978).

[c] Model A, Probit $\% = -1.625 + 1.543$ Log (dose); Model B, $\% = -1.48 + 0.389 \times 10^{-2}$ (dose); Model C, $\% = 0.3565 \times 10^{-2}$ (dose); Model D, $\% = [1 - e^{-\beta(\text{dose})}]\ 100$, where $\beta = 0.38 \times 10^{-4}$.

RESULTS AND DISCUSSION

The incidence of hepatic angiosarcoma in subgroups of 9677 workmen with respect to their duration of exposure are given in Table 2. These workers include 95.1% of the 10,173 in the cohort study; the remainder could not be traced.

The atmospheric concentrations of vinyl chloride to which these workers had been exposed were not quantitated, except subjectively into high, medium, and low categories. Since the time-weighted-average (TWA) exposure recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) prior to 1972 was 500 ppm and subsequently 200 ppm until adoption of the Occupational Safety and Health Act standard of less than 1 ppm in 1974, it is assumed that even those exposures subjectively deemed low were high. Indeed, it is reasonable to expect the TWA exposures of 200 ppm and greater for 8 hr were common rather than the exceptions.

Table 3 depicts the average theoretical rat equivalent daily doses of biotransformation products of VC received by workers exposed to 200 or 500 ppm for 8 hr daily, 5 days/week adjusted for the fraction of their working life during which exposure occurred. The doses, v, are expressed as micrograms per 8 hr and were calculated from Eq. 3 (given under Introduction) multiplied by the fraction of an assumed 35-year working life during which exposure occurred.

Having estimated the rat equivalent daily doses of biotransformation products of VC received by the various subgroups of 9677 workmen exposed to a TWA of 200 or 500 ppm VC, the predicted incidence of hepatic angiosarcoma for each subgroup was calculated (Table 4). Examination of the data in this table indicates that Models C and D overestimate the incidence of hepatic angiosarcoma experienced by these workers while Model B underestimates the incidences. Models C and D may overpredict because they do not address either the enzymatic biotransformation of VC or repair of the lesion leading to development of angiosarcoma, both of which are likely to be distributed normally in human or animal populations.

It may be argued that Models C and D overpredict because the recommended TWA exposure values of 200 or 500 ppm VC are

TABLE 2

INCIDENCE OF ANGIOSARCOMA IN 9677 WORKMEN EXPOSED TO VINYL CHLORIDE[a]

Population	Duration of exposure (years)	Mean exposure duration (years)[b]	Fraction of working life[c]	Observed angiosarcomas
4384 (0.31)[d]	< 4	2	0.06	1 (18 years)[e]
2339 (0.27)	5–9	7	0.20	0
946 (0.58)	10–14	12	0.34	2 (15 and 23 years)
1007 (1.0)	15–19	17	0.49	2 (18 and 19 years)
677 (1.0)	20–24	22	0.63	0
324 (1.0	25+	27	0.77	0
Total 9677				

[a] From "Epidemiological Study of Vinyl Chloride Workers", Final Report January 1978, prepared by Equitable Environmental Health, Inc., Rockville, Md., for Manufacturing Chemists' Association, Washington, D.C.

[b] Assumed mean duration of exposure.

[c] Mean duration of exposure divided by 35 years.

[d] Fraction of population incurring first exposure 15 or more years prior to study.

[e] Duration between first exposure and diagnosis.

higher than those actually incurred by workers included in the epidemiological study. Undoubtedly, some were exposed to smaller levels. Many were reported exposed to much higher levels; in some cases at or above the odor threshold of approximately 3500 ppm. Unfortunately, in the absence of analytically determined exposure levels, approximations of the actual TWA values must be used. For a TWA exposure of 100 ppm VC, the predicted number of workers developing angiosarcoma in this epidemiological cohort are 4, 0, 30, and 32 for mathematical Models A, B, C, and D, respectively. For a 50-ppm TWA, the corresponding numbers are 1, 0, 17, and 18. Thus, utilizing values for TWA exposures which are thought to underestimate the actual exposures appear to overpredict still the number of workers developing angiosarcoma of the liver when mathematical Models C and D are used, albeit Model A apparently underpredicts when a TWA exposure of 50 ppm is used.

When a TWA of 200 ppm is utilized to represent the atmospheric concentration to which these workers were exposed, the predicted incidence of angiosarcoma of 10 cases using Model A compares favorably with that experienced, five cases. For a significant number of workers, the time elapsed since initial exposure has yet to reach 15 years, the shortest time needed for development of angiosarcoma in 1 of 5 of the afflicted workers (Table 2). Thus, it may be

TABLE 3

AVERAGE THEORETICAL RAT EQUIVALENT DAILY DOSES OF BIOTRANSFORMATION PRODUCTS RECEIVED BY A 70-kg HUMAN EXPOSED TO 200 OR 500 ppm VINYL CHLORIDE FOR VARIOUS FRACTIONS OF AN ASSUMED 35-YEAR WORKING LIFE

Mean exposure duration (years)	Fraction of working life	v, micrograms per 8 hr averaged over 35 hr[a]	
		500[b]	200
2	0.06	60	38
7	0.20	200	125
12	0.34	341	213
17	0.49	491	306
22	0.63	631	394
27	0.77	771	481

[a] $v = [1675\ \mu g/8\ hr \cdot S\ \mu g/liter]/[860\ \mu g/liter + S\ \mu g/liter] \times$ (fraction of working life).

[b] Parts per million.

TABLE 4

PREDICTED NUMBER OF ANGIOSARCOMAS IN WORKERS EXPOSED TO 500 OR 200 PPM VINYL CHLORIDE 8 HR/DAY, 5 DAYS/WEEK FOR VARIOUS FRACTIONS OF A 35-YEAR WORKING LIFE VERSUS THE NUMBERS OBSERVED USING BIOTRANSFORMATION AND ANGIOSARCOMA INCIDENCE DATA FROM RATS AND FOUR MODELS FOR EXTRAPOLATION[a]

		Angiosarcomas predicted (Models)[b]							
		A		B		C		D	
Population	Angiosarcomas observed	500[c]	200	500	200	500	200	500	200
4384	1	0.2	0.0	0	0	9.4	5.9	10.0	6.3
2339	0	2.4	0.8	0	0	16.7	10.4	17.7	11.1
946	2	3.0	1.1	0	0	11.5	7.2	12.1	7.6
1007	2	6.8	2.7	4.0	0	17.6	11.0	18.6	11.7
677	0	7.3	3.0	6.6	0.3	15.2	9.5	16.0	10.1
324	0	4.9	2.1	4.9	1.3	8.9	5.6	9.4	5.9
Total									
9677	5	25	10	16	2	79	50	84	53

[a] Observed number of angiosarcomas from "Epidemiological Study of Vinyl Chloride Workers," Final Report January 1978, prepared by Equitable Environmental Health Inc., Rockville, Md., for Manufacturing Chemists Association, Washington, D.C.

[b] Model A, Probit $\% = -1.625 + 1.543$ Log (dose); Model B, $\% = -1.48 + 0.389 \times 10^{-2}$ (dose); Model C, $\% = 0.3565 \times 10^{-2}$ (dose); Model D, $\% = [1 - e^{-\beta(\text{dose})^3}]\ 100$ where $\beta = 0.38 \times 10^{-4}$. The constants in these models were obtained using the biotransformation and angiosarcoma incidence data for rats exposed to vinyl chloride (Gehring *et al.*, 1978).

[c] Parts per million.

anticipated that a few additional cases of hepatic angiosarcoma will occur in this population. It is comforting that an epidemic of cases, as has been envisioned by some, is not to be anticipated.

As indicated in the beginning of the paper, the previous attempt to extrapolate data from experiments in rats to predict the occurrence of hepatic angiosarcoma in vinyl chloride workers appeared to overpredict the observed incidence even when differences in the biotransformation of VC to active products by humans and rats were incorporated in the extrapolation.

The foregoing analysis using a probit percentage incidence model (Model A) has revealed that data collected in experiments on rats may be used to predict the incidence of hepatic angiosarcoma in humans with reasonable accuracy. Further verification of this model will be assisted greatly by determination of the rate of biotransformation of VC by humans exposed to sufficient concentrations of VC to allow such measurement. Currently, this must be estimated by the rate of biotransformation in rats and its assumed relationship to body surface area (Gehring *et al.*, 1978). Nonetheless, the correlation between predicted and observed incidence of hepatic angiosarcoma in vinyl chloride workers seems to justify both the assumptions and the model (Model A, Probit %) used to make the predictions.

Since the predicted incidence of hepatic angiosarcoma in humans using results from studies in rats appears justifiable, it is of interest to use the same procedures to estimate the incidence in workers exposed to 1 ppm 8 hr/day for a 35-year working life, the upper limit of the current Occupational Safety and Health Act standard. These predictions are shown in Table 5 for all four models.

Models C and D predict an incidence

TABLE 5

PREDICTED INCIDENCE OF ANGIOSARCOMA IN WORKERS EXPOSED TO 1 ppm VINYL CHLORIDE 8 HR/DAY, 5 DAYS/WEEK FOR 35 YEARS USING BIOTRANSFORMATION AND ANGIOSARCOMA INCIDENCE DATA FROM STUDIES IN RATS[a]

(A) Probit % or logarithm probability
1.5×10^{-6}% or 1.5/100,000,000

(B) Linear not forced through origin
None predicted below exposures of 98.7 ppm.

(C) Linear forced through origin
1.7×10^{-2}% or 1.7/10,000 or 177/1,000,000

(D) One-hit model (CAG)
1.89×10^{-2}% or 1.9/10,000 or 189/1,000,000

[a] Rat equivalent daily dose of biotransformation products received by workmen exposed for 8 hr to 1 ppm vinyl chloride is:
V = [1675 μg/hr·2.56 μg/liter]/[860 μg/liter + 2.56 μg/liter] = 4.97 μg/8 hr.

comparable to that experienced by workers exposed to much higher levels, again revealing their inadequacy because of overprediction. Model B, although a linear model, predicts zero response at 98.7 ppm VC. Thus, exposures to levels below this are not predicted to induce hepatic angiosarcoma. Using what appears to be the most reliable model (Model A, Probit %), the predicted incidence of hepatic angiosarcoma is 1.5×10^{-6}% or 1.5 cases in 100,000,000 workers. It is emphasized that use of Models A, C, and D to predict the incidence of hepatic angiosarcoma in workers exposed to 1 ppm VC assumes no threshold or even an inflection point in the dose–response curve (even though a threshold might occur).

In summary, the use of animal data for the assessment of risk in humans exposed to a chemical is not as mystical as frequently assumed. Dose–response data for the induction of angiosarcoma in rats exposed to various levels of VC together with attendant biotransformation data have been used to estimate, reliably, the risk of developing angiosarcoma in persons exposed to VC. There is every reason to believe that similar data can and should be used in the assessment of risk of exposure to specified levels of other substances.

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E-2

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Cancer Mortality in U.S. Counties with Plastics and Related Industries

by Thomas J. Mason*

Counties in the United States have been identified with chemical establishments whose primary manufacturing processes use vinyl chloride. Site-specific cancer mortality comparisons have revealed an excess of multiple myeloma in males associated with two of the manufacturing categories, synthetic rubber and synthetic fibers. A causal relationship between these manufacturing categories and multiple myeloma could not be established. An industry-based assessment of the occupational contribution to this excess is needed to evaluate the etiologic importance of this relationship.

Introduction

Angiosarcoma of the liver has been identified among workers who are heavily exposed to vinyl chloride (*1,2*). There is the possibility that individuals residing in areas with manufacturing plants using vinyl chloride may be exposed to this chemical. The present investigation of site-specific cancer mortality by county evaluates the risk of malignancy among residents of counties in the United States with possible environmental exposure to vinyl chloride.

Methods

The 1963 Census of Manufacturers (*3*) was used to identify counties with chemical establishments identified by Standard Industrial Classification (SIC) codes 2821–2824. These establishments are engaged primarily in manufacturing plastics materials and synthetic resins (SIC 2821), synthetic rubber (SIC 2822), cellulosic man-made fibers (SIC 2823), or synthetic organic fibers (SIC 2824). Vinyl chloride is not used in manufacturing cellulosic fibers. The category was included, however, to complete SIC Groups No. 282 which was selected to represent plastics and related industries. The number of people employed in each of the four manufacturing categories was then obtained for individual counties in the United States. As such this is a conservative estimate because classification is a function of the main items manufactured. Counties in each of the four manufacturing categories were ranked on the proportion of the total county population employed. Those counties in the upper quartile of the distribution of nonzero proportions for each manufacturing category were retained as study counties. As a comparison group, two counties were chosen for each study group county, matched by state and the per cent of the population living in urban areas (*4*).

Site-specific cancer mortality rates were calculated for the white population in study and control counties as well as the total United States for the period 1950 to 1969 and its four 5-yr component intervals. Mortality data by age, race, sex, cause of death, and county of usual residence were provided by the National Center for Health Statistics. Population estimates were obtained from published census statistics of 1950, 1960, and 1970, and intercensal estimates were derived by linear interpolation. All rates were age-adjusted by the direct method with the total U.S. population 1960 as the standard, and are expressed per 100,000. Rates were calculated for 29 individual sites and 6 combined sites (*5*). The variance

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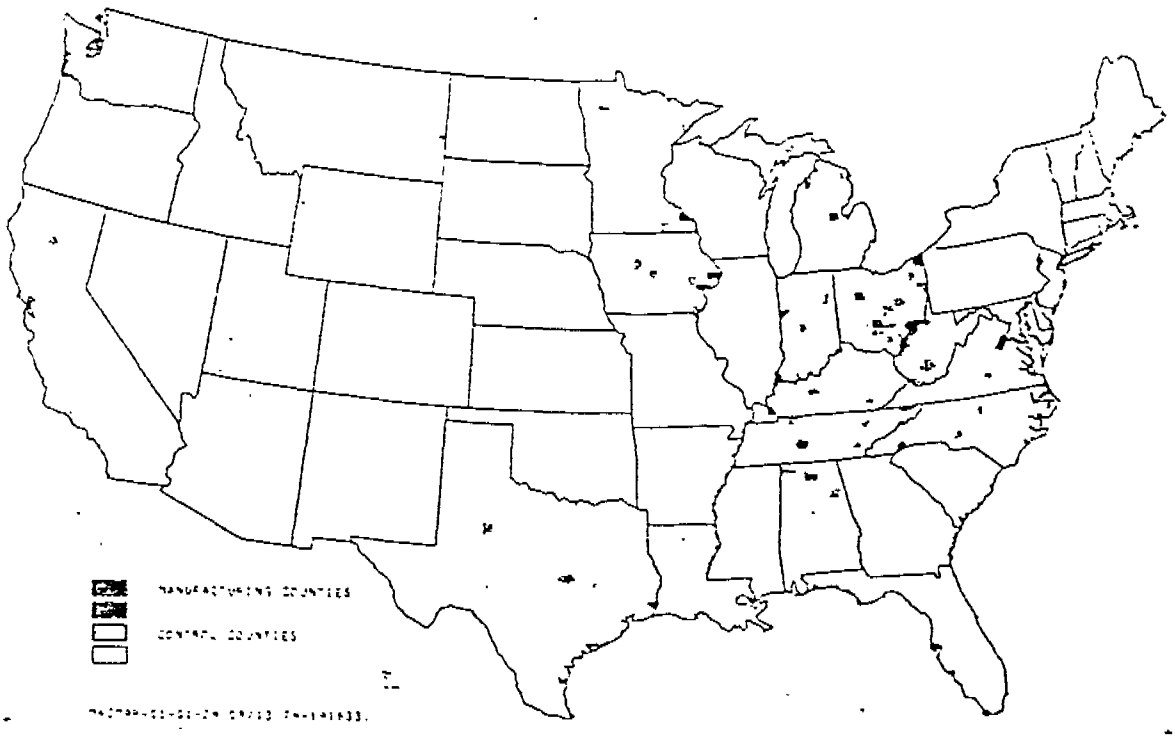

FIGURE 1. Study counties with chemical establishments primarily engaged in manufacturing plastics materials and synthetic resins with associated controls. Upper 25% of counties ranked on proportion of their total 1963 population employed in manufacturing category SIC 2821 and controls.

for each mortality rate was calculated by following the methodology of Chiang (*6*). Comparisons for males were made to the total United States as well as to control counties, utilizing a standardized normal test of significance at $p = 0.05$ (*7*). Comparisons for females were made for only those sites for which a significant male excess had been detected.

Results

Figures 1–4 identify study counties (upper 25% of the distribution of proportions of individual county populations employed in each manufacturing category) and their respective controls. The geographic patterns are distinct for each category, since no county satisfied the selection criterion for more than one type of manufacturing. Demographic characteristics for individual counties (Table 1) were taken from the 1960 Census (*4*). There are marked differences for urbanization between the categories, i.e., synthetic rubber manufacturing takes place in highly urbanized areas, whereas fibers are made in rural places. Age-adjusted cancer mortality rates for each manufacturing category were compared initially to total U.S. rates, and then to control counties. Table 2 presents only those rates for sites in white males which were significantly ($p < 0.05$) greater than the total U.S. and control counties. No anatomic site of cancer was found excessive in more than one manufacturing category for the 20-year period 1950–69. Also, no significant excesses were found for counties manufacturing cellulosic fibers.

Due to disease classification changes in 1958, rates for primary liver cancer [ICD 155.0, Seventh Revision ICD (*8*)], were calculated for the interval 1958–1967. This includes angiosarcoma deaths which were not separable from other forms of liver cancer in our mortality data. Of the counties considered, only those with synthetic rubber manufacture had

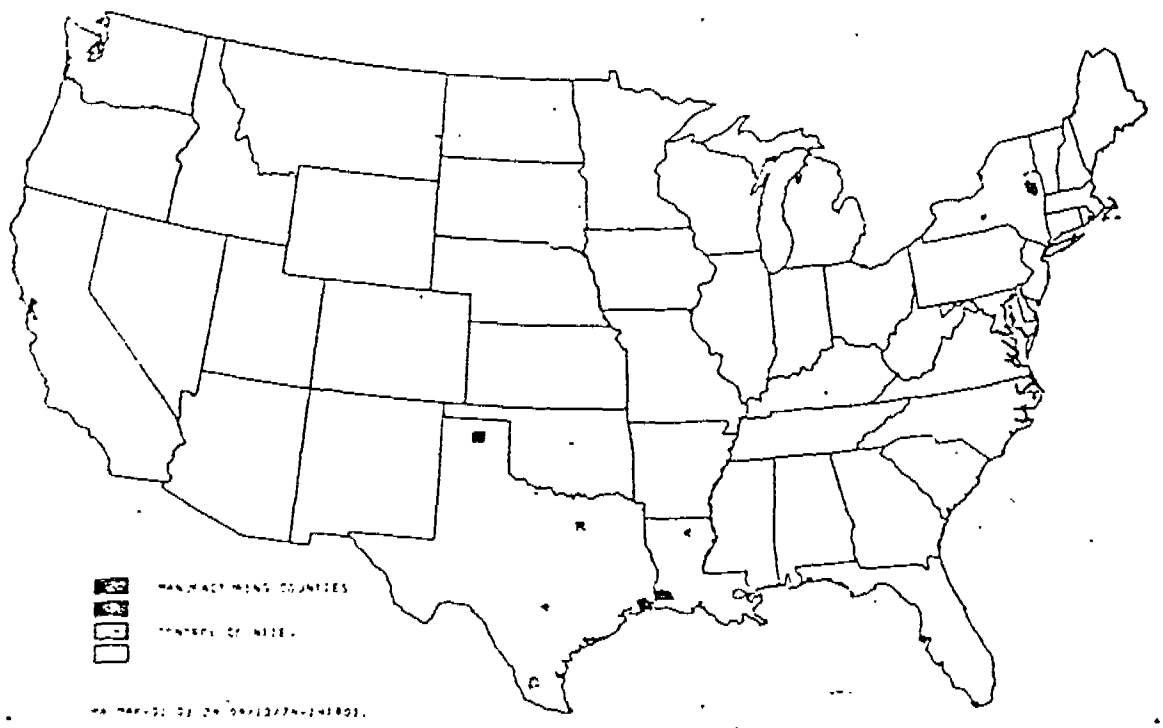

FIGURE 2. Study counties with chemical establishments primarily engaged in manufacturing synthetic rubber with associated controls. Upper 25% of counties ranked on proportion of their total 1963 population employed in manufacturing category SIC 2822 and controls.

consistently greater rates for liver cancer in general than the total U.S. rate of 1.34 for white males. However, the rate of 2.71 for counties manufacturing synthetic rubber was not significantly greater than that of 2.03 for their control counties.

Table 1. Characteristics of counties for manufacturing categories and controls.

	Plastics (SIC 2821)	Synthetic rubber (SIC 2822)	Cellulosic fibers (SIC 2823)	Synthetic fibers (SIC 2824)
Number of counties	21	4	5	5
Total population, 1960	979,417	514,649	130,105	220,798
Range employed in the specific category, %	0.5–8.7	0.6–2.4	4.3–10.1	2.4–4.4
Urban, %*				
Manufacturing	50.2	80.2	33.9	43.1
Control	47.0	90.4	48.2	41.7

*Weighted averages of individual county estimates.

Comparisons of data for females by manufacturing category were restricted to those anatomic sites for which a male excess had been detected. The only site with a significant excess in comparison to both total U.S. and controls was lung cancer in counties with synthetic rubber manufacture. The rates were 7.74 (study group), 6.72 (control), and 6.29 (total U.S.).

Time Trends Associated with Manufacturing Categories

Time trends were investigated by subdividing the interval of study (1950–1969) into four 5-yr intervals and comparing mortality rates for all sites of cancer which were included in the 20-yr comparisons. Significant differences for males were detected for two sites (cancer of the rectum and multiple myeloma) which were not at excess for the total time period, and

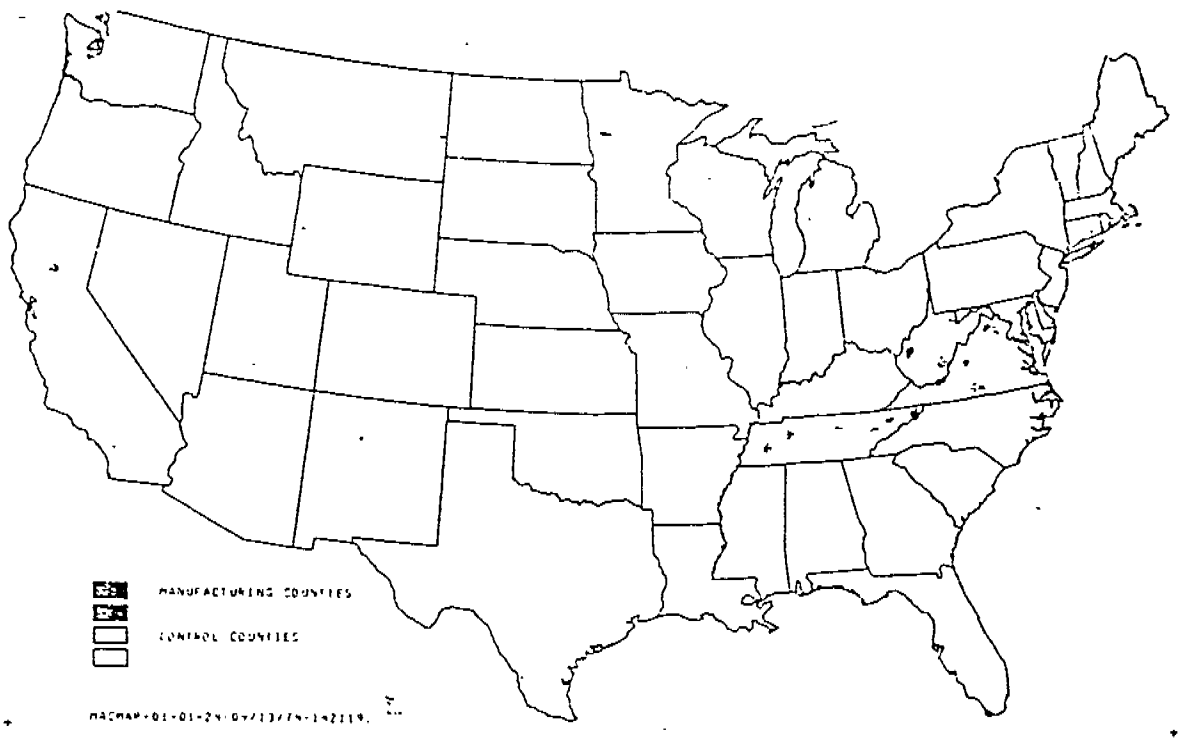

FIGURE 3. Study counties with chemical establishments primarily engaged in manufacturing cellulosic man-made fibers with associated controls. Upper 25% of counties ranked on proportion of their total 1963 population employed in manufacturing category SIC 2823 and controls.

Table 2. Age-adjusted mortality rates per 100,000 white males by manufacturing category for cancer sites which were significantly ($p < 0.05$) greater than the total U.S. and control counties (1950–1969).

	Mortality rates per 100,000		
	Manufacturing counties	Total U.S.	Control counties
Plastics (SIC 2821)			
Testis (ICD 178)[a]	0.91	0.83	0.71
Other endocrine (ICD 195)[b]	0.39	0.31	0.24
Synthetic Rubber (SIC 2822)			
Nasal sinuses, etc. (ICD 160)	0.73	0.43	0.37
Lung (ICD 162,163)	48.69	37.98	45.08
Bladder (ICD 181)	7.84	6.78	6.35
Synthetic Fibers (SIC 2824)			
Multiple myeloma (ICD 203)	2.24	1.76	1.79

[a] All ICD numbers refer to the International Classification of Diseases, Sixth Revision (9).
[b] Includes suprarenal, parathyroid, thymus, pituitary, and pineal glands.

these were excessive only in the interval 1965-1969. For counties manufacturing plastics materials and synthetic resins, cancer of the rectum in males remained constant in contrast to a decline in the control counties and the total U.S. The rates were 7.30 per 100,000 per year for manufacturing, compared to 5.24 in control counties and 6.62 in the total United States. For females, mortality rates for rectal cancer declined over time in both manufacturing and control counties. Mortality rates for multiple myeloma among males in counties with synthetic rubber manufacture did not differ from controls and total United States through 1964. For 1965–1969, however, the rates were 3.46 (study group), 2.11 (total U.S.), and 2.0 (control). There was no comparable difference among females.

Decreasing Trends

Mortality rates decreased in time for cancer

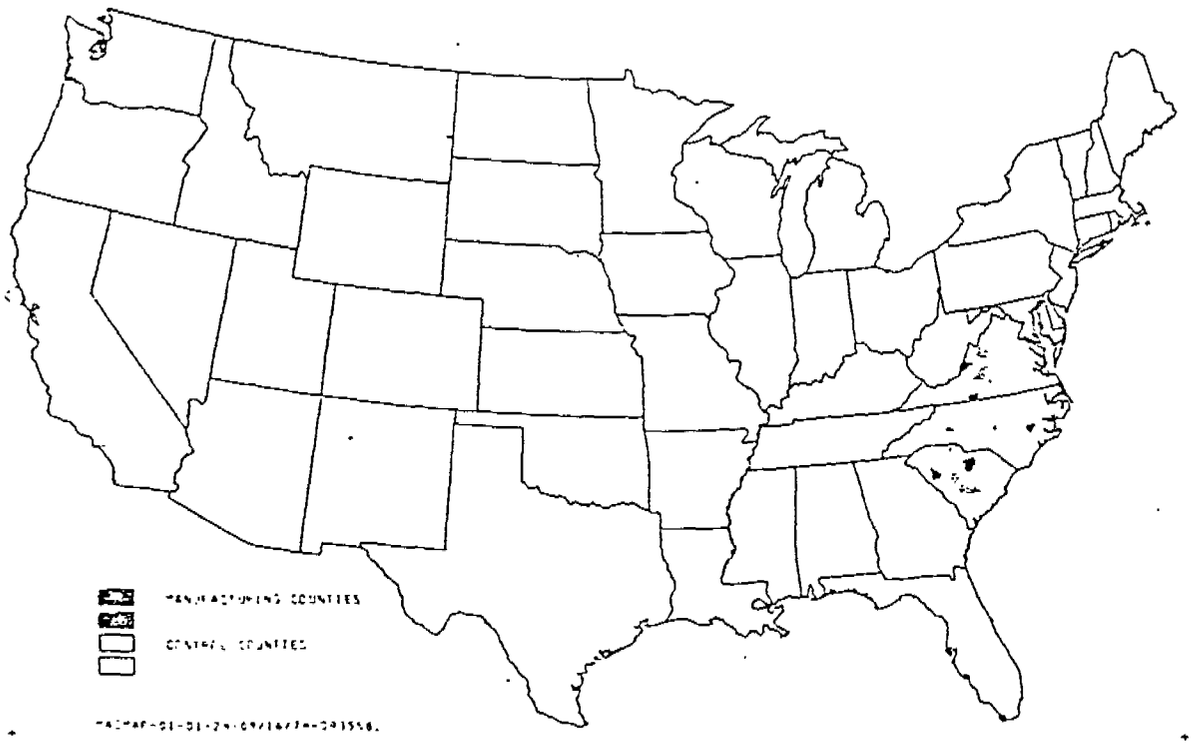

FIGURE 4. Study counties with chemical establishments primarily engaged in manufacturing synthetic organic fibers with associated controls. Upper 25% of counties ranked on proportion of their total 1963 population employed in manufacturing category 2824 and controls.

of the testis in counties with plastics and synthetic resin manufacture, and for cancer of the nasal cavity and accessory sinuses among males in counties with synthetic rubber manufacture. The rate of decline for testis was greater for manufacturing counties than control counties and total United States. For nasal cavity and accessory sinuses, mortality rates declined at a greater rate for control counties than the total U.S. and counties with synthetic rubber manufacture.

Increasing Trends

Lung cancer among males increased at a greater rate in control counties than in counties with synthetic rubber manufacture. The increase in these manufacturing counties was greater than for the total U.S. For all other sites given in Table 2 (other endocrine, bladder, and multiple myeloma) the rate of increase was greater in the manufacturing counties than the controls, and also greater for both county categories than the United States rate for change.

Discussion

This investigation of the possible health hazard to residents of counties in the United States with chemical establishments using vinyl chloride has several limitations. The effect of confounding variables on the results could not be completely controlled for. The selection criteria for control counties takes into consideration the effect of urbanization and also regional differences in diagnosis. However, the effect of cigarette smoking which is associated with cancers of the lung and bladder (*10*) could not be controlled for. The finding of excess mortality for lung cancer among men and women in counties with synthetic rubber manufacture could be due to differences in smoking habits, and not be directly related to the manu-

facturing process. There is also a dilutional effect which may prevent the identification of excesses among small subsets of the population with relevant exposure. The reported excess of angiosarcoma of the liver among vinyl chloride workers was not detected in this investigation. This is due to the grouping of diagnoses in disease classification as well as the small number of cases. No refinement of the data to smaller population units than counties, however, was possible.

Mortality rates for cancers of the nasal cavity and accessory sinuses and bladder among males were excessive only in counties with synthetic rubber manufacture. This finding may be unrelated to the manufacturing of synthetic rubber, but is consistent with previous findings suggesting that chemicals may be carcinogenic at the sites of absorption and excretion (*11*).

Occupational studies have reported excess mortality due to cancers of the digestive system, liver and biliary tract, lung, brain, and lymphatic and hematopoietic tissues among vinyl chloride workers (*1,2*). The only site-specific comparison which detected increases for males in more than one of these manufacturing categories was for multiple myeloma. Mortality rates for this site were greater for counties with synthetic rubber and synthetic fiber manufacture than their corresponding controls and the total United States. An excess of multiple myeloma in farmers has been reported (12). This may relate to the male excess in the rural counties (43% urban) with synthetic fiber manufacture. However, it does not explain the finding of an excess for males in counties with synthetic rubber manufacture (80.2% urban). Multiple myeloma is included in the broad classification for cancers of lymphatic and hematopoietic tissues. An evaluation of the contribution of mortality from this site to the excess for the broader classification among vinyl chloride workers is needed.

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The critical review of this manuscript by Robert W. Miller, M.D., Joseph F. Fraumeni, Jr., M.D., and Robert Hoover, M.D. is gratefully acknowledged, as well as the technical assistance of Frank W. McKay in the computerized preparation of the figures.

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FACT SHEET

VINYL CHLORIDE AND HEALTH

When any questions of employee or community health arise, such as occurred during the Burlington Township Planning Board hearings on Tenneco's plant modernization program, everyone involved with the facility is naturally concerned.

Tenneco management firmly and sincerely believes that neither our Burlington employees nor the the community have any cause for concern. Our confidence is based on two factors:

1) Comparison and evaluation of all the scientific data compiled by independent sources on this subject.

2) The actual experience of vinyl chloride plants during the 40 years the industry has been operating in this country.

The issues and the facts can be summarized as follows:

DOES EXPOSURE TO VINYL CHLORIDE MONOMER (VCM), THE RAW MATERIAL USED BY TENNECO'S BURLINGTON PLANT, INCREASE THE RATE OF BIRTH DEFECTS IN CHILDREN?

Facts:

1) The principal research cited at the Planning Board hearings to indicate increased risk was a 1974 study of communities in Ohio with vinyl plants which showed a higher-than-normal rate of birth defects. The researcher attributed these to exposure to vinyl chloride.

Following publication of this study, the Center for Disease Control (CDC) of the U.S. Public Health Service conducted two investigations of its own. The first, which reviewed the original work in Ohio, concluded that the evidence available "did not establish any association between (birth defect) cases and vinyl chloride exposure." Specifically, it found that none of the parents of the affected children had ever worked in a vinyl plant.

The CDC's second investigation studied Charleston, West Virginia, site of a vinyl chloride plant since 1948. The CDC concluded that "no relationship between infants with malformations and parents' exposure to vinyl chloride could be established."

2) Many other studies with mice and rats in the U.S. and England, and conducted at exposure levels ranging from 50 parts per million to 50,000 parts per million, have produced no evidence that vinyl chloride causes birth defects. For example, a study for the Consumer Product Safety Commission (CPSC) on these animals failed to detect any evidence of birth defects caused by vinyl chloride monomer.

CAN EXPOSURE TO VCM CAUSE CANCER AMONG EMPLOYEES OR PERSONS LIVING IN THE COMMUNITY?

1) When the question of possible risk was first raised, the federal Environmental Protection Agency (EPA) calculated

that, based on national mortality rates, for the 10 years between 1964-74 there should be only 6 cases of angiosarcoma among 5 million people if vinyl chloride posed no risks. The EPA then studied the 5 million people living within a five-mile radius of vinyl plants in the U.S. and found not 6 angiosarcoma cases during that period but only 3. In other words, there were actually fewer cases than would have been expected if no vinyl chloride plants existed in these communities. It should also be noted that during the period covered by these studies, vinyl chloride emissions were not controlled. Since then, permissible emission levels have been drastically reduced by the Occupational Safety and Health Administration (OSHA).

2) Tenneco's health records include no cases of angiosarcoma (liver cancer - the type of cancer thought to be associated with exposure to vinyl chloride monomer) in any plant employee and Tenneco has been operating vinyl plants for more than 20 years.

3) In the previously-mentioned CPSC research, in which rats and mice were tested at VCM exposures up to 50,000 parts per million, no angiosarcoma cases were found.

4) Vinyl chloride used to be used as a propellent in hair sprays, which brought relatively high concentrations into close proximity with a woman's face. There are no indications that this exposure produced angiosarcoma among women.

CAN DUST OF POLYVINYL CHLORIDE (PVC), THE PLASTIC RESIN PRODUCED BY THE BURLINGTON PLANT, CAUSE CANCER?

Facts:

1) Scientific studies indicate PVC dust poses no health hazard to people, animals or plants.

2) During more than 40 years of PVC production, extensive research has consistently shown that employees in vinyl plants are as healthy as workers in other industries, and healthier than the general population.

3) National Cancer Institute statistics show that Burlington County's cancer mortality rate is 9% below the New Jersey State average.