



DOW CHEMICAL U.S.A.

21 September 1977

MIDLAND, MICHIGAN 48640

Dr. Vernon E. Rose
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Documentation and Standards
Development
National Institute for Occupational
Safety and Health
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Dear Dr. Rose:

Attached are my comments on the draft Vinyl Compounds criteria document. These comments represent my inputs as a consultant and do not constitute positions of The Dow Chemical Company.

Generally, as will be seen by my comments, I find the document unacceptable scientifically. There are many errors and in some cases untrue statements. Furthermore, the document seems to have been developed by people possessing preconceived bias. Finally, judgmental statements are perceived frequently to have been developed using capricious bias. To some degree, this has been fostered by inclusion of this group of vinyl compounds into one document. Frequently, similar information is used to render judgments restricting exposure to one compound, but not restricting exposure to others.

Very critical is the hypothesis used to develop a standard for vinyl chloride. Although setting forth this hypothesis is scientifically acceptable, an objective scientist is obligated to test his or her hypothesis. A simple test of the hypothesis reveals that it overestimates by many orders of magnitude the incidence of angiosarcoma which has been observed in exposed vinyl chloride workers.

In conclusion, I urge strongly that NIOSH:

- 1) Prepare a document for each material separately.
- 2) Prepare each document more accurately representing the data available.
- 3) Reassess the apparently scientific basis for arriving at a standard.

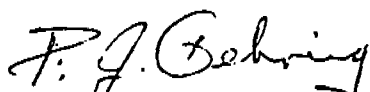


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- 4) Develop consistency in using data to render judgments regarding standards. In this regard, NIOSH should deem all compounds covered within this document as "Cancer Suspect Agents". I do not concur with the judgment of NIOSH. However, whatever tact NIOSH takes, it should be consistent.

My foregoing statements and comments on the document may seem harsh but they are submitted in a constructive sense. NIOSH is an important agency with an essential mission. I hope they will not negate this essential role by impetuous and capricious actions.

Respectfully submitted,



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Enclosure

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SPECIFIC COMMENTS ON DOCUMENT FOLLOW:

Page 1, lines 13 & 14 - These standards are not based on health effects! Rather they reflect subjective evaluation of possible health effects. For vinyl chloride and vinylidene chloride, the recommended health standards are based on analytical chemistry capability.

Page 7, lines 207 through 208 - I request that NIOSH produce data substantiating that the techniques to implement the recommended standards are valid, reproducible, and available. Subsequently, these data should be submitted to a group of experts capable of assessing them; not the current group of consultants. I believe that the indicated statement is speculative-unsubstantiable with data. Furthermore, NIOSH must establish the need for such techniques and, most importantly, assess the hazard of instituting such technology relative to the hazard against which they wish to protect.

Page 7 & 8, line 221 & 222 - Inclusion of vinylidene chloride with vinyl chloride is biased and speculative. At least be consistent! If NIOSH wishes to use data like that used to deem vinylidene chloride a carcinogen, the same data should be used to regulate similarly vinyl bromide, vinyl fluoride, vinylidene fluoride, and very likely vinyl acetate. Furthermore, if NIOSH wishes to group vinyl compounds into one document they should be consistent. Therefore, add to the Document other vinyl compounds; for example, perchloroethylene, trichloroethylene, acrylonitrile, vinyl benzene, vinyl methane, vinyl ethers, vinyl esters, vinyl pyrrolidinones, acrylic acid and its esters. Selection of the vinyls covered in the current document is unscientific and arbitrary.

Page 8, lines 222 and 223 - NIOSH concluded in the text of the document that malformations, fetal deaths, and heritable changes were not judged to be associated with exposure to these vinyl compounds. Why do they say here that these effects need to be considered hazards of vinyl compounds? Either NIOSH believes these effects are or are not real. Which is it?

Page 9 - Why can standards be set for cis- and trans-dichloroethylene and not vinyl fluoride and vinylidene fluoride? More pertinent data exist for the latter compounds.

Page 9, line 273 - There exist data assessing the value of annual medical examinations in preventive medicine. Recommendation for annual medical examinations is subjective. Why not base such recommendations on data rather than supposition?

Page 11, lines 300-302 - Curiously, it is not recommended that employees be told that vinyl fluoride and vinylidene fluoride are mutagenic to yeast. Why?

Page 11, lines 303 and 304 - Does NIOSH mean to subject employees to the greater hazard of medical examination (transportation, blood drawing, etc) than incurred by exposure to, example, 100 ppm vinyl chloride for 15 minutes? NIOSH should be very conscientious in assessing the hazards incurred if these recommendations are instituted!

Page 12, line 344 - NIOSH must be consistent. I do not accept personally their judgment that vinylidene chloride should be labeled a cancer Suspect Agent; however, assuming this judgment is proper, then vinyl fluoride, vinylidene fluoride, vinyl bromide, as well as vinyl acetate should be labeled thusly.

Page 13, line 383 - Add following between needed and to in this line ". . . and when feasible and when such controls do not constitute to the worker a hazard greater than that incurred via exposure to a specified level of the compound in question."

Pages 15, 16, 17, and 18 - The acceptability of the data given in these tables should be submitted to a panel of experts for validation.

Page 19, lines 636-645 - A recommendation that the indicated impervious clothing be worn constitutes, very likely, a hazard greater than that against which NIOSH proposes to protect the worker. How can NIOSH make such a recommendation without assessing the competing hazard of their recommendation?

Page 19, lines 656-665 - Since the concept of hazard proposed by NIOSH is different markedly than my own and very likely others, I recommend that NIOSH be charged with preparing a brochure which can be given every employee. I certainly could not profess the necessity of the NIOSH recommendations if instituted since they are at best arbitrary.

Page 20, line 667 - This statement implies vinylidene chloride is a human carcinogen. This is not the case.

Page 20 - Effects on evaluations of fetal development have been judged not to be a hazard by NIOSH. Are they or aren't they? If the latter, include the other vinyl compounds as stated previously.

Page 20, line 691 - Add following--"Whenever feasible automated equipment should be used to preclude worker exposure? I don't believe the need for this statement but if NIOSH believes that the carcinogenic hazard of these compounds is real and significant than NIOSH should advocate the elimination of workers from such hazardous jobs whenever feasible.

Page 21, line 707 - Add other vinyl compounds for reasons previously stated.

Page 21, line 716 - Define "affected".

Page 22 - In all cases NIOSH is obligated to assess the hazard of instituting emergency procedures versus the hazard of exposure to specified levels of the compound in question.

Page 22, line 743 - To what degree of certainty must containers be stored in a safe manner?

Page 22, line 754 - ". . . is not a hazard." To what degree of certainty?

Page 22, line 769 - Again, I request NIOSH to study thoroughly and evaluate the hazard of such protective equipment versus the hazard of specified levels of exposure to the chemicals in question.

Page 24, lines 782 and 783 - Include other vinyl compounds as well as vinyl chloride and vinylidene chloride for consistency.

Page 24, lines 787-790 - I request data showing the necessity of this precaution.

Page 24, lines 791-793 - Does this precaution suggest that oral ingestion constitutes a greater hazard than either inhalation or skin absorption? This is the traditional type of unscientific garbage added to documents with no scientific basis.

Page 25, line 803 - To what level of occupational exposure? Does this include an individual working in another plant two blocks away?

Page 25, line 825 - Why once a week?

Page 26, lines 835-839 - Has an analysis of such record keeping been made, cost benefit? I grant that extensive record keeping is justified if the objectives can be justified and such records can be recalled for useful purpose. If this recommendation is retained, it should apply to all sectors, government and university employees as well. Indeed, all recommendations must be applied equally to all sectors.

Page 28, line 878, No. 4 - It is the responsibility of NIOSH to establish that these standards can be attained with existing technology. They have not done so in this document.

Page 28, line 884 - Vinyl bromide, vinyl fluoride, and vinylidene fluoride must be equated to vinylidene chloride in their potential carcinogenic activity. Be consistent.

Page 29, lines 897-898 - If NIOSH accepts this statement, apply it uniformly.

Page 30, lines 924-928 - Data showing what is claimed in these lines for vinyl compounds are nonexistent.

Page 31, line 959 - 2.2M in U.S.? What is basis for this estimate? If true, why hasn't the prevalence of angiosarcoma increased tremendously?

Page 32, line 964 - Is vinylidene chloride more of a structural analog than other vinyls? Please supply the chemistry which supports this contention!

Page 39, line 1137 - Is NIOSH suggesting that angiosarcoma induction is reversible?

Page 40, line 1155 - Add following to sentence ending in this line, "... of course hepatic carcinoma in one worker does not establish cause-effect since the expected background incidence would predict some cases of this type of disease in the large number of workers exposed".

Page 41 - Merely stating occurrence of syndromes observed even in an exposed population is scientifically unacceptable. Was the incidence of such occurrences greater than expected or not?

Page 42, lines 1186-1195 - Again, how does incidence compare with that of controls? Perhaps uninterpretable data should be relegated to a section of the document called "Interesting and Uninterpretable Information".

Page 43, line 1207 - What is free HCl?

Pages 44 and 46 - Estimate exposure levels! How can NIOSH include such data without estimating exposure levels; at least subjectively. Shall the future be based on qualitative analysis?

Page 48 - Again, an estimate of exposure level is needed. Why not indicate that most of the syndromes referred to are the result of conditions leading to exposure many-fold higher than that currently practiced.

Page 58, lines 1547-1550 - Uniquely?

Page 58, lines 1554-1556 - This is an abstract finding. People get dizzy smelling perfume.

Page 58, line 1564- Recent data indicate that the incidence of spontaneous angiosarcoma may be higher than thought previously.

Page 58, lines 1573-1585 - I believe Dr. Popper indicated that some of these angiosarcomas were not the same type as those seen in vinyl chloride workers. Check this. Don't inflate the problem unnecessarily.

Page 62, line 1637 - Twenty-five not 21.

Page 69, lines 1779-1781 - What was Popper's evaluation of the relevance of these cases?

Page 71, lines 1806-1809 - Put in perspective! Characteristics of lesions in these cases versus those seen in PVC workers were, I believe, different. Juvenile versus adult occurrence of disease needs to be pointed out. How much vinyl chloride can be carried home on clothing? Some elementary physical chemistry should be recalled prior to making such inflammatory suggestions.

Page 73 - What else did this insulated wire-chewer chew? How about petroleum products contaminating the wire, also flux?

Page 74, starting line 1874 - With respect to the cited study, I don't believe that range of typical exposure to vinylidene chloride exposure of 0-5 ppm, line 1880, can be substantiated with data. Please supply these data! I am not interested in data attained after the problem was perceived but rather historical data during which it was developing.

As stated, the write-up suggests that vinylidene chloride was the only substance present. In reality, almost 50 other chemicals were present. Since there is no scientific basis to single out vinylidene chloride, why hasn't NIOSH listed the other chemicals together with their after the incident exposure ranges? Obviously, NIOSH has selected a subjective-biased reporting of facts rather than a scientific approach.

Page 80, lines 2003-2014 - These were EEG changes resulting from acute exposure. Since EEG changes are more serious than dizziness previously cited for vinyl chloride, the following sentence should be added. "These alterations constitute a potentially-grave effect of exposure to vinyl acetate and hence need to be protected against. . . ." Consistent with NIOSH philosophy, the concentration recommended for the workplace should be no greater than 0.006 mg/Cubic meter unless of course mind modification is not as serious a consequence as cancer.

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Page 81, lines 2030-2034 - Should not it be indicated that essentially all cases of angiosarcoma in the U.S. came from a few locations, indeed two? Doesn't NIOSH believe this is of importance in establishing cause-effect? At least scientifically, a scientific document should retain this perspective since it indicates either excessive exposure or a uniquely susceptible population!

Page 82, lines 2051-2057 - Since activation of vinyl chloride to an active product is necessary for carcinogenesis, and since this activation is saturable, a most important parameter for assessing exposure is duration. NIOSH should analyze this aspect! For example 6-hr exposure to 250 ppm is considerably worse than 3-hr exposure to 500 ppm.

Page 82, line 2063 - Is this a conclusion which can be substantiated? Short duration for development in some cases indicates it is not.

Page 83, lines 2084-2092 - Should not the even greater inadequacies of studies by others discussed in this document be stated? It seems that NIOSH has pointed out selectively inadequacies when the results do not fit the boundaries of their preconceptions.

Page 91, lines 2232-2233 - Since the restriction cited for the Dow study applied to others as well, this same statement should be included in the critique of all other such studies. Also, in the critique of other studies it should be indicated that the exposures were high.

In line 2233, it is stated that the reliability of the statistics is very low. How low is it? Is the reliability less than that used to assess animal experiments in which less than 100 animals were used?

Page 91, line 2234 - It should be stated that the Nicholson (1974) study was conducted on workers from one of those few locations where angiosarcoma occurred. This is essential to put the results in proper perspective.

Page 92, lines 2261-2262 - Again put statement in perspective! What is the statistical probability that the glioblastoma and 2 lymphomas were caused by exposure to vinyl chloride? It is possible that any condition seen in vinyl chloride workers is related to exposure. Since unfortunately spontaneous disease is a fact of life some judgment must be executed.

Page 92, line 2265 - Doesn't NIOSH have the responsibility to put in perspective the phrase "...more cases may be forthcoming". How true has this prediction been?

Page 92, line 2271 - Interestingly, NIOSH accepts here exposures initiated less than 10 years before time of study. Is this consistent? Note page 91, line 2232.

Page 93, line 2276 - Was the death rate of other unlisted causes decreased or is it important to indicate only those causes for which the death rate was greater?

Page 93, lines 2283-2326 - Other vinyl chloride associated disease should be indicated as these give an indication of exposure. To reiterate, for scientific perspective it should be indicated that the distribution of affected employees has been sporadic rather than diffuse suggesting either unique susceptibility or exposure to high doses and dose dependency.

Page 100 - Shouldn't it be pointed out that the cited Infante work included selection bias in that workers exposed to low levels of vinyl chloride were grouped arbitrarily with controls?

Page 101, line 2589 - The study cited here is very poor; numbers are too small and matched controls are needed for such a study. Also, one spot sample for cytogenetic evaluation is absolutely inadequate. What type of chromosomal alterations were seen? Shouldn't NIOSH assess these deficiencies as they have when a study does not indicate an effect?

Page 107, lines 2611-2618 - To what level of vinyl chloride had these people been exposed? Were they incurring exposures consistent with those prior to recognition of the possible health effects of vinyl chloride? If yes, then it should be stated thusly.

Page 114, lines starting 2780 - Why present interim data when final report is covered?

Page 115, line 2798 - It should be pointed out what the tumors were with respect to type and the number of animals in which observations were made. Was this study designed adequately to support the conclusion? I believe not.

Page 115, lines starting 2800 - This constitutes an exceptionally poor critique of Maltoni's excellent work. What was dose response? What was time to development?

Page 117, line 2839 - It should be indicated that the mice were suffering severe effects other than cancer and that secondary carcinogenesis may explain the response. This is particularly true for tumors other than angiosarcoma! Secondary stress induced cancer in mice is a fact which cannot be ignored.

Page 120, lines 2913-2916 - Certainly these data indicate lucidly the unique susceptibility of mice, do they not?

Page 121, line 2941 - Define all.

Page 124, line 3009 - It should be pointed out that olive oil lowers GSH, a compound found in the body, particularly liver, needed to detoxify the active metabolite of vinyl chloride.

Page 131, lines 3144-3146 - What the devil is this statement made for? Torkelson et al not only discerned and reported an increased liver weight in 1961 but also recommended lowering of acceptable exposure for workers. Also, are the authors suggesting that all compounds shown to increase liver weight will lead to vinyl chloride type syndrome?

Page 141, line 3352 - Typographical errors.

Page 145, lines 3475 and 3483 - Typographical errors.

Page 148, lines 3601-3602 - This is an unwarranted inclusion. How can a factual scientific document include concepts that defy physical-chemical reality as well as amply biological data refuting the claim that vinyl chloride accumulates in fatty tissue?

Page 149, line 3618 - See Table. Evidently the authors did not read the article they cite.

Page 154, lines 3788-3789 - An astute observation which should be tempered with the fact that almost routinely the liver is found to contain the greatest concentration of radioactivity regardless of the compound being studied.

Page 155, line 3804 - Typographical error.

Page 156, line 3828 - Although I believe I was one of the first to point out the possibility of chloroethylene oxide being the active metabolite of vinyl chloride, I believe it should be called speculative. Indeed some data suggest it is a red herring.

Page 160, lines 3903-3910 - This is stated poorly. Indeed, its beyond comprehension.

Page 161, line 3940 - Olive oil reduces GSH levels!

Page 163, line 3980 - It should be stated that marked maternal toxicity occurred in mice exposed to 500 ppm.

Page 165, line 4030 - Authors conclusions state that vinyl chloride alone was not consistently embryotoxic in the three species studied. Authors consider skeletal anomalies observed to be minor variations and still do. What evidence does NIOSH have to the contrary? Do they profess that these deviations be deemed teratogenic for all compounds? If so, this should be published for scientific assessment.

Page 165, line 4033 - Authors do not consider dilated ureters to be a minor soft tissue variation, but indeed a malformation. However, this particular malformation has been observed in control fetuses in this species (4.4% of litters). Thus, the authors do not feel that the occurrence of only dilated ureters in fetuses of Sprague-Dawley rats constitute a teratogenic effect. Such skeletal modifications as delayed ossification of bones, vertebral spurs, and unfused bones are interpreted to be minor variations as stated in the test. If NIOSH has a different interpretation, it should be published for critical review.

Page 165, lines 4035-4037 - The authors of the criteria document have misrepresented the work of the authors of the paper cited. The authors of the paper cited presented all anomalies which occurred. Their conclusion was that "vinyl chloride alone did not cause significant embryonal or fetal toxicity and was not teratogenic in any of the species at the concentrations tested".

I must add that the conclusions of the authors are based on long experience in teratology, as well as a working knowledge. I object to less expert people reinterpreting out of context the data. If NIOSH possesses some new concepts regarding interpretation of teratology studies, they should publish them for review by the experts as others have done.

Page 169, line 4117 - What is a stripe of midzonal necrosis?

Page 172, line 4171 - In this line vinyl chloride is mistakenly used for vinylidene chloride. This points out the hazard of preparing criteria documents for groups of compounds. It also is evidence of the selective bias used to develop the section on vinylidene chloride. Is it not?

Page 173, line 4199 - Midwest Research Institute tried to expose rats and mice to 50 ppm VDC, but because of miscalculation wound up exposing them to 55 ppm. (Lee, Oral Report at NIEHS Conference, Bethesda, MD., May 2, 1977.)

Page 173, line 4205 - Death of mice after 13 days exposure to 55 ppm suggests this exposure level is above a "maximum tolerated dose." The observance of liver and kidney injury is consistent with known toxicity for mice. Maltoni has reported kidney toxicity in mice and we have seen kidney and liver toxicity in mice in a recent unpublished study.

Page 174, line 4217 - The report says there were no mammary tumors in mice exposed to VDC. The report at the International Congress of Toxicology says there were mammary tumors in mice. Which is correct?

Page 174, lines 4219-4220 - This report says 55 ppm VDC caused hemangiosarcoma in livers of rats. That is not true. This observation was not made in earlier reports and it was confirmed with MWRI by phone with Dr. J. Winston) that no hemangiosarcomas were seen in rats.

The following table of data on mice was presented by Dr. Lee at the NIEHS Conference referred to above.

	50 ppm <u>vinyl chloride</u>	55 ppm <u>vinylidene chloride</u>
Acute deaths	none	2
Chronic deaths	2	3
Tumors of lung	12	7
Mammary tumors	9+2	none
Hemangiosarcomas of liver	3	3

The similarities in chronic death, lung and liver tumors for the two materials are striking and very different from Maltoni's results of VDC exposure of mice. Maltoni could not keep mice alive at 50 ppm VDC.

Maltoni, Viola, and Dow have all reported on studies of VDC in rats, both by inhalation and oral administration, and have not seen an increased evidence of tumors. All of this work has been made public in interim (Maltoni and Dow) or final (Viola) reports but is not included in the Criteria Document. They should be included. NIOSH has these reports why have they been excluded?

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The differences in response to VDC of mice and possibly rats at MWRI and elsewhere and the similarities in the response of mice to VC and VDC at MWRI cause one to wonder about the composition of air in the VDC chamber. Could significant amounts of VC have been present? In any case, there are uncertainties and discrepancies in reports of the MWRI work that must be removed if the work is to be relied upon for public policy setting.

Page 175, lines 4236 and 4237 - I concur totally; also true for other references cited throughout document. To be consistent, shouldn't such an evaluation by NIOSH of various works be stated uniformly when applicable?

Page 190, line 4619 - Typographical error.

Page 195, lines 4792 through 4794 - Data are given which are not consistent with those in Table from which they were gleaned, page 196.

Page 196, line 4850 - Binding

Page 200, line 4920 - If origin of authors is to be identified, do it consistently. I perceive identifying an industrial source as a possible attempt to discredit the work, because of source rather than quality.

Page 202, line 4967 - This study cannot be deemed long-term. .

Page 203, line 4984 - Designate the type of changes occurring in Kupffer cells. This is important! Also true on numerous occasions in next few pages.

Page 214, lines 5237-5239 and lines 5244-5246 - Note that vinyl fluoride and vinylidene fluoride have an effect on the kidney. Also note that vinylidene fluoride is a reasonably potent kidney toxin. Since these compounds have similar toxic manifestations as their chlorinated analogs, since they cause mutations in yeast, and since they are equally likely to be metabolized through an epoxide, why has NIOSH not judged them similarly to vinylidene chloride? Be consistent in use of judgmental information. Either deem these "Cancer Suspect Agents" or change the labeling for vinylidene chloride! Later, on this page line 5250 through 5252, kidney damage is attributed to fluoride ion. This, I believe, to be unwarranted supposition.

Page 215 - Since vinyl fluoride is mutagenic, it should be treated as vinylidene chloride has been for displaying such activity.

Page 216, line 5296 - Typographical error.

Page 218, lines 5336 and 5337 - Since vinylidene fluoride is mutagenic and possesses a potential like that of vinylidene chloride to cause toxicity, it should be treated similarly.

Page 226, line 5516 - Unless the data on page 214 are negated, this statment is untrue.

Page 227, lines 5530 and 5531 - I do not concur with this statement.

Page 227, line 5533 - Unless I am mistaken, neither 5 nor 25 ppm vinylidene chloride have been reported to cause liver and kidney damage. A mild-reversible-hepatic alteration has been cited in an interim report by Dow on rats in a lifetime study and Maltoni has reported kidney injury in mice exposed to 25 ppm. However, neither of these studies have been covered in the criteria document. What data were used to support the cited statement?

Page 227, lines 5536 and 5537 - Vinyl fluoride and vinylidene fluoride also cause kidney damage.

Page 228, lines 5562-5564 - This is not true! We know the levels were at least consistent with the TLV's of the time and orders of magnitude higher than those now being incurred.

Page 229, lines 5572 and 5573 - Statement is not true!

Page 229, lines 5574-5576 - Two other reports on studies in rats show negative effects in rats and hemangiosarcomas were not seen in rats in the study cited!

Page 229, last line - I do not understand how NIOSH has concluded that there exists dose-response relationships for cytogenetic studies in humans but not cancer studies. Explain please!

Page 230, lines 5587-5592 - All compounds in the document in accordance with NIOSH judgment are potentially carcinogenic and should be treated and handled similarly.

Page 231, lines 5615-5621 - These are not appropriate statements since activation is required for the carcinogenicity of vinyl chloride and this is a saturable process. Direct reactivity cannot be related to toxicity.

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Page 232, lines 5634-5636 - Also true for vinyl bromide, vinyl fluoride and vinylidene fluoride.

Page 232, line 5638 - 2-Chloroethylene oxide has not been demonstrated definitively and very likely constitutes a convenient fiction.

Page 233, line 5645 - This statement implies direct alkylation activity which does not seem to occur to a significant degree.

Page 278, line 7006 - Add to following between "industries" and "where" ". . . universities, government or any other organization. . . ."

Page 297, line 7021 - To be consistent with judgmental policies being used by NIOSH add "Automated systems should be developed to eliminate need for workers in vinyl chloride industries and hence their exposure".

Page 283, lines 7107-7108 - For what purpose? This is tokenism, busy work with no purpose.

Page 283, lines 7116 and 7117 - Please provide data attesting to need for this.

Page 284, lines 7132-7143 - NIOSH must assure that all recommended precautions do not constitute a hazard greater than that against which they desire to protect. Therefore, I request such data.

Page 286, lines 7186-7187 - Is ingestion worse than inhalation or skin absorption? What is basis of this recommendation other than that it is traditional anyway?

Pages 288, 289, and 290 - Same practices recommended for vinyl chloride and vinylidene chloride should be recommended for vinyl bromide, vinyl fluoride, vinylidene fluoride, and vinyl acetate as well.

Page 300, lines 7484 and 7485 - So what? Can these be attributed to exposure?

Page 304 - This is a hypothetical approach which is scientifically acceptable as an initial hypothesis. To assess the boundaries of this hypothesis, let's determine what Maltoni's data predicted the incidence of cancer should be in workers:

Rats exposed to 500 ppm for 4 hrs:

- 1) 500 ppm = 1.28 mg/l air.
- 2) Rats breathe $\approx$ 1 liter air/10 min or 6 l/hr.
- 3) Hence rats exposed to 500 ppm for 4 hrs obtain
 $(6)(4)(1.28) = 30.72$ mg or $\approx$ 76.8 mg/kg.
- 4) Total dose received by Maltoni's rats
 $76.8 \text{ mg/kg/day} \times 5 \text{ days/week} \times 52 \text{ wks} \approx 20 \text{ g/kg}.$

Man exposed to 500 ppm:

- 1) 500 ppm = 1.28 gm/M³
- 2) Man breathes 6 to 10 M³/8 hr day or
7.68 gm/day or for a 70 kg man
109 mg/kg/day.
- 3) Since men were in the past exposed to 500 ppm for
as much as 30 years their total dose would have been:

 $109 \text{ mg/kg/day} (5 \text{ days/week}) 52 \text{ wks/yr} \times 30 \text{ yr}.$
 $\approx 850 \text{ grams/kg}$ or approximately 40 times the dose
inducing a 12% incidence of angiosarcoma in rats.

Even if the exposures were as little as 100 ppm, the dose received per kg would have been 8 times greater than the dose producing 12% angiosarcoma in rats.

In deriving a recommended standard, doesn't it seem a little inconsistent to use a hypothesis which predicts an incidence of angiosarcoma in man far greater than that observed. The incidence in men exposed to vinyl chloride has been estimated to be 0.02 to 0.04%. Hence even using a 12% predicted incidence over predicts the incidence by 300-fold. Assuming a linear extrapolation, the overprediction ranges from 2400 to 12,000. I realize that I have not included vacation and such but the ridiculous overprediction cannot be resolved by little adjustments. I do not know how much dilution there is in the cited incidence of angiosarcoma of 0.02 to 0.04% in vinyl chloride workers by inclusion of some folks exposed to smaller amounts, but even if diluted by an order of magnitude the conclusion must be that the hypothesis used by NIOSH is not valid.

I strongly urge that NIOSH go back to the drawing board and develop a somewhat more rational hypothesis that can conform better to the boundaries of our very valuable, even though unfortunate, human experience.

Page 304, lines 7576-7579 - This statement is not true unless NIOSH wants to ignore excision and postreplication repair.

Page 305, line 7583 - Vinyl chloride has little capacity for intrinsic alkylation; it must be activated.

Page 305, lines 7597-7598 - This is not true!

Page 306, lines 7602-7605 - See comment above, page 304.

Page 306, line 7617 - As indicated previously, vinyl bromide, vinyl fluoride and vinylidene fluoride are also mutagenic. To be consistent with the judgmental criteria used by NIOSH to deem vinylidene chloride a carcinogen, deem these thusly. Also, a case can be made for vinyl acetate which is almost equally as strong.

VINYL COMPOUNDS CRITERIA DOCUMENT
ANSWERS TO EXTERNAL REVIEW QUESTIONS

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September 22, 1977

VINYL COMPOUNDS CRITERIA DOCUMENT
ANSWERS TO EXTERNAL REVIEW QUESTIONS

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1. Critical biological effect will vary with exposure level. For instance, the critical biological effect for vinylidene chloride administered to rats in the range of 25-75 ppm levels is mild reversible liver changes. Without reference to specific exposure levels, there can be no meaningful answer to this question.
2. Vinyl Chloride:
 - a. I do not believe the recommended standard is justified by the available data nor supported by reported human health effects. The recommended standard is purely judgmental. Furthermore, there has been no data presented to support the statement that compliance with the recommended standard can be achieved by existing technology.
 - b. No, I do not agree with the recommended standard. The new standard which NIOSH is proposing appears to be unjustifiably restrictive since no effort has been made to definitively assess the added benefit which might be derived through its implementation. There are no data to indicate the current OSHA standard is inadequate.
 - c. I believe the available data supports an 8-hour 10 ppm TWA standard for vinyl chloride.

Vinylidene Chloride:

- a. Same as above (2-a) for vinyl chloride.
- b. No. The draft document treats vinylidene chloride as a human carcinogen. The data do not substantiate such a conclusion.
- c. The data again support a 10 ppm TWA standard for vinylidene chloride.

Other Vinyl Compounds:

- a. I believe the data presented shows that vinyl bromide, vinyl fluoride and vinylidene fluoride are no less of a hazard than vinyl chloride or vinylidene chloride. Based on supporting arguments presented in the document, particularly chemical/biochemical reactivity which places vinyl bromide at the top of the biochemical reactivity list of the vinyl compounds, the recommended standard for vinyl bromide is inconsistent with those recommended for vinyl chloride and vinylidene chloride. Furthermore, the mutagenic activity in microorganisms indicates that for VCM and VDC, reactive electrophiles are likely produced. If such information is going to be used by NIOSH to justify restrictions

for VCM and VDC, these restrictions should be used consistently for all chemicals in the document. In addition to the foregoing, similar arguments can justify similar restrictions for vinyl acetate and cis/trans 1,2-dichloroethylene as well.

- b. No.
 - c. For consistency in interpreting the data, the standards for vinyl bromide, vinyl fluoride and vinylidene fluoride should also be a 10 ppm TWA.
3. No. Interpretation of the data is judgmental, inconsistent, and, in some cases, purely speculative. No data is presented to show that sufficient technology or analytical techniques exist to permit reliable compliance with the recommended standard. Recommended standards for several of the vinyl compounds are unsubstantiated by biological or toxicological data, and are arrived at by mere projections based on property and reactivity data.

The most glaring example of purely judgmental decision-making by NIOSH in the document is the recommended standard for vinyl chloride. NIOSH has apparently selected data to fit their conclusion and has disregarded those studies which do not support their position, primarily the published reports of human experience studies. In recommending a standard for human exposure, it is ludicrous to give more weight to data collected from small numbers of animals than to the human data available on vinyl chloride, involving far more "real-life" subjects.

There can be no doubt that exposure to high concentrations of vinyl chloride can cause serious injury or death. However, the document omits or dismisses well-documented reports which demonstrate no effect in employees exposed for long periods of time at levels well above the current OSHA standard of 1 ppm.

The following are published reports by The Dow Chemical Company and others which NIOSH has failed to adequately consider despite the fact that they demonstrate no effect at levels of human exposure which exceed the existing OSHA standard of 1 ppm. Copies of these papers are appended.

- I. The Correlation of Clinical and Environmental Measurements for Workers Exposed to Vinyl Chloride, C. G. Kramer, M. D. and J. E. Mutchler, Industrial Hygiene Association Journal, Volume 33, Pages 19-30, 1972.

This report on men exposed as long as 25 years demonstrates a close response relationship of their clinical chemical parameters with their career time-weighted-average exposure to vinyl chloride.

- II. Vinyl Chloride Exposure in a Controlled Industrial Environment. A Long Term Mortality Experience in 594 Employees, M. G. Ott, R. R. Langner and B. B. Holder, M. D., Archives of Environmental Health, Volume 31, pages 333-339, 1975.

Employees were grouped into four categories according to the highest level of vinyl chloride exposure experienced for at least one month.

The authors concluded that:

"No adverse malignancy effects were demonstrated in the lower-exposure categories. TWA's ranged from approximately 10 ppm in the low-exposure category to about 100 ppm in the intermediate category. It should be cautioned that the number of individuals exposed over a relatively long period of time, 10+ years for example, in these exposure groupings was small as evident from Table 8. Thus, it was not possible to examine effects due to differences in exposure duration among the lower exposure groups.

An increase in deaths due to malignant neoplasms was noted among employees in the highest exposure category. The individuals in this category experienced repeated excursions of several thousand parts per million vinyl chloride or were exposed to TWA concentrations of 200+ ppm over time spans from one month to 18 years. These same individuals also worked for periods of time at varying lower levels of exposure."

- III. Mortality Study of Workers in the Manufacture of Vinyl Chloride and its Polymers, I. R. Tabershaw, M. D. and W. R. Gaffey, JOURNAL OF OCCUPATIONAL MEDICINE, Vol. 16, No. 8, Pages 509-518, 1974.

This early publication is currently being updated by the companies supporting the research on vinyl chloride being coordinated by the Manufacturing Chemists Association. The conclusions of the 1974 report have not changed. Angiosarcoma of the liver was found only in the most highly exposed group. The same is true for other types of cancer which though they were not statistically increased beyond the control, were found to be higher only in the most highly exposed group. The lower exposure group which had exposure well in excess of 1 ppm based on description of the old procedures, was found to have less tumors than the higher group or the controls.

- IV. Mortality Experience of Workers Exposed to Vinyl Chloride Monomer in the Manufacture of Polyvinyl Chloride in Great Britain, A. J. Fox and P. F. Collier, British Journal of Industrial Medicine, Volume 34, Pages 1-10, 1977.

This study is similar to the mortality study in the U.S. reported in III. above. Two cases of angiosarcoma of the liver were found, both in the most highly exposed group. This group had exposure greater than 200 ppm and probably greater than 500-1000 ppm. The lower exposure group who had exposures of 25 ppm or less had no angiosarcoma cases. Other cancers were not increased in either the high or low exposure groups.

- V. Vinyl Chloride Cytogenetics, D. J. Picciano, R. E. Flake, M. D., P. C. Gay, M. D. and D. J. Kilian, M. D., JOURNAL OF OCCUPATIONAL MEDICINE, Vol. 19, pages 517-520, 1977.

Previous reports of cytogenetic changes in highly exposed polyvinyl chloride production workers prompted this study on a population of 209 men who had a relatively low exposure for up to 28 years. The average duration of exposure was 48.3 months.

The authors reported:

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.

Since these reports consistently show no observed effect of vinyl chloride exposure at levels well in excess of 1 ppm, it is apparent that NIOSH has chosen to ignore them in the development of the recommended standard. Proper consideration of these studies leads to the conclusion that 1 ppm is probably too restrictive a standard already, and that any lower value would demand a waste of resources.

4. In my opinion, the differing hazards that are associated with each of the vinyl compounds warrants treatment of each compound in a separate document. Conversely, if a document is to be all inclusive, why not include ethylene, trichloroethylene, perchloroethylene, and acrylonitrile?
5. Yes. The scope of the document is too broad. It includes one known carcinogen, which prejudices the thinking regarding the unknown health hazards of the other compounds in the document. Lacking substantiated toxicological data, the document relies on structural similarities, physical property and biochemical reactivity data to assess the possible hazards of the other vinyl compounds in the document. This guilt by association inference should be eliminated or mitigated.

Not only has an inclusion of these vinyl compounds in one document allowed unjustifiable extension of data on one to another, but, even more seriously, this extension has not been made uniformly.

(See also answers to 3 and 4 above).

6. Yes, only because it is more easily detoxified. However, if one professes the one molecule theory of carcinogenicity, mediated by reaction of an electrophile with DNA, then vinyl acetate must be considered a carcinogen. I accept the possibility of such a mechanism, although the probability of such is essentially nil.
7. In my opinion, relationships between structures and biological activities of the vinyl compounds are overly addressed in this document. For example, the known carcinogenicity of vinyl chloride is improperly extended to vinylidene chloride based on similar structural and metabolic data, where only questionable animal and no human carcinogenic data exist on vinylidene chloride. I believe that disproportionate importance has been placed on structural/biological relationships in developing the recommended standards. In doing so, there is certainly an inconsistency in applying these relationships to the recommended standards. For example, vinyl bromide, although ranked highest in biological reactivity, has a much higher recommended standard than either vinyl chloride or vinylidene chloride.

As indicated before, consistent adherence to structural similarity should result in condemnation of vinyl bromide, vinyl fluoride and vinylidene fluoride.

8. The data do support common mechanisms mediated by reaction of an electrophile with DNA. However, competing forms of toxicity, as well as different efficiencies for detoxification, result in different manifestations of toxicity.
9. At first it must be pointed out that there is a difference between toxicity and hazard since the latter implies exposure to amounts sufficient to cause toxicity. In this regard, I have already expressed that the restrictive levels recommended by NIOSH for vinyl chloride and vinylidene chloride are far lower than those required to constitute a measurable hazard.
10. a. No.
b. Frequency of the medical exams should not be mandated on an annual or other required schedule. Frequency should be left to the professional judgment of the physician based on such factors as employee age, work history, exposure levels, previous alth history, etc.

The frequency of medical exams could be reduced if recommended exposure levels are met and the health of the individual employee and/or the surveyed group can be shown to be similar to a non-exposed group over a period of years.

Since the frequency of physical examinations for preventative health care has been assessed for efficiency, NIOSH should refer to such literature to develop intelligently rather than by supposition the frequency to be used.

As defined for vinyl and vinylidene chloride, medical exams would be required for all employees "occupationally exposed", which, in essence, means any exposure. This seems unnecessarily stringent and would, in contrast to the current OSHA standard for VCM, apply to fabricators and processors of PVC.

The point that "medical attention shall be provided promptly to any individual suspected of being overexposed to vinyl compounds" presents serious practical problems. With the low ceiling concentrations and TWA's recommended in the document, and the word "suspected" in the requirement, this will, in effect, require that "medical attention" (not defined in the document) be provided and administered in the plant on a nearly continuous basis.

Is NIOSH proposing that medical exams and clinical workup such as that cited in the document be conducted on an individual who, for example, has had a 15-minute exposure to 10 ppm vinyl chloride? If this is the case, has NIOSH considered the health hazards of such medical workup? Should NIOSH not always consider the hazards inherent to their recommendations versus those which may be incurred by exposure to the compounds they wish to regulate?

- c. Why has NIOSH singled out the heart and nervous systems as targets for the vinyl compounds with respect to those concentrations which may occur in the work environment, as required by the preplacement and periodic medical exams? The clinical test measurements are not specific and elevations are not necessarily an indication of overexposure.
 - d. None. Indeed those recommended to be instituted when an over-exposure occurs are of no value.
11. a. Many of the work practices seem excessive and nonproductive. Adherence to the proposed exposure limits is strictly based on engineering controls, yet no information is presented to demonstrate that such control technology exists. In addition to strict reliance on engineering controls, respirator use is extremely limited. There is no allowance for jobs such as filter changing. If engineering controls cannot meet the exposure standard and respirators are not allowed for compliance in any but the specified situations, what alternative would an operation/process/plant have but to shutdown?

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I request that NIOSH furnish to this external review panel the data and information on which it has based its judgment that sufficient technology exists, including process technology and engineering controls, to permit compliance with the recommended standards. Furthermore, this information should be submitted to a panel of experts representing process engineering, manufacturing and industrial hygiene areas of expertise, which would be much better qualified than this external review panel to judge the feasibility and applicability of such information to compliance with the recommended standard.

In order to protect all employees with exposure to the vinyl compounds, recommended work practices should be extended not only to industrial employees but to those employed in universities, the government, independent laboratories, etc.

Whatever work practices are recommended, NIOSH should assume the responsibility of showing that such practices are not going to constitute a hazard greater than those they propose to eliminate. For example, a work practice requirement of wearing a rubber "slicker" suit for extended periods in a hot, humid area such as the Gulf Coast may pose the more serious hazard of heat exhaustion to the employee.

The definition of a Regulated Area is so broad as to include, in the case of vinyl chloride and vinylidene chloride, any place in the plant where these compounds are present (definition of occupational exposure for VCM and VDC). Besides inclusion of VCM/PVC plant areas now permitted to be deregulated under the current OSHA standard for VCM, this definition will extend to the downstream fabrication and processing of polymers. Is this warranted by the data?

The excessive recordkeeping, monitoring, medical surveillance, etc. required for employees who enter and work in regulated areas greatly increases the resources needed to comply with the recommended standard over that of the current OSHA standard for VCM. Doesn't this demand an unwarranted waste of resources?

Prior to making any recommendations for recordkeeping, NIOSH should make a critical analysis of which records are needed and how they are to be used. Has NIOSH done this, and if so, what are the results of the analysis?

The requirements for showers and clothing changes are excessive. How is one to enforce these and the requirements for washing hands prior to eating, smoking, using toilet facilities? Does NIOSH have data to justify these requirements? At the low recommended levels and in consideration of the physical properties of these materials, is there reason to expect hazardous residual levels of these materials on the persons of exposed employees?

Recordkeeping on all persons entering vinyl chloride and vinylidene chloride areas is required - this applies a carcinogen standard to vinylidene chloride. Why? Why isn't this requirement applied to the other vinyls?

Is not 15 minutes for washing skin contacted with liquid vinyl chloride too long? What is vinyl chloride contact? (EPA standard says that 10% VCM is vinyl chloride).

- b. Essentially very little of this document addresses itself to non-toxicological hazards, such as flammability. It should be mentioned that vinyl chloride and vinylidene chloride containers should also be kept from heat, sparks, and flame.

- c. No

12. Eye and face protection - satisfactory.

Respiratory protection - the situations where compliance with the recommended standard by the use of respirators is permitted are too restrictive. In the absence of sufficient engineering controls, certain operations could not be performed if respirators were not allowed for compliance.

At the recommended low levels for vinyl chloride and vinylidene chloride, cartridge or canister-type respirators could be allowed.

- 13. a. First of all, as for the work practices section of the document, I believe that the sampling and analytical procedures recommended by NIOSH for the vinyl compounds should be reviewed by a group of experts knowledgeable in this field, and not by this external review panel.

The objective of the monitoring program should be to insure protection of the worker by checking whether exposure levels are maintained at acceptable concentrations. The proposed sampling and analytical techniques require exposure and development of data over a long period of time. They are not suitable for continuous or short-term multiple location analysis and alarming to inform the employee of the levels to which he is being exposed so that corrective action can be taken if necessary.

There seems to be serious question as to whether the proposed sampling and analytical techniques would be workable in production plant units. Has NIOSH considered this point? If so, the supporting data should be provided. Has NIOSH addressed the practical questions of having to sample each employee for 15 minutes each time he performs a task involving high potential for exposure to the vinyl compounds, and doing this once a week, up to three shifts per day? The added requirement of performing this sampling and analysis each time any condition

in the plant changes places an unwarranted burden on the monitoring program.

- b. Has NIOSH validated the recommended sampling and analytical techniques? If so, this information should be provided. There is no supporting information presented in the document that addresses and validates the sensitivity and variability to be expected in using the recommended methods. What about recovery of the sample from the charcoal tubes when measuring the low recommended concentrations? Are these compounds irreversibly absorbed at low concentrations?
 - c. The solvent flush technique recommended does not enhance reproducibility. To use the recommended technique in the high humidity of the Gulf Coast area, a sample time of 50 minutes would be indicated, which would further reduce sensitivity.
 - d. Does NIOSH have data on possible interferences with these methods? At the recommended low levels of the standard, low concentrations of interferences that could be present due to neighboring plants, impurities, etc., could become significant. Has the variation in interferences from column to column been considered by NIOSH?
 - e. Variations in the recommended method may be appropriate, such as larger charcoal tubes, greater flow rates, different types of charcoal, different columns, using more desorption solvent, etc. to achieve reliable sensitivity. The question of a better method should also be addressed from the standpoint of the method which best protects the employee. In this case, a method which is suitable for continuous measurement of exposure levels is preferable. Has NIOSH considered this?
14. If the data on vinylidene chloride are adequate to justify labeling it a cancer-suspect agent, than why has NIOSH not used similar data on the other vinyl compounds to cause them to also be labeled cancer-suspect agents?
- Does labeling and posting of signs in English and the predominant language of non-English reading employees apply to every case or only certain geographic areas? This is impractical in many instances.
15. No additional requirements. If NIOSH has reached the conclusion that vinyl chloride and vinylidene chloride are not teratogenic and do not cause reproductive effects, why should any reported adverse effects even be mentioned to employees? Counseling of employees is required under the medical section - is this "overkill" by again requiring informing of employees of possible adverse health effects?

16. a. The risks are overstated in the document. Inferences are continually made that vinyl chloride and vinylidene chloride may cause cancer, mutations, or terata in humans when the data shows that at currently practiced exposure levels, the risks are negligible, let alone at the lower recommended levels.

For vinyl chloride, human data at low exposure levels, even well in excess of the current 1 ppm TWA, has virtually been ignored. This data shows no adverse risk of cancer, mutations, or terata. Proper consideration of these studies leads to the conclusion that 1 ppm is already too restrictive as a standard and that any lower value is a waste of resources.

For vinylidene-chloride, there is no substantiated evidence to conclude that VDC is a human carcinogen, mutagen, or teratogen.

- b. A paper by Brian MacMahon, M.D., of the Harvard School of Public Health, titled "Vinyl Chloride and Human Reproduction", is appended. This is a critique by Dr. MacMahon of the existing literature on observations relating vinyl chloride exposure to risk of fetal defect or death. Dr. MacMahon reaches the conclusion that "the literature to date contains no credible evidence that vinyl chloride has actually caused mutations, fetal anomalies or fetal death in humans". This paper will be submitted to the EPA in the near future by the Society of the Plastics Industry.

Why has NIOSH not included for consideration the data presented by Dr. L. W. Rampy, of The Dow Chemical Company, on the interim results of chronic toxicity studies of vinylidene chloride in rats at the NIOSH meeting on vinylidene chloride, April 22, 1977, in Rockville, Maryland. This data were also given in a written form to NIOSH, and their exclusion from the draft document is questioned.

Further reports of the MCA-sponsored work on vinylidene chloride conducted at Dow also were not considered by NIOSH in the draft document, including a 3-year reproductive study on rats and a cytogenetic study on rat bone marrow cells.

17. Cytogenetic studies on vinyl chloride workers and birth defect studies on vinyl chloride worker families and communities with VCM/PVC plants have allowed no firm conclusions on genetic effects of vinyl chloride. See the appended critique by Dr. Brian MacMahon referred to in 16-b above.

The draft document largely speculates on possible genetic effects of vinyl chloride and vinylidene chloride based on mutagenic studies, limited teratology data on animals, and the inconclusive studies on humans. Studies of human experience at low dose levels shows no

genetic effects of vinyl chloride. NIOSH has concluded in the document that vinyl chloride and vinylidene chloride are not teratogenic and do not cause reproductive effects. Why then, is this point being pressed?

18. The recommended approach to regulating mixtures of the vinyl compounds is unworkable from a practical standpoint. How has this conclusion been achieved? How is it justified? Has the analytical method been validated for mixtures of the vinyl compounds, particularly when total exposure concentration of the vinyls would be required to meet the vinyl chloride ceiling of 0.1 mg/m³?

Does the recommended approach assume that all vinyl compounds have the same hazards? If so, why not have one standard in the first place?

One study cited (Jaeger, et.al., lines 4067-4077) states that high concentrations of vinyl chloride protected the specimen from any adverse effects of vinylidene chloride. If this is so, is the converse true?

19. A copy of a recently completed paper, "Resolution of Dose-Response Toxicity Data for Chemicals Requiring Activation: Example - Vinyl Chloride", by P. J. Gehring, P. G. Watanabe, and C. N. Park, is attached. This paper offers a reasonable explanation of the carcinogenic dose-response data on vinyl chloride, and permits an extrapolation of the data to humans in order to predict carcinogenic incidence. This new approach is suggested for consideration by NIOSH.

The remaining studies on vinylidene chloride being conducted at Dow under the auspices of the MCA will be reported in the near future. Since much of the data from these studies will represent the first published reports of long-term exposure to vinylidene chloride, it is suggested that NIOSH take them into consideration before making any final recommendation for a vinylidene chloride standard.