DOW CHEMICAL U.S.A.

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MIDLAND, MICHIGAN 48640

October 5, 1977

Mr. Vernon E. Rose, Director
Division of Criteria Documentation
and Standards Development
National Institute for Occupational
Safety and Health
5600 Fishers Lane
Park Building, Room 3-18
Rockville, Maryland 20857

REQUEST FOR INFORMATION - VINYLS (F.R., VOLUME 42, NO. 131, FRIDAY, JULY 8, 1977

Dear Mr. Rose:

In response to your Federal Register request, we would like to call your attention to the extensive information on vinyl chloride and vinylidene chloride which The Dow Chemical Company has supplied to NIOSH over the past one and one-half years, including:

1. A letter dated April 2, 1976, with several enclosures, from James W. Conder to the Acting Director, Division of Criteria Documentation and Standards Development, with information on vinylidene chloride. This was sent in response to a January 5, 1976, Federal Register notice requesting information relevant to the establishment of a safe and healthful occupational environment for vinylidene chloride.

2. A letter dated August 27, 1976, from our Mr. E. R. Smith to the Director, Division of Criteria Documentation and Standards Development, with enclosures, sent in response to the Federal Register notice of July 29, 1976, requesting new information or data pertinent to an update of a vinyl chloride criteria document.

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3. Two letters sent in March, 1977, one from our John M. Lanham, M.D., and one from our Mr. J. P. Strasser, in response to a February 25, 1977, letter from John F. Finklea, M.D., to H. C. Scharnweber, M.D., of Dow, requesting information and answers to several questions concerning occupational exposure to vinylidene chloride.

4. Presentations by personnel of Dow's Toxicology Research Laboratory at an April 22, 1977, NIOSH meeting on vinylidene chloride in Rockville, Maryland. These presentations concerned the MCA-sponsored studies on vinylidene chloride conducted at Dow.

5. Considerable information presented and transmitted to NIOSH and to SRI personnel during a June 14, 1977, plant visit to Dow's Oyster Creek Division Vinyl Chloride Unit and the vinylidene chloride plant in our Texas Division, both at Freeport, Texas. A copy of the transmittal letter which accompanied this information is enclosed.

Enclosed are two new reports on vinyl chloride which should be of interest to NIOSH. The first is a recently completed paper by P. J. Gehring, P. G. Watanabe, and C. N. Park of The Dow Chemical Company, entitled, "Resolution of Dose-Response Toxicity Data for Chemicals Requiring Activation: Example - Vinyl Chloride". This paper presents a new, sensible, and logical approach for assessing the potential carcinogenicity of a material such as vinyl chloride, and permits a reasonable extrapolation of the animal data on vinyl chloride to humans to predict carcinogenic incidence.

The second paper, "Vinyl Chloride and Human Reproduction", by Brian MacMahon, M.D., of The Harvard School of Public Health, is a critique 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 deaths in humans". This paper will be submitted to the EPA in the near future by the Society of the Plastics Industry.

NIOSH should also be aware that the remaining MCA-sponsored studies on vinylidene chloride being conducted at Dow's Toxicology Research Lab will be reported in the near future. The data from these studies should be considered by NIOSH before making any recommendation for an occupational standard for vinylidene chloride, since they will represent the first published reports of long-term exposure to vinylidene chloride.

We strongly believe that based on dissimilarities in toxicity and health hazards, vinyl chloride and vinylidene chloride should differ not only in exposure limits, but also monitoring requirements, work practices, medical surveillance and other aspects of a standard.

We sincerely hope that the information which we have provided to NIOSH in the past, as well as the enclosed papers and any future reports we may provide, will be helpful in arriving at reasonable occupational health standards for vinyl chloride and vinylidene chloride. Please contact us if we can be of further assistance.

Very truly yours,

James W Conder

James W. Conder
Health and Environmental Research

bms

Encs.

bcc: P. J. Gehring, 1803
F. D. Hoerger, 2030
C. C. Kazmierski, 2020
C. F. MacGowen, Washington, D. C.
E. R. Smith, 2020
J. P. Strasser, 1603

DOW CHEMICAL U.S.A.

BENNETT BUILDING
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June 14, 1977

Dr. Alfred Milbert
Division of Criteria Documentation
and Standards Development
National Institute for Occupational
Safety and Health
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Milbert:

Re: VINYLS CRITERIA DOCUMENT

Attached is a compilation of the presentations made on vinyl and vinylidene chloride during your June 14, 1977, visit to our Oyster Creek Division.

We believe the data and information presented, which is based on over 30 years experience, supports the following recommendations:

Vinyl chloride and vinylidene chloride, though structurally similar, are quite dissimilar in their toxicity and health hazards. Consequently, they should not be covered by a single occupational exposure standard. We strongly believe that separate requirements should apply not only to the permissible exposure limits for the two materials, but also to monitoring, work practices and other sections which make up the framework of a standard. (See enclosures I-B, I-C, II, III-A and III-B)

After more than two years of operating under the current OSHA standard for vinyl chloride, we believe certain requirements are overly restrictive and do not materially contribute to a healthful workplace. These include:

A. Scope - recent technical advances in reducing residual monomer levels in polymers now support exempting packaging, storage, and handling

operations of polymers from the vinyl chloride standard. This includes the exemption of fabricators. (See enclosure I-C)

B. Monitoring - frequency of monitoring requirements are unnecessarily stringent, particularly for a continuous operation such as a monomer plant. Once a baseline has been determined over a period of time, monitoring results would not be expected to change unless some significant change occurs in the process. (See enclosures I-A and II)

C. Regulated Area - the daily roster requirements for regular employees are absolutely unnecessary, since this information is well documented by employment records. (See enclosures I-A and I-C)

D. Methods of Compliance - requirements for updating written plans should be changed from six months to one year. (See enclosure I-C)

E. Medical Surveillance - as in the case of monitoring, once a baseline has been determined on an employee with respect to his exposure levels, medical history, age, etc., the frequency requirement of medical examinations could be flexible. Professional medical judgment should be allowed in the surveillance program. (See enclosure IV)

F. Signs and Labels - requirements for labelling polymers should be dropped, as residual monomer levels in polymers have been drastically reduced since original issuance of the standard. (See enclosure I-C)

G. Reports - the 24-hour reporting requirement should only apply to extreme emergencies, which should then be better defined. (See enclosure I-C)

Because of our unique situation in producing vinyl chloride and vinylidene chloride in close proximity (and their subsequent use as co-polymers), some of our procedures and controls tend to overlap. We would point out, however, that if vinylidene chloride were produced and used in physically separated facilities, the stringent controls required by the OSHA VCM standard would not be warranted for vinylidene chloride, based on dissimilar chronic health hazards. (See enclosures I-B, I-C, III-B)

Dow strongly desires to have one of our technical experts serve on the external review committee for the vinyls criteria document. With our lengthy experience and comprehensive programs involving vinyl chloride and vinylidene chloride, we could provide technical breadth and depth in the areas of manufacturing, engineering, work practices, industrial hygiene and toxicology. We would appreciate your consideration and response on this point.

We sincerely hope that the information presented during your visit and the accompanying compilation will aid in your criteria effort. If we can be of any further assistance, please feel free to contact us.

Very truly yours,

James W. Conder

James W. Conder
Health and Environmental Research

cd

cc: Vernon E. Rose, NIOSH
Richard Thomas, SRI

Enclosures

I. Manufacturing Processes and Work Practices for Vinyl Chloride and Vinylidene Chloride

Presentations include:

--Basic process description
--Work practices/procedures to minimize employee exposure
--Engineering controls
--Safety practices
--Personal protective equipment
--Employee training and education
--Emergency procedures
--Sign posting and labeling
--Monitoring systems

A. Vinyl Chloride - C. C. Bird

B. Vinylidene Chloride - M. B. Tracy

C. Vinylidene/Vinyl (Saran) Polymers - R. L. Dostal

II. Industrial Hygiene Practices for Vinyl and Vinylidene Chloride - R. R. Langer

Including:

--Typical employee exposure levels
--Area monitoring
--Personnel monitoring
--Analytical method

III. Toxicology of Vinyl and Vinylidene Chloride

A. An Assessment of the Toxicology of Vinyl Chloride - T. R. Torkelson

B. Vinylidene Chloride Toxicology - J. M. Norris

IV. Medical Surveillance for Employees Exposed to Vinyl and/or Vinylidene Chloride - P.C. Gay, M.D.

Including:

--Current Surveillance Programs
--Assessment of medical surveillance required by OSHA Standard for vinyl chloride

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RESOLUTION OF DOSE-RESPONSE TOXICITY DATA FOR CHEMICALS REQUIRING METABOLIC ACTIVATION: EXAMPLE - VINYL CHLORIDE

BY: P. J. Gehring, P. G. Watanabe and C. N. Park

July 12, 1977

Toxicology Research Laboratory
Health and Environmental Research
Dow Chemical, U.S.A.
Midland, Michigan 48640

This study was funded by the companies supporting the vinyl chloride projects being administered by the Manufacturing Chemists Association, Washington, D.C.

ABSTRACT

The toxicity of many chemicals results from biotransformation products formed from the chemical rather than to the chemical per se. In such cases, the incremental response may become diminishingly smaller with increasing dose or exposure because activation of the chemical to the toxic form follows apparent Michaelis-Menten rather than apparent first-order kinetics.

To illustrate this concept, rats were exposed to concentrations ranging from 1.4 to 4600 ppm vinyl chloride for 6 hours and the total amount metabolized determined. The amount metabolized followed apparent Michaelis-Menten kinetics. For rats, the logarithmic probability incidence of angiosarcoma versus the amount of vinyl chloride metabolized rather than the exposure concentration of vinyl chloride is linear. Assuming no threshold inspite of evidence to the contrary, extrapolation of the data below the range of doses causing experimentally observable responses predicted an incidence of 0.01% hepatic angiosarcoma in rats exposed to 4.6 ppm vinyl chloride. Theoretical extention of the extrapolation to humans after adjusting for metabolic and body mass differences was undertaken. The theoretical extrapolation for man exposed daily for 8 hours to 1 ppm suggests an incidence of 1.5 per 100,000,000. This theoretical incidence, although a likely

overestimate because of a less than predicted incidence in men exposed to 200 ppm and greater as well as evidence for a threshold in rats, is less than that expected to occur spontaneously. It is concluded that pharmacokinetic parameters must be elucidated before designing toxicological experiments or before interpreting the results therefrom.

INTRODUCTION

There exists a great deal of uncertainty in predicting the potential response of exposure to chemicals at concentrations below those producing an experimentally discernible response. This is particularly true when the response to the chemical in question is oncogenesis. Statistical projections recommended for assessing the risk of exposure to doses of oncogenic chemicals less than those producing an observable response include those based on logarithm probability curves (probit curves), logistic curves or linear curves (one-hit curves), (FDA Advisory Committee on Protocols for Safety Evaluation, 1971). One of the most commonly used statistical projections for risk assessment has been that promoted by Mantel and Bryan (1961) in which a logarithm probability projection with a slope of one is utilized. A flaw innate to all of these methods is that the dose-response information used to make the projection is based on the dose of chemical administered to the animal rather than the quantity of the administered dose giving rise to the response; the latter may either increase or decrease disproportionately as the administered dose is increased.

The use of high doses to reveal the chronic toxicity incurred with exposure to a chemical is a common, scientifically

defensible practice if judgment and scientific rationale is used in designing the experiments and in assessing the resulting data. Such doses overwhelm frequently the enzymatic processes for activation of the chemical to the toxic form or for deactivation of the toxic form to an innocuous form. In this paper, it is demonstrated how the dose-dependent activation of vinyl chloride to an oncogenic product must be considered in resolving the dose-response of rats exposed via inhalation to vinyl chloride.

METHODS

Material.

Vinyl chloride (^{14}C-labeled) was synthesized from (1,2-^{14}C) 1,2-dichloroethane (New England Nuclear, Lot #819-221 and 819-292, 5.0 and 4.8 mCi/mmole, respectively) directly prior to use (Wagner, et al., 1975). Non-labeled VC (Matheson Gas Products) of 99.9% purity was mixed with the ^{14}C-material to obtain the desired specific activity.

Animals.

Male, Sprague-Dawley rats (Spartan Research Laboratory) weighing 200-250 g were used throughout the study. Food and water were provided ad libitum except during the exposure. Exposures were conducted between 9:00 a.m. and 3:00 p.m. (EST). Groups of 3-6 rats were exposed to various concentrations of ^{14}C-VC for 6 hours.

Exposure and Procedure.

The rats were exposed by inhalation under dynamic conditions in a 30 ℓ glass inhalation chamber. The mean analytical concentrations of VC measured by gas chromatography were 1.4±0.3 (SD), 9.3±0.2, 24.7±1.4, 51±2, 109±23, 250±2, 511±11, 1020±13, and 4600±311 ppm. Details of this exposure and the method of analytical determinations have been reported previously (Watanabe, et al., (1976a). Immediately following

the 6-hour exposure to various concentrations of ^{14}C-VC (1.4-4600 ppm) the rats were killed by a blow to the head, and the carcass was analyzed for total radioactivity (Watanabe, et al., 1976b). Since radioactivity found in the carcass was non-volatile, this radioactivity represented the total amount of VC metabolized.

RESULTS

Consistent with the results of previous studies (Watanabe, et al., 1976a and 1976b), the metabolism of VC by rats does not increase proportionately with increasing concentrations of VC being inhaled (Table 1). The nonlinearity of the amount of VC metabolized during 6 hours of exposure to various concentrations of VC appeared to be in accordance with Michaelis-Menten kinetics as described by the equation:

$$v = \frac{V_m S}{K_m + S} \quad . \qquad (1)$$

In this equation, v and V_m, are the velocity and maximum velocity respectively for the biotransformation of VC expressed as μg equivalents VC metabolized per 6 hours. S and K_m are the concentration of VC being inhaled and the Michaelis constant expressed as μg VC/ℓ air, respectively.

To ascertain whether Michaelis-Menten kinetics were applicable, the data in Table 1 were analyzed in accordance with the linear Woolf-Augustinson-Hofstee transformation of the Michaelis-Menten equation (Segel, 1976),

$$v = -K_m \frac{v}{S} + V_m \qquad (2)$$

It can be seen from the plot (Figure 1) that the data appear to lie along a straight line thus verifying, at least visually, the Michaelis-Menten model. V_m and K_m can be estimated by the ordinate intercept and the slope of the line or they can be estimated directly by fitting the nonlinear Michaelis-Menten model. Both procedures yield similar parameter estimates. The estimates derived by fitting the model directly are 8558±1147 (SD) µg VC metabolized and 860±159 (SD) µg VC/ℓ air for V_m and K_m respectively.

Once a means is obtained to calculate the amount of VC metabolized by rats as a function of exposure, it is then possible to relate the untoward effects associated with VC exposure to the amount biotransformed rather than the exposure concentration of VC per se incurred by rats exposed to VC.

Maltoni and Lefemine (1975) reported the incidence of hepatic angiosarcoma in rats exposed to different concentrations of VC, 4 hours/day, 5 days/week for 12 months and subsequently held for observation until death (Table 2). Before attempting to relate these data to the amount of VC biotransformed in accordance with the Michaelis-Menten equation using the previously determined values of V_m and K_m, the value for V_m must be adjusted for the shorter exposure duration used by

Maltoni and Lefemine, 4 hours versus 6 hours. This adjustment is accomplished by multiplying V_m by 4/6. Thus, the amount of VC biotransformed daily by rats exposed to the various concentrations used in the experiment of Maltoni and Lefemine can be calculated from the equation:

$$v = \frac{5706 \left(\frac{\mu g\ VC}{4\ hr}\right) \cdot S\left(\frac{\mu g}{\ell}\right)}{860 \left(\frac{\mu g}{\ell}\right) + S\left(\frac{\mu g}{\ell}\right)} \qquad (3)$$

The resulting values for v are given in Table 2.

Figure 2 depicts a logarithm probability plot (probit plot) of the incidence of hepatic angiosarcoma observed in rats by Maltoni and Lefemine (1975) versus the amount of VC biotransformed for 4 hours of exposure, v, or the exposure concentration, S. The incidence of hepatic angiosarcoma in rats is linear with respect to log v but not log S. The line drawn for log v versus tumor incidence (Figure 2) was determined by using a probit regression analysis program, and the equation relating the incidence of hepatic angiosarcoma to log v was:

$$\text{probit response} = -1.625 + 1.543 \log v \qquad (4)$$

Using the foregoing equation, a projection below the levels of exposure producing an experimentally discernible response has been made (dashed line). Assuming no threshold for the induction of angiosarcoma in rats exposed to VC, the exposure concentration producing one angiosarcoma in 10,000 rats can be calculated. The probit percent representing an incidence of 0.01% is 1.28. Substitution of this value into the equation (4) yields:

$$\text{Log } v = 1.8827$$

$$\text{Antilog } v = 76.33 \text{ µg VC metabolized/4 hours}$$

Using equation 3, the concentration of exposure to VC needed to give this value for v is 11.66 µg/ℓ or 4.6 ppm (95% confidence limits are from .08-22.2 ppm). Hence, exposure of rats to 4.6 ppm VC for 4 hours daily, 5 days/ week for 1 year can be expected to produce one angiosarcoma per 10,000 rats if the dose-response curve remains valid at exposures less than those producing a discernible experimental response.

DISCUSSION

For many chemicals, toxicity may not be a function of exposure to the chemical per se, but rather to a biotransformation product of the chemical. Frequently, production of a toxic metabolite is dependent upon enzymatically mediated reactions which are classically described by Michaelis-Menten kinetics. Since enzymatically mediated reactions are concentration-dependent and saturable, toxicity resulting from exposures to chemicals requiring activation to a toxic form cannot be related directly to the magnitude of exposure or dose. In such a case, it is necessary to determine the amount of the chemical undergoing biotransformation as a function of dose or exposure before a meaningful dose-response relationship can be established.

There is considerable evidence that vinyl chloride requires bioactivation to produce tumors. Metabolic activation is required to induce mutations in bacteria exposed to VC (Bartsch, et al., 1975; Malavielle, et al., 1975; Rannug, et al., 1974). Covalent binding of ^{14}C to hepatic macromolecules in rats (Watanabe, et al., 1977) exposed to ^{14}C-VC also requires bioactivation. Covalent binding of electrophiles to DNA has been associated with tumorigenesis.

For vinyl chloride-induced hepatic angiosarcoma in rats, a logarithmic probability plot (probit plot) of the incidence versus the amount of vinyl chloride metabolized, v, over a range of exposures from 50 to 10,000 ppm VC gives a classical straight line, Figure 2. The dose-response relationship is not a straight line when plotted as a function of the exposure concentration, S. These results support further the conclusion that VC requires biotransformation to an active metabolite for tumorigenesis. Furthermore, a more reasonable evaluation of the dose-response data for vinyl chloride induced tumorigenesis requires knowledge of the amount of VC activated as a function of exposure.

After arbitrarily excluding data acquired from rats exposed to concentrations of VC exceeding 500 ppm in the experiment of Maltoni and Lefemine (1975), Schneiderman, et al (1975) extrapolated the remaining data to predict an incidence of 0.01% hepatic angiosarcoma in rats exposed to 1 ppm VC. This number is reasonably close to our prediction of 4.6 ppm VC for the same incidence. If Schneiderman, et al had used all of the data, a dose-response curve with an unrealistically shallow slope would have resulted and the predicted level causing 0.01% hepatic angiosarcoma would have been much smaller, on the order of 0.00001 ppm.

The concepts developed herein allow use of all of the data presented by Maltoni and Lefemine (1975) to construct a dose-response curve on a scientifically defensible basis. Assuming that the resulting dose-response curve can be projected beyond the range of the experimentally discernible responses, the exposure concentration required to produce an incidence of 0.01% hepatic angiosarcoma in rats is 4.6 ppm.

Aside from interpreting toxicity data for chemicals requiring activation to a toxic form, there are some practical implications of the concepts presented herein for designing experiments to assess the toxicity, including carcinogenicity, of such chemicals. For these chemicals, increasing the concentration above the apparent K_m will produce diminishingly smaller increments in the response; no increase in the response is to be expected when the exposure concentration is 2 or 3 times K_m. Since total dose is a function of exposure time as well as concentration, it is important to determine the effect of exposure time on the response. As shown in Equation 3, the only parameter influence by exposure time is V_m, which is increased linearly with time. Therefore, after the concentration to which the animals are exposed becomes 2 to 3 times K_m, the amount metabolized, v, will increase linearly with increasing exposure time. For

this reason, the gradation of incidence of angiosarcoma in rats exposed to high concentrations of VC will become a function of exposure time rather than concentration. This reasoning makes it imperative that the duration of exposure as well as exposure concentration be considered in evaluating the results of epidemiological studies of people exposed to high concentrations of VC in the work environment.

Unless the dose-dependent, Michaelis-Menten type pharmacokinetic parameters are resolved prior to designing the experiment, the results may be useless for characterizing the dose-response function for the untoward effects observed. Thus, the current approach using the maximum tolerated dose as defined presently and fractions thereof, may be scientifically unsound if the objective is to assess the potential toxicity of exposure to much lower doses or exposures.

For some chemicals detoxification of the chemical per se or reactive metabolites formed from the chemical may also be dose-dependent and saturable leading to a build-up of toxic materials. In such cases, the incremental responses to increasing doses or exposures will become disproportionately larger rather than smaller (see Gehring and Blau, 1977).

In the foregoing analysis of the dose-response data for the induction of angiosarcoma in the rat, no threshold for the response was assumed. As indicated extrapolation below the range of doses causing an observable response may overestimate the response in rats because there is evidence that detoxification of reactive metabolites of VC may occur more efficiently in rats exposed to concentrations of VC below 50 ppm (Watanabe, et al, 1976c). Indeed, further analysis of the data reported by Maltoni and Lefemine (1975) also provides an indication of a practical threshold. In a subsequent presentation of these data, it was revealed that the latency for the development of hepatic angiosarcoma was respectively 64, 70, 78, 81, 79 and 135 weeks for rats exposed to 10,000, 6,000, 2,500, 500, 250 and 50 ppm VC (Maltoni, 1975). These results indicate that at the low level of exposure the time required for induction exceeds considerably the mean life expectancy for rats of approximately 104 weeks. This is consistent with the work of others suggesting that multiples of a lifetime may be required for expression of cancer in response to low doses of a carcinogen (Druckney, 1967 and Albert and Altshuler, 1973). Thus, extrapolation of the data obtained for rats below the range of exposures causing a discernible response may be expected to overestimate the projected incidence.

The ultimate objective of a toxicological study is to develop data which can be used to assess the potential risk in man. Although such extrapolation is fraught with uncertainties, it is worthwhile to utilize the concepts presented herein to achieve this objective. The basic assumptions made are:

1) Induction of angiosarcoma is related to the amount of reactive metabolite of VC per unit of mass.

2) Exposure of rats for 12 months approximates exposure of workers for their working life.

3) There is no threshold for the induction of angiosarcoma in either rats or man which probably overestimates the assumption of risk as discussed above.

4) The efficiency of the metabolic processes involved in the conversion of VC to the reactive form is proportional to the body surface area. Since data for the biotransformation of VC by man are not available, the most logical basis for translation of the animal data to man would seem to be on the basis of body surface area.

The last assumption deserves comment. There are considerable data in the literature showing that metabolism in general and other physiological parameters as well are relatable directly to the surface area of the body (see Schmidt-Nielsen, 1970 and Pinkel, 1958). For this reason, administration of biologically active chemicals to various species frequently gives an equivalent response when the dose is administered in proportion to the surface area of the body, that is dose per square meter of body surface (Pinkel, 1958). This relationship is gaining recognition in estimating the risk incurred by man from exposure to chemicals in the environment (Committee on Safe Drinking Water, National Research Council, 1977). In utilizing this relationship it must, however, be recognized that the original relationship was developed for biologically active agents. Since metabolism and other physiological processes involved in detoxification are more active in smaller animals, the dose of a biologically active chemical per unit of mass required to produce a given effect increases as the body mass decreases, while the dose per unit surface area remains relatively constant. However, for a chemical requiring activation to the biologically active toxic form, the total amount transformed will be roughly proportional to the body surface area. Since toxicity is a function of the concentration of the active form in tissue, this total amount transfromed must then be normalized for mass to estimate an equivalent response.

Using aforementioned rationale, the maximum velocity, V_m, for a 70 kg man can be estimated by calculation using the V_m value obtained for a 0.250 kg rat. The V_m of man for VC will be :

$$V_m \text{ (man)} = V_m \text{ (rat)} \left(\frac{1.85 \text{ sq m}}{0.045 \text{ sq m}}\right)$$

or

$$V_m \text{ (man)} = (8558 \text{ µg/6 hr}) \left(\frac{1.85 \text{ sq m}}{0.045 \text{ sq m}}\right) = 351829 \text{ µg/6 hr}$$

where the values 1.85 and 0.045 sq m are the body surface areas of a 70 kg man and a 0.250 kg rat, respectively (Pinkel, 1958). For an 8 hour exposure, the value is 469105 µg/8 hr. In order to use this number to theoretically estimate the response in man using data collected in rats, the V_m for man must be adjusted to a mass equivalent to that of rats since toxicity is a function of concentration in tissue. To do this the number is divided by 70 kg/0.25 kg or 280. The resulting V_m for man on a mass equivalent basis to that of rats is 1675 µg/8 hr. Using this value, the amount of VC transformed to a reactive form by man on a mass equivalent basis to rat is given by the equation:

$$V \text{ µg/8 hr} = \frac{1675 \text{ µg/8 hr} \cdot S \text{ µg/ℓ}}{860 \text{ µg/ℓ} + S \text{ µg/ℓ}} \qquad (5)$$

Using this equation, the amount of VC transformed by man on a mass equivalent basis to rats was calculated as a function of exposure concentration and the expected incidence of angiosarcoma estimated from equation 4 (Table 3).

For men exposed to greater than 200 ppm VC, the incidence of angiosarcoma has been reported to be 0.02% (Fox and Collier, 1977). Hence, the theoretical calculated incidence using data from rats exceeds that currently detected by approximately 50 fold. This may indicate that people are less sensitive than rats to the induction of angiosarcoma or it may indicate that a practical threshold for the induction of angiosarcoma had been attained. Consistent with this latter possibility is that V on a mass equivalent basis to rats for men exposed to 200 ppm is 625. This number lies below that for rats exposed to 50 ppm. As indicated previously, angiosarcoma observed in rats exposed to 50 ppm occurred only in a rat that lived 135 weeks. Further, this rat did not die as a result of the angiosarcoma but was killed. Thus, as indicated previously, projection of the data collected in rats below the range of exposures producing an observable response may overestimate the incidence.

Inspite of the likelihood of overestimating the incidence of angiosarcoma in rats or man, the incidence predicted for people exposed to 1 ppm, the current OSHA (Occupational Safety and Health Act) standard, is very small (1.5 per 100 million). This value which is likely an overestimate is below the expected incidence of spontaneous angiosarcoma reported to be 20 to 25 cases in the U.S. annually (Makk, et al, 1976).

In summary, it has been demonstrated that the incidence of VC induced angiosarcoma in rats is relatable not to the concentration of exposure but rather to the amount of VC biotransformed. Biotransformation of VC by rats is a dose-dependent process characterized by Michaelis-Menten type kinetics. The concepts evolved from this analysis reveals why pharmacokinetics must be considered in designing toxicology experiments as well as in interpretation of the resulting data. Having characterized the dose-response for induction angiosarcoma in rats as a function of the amount of VC biotransformed, a theoretical estimate of the incidence expected to occur in exposed men was undertaken using the data collected in rats. For daily 8 hr exposures to 1 ppm, the predicted incidence is 1.5 in 100,000,000 which is less than that expected to occur spontaneously. This predicted

incidence is likely an over-estimate of that which will occur as a result of exposure to 1 ppm because there is some evidence for at least a practical threshold in both rats and man. There are no illusions that this estimate by extrapolation of data outside the range of doses causing experimentally observable responses and subsequently to man is without flaws. However, the rationale used represents a new approach which utilizes more logic than methods employed currently for such extrapolation.

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LEGENDS

Figure 1. Metabolism of vinyl chloride analyzed in accordance with the Woolf-Augustinson-Hofstee linearized form of the Michaelis-Menten equation. Values of v and v/S were taken from Table 1. The line was fit by linear regression analysis. The correlation coefficient, R, was 0.88.

Figure 2. (a) Metabolism of vinyl chloride expressed as log v ($\frac{\mu g \text{ VC metabolized}}{4 \text{ hr}}$) versus percent incidence of hepatic angiosarcoma (probability scale). (b) Exposure concentration expressed as log S (ppm) versus the percent incidence of hepatic angiosarcoma. The probit equivalents of the percent incidence are shown on the right hand ordinant. The solid line is the best fit for experimentally observed responses while the dashed line represents extrapolation below those doses producing an observable response assuming no threshold.

R&S 105591

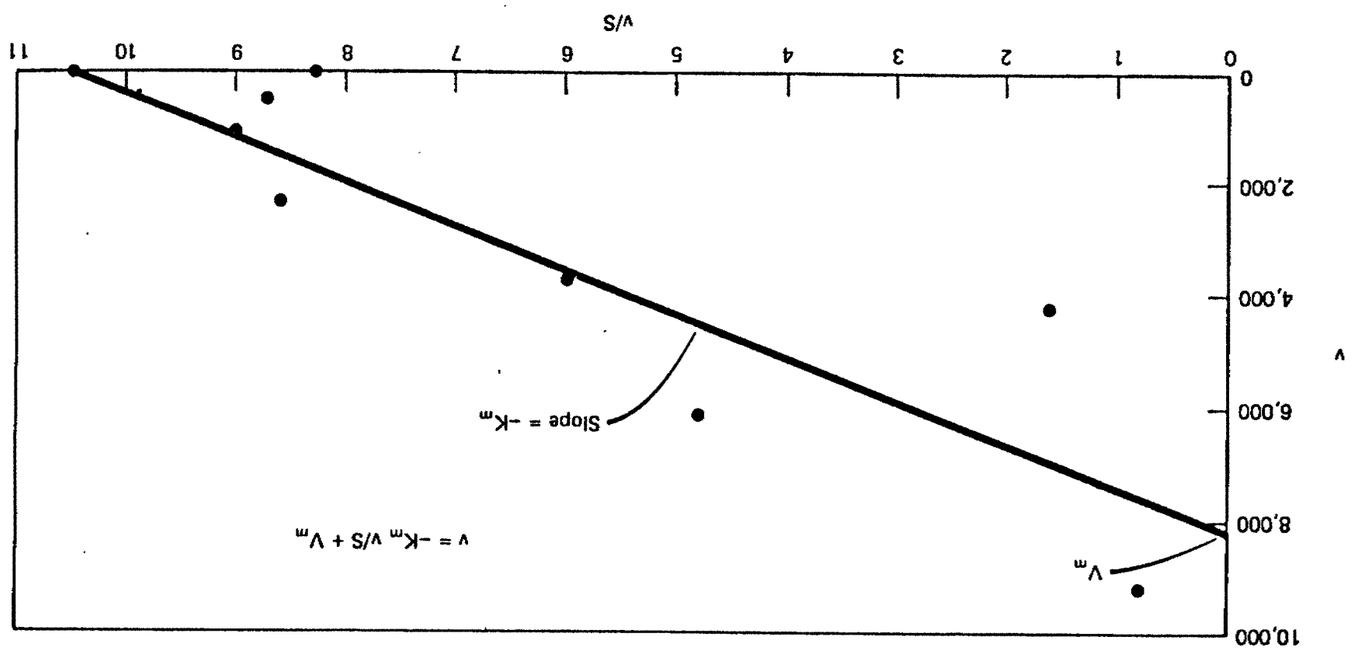
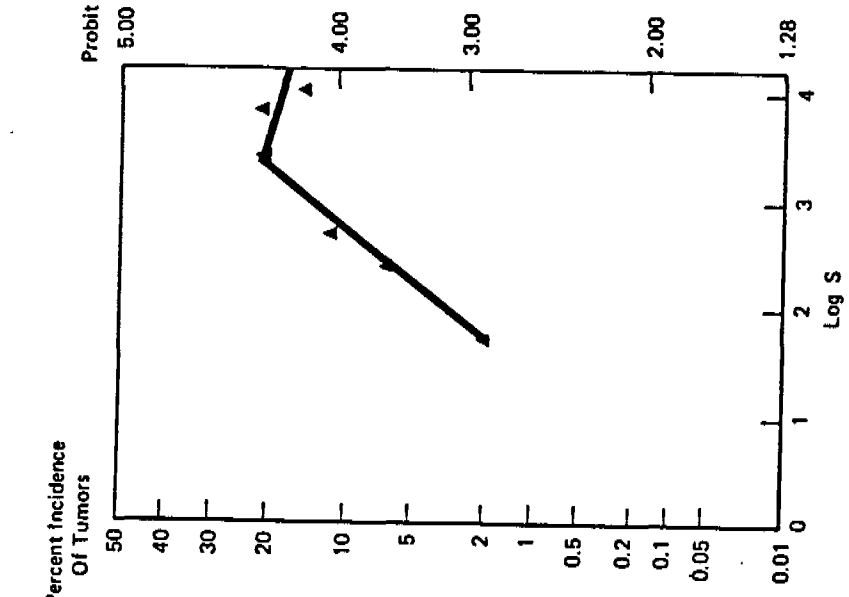
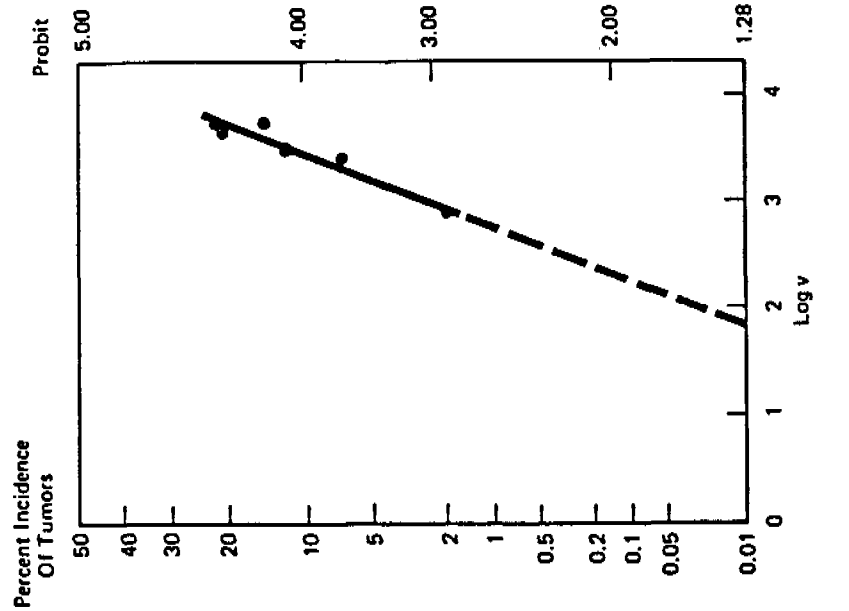


FIGURE 1

FIGURE 2



(b)



(a)

R&S 105592

TABLE 1

Parameters for Describing the Metabolism of Inhaled Vinyl Chloride (VC) Using Michaelis-Menten Kinetics

Exposure Concentration S (ppm VC)	S (µg VC/ℓ air)[a]	v µg VC metabolized / 6 hr[b]	v/S
1.4	3.6	30±3[c]	8.33
9	23.0	242±26	10.52
25	64.0	557±42	8.70
51	130.6	1181±93	9.04
109	279.0	2406±173	8.62
250	640.0	3826±345	5.98
511	1308.2	6263±355	4.79
1020	2611.2	4257±765	1.63
4600	11776.0	9255±1467	0.79

[a] 1 ppm VC = 2.56 µg VC/ℓ air

[b] Determined from the total radioactivity in the carcass

[c] Mean ± standard deviation

TABLE 2

Correlation Between Exposure Concentration of Vinyl Chloride, Metabolism and Induction of Hepatic Angiosarcoma in Rats

Exposure Concentration S (ppm VC)	S (μg VC/ℓ air)[a]	v $\frac{\mu g\ VC\ metabolized}{4\ hr}$[b]	log v	Percent Incidence of Hepatic Angiosarcoma[c]
10,000	25,600	5,521	3.742	15
6,000	15,360	5,403	3.733	22
2,500	6,400	5,030	3.702	22
500	1,280	3,413	3.533	12
250	640	2,435	3.386	7
50	128	739	2.869	2

[a] 1 ppm VC = $2.56\left(\frac{\mu g\ VC}{\ell\ air}\right)$

[b] V_m corrected for 4 hour exposure, $8558\ \left(\frac{\mu g\ VC\ metabolized}{6\ hr}\right) \cdot 4/6 = 5706\ \left(\frac{\mu g\ VC\ metabolized}{4\ hr}\right)$

$$v = \frac{5706\left(\frac{\mu g\ VC}{4\ hr}\right) \cdot S(\mu g/\ell)}{860(\mu g/\ell) + S(\mu g/\ell)}$$

[c] From Maltoni and Lefemine (1975).

TABLE 3

Theoretical Amounts of Reactive Product Formed From VC By a 70 kg Man Exposed Continuously For 8 Hours and the Corresponding Expected Incidence of Angiosarcoma as Predicted From Data Collected in Rats Assuming No Threshold

Exposure Concentration		v $\frac{\mu g \text{ VC metabolized}^b}{8 \text{ hr}}$	Log v	Probit Response[c]	Theoretical Percent Incidence of Angiosarcoma[c]
ppm	µg/ℓ[a]				
200	512	625	2.79	2.68	1.02
50	128	217	2.34	1.98	0.11
5	12.8	24.6	1.39	0.52	3.74×10^{-4}
1	2.56	4.97	0.70	-0.54	1.5×10^{-6}

[a] 1 ppm = 2.56 µg/ℓ.

[b] v has been calculated using the Michaelis-Menten equation after calculating the V_{max} for man from the V_{max} determined for rats. This calculation was made by assuming V_{max} is proportional to body surface area snd subsequently adjusting it to a mass equivalent to that of rats. See text.

[c] The expected probit response was calculated from probit equation 3 (text). Subsequently the theoretical percent incidence of angiosarcoma was determined from the respective probit.

August 11, 1977

VINYL CHLORIDE AND HUMAN REPRODUCTION

Brian MacMahon, M.D.

This review covers the existing literature on observations relating vinyl chloride exposure to risk of fetal defect or death. With one exception (John et al., 1977) the studies reviewed are based on observations in humans. The report of John et al. appears to be the only published work on teratogenicity of vinyl chloride in laboratory animals. The reports of vinyl chloride mutagenesis in bacteria have not been reviewed. They lie outside the area of competence of this reviewer; in addition, while indicative of the need to regard vinyl chloride as a potential mutagen and/or teratogen, such reports do not address the question of whether vinyl chloride does in fact produce fetal death or defect in the doses to which humans are exposed.

The report consists of a brief summary of the author's assessment of the present status of the field, followed by evaluations of the individual reports sent to the author by Dr. Torkelson and others identified by search of the medical literature. A few of the items sent by Dr. Torkelson will not be found here. The reasons are given in an Appendix (page 21).

Summary

The questions of mutagenicity and teratogenicity of vinyl chloride, though inter-related to some extent, should be considered separately.

The available evidence, while not definitive, suggests that vinyl chloride probably is a mutagen and that this mutagenicity may have relevance to humans. The evidence supporting this view is as follows:

1. The demonstrated mutagenicity of the compound in at least some bacteria.

2. The apparent high prevalence rate of chromosome breaks in peripheral lymphocytes of heavily exposed workers. As noted later in this report (page 19), the evidence of chromosome breakage in humans leaves much to be desired. A larger study, with greater attention to subject selection than characterizes previous reports, would seem to be a high priority item since a substance that is capable of producing the chromosome abnormalities described in the reports of Purchase et al., Ducatman et al. and Funes-Cravioto et al. is almost certainly capable of inducing other, non-visible mutations both in somatic and in germinal cells. This line of evidence seems at present to be by far the most relevant to the question of the mutagenicity of vinyl chloride in man.

3. The carcinogenicity of vinyl chloride for the human liver. Not all

Edmonds, L.D., Anderson, C.E., Flynt, J.W.Jr. and Heath, C.W. Jr. (1976). Congenital central nervous system malformations, Kanawha County, West Virginia. Public Health Service - CDC-Atlanta, EPI-76-60-2. Manuscript. ("Not for publication").

(Note: I have not seen this manuscript published but know that it has been submitted to at least one journal for consideration for publication. It was not accepted by that journal but will probably be published somewhere in the near future).

During 1970-74 there were 7 U.S. counties in which (a) a PVC production plant was located, and (b) hospitals representing more than 50 percent of the births participated in the birth defects monitoring program (BDMP) of the Center for Disease Control, Atlanta, Ga. Two of these seven counties had rates of central nervous system defects significantly in excess of national rates for hospitals reporting to the BDMP; one was Lake County, Ohio (Painesville) which was studied previously by Edmonds et al. (1975); the other was Kanawha County, West Virginia. There are two relevant aspects of this paper-patterns in the rates for Kanawha County and a case-control study of the cases themselves and their parents.

Rates of CNS defects are based on two sets of data - the BDMP and the state vital record system. For the former, national BDMP rates are used for comparison; no comparison rates are presented for the latter. The rates are highest in BDMP data in 1971 and in the state data in 1970. The state data show a marked decline in 1973 and 1974; in the BDMP data the rate in 1974 (and in preliminary data for 1975) was similar to the total U.S. rate. The high rate in 1970-73 was manifested by all three major CNS defects - anencephaly, spina bifida and hydrocephaly - as well as by the category "other CNS" defects.

For the case-control study, two controls were selected from vital statistics records for each confirmed CNS defect in a resident of Kanawha County ($n = 47$). It is not clear why two controls were selected since only the case parents and one of the controls (randomly selected) were interviewed. No information on the other control is used. The interviews were by telephone. There were no differences between case and control parents in frequency of working in the PVC plant or in location of work-place or residence in respect to distance from the plant. Only two of the fathers of cases, five of the fathers of controls and none of the mothers in either group had ever worked in the PVC plant.

Comment

This study uses simple and standard epidemiologic procedures and provides little on which to comment. It would be of interest to know the reason why 59 cases in Table 1 is reduced to 47 in Table 3. If this was primarily because of misdiagnosis or miscoding it would raise questions as to the accuracy of the BDMP data. If, on the other hand, the 12 excluded cases were mostly non-residents of the county it would appear that rates for non-residents (born in the county) were as high as those for residents. One can estimate from the numbers of cases and rates in the three tables that the number of births to non-

Edmonds, L.D., Falk, H. and Nissim, J.E. (1975). Congenital malformations and vinyl chloride. (Letter to the Editor) Lancet, ii: 1098.

Following the report of Infante (1976) (reported in 1975 but published in 1976), data from the birth defects monitoring program (BDMP) of the Center for Disease Control were examined. Two hospitals participating in the BDMP are located in cities with vinyl chloride polymerisation plants - one in Pennsylvania and one in Painesville, Ohio, one of the three cities studied by Infante. Congenital malformation rates reported from these two hospitals during 1970-74 are compared with rates from all the reporting hospitals in the respective states.

No increase in rates was seen in the Pennsylvania hospital.

In the Painesville hospital it is stated that "an increase, primarily in anencephaly and spina bifida, was noted...". Data are given only for anencephaly and spina bifida, the rate for each malformation being a little over twice the rate for the state.

In Painesville, two "control" (normal) infants were selected for each of the 15 known cases and information on residence and occupation of parents of cases and controls obtained from medical records. In addition, parents of 14 of the 15 cases were interviewed. None of the interviewed parents of cases had ever worked at either of the two polymerisation plants. None of the parents of cases or controls lived within 2 miles of the plants. A significantly higher proportion of mothers of controls than of cases lived within 10 miles of a PVC plant, but this is attributed to a chance finding among multiple comparisons.

Comment

It is not surprising that a high rate of anencephaly and spina bifida was found in Painesville, since the data cover almost the same years as those of Infante (1976). For 1970-73 (for the whole city)Infante found 13 cases of "central nervous system" defects, while for 1970-74 (in this one hospital) Edmonds et al. found 15 cases, suggesting that most of the births to residents of the city occur in this one hospital and that there is considerable overlap between the two series.

The fact that no link could be found between cases of anencephaly and spina bifida and either of the two VC polymerisation plants, as well as the lack of increased rates in the Pennsylvania hospital, indicates that it is not the presence of the two plants which is responsible for the high malformation rate in Painesville. The most likely explanation seems to me to be random fluctuation.

There is a small numerical error in this letter. The total of 15 cases includes one that was not reported to BDMP but was identified by search of birth certificates. Since this search was not undertaken for the entire state data (or, at least, it is not stated that it was) the state data in the table relate

Infante, P.J. (1976). Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. Ann. N.Y. Acad. Sci., 271: 49-57.

Data are presented on rates of congenital malformation and of certain neoplasms in three communities in Ohio containing polyvinyl chloride production facilities. Only the congenital malformation data are relevant to this review.

The three communities and the number of livebirths during the four years studied (1970-73) are Ashtabula (1,900), Painesville (1,381) and Avon Lake (738). The sources of information on congenital malformations are the routine reports on certificates of birth. Most of the data are limited to livebirths but some information is given on neural tube defects in stillbirths.

The author notes that the total reported malformation rate for the three index cities combined is almost twice as high as for the state as a whole or for the balance of the three counties in which the index cities are located. In two brief paragraphs at the top of page 52 it is stated that the differences "did not appear to be" related to race or maternal age, that the differences were observed for children born in the same hospital but to parents not resident in the city (seeming to rule out reporting bias) and that urban-rural differences were not "significant" in three other county-city combinations matched to the index areas on population size. However, no data are given on these three points.

The three index cities are then compared with 10 other cities located in the same three counties. Two of the other cities had higher malformation rates than the index cities. One of them (North Ridgeville) was "proximate to" one of the index cities (Avon Lake) and the data for that city were therefore combined with those for the three index cities to give observed and expected numbers of malformations by site, expected values being based on state averages. Observed values exceed expected in 13 of the 17 categories of malformation.

Data for central nervous system defects are given for stillbirths as well as livebirths. For stillbirths and livebirths combined, CNS defects were approximately three times as frequent in the four communities (3 index cities plus North Ridgeville) as in the state as a whole. Type of CNS defect is given for stillbirths but not for livebirths.

Comment

There are several potential sources of error in this study, but it is not easy to see how any one of them could account for the principal finding of a high malformation rate in the three index cities. I am fairly well convinced that the finding results from a combination of chance, reporting differentials and epidemiologic gerrymandering.

Birth certificates are a notoriously poor source of information on congenital malformations. The rate for the state of Ohio as a whole (about 10 per 1,000 livebirths) suggests that only about half the medically significant malformations are being reported. However, incomplete reporting would not account for the findings unless there were bias, as well as incompleteness. The

of recognizing the error involved and the suggestion it leaves with the reader that similar kinds of selection may have occurred at other steps in assembly of the data.

The feature of the data that is most suggestive that the high malformation rate in the three cities is an artefact is that a wide variety of malformations are involved. The author focuses attention on the central nervous system defects, because of their usual severity, but, as noted above, 13 of the 17 categories examined are in excess and, among the more common groups, oral clefts, club foot and anomalies of the upper alimentary tract and genital organs are all substantially in excess. The known teratogenic agents in humans and in experimental animals have considerable specificity in the malformations they produce. It seems unlikely that any agent would produce the variety of malformations found in excess in these cities. A much more likely explanation is some artefact - such as reporting differentials - that would apply to all categories of malformation. "Clubfoot", which shows a three-fold increase in these data, is a diagnosis whose frequency is particularly dependent on diagnostic and reporting practices and which seems unlikely to be caused by a specific teratogen - much less a mutagen.

There is a good deal of imprecise wording in the paper which does not inspire confidence in the rigor of those parts of the analysis which must be taken on faith. For example:

(1) In the "Discussion and Summary" (page 56) the statement is made that "anomalies of the central nervous system appear to be of the greatest concern". But why? Earlier in the text it is stated that this is because of the "severity of the defects involved". That is, this is not a conclusion that arises from the data. In addition, while most anomalies of the central nervous system are severe, some are not. We are not told what type of CNS malformations occurred among the livebirths, which contributed 17 of the 25 cases.

(2) No distinction is made between mutagenesis and teratogenesis and the text slips from one to the other as though the words were interchangeable, which they are not.

(3) Similarly, the text on page 24 slips from "central nervous system defects" to "anencephaly, spina bifida and hydrocephaly". It is true that these usually constitute the majority of CNS defects, but we are never reassured on this point by a statement as to the types of CNS defect found among the livebirths.

On a more trivial level:

(4) I am unable to square the numbers in Table 3 with those in Table 4. In Table 3 the four communities contribute 105 cases but in Table 4 there are 114. I suspect that Table 3 is based on malformed infants while Table 4 is based on malformations, some infants exhibiting more than one. However, no explanation is given by the author.

(5) The ICDA codes for CNS defects in Table 4 are incorrect.

Infante, P.F., Wagoner, J.K., McMichael, A.J., Waxweiler, R.J. and Falk, H. (1976). Genetic risks of vinyl chloride. Lancet, i: 734-735.

And related correspondence:
Paddle, G.M. (1976). Lancet, i: 1079
Infante, P.F. et al. (1976b). Lancet, i: 1289-1290

This study is based on data obtained by interviewing 95 workers exposed to vinyl chloride monomer (VCM) and 158 workers ("controls") with no or very little such exposure. The controls worked with polyvinyl chloride or rubber; the proportions from each of these two groups are not given. In addition to broader questions on health status, the interviewees were asked for information on conceptions and fetal deaths experienced by their wives. From employment records, the conceptions were distinguished as occurring "prior to husband's exposure" or "subsequent to husband's exposure". It is not stated how this distinction is made for workers with no exposure, though one can infer that it was in terms of entry into current job category. The question is of some importance because of differences between exposed and control groups in the proportion of conceptions occurring prior or subsequent to "exposure" (see below).

The principal finding is that fetal death rates, adjusted for paternal age, were significantly high among wives of VCM workers after exposure than among wives of controls or among wives of VCM workers prior to exposure. The high fetal death rates were seen only among conceptions occurring to workers aged less than 30 years. The trend persisted when families reporting more than two abortions were excluded and when data collected by individual interviewers were examined separately. The mean interval between fetal loss and time of interview was about two years less for controls than for VCM workers, suggesting that the probability of recall should have been at least as high for the controls as for the exposed workers.

The letter from Paddle (1976) notes the erratic behavior of the fetal death rates when adjusted for paternal age and suggests that additional information be provided. The authors' response (Infante et al., 1976b) gives an important table showing pregnancies and fetal deaths by paternal age. The text of the authors' response provides little additional information.

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. These include:

1. The small numbers on which the rates - and particularly the age-specific rates - are based. Although statistical significance is achieved in some comparisons, the general tenor of the article is such that one can have little confidence that this was not the result of post-hoc grouping of data - the "gerrymandering" so evident in another paper by the senior author of this article (Infante, 1976).

Table 1 and the differences found to be formally significant. However, when examining the effect of excluding women with more than two abortions (page 735) it is deemed sufficient to note that "the trend was maintained". It is not remarked that the trend was considerably reduced and that the residual difference is almost certainly not significant. (The data are not given actually to permit significance testing after exclusion of repeated aborters.) The table provided in response to Dr. Paddle's letter (page 1289) reveals a most striking difference in the paternal-age distribution for conceptions before exposure. As already noted, this difference is puzzling as to its implications to the definition of the study groups. In addition, the difference is so marked as to make the comparison even of age-adjusted rates almost meaningless. In contrast, the age distributions of conceptions after exposure are quite similar in exposed and control families - a fact which suggests that a difference in the definition of onset of exposure is responsible for at least part of the difference in paternal-age distributions of conception prior to exposure. On page 735, column 1, the authors compare the age-adjusted fetal death rate of 6.1% for VCM workers prior to exposure with that of 15.8% for the same group after exposure. This comparison is not valid since the two rates have been adjusted to different standards - the 6.1% to the controls before exposure and the 15.8% to the controls after exposure. A valid comparison, using the same standard for adjustment of both rates, indicates that the actual difference is less than the 6.1:15.8 comparison suggests. For example, using the age distribution of all control conceptions as a standard, I obtain age-adjusted rates of 9.8% and 14.8% for the VCM group before and after exposure. As the authors would point out, the trend is still present and if the significance test has been carried out correctly it would not be affected. But the authors' lack of recognition that their comparison is not a valid one is disturbing.

The most obvious deficiency in the text of this paper is the inadequacy of the description of sources of data - even after the additional description provided in response to Paddle's letter. We are nowhere told how many eligible workers there were in the various groups or what the response rates were in exposed and control groups. The question of response rates is dealt with in the statement that "Group-participation rates ranged from 62 to 77%". We are not told which ends of the range applied to which groups. In addition, 62 to 77% is a broad range and seems inconsistent with the later statement (page 1289) that "The range for response rates....were similar for the study and control groups". There were two groups of controls (PVC and rubber workers), so some kind of range can be envisaged there, but was there also a range within the "study group" (exposed)? The reader should not be required to puzzle such things out - particularly when no matter how hard he puzzles the answer is not to be found in the paper.

There are other statements which may not have such important implications as definition of the study groups and exposure times but nevertheless give the reader pause for thought. For example, it is stated that a "similar number" of rubber workers were selected for study (page 734), but the context does not indicate what the number is similar to - the number of VCM workers, PVC workers or both (presumably it cannot have been the latter but that is only by implication). There is a sentence on page 734: "Although the underlying distributions differed, mean paternal ages were virtually the same - 30.4 versus 30.2 years". The reference is clearly to the VCM workers <u>subsequent</u> <u>to</u> exposure, yet subsequent to exposure the underlying distributions do <u>not</u> differ - it is prior to exposure

Infante, P.F., Wagoner, J.K. and Waxweiler, R.J. (1976c). Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. Mutation Res. 41: 131-142.

This is an overview of work published elsewhere by these same authors. With respect to fetal mortality and congenital malformations, the data are the same as those published by Infante (1976) and Infante et al. (1976) and reviewed in this report. Even much of the text is identical with that of the other publications. The only additional information in this paper is some detail on the results after exclusion of women with more than one fetal death (Table VIII); the data add little to the previous publication.

Comment

Having the same data as the other publications of these authors, this paper is subject to the same criticisms. It contains also a number of minor errors. The numbers for specific defects listed in Table V are the same as in Infante (1976), but the total (109) does not square with either Table 3 or Table 4 of Infante (1976) - tables which, as noted in the review of that paper, do not square with each other either. If there is a good reason for this discrepancy, it is not given. Two of the authors are omitted from the citation of the authors' previous paper on "Genetic risks of vinyl chloride" (ref. 7a).

I have not reviewed in detail the sections of this paper dealing with carcinogenesis, but one point could not escape attention. It is perhaps relevant to this review in that it seems to reflect the authors' general attitude to data. On page 133, the authors state: "The excess in mortality from cancer of the lymphatic and hematopoietic systems was not significant; however, the SMR increased from 159 to 176 with an increase in latency. These comparisons show the importance of latency when looking for occupationally-induced cancers". Clearly, although recognizing the lack of statistical significance, the authors imply that there is some meaningfulness in the change from 159 to 176. Reference to Table II indicates that these SMRs are based on ratios of 4 to 2.5 and 3 to 1.7, respectively.

In sum, this paper adds nothing to previous publications.

John, J.A., Smith, F.A., Leong, B.K.J and Schwartz, B.A. (1977). The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats and rabbits. Toxicol. Appl. Pharmacol. 39: 497-513.

In three species the effects on fetal development of maternally inhaled vinyl chloride at several concentrations was studied. Some groups of animals received simultaneously 15% ethanol in their drinking water since the primary pathway of metabolism is thought to be blocked by ethanol. This suggestion is supported by the fact that maternal toxicity was enhanced in nearly all comparisons of animals receiving ethanol with those receiving the same dose of vinyl chloride without ethanol.

Maternal toxicity(primarily decrease in total weight gain and decrease in liver weight) was found in mice receiving 50ppm vinyl chloride with ethanol or 500 ppm with or without ethanol. In rats and rabbits, no maternal toxicity was evidenced at 500ppm. Rats showed such toxicity at 2500ppm, with or without ethanol, and rabbits at the same level but only with ethanol.

The levels of vinyl chloride concentration at which maternal toxicity is apparent correspond to the levels at which effects on fetal development appear - that is, in mice at 50ppm with ethanol, in rats at 2500ppm with or without ethanol, and in rabbits at 2500ppm only with ethanol. The toxic effects on the fetus were manifested mainly by evidence of fetal detah (decreased litter size, frequency of resorptions) and decrease in fetal weight and length. Decrease in fetal weight or length was not seen in any of the exposed groups of rabbits.

In none of the three species did gross anomalies occur in exposed animals with a frequency significantly greater than in controls. However, some skeletal anomalies occurred significantly more often among mice exposed to 50ppm with ethanol and to 500ppm with or without ethanol and among rats exposed to 2500ppm with ethanol. Although the incidence of skeletal anomalies was high among rabbits exposed at 500ppm, it was not higher than controls among those exposed at 2500ppm. Many statistical comparisons are made in this paper and the significant increase in skeletal anomalies for rabbits exposed at 500ppm is probably a chance finding.

Comment

Although outside the area of this reviewer's expertise, this appears to be an excellent study, the experimental data being meticulously examined and described. In view of the many comparisons made, some of the formally significant differences may be attributable to chance. Nevertheless, a pattern emerges of impaired fetal development at concentrations of vinyl chloride exposure that produce maternal toxicity. Congenital malformations are not a prominent feature of the fetal toxicity. However, the authors' statement (page 513) that "exposure of pregnant mice, rats, and rabbits to vinyl chloride by inhalation was not teratogenic at the concentrations tested", repeated in essence in the Summary

Reports of chromosome breakage in workers exposed to vinyl chloride:

Ducatman, A., Hirschhorn, K. and Selikoff, I.J. (1975). Mutation Res., 31: 163-168

Funes-Cravioto, F., Lambert, B., Lindsten, J. et al. (1975). Lancet, i: 459

Purchase, I.F.H., Richardson, C.R. and Anderson, D (1975) Lancet, ii: 410

ibid (1975). Proc. Roy. Soc. Med. 69: 290-291

Fleig, I (1976). Quoted by de Boer, L. Proc. Roy. Soc. Med. 69: 292

Fleig (1976) is said to have reported a study in which chromosome abnormalities were no more common in a group exposed to vinyl chloride than in controls. However, no details are given. The other reports in this series all indicate a higher rate of chromosome breaks in the peripheral lymphocytes of occupationally-exposed subjects than in controls. In addition, Purchase et al. (1976) report briefly on an experiment in which 15 male mice were heavily exposed to vinyl chloride and then mated. There was no evidence of production of dominant lethal mutations, as assessed by fetal death or resorption among the offspring.

Comment

These studies must be regarded as suggestive of the potential of vinyl chloride for producing visible chromosome damage and therefore, by implication, of invisible genetic mutation at least in somatic cells. However, even the accumulated evidence from all three positive studies leaves much to be desired and a more definitive study is clearly needed. Only in the study of Purchase et al. are the numbers at all convincing (56 exposed and 24 controls). The study of Ducatman et al. is based on only 11 exposed subjects and 10 controls; that of Funes-Cravioto et al. on 7 exposed and 3 controls. None of the four reports (data from one of the studies are reported twice) describes how the study subjects - either exposed or control - were selected from among the many who could presumably have satisfied the criterion of being exposed or not. From only one study (Ducatman et al.) are data on age given and in that study the mean age of the controls was substantially lower than that of the exposed subjects. In one study (Funes-Cravioto et al.) the highest frequency of abnormal cells was found in subjects with the shortest duration of exposure, and in another (Purchase et al.) the frequency of abnormalities is only slightly, and not significantly, higher in the group with the greatest intensity of exposure.

The negative result of the lethal dominant mutation experiment reported

Appendix. Documents sent by Dr. Torkelson but not reviewed in this report.

(Numbers refer to the list of documents accompanying Dr. Torkelson's letter to Mr. John Lawrence, dated May 12, 1977)

1. Infante (1975). This is the manuscript of a report which was subsequently published. The published version is reviewed (Infante, 1976). There are no substantive changes from the manuscript to the published report.

3. Infante et al. (1976). Subsequently published (item #10) and reviewed.

5. John et al. (1977). Subsequently published (item #8) and reviewed.

7. An earlier version of Edmonds et al. (1975) (item #2), which is reviewed. The text of this version differs a little from the published report but the data are identical. This is probably also reference #2 in Edmonds et al. (1975),but I have not been able to locate the original of this reference.

August 11, 1977