Roy T. Gotteman
Director

The Vinyl Institute

File: Vinyl Chloride/ Cancer

March 22, 1985

To: Robert Buehler @ BF Goodrich, Washington,D.C.

George Snider, Jr. @ BF Goodrich, Cleveland

Subject: Critique of Repace and Lowery's Paper on Cancers Due to VCM Exposure

John Barr, of Air Products, has reviewed the Repace and Lowery paper at my request.

I attach copies of his comments and papers he has provided.

The conclusion is that this paper uses information that is dated, the estimates are inflated as to cancer deaths -- in short, the paper is a biased and erroneous estimate.

For your information and comments.

Regards.

Roy

A Division of
THE SOCIETY OF THE PLASTICS INDUSTRY, INC.
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Roy T. Gottesman
Executive Director

The Vinyl Institute

March 15, 1985

To: Mr. John Barr
@ Air Products and Chemicals

Dear John:

Attached is the Repace and Lowery paper that I discussed with you on the phone today along with the critiques by Elizabeth Anderson and Dr. Sorrel Schwartz of Georgetown Univ. The source of the <27 cancer deaths due to vinyl chloride is the 1975 USEPA Proposed Standard for Vinyl Chloride under NESHAPS.

As discussed, I would greatly appreciate your review of the attached, your comments and copies of any publications that discredit this assessment on cancer deaths due to vinyl chloride. As you pointed out, this was an estimate prior to the installation of the control devices to comply with the OSHA and EPA standards.

Please return thse papers to me and thanks for your help.

Roy

Roy Gottesman

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Air Products and Chemicals, Inc.
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18 March 1985

Dr. Roy T. Gottesman
Director, The Vinyl Institute
355 Lexington Avenue
New York, NY 10017

Dear Roy:

I have reviewed the paper by Repace and Lowray on passive smoking for its reference to vinyl chloride as being responsible for 27 deaths per year in the general public. There is no support for that number.

There is a statement on p. 22 that "table 5 given a comparison of the estimated risk of passive smoking to risks estimated by the US EPA for the carcinogenic hazardous air pollutants currently regulated under Section 112 of the CAA". This would lead a reader to assume the risks presented in the referenced table are the current risks from those pollutants. The heading to the table states, however, that the mortality is before control, leading to the question of why the data are presented if they are known to be inaccurate.

Vinyl chloride is listed as "<27 CDs per year", and the reference is 40 FR 59532, proposed VC standard. I no longer have that document available to me, but the preamble to the standard as promulgated at 41 FR 46560 says that the EPA estimated by the linear dose response curve a range of "from less than 1 to 10" cases of ASL per year, and 0.1 to 0.01 times that many cases by the log prohibit model. They also stated that "an equal number of primary cancer at other sites" is expected "for a total of somewhere between less than one to twenty cases per year". It went on to say that regulations is expected to reduce the amount of VC emitted by 95%, and the number of cases "at least in proportion" to that reduction.

These estimates come from an unpublished report by Kusmack and McGaughy, in December of 1975, and are based on very scanty, and selected (by them) data. You will find a discussion of that estimate in the paper I presented at New Orleans in 1982, and in a longer discussion in the draft Chapter for the New Encyclopedia of PVC whch I sent you last year. Their estimate has been widely quoted as 20, with no "up to" or other qualifier used.

For example, see Anderson, et al., Risk Analysis 3 277 (1983) table V(b). There VC is listed for 20 deaths before regulation, 1 after.

This is not exactly news. As 41 FR 46560 stated in October of 1976, the "up to 20" estimate was expected to be reduced "at least by 95%".

Ray Albert, the "father" of the CAG group at EPA confirmed this in 1978 in a letter to the General Counsel of EPA in which he gives the same before/after figures which Anderson published in 1983.

The EPA proposal to amend the VC standard says at 50 FR 1182 that "the risk attributed to exposure to VC. . . have been estimated to be 0.28 cases per year for ASL and 0.55 cases per year for all cancer". This is based on 95% reduction figure, but for some reason the starting point had dropped to eleven. If you have kept up with our contacts with EPA on this review of the VC standard, you will remember that they published data showing that the reduction actually has been over 99%, in the TRW report EPA-450/3-87-003, February 1982.

The point must be made that all of these "estimates" are subject to serious questions of validity. See my APCA paper. The fact is that neither EPA nor CDC has ever found even one person, not to mention 20 per year for 40 years, who has any indication of health effects from ambient exposure to VC.

The use of table 5 by Repace and Lowrey can best be characterized as yet another careless misuse of faulty data in a manner more suited to serving the desired ends of the author than the search for truth. The error is made more egregious by the fact that both Anderson and H. Gribb, the person who actually prepared the "review" of the paper for her, are listed as authors of the 1983 Risk Analysis paper, and thus are presumed to be aware of the data used in their paper. Their failure to recognize the error in this paper suggests either a lack of concern for the contents of the paper being reviewed or a disregard for the presence of erroneous data.

I paid little attention to the rest of the paper by R&L. The EPA recently has acknowledged that it has been following a will'o'wisp in the hazardous air pollutant area, and has been busy writing papers trying to justify some new area to regulate, such as indoor pollution. This is one such self-serving attempt. Note that none of the reviewers gave any real support to the basic concepts of the paper.

I hope that this is useful to you. More details can be furnished if needed, but the basic facts are that the "27" number is wrong, and was used in an incorrect context. If there are any cases, they are "less than" 1 per year by several orders of magnitude.

Sincerely yours,

John T. Barr, Manager
Regulatory Response

JTB:csb

82 9 2

Risk Assessment for Vinyl Chloride in Perspective

John T. Barr

Air Products and Chemicals, Inc.
Allentown, Pennsylvania

For Presentation at the 75th Annual Meeting of the Air Pollution Control Association

New Orleans, Louisiana June 20-25, 1982

Introduction

The combination of circumstances which found the carcinogenic hazard of vinyl chloride (VC) being discovered at about the same time as the science of risk analysis was undergoing rapid development, and the great commercial interest and long history of use of the substance has resulted in a body of literature and pharmacological data greater than one can expect to have for most substances. It is therefore instructive to review the many risk assessments which have been prepared for VC against the available biological information to determine if we can evaluate the extrapolation methods used, and to discuss the current regulations for VC in light of this comparison.

Hazards of Vinyl Chloride

It is necessary to decide first which of the hazards presented by VC should be the basis for the risk estimation. The substance presents the acute hazards of frostbite from exposure to the liquid, of anesthesia at concentrations over 8,000 ppm and suffocation at higher concentrations (von Oettinger, 1955). It also forms explosive mixtures in air above 3.75 volume percent, and so the efforts to control the physical safety of operations generally preclude exposure to acutely toxic concentrations.

These control efforts were reinforced in the mid-1960's where it was discovered (Suciu, 1963) that workers who had been exposed to very high levels of VC developed "vinyl chloride disease," the primary manifestation of which was acroosteolysis (AOL), a degenerative disease of the bone tufts in the hands, and more rarely of the feet and lumbar region. Although crippling to some degree, this disease is not fatal, and is at least partially reversible if exposure is eliminated (Graniger, Walker and Ward, 1980).

Almost ten years later it was found that some of the workers having similar exposure also were developing angiosarcoma of the liver (ASL), a rapidly fatal disease. Oddly enough, there is only one possible case of a worker developing both AOL and ASL (Stafford, 1981) among the 80-plus cases of AOL and 90-plus cases of ASL now known worldwide, although both are diseases of the vascular system. Several large epidemiology studies were conducted on workers exposed to VC (Baxter and Fox, 1976; Chiazze, 1980; Duck, Carter and Coombu, 1975; Equitable Environmental Health, 1978; Fox and Collier, 1977; Frentzel-Beyme, Schnitz, and Theiss, 1978; Theriault and Allord, 1981), and ASL was the only fatal disease found consistently to be in excess in these

persons. Animal studies have shown an excess of tumors at other sites, but the lowest exposures at which these occur are considerably higher than that for ASL. For example, Maltoni (1979) reported the following data:

Site	Concentration For Significant Elevation
Forestomach papillomas:	30,000 ppm
Neuroblastomas:	10,000 ppm
Zymbal gland carcinomas:	10,000 ppm
Nephroblastomas:	250 ppm
Liver angiosarcoma male:	200 ppm, 50 mg/kg
female:	50 ppm, 16.7 mg/kg
Mammary adenocarcinoma:	5 ppm

The low concentration for onset of mammary tumors was of concern when a preliminary study of fabrication employees reported an excess of breast tumors (Chiazze, et al., 1979) but a follow-up case-controlled study (Chiazze, 1980) found no association between the cases and VC exposure. The largest study of VC-PVC workers in the United States reported slight excesses of brain and lung tumors (Equitable Environmental Health, 1978), but this was not seen in the other studies referenced above. The excess of brain tumors was small, and not dose- or exposure-related. The overall excess of lung tumors resulted from an excess in one plant only, and reexamination of those cases also showed no association with VC exposure (Waxweiler, 1978).

Vinyl chloride has been found to be active in several in vitro mutagenetic tests with bacteria and yeasts (Hopkins, 1979) and it appears to cause chromosome abnormalities in exposed workers, but these changes are reversible when exposure is reduced (Hansteene, 1978) and several studies of neighborhoods around PVC plants have failed to show a supportable association with birth defects (Edmonds, 1975, 1976). It is not a teratogen in rodents (Johns, 1977).

Therefore it appears reasonable to assume that if there is any significant chronic risk other than ASL, it is considerably smaller than that for ASL, and that an adequate risk assessment can be based on only the liver tumors.

Review of Risk Assessments

1. Schneiderman, 1975

One of the first attempts to utilize animal data to estimate risks at very low exposures was that of Schneiderman, Mantel and Brown (1975). They used preliminary Maltoni results to compare the estimates obtained from three possible mathematical models. The 99% assurance level of a "safe" dose at a lifetime risk of 10^{-6} was estimated from several extrapolation models as follows:

Log Probit (slope = 1)	73 ppb
Logit (slope = 3.45)	119 ppb
Logit (slope 2.3, one-hit)	2.1 ppb

The authors discussed the recognized difficulties of extending these rat data to humans and of providing animal experiments that could answer satisfactorily the question of human risk at very low doses.

2. Kuzmack and McGaughy, 1975

The EPA was the first group to attempt a human risk assessment for vinyl chloride (Kuzmack and McGaughy, 1975). This pioneering effort attempted to use both animal and human data, and to show comparative results from both the linear and log-probit models. It concluded that there was an individual risk of 71 x 10^{-6} per ppm of lifetime exposure to VC by the linear extrapolation method, and that the log-probit results were one-tenth to one-hundredth of that.

This effort is subject to several serious criticisms. The exposure data used for human experience was that from a group with less than average exposure, while the ASL rate was chosen from only those plants which did report cases, and ignored the remainder of the population. Thus, their incidence rate of 7.5% compares to an actual figure of about 0.1%.

They used as their primary method a linear extrapolation of rat data, which often has been seen to overestimate the actual rates by at least two orders of magnitude, and they assumed the total cancer rate to be twice that found for ASL.

This same estimate was used by the EPA (1979) to estimate the concentration of VC in drinking water which would produce various levels of risk. These estimates are, of course, subject to the same criticisms.

Nisbet (1978) challenged the estimate of Kuzmack and McGaughy (1975) when it was used by Wilson in testimony before the OSHA hearing on its generic cancer policy. Nisbet stated that his calculations showed the risk to be 10-30 times greater, by the same calculation method. Wilson (1978) suggested several flaws

in the Nisbet procedur
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including the fact that he chose for his
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zymbal glands, which have no counterpart
and Kuzmack and McGaughy had used a
to account for possible cancer at other
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Albert (1978) applied
tially carcinogenic a
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is same general procedure to other poten-
pollutants in the United States and
annual cancer deaths as follows:

Arseni	15.6
Benzen	77.8
Cadmiu	26.2
Coke o	149.5
VC (af	1.0
regulation)	

3. Gehring, 1979

Gehring, et al., (197
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Although not considered by the authors,
dels match rather closely the total U.S.
al ASL at an assumed 1,000 ppm exposure.
s no incidence below 99 ppm in humans.
s a human risk of 1.5 x 10^{-8} at 1 ppm
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A limitation of the G
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ing procedure is that it uses partial
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several deaths have occurred since then.
entire population, but only the employees
t certain criteria for data retention and
e Stafford (1981) data does cover the
tends the history for seven years. The
s not known, but a reasonable estimate,
urnover rates and the number of plants
study, is certainly not less than 25,000.
incidence of about 0.1%. Of these, the
to substantial exposures would be about
ne time. Multiplication by 25 plants,
r the turnover during this period, would
exposed persons, for an effective inci-

dence of just over 1%. Personal experience would indic ; that, for the period prior to 1964, when all of the first exp ıres of the fatal 26 cases had occurred, the average exposures this highly exposed group certainly was in excess of 1,000 p for the working day. Maltoni (1979) found a 1% incidence at ab . 1-10 ppm in rats. Calculation of the dose equivalent t ı 1% incidence in rats gives 0 ppm by the linear method and ı ppm from the log-probit equation for the combined Maltoni i ılation experiments. This crude and subjective estimate would ın say that man is about 100 times as resistant as the rat to inhala- tion, a figure generally in agreement with other estima ; (NCAB, 1979).

4. Food Safety Council 1978, 1980

The Food Safety Council has recommended (FSC, 1978) the ıe of the gamma multi-hit model because of its flexibility in ındling dose response data of varying curvilinearity at low dos It has calculated (FSC, 1980) the maximum likely and lower ⁷.5% limit doses for substances at various risk levels and w ı different models. For VC, at 10^{-6} risk, these results ı as follows (based on early Maltoni data):

One-hit	2.0×10^{-2} ppm
Armitage-Doll	2.0×10^{-9} ppm
Weibull	2.1×10^{-10} ppm
Multi-hit	$3.9 \times 10^{-}$ ppm

For this substance, the goodness of fit of the Weibull ıel (0.56) was superior to that of the multi-hit (0.32). N ːher of the other two models gave acceptable fits. This was in ırt because of the concave shape of the curve, which includ all of the high doses in the dose response data.

5. Dow, 1979

A Dow Heath Team performed a relative risk estimation f several compounds (Langer, et al., 1979) which considered proba ı expo- sure, the consequence of exposure, the physical state c the substance during processing, and the current exposure s ıdards. This resulted in a value of 480 for VC in a "closed sys ı but with employees in the vicinity." The same procedure as ɔned hazard rating values to some other substances as follow benzene, 10; phosgene, 410; hydrogen sulfide, 5; arsine),700; and bis-chloromethyl ether, 69,700. In a batch operati with occasional manual handling, the hazard rating for VC ir ɛased to 9,700 by this method.

6. Mehir, 1980

Mehir, et al., (1980) conducted a series of tests for t Consumer Product Safety Commission, a part of which consisted of ‹posing rats and mice to a series of short, high exposures, rat r than

the usual extended low dosage. They included one-hour exposures to rats and mice at 50, 500, 5,000, and 50,000 ppm, 10 and 40 hour exposures at 500 ppm, and 49 and 100 one-hour exposures at 50 ppm. After lifetime observation they found no effects on rats, or their offspring, nor on mice exposed to less than 500 ppm. Those exposed to over 500 ppm developed pulmonary adenomas, but they also had suffered from pneumonitis.

They considered the published data on animal exposures and concluded that there was a lifetime dose below which no oncogenic response is seen. This was estimated to be 5,000 ppm-hrs for mice and greater than 50,000 ppm for rats, regardless of whether the dose was administered over a short or long period. This concept of equality of effectiveness for all modes of exposure does not have general acceptance and would not appear to be correct, based on our present understanding of carcinogenesis. Dose-rate effects are, of course, well known. However, the degree to which this can be extended to all types of effects is not known.

These authors also used the Crump-Guess model (Crump, Guess and Deal, 1977) to evaluate their data on mouse pulmonary cancer, and estimated that exposure to 5,000 ppm VC doubles the probability of cancer, while 50,000 ppm increased the risk nine-fold. In view of the fact that pneumonitis was present in all animals exposed above 500 ppm, it is questionable if this was a direct oncogenic response, or the result of an nongenetic event because of severe lung damage. Maltoni (1979) also reports an increase in lung tumors in mice, but not in rats or hamsters. Thus, the significance of this finding to risk in humans is questionable.

7. Anderson, 1980

Anderson, et al., (1980) extended the work of Gehring, et al., (1978 and 1979) to incorporate the amount of metabolic products from VC which actually was bound to the DNA of exposed rats, (Gehring and Blau, 1977) rather than the total amount metabolized. They assigned various values to the parameters in a Michaelis-Menten equation depicting the kinetics of the metabolic process, and compared the results from extrapolation to low doses by log-probit and multi-hit models. They found that the two extrapolation models responded quite differently to these variations at very low doses, and that it was not possible to select one model as the more appropriate from the high-dose data. Use of the values of Gehring for the primary parameters, gave estimates of the dose equivalent to lifetime risks of 10^{-7} of less than 1 ppm for the probit model and less than 2 ppm for the multistage model, a correspondence which the authors pointed out was better than the precision of interspecies comparisons.

8. EPA, 1980

The final version of the water quality criteria document for VC (EPA, 1980) used a different approach for risk estimation. The slope of the incidence of all tumors at the lowest doses of Maltoni experiment BT-1 was adjusted for the fraction of exposure, the equivalent feeding level to give the same blood concentration of VC as by inhalation (see Withey and Collins, 1976), and the ratio of the surface area of humans vs. rats, to produce an estimate that a lifetime risk of 10^{-5} would be caused by drinking 2 l/day of water containing 20 g/l. There is some confusion in the mathematics given in the report, and the assumptions on which the adjustments are made are far from having general acceptance, although generally following NAS recommendations. It appears that this procedure overstates the risk by several orders of magnitude.

9. NAS, 1980

The National Academy of Science (1977) calculated the upper 95% confidence limit for risk from drinking water containing vinyl chloride from the probabilistic multistage model and early Maltoni rat data. They report (NAS, 1980) a lifetime risk of 10^{-6} as being equivalent to 3.0810^{-5} mg/kg/day. For a 70 kg person consuming 2 l/day, this would calculate to an acceptable level of 1 g/l. The difference between the EPA and NAS numbers comes from the different curve-fitting methods for the animal data.

10. Gaylor and Kodell (1980) applied linear "interpolation" to the same early Maltoni data used by the Food Safety Council (1978) to arrive at a predicted maximum risk of 10^{-6}. The upper 97.5% confidence limit of the animal data was taken as one point on the interpolative line, and zero incidence at zero exposure as the other. This produced a lower 97.5% confidence limit dosage of 7.1×10^{-4} ppm for a lifetime risk of 10^{-6} in rats. Their application of the Armitage-Doll multistage model gave 5.2×10^{-2} ppm as the dosage at 10^{-6} lifetime risk compared to 2×10^{-2} by the Food Safety Council. The difference is due to alternative assumptions on the value of the exponential dose term.

11. Crump and Guess (1980) reviewed some of the earlier risk estimates for vinyl chloride in drinking water, and recalculated the risks, using the one-hit and multistage models. They arrived at an upper 95% confidence limit of lifetime risk for drinking water containing 1 g/l of VC of 4×10^{-6}, based on early Maltoni inhalation data. Using the assumption that a 0.2% incidence of ASL in workers had resulted from a lifetime exposure of 70 g/kg, they obtained a maximum likelihood risk of 10^{-6} from 0.34 g/l by both the multistage and linear models, with 95% lower confidence limits of the same risk at 0.24 g/l. These two models reduce to a linear form when used at very low doses and with the assumption of no threshold value.

These authors cite EPA data on the occurrence of VC in public water supplies which by their methods yield a lifetime risk of 3.7×10^{-6}, or 12 deaths per year from this cause in the United States. None of these has been observed, despite the accumulation of 15 years' data on ASL deaths (Popper, 1978).

12. Scott (1981) ascribed the decreased incidence of tumors in rats at the higher doses to a cell killing process, and adopted the Weibull model to account for this. Application of the model to some early Maltoni data produced a curve which fit the data from 50-10,000 ppm. He did not attempt to extrapolate to doses beyond the experimental range.

13. Carlborg, 1981, also applied the Weibull model to 31 bioassay reports on a variety of animal carcinogens. He concluded that the one-hit model was not appropriate and that carcinogens could be divided into categories according to the shape of the curve, e.g., concave or convex. He found that the early Maltoni data on VC fell into the former category. Application of his parameter estimates to those data, assuming no spontaneous incidence of ASL, gives 2.5×10^{-8} ppm for a lifetime risk of 10^{-6} for rats. Later calculations including all of the published Maltoni data did not change the results significantly (personal communication).

He found the Weibull shape parameter to be approximately 0.5, which is assumed to be the number of stages for tumor initiation. This is consistent with the finding by Gehring (1977) of a saturable metabolic path which produces the proximate carcinogen. It also suggests that the number of "stages" is the number of finite-rate steps before the rate-limiting step. There may be other stages following, but they are not rate controlling. Actually, there appears to be at least two saturable mechanisms involved in the pharmacokinetics of VC, the metabolism to the ultimate carcinogen and the detoxification by sulfhydryl groups.

14. One further evaluation of human risk can be made from the experience of persons residing near VC-PVC plants. The EPA estimated (Kuzmack and McGaughy, 1975) that five million persons lived within five miles of these plants, and were exposed to an annual average concentration of 17 ppb. The present distribution of plants was generally well-established by 1959, thus we have 22 years of history, or about 110 million person-years. About five or six of these plants, with 1-2 million neighbors, go back another 20 years, but these data are not firm enough for inclusion.

The fact that no case of ASL has been confirmed as arising from these ambient exposures places the upper bound of risk at less than 2.7×10^{-7} per ppm-yr. It is believed that the exposure data were overestimated by EPA, and thus this result may be too low, but it is in the same general range as that arrived at by Gehring (1979) and Anderson (1980) after making corrections for pharmacokinetics.

Extending this crude calculation, these five milli persons are now supposed by EPA to be exposed to 0.2 ppb (prob y a high figure), which would predict no more than 0.0003 d hs per year, or one per 3,700 years in that whole population du o VC exposure. But it also must be recognized that with approxima y 20 cases per year of ASL in the general population, there c be expected from a purely statistical basis that there should one case every two years or so among this group of 5 millio lant neighbors.

The results of these estimates discussed above are comp ed in Table I, after conversion to a uniform 10^{-6} lifetime risk. Esti es 5, (Dow 1979) and 12 (Scott, 1981) were not in a form to permit is comparison. See OSHA, (1980), for references to a few other estimat that were not considered here.

It can be seen that the results fall into two major cat ories, those which project that the risk of 10^{-6} occurs at exposures greater than 1 ppm, and those which find that risk in the ppb r e. The estimates which yield the higher allowable exposures ar ased on human data (Nos. 3, 7 and 14) or use a log-probit extra lation model (No. 2, second estimate), or predict a threshold (No. 6 The remainder generally are based on the linear, non-thresh model, and make no biological correction. The result is a differe of 3 or 4 orders of magnitude. The estimates which yield the hig allowable exposures are in better agreement with human experience an are those of the other group.

Additional Data

All of the extrapolations reported here have used for t original Maltoni data from his experiment BT-1. He has now repo d (Maltoni, 1979) three other comparable inhalation experiments on same strain of rats, and one on another strain, in addition to two estion studies. The results of these experiments are shown in gure 1, on a log-probit scale. It can be seen that they all follow imilar pattern, but that there are large variations in slope b een the various data groups. Table III contains the log-probit uations calculated from some of the individual experiments, and rious groups of experiments. Excellent fits are obtained for a sing experiment, as would be expected from the small number of data poin , but adequate fits are obtained for the group as a whole. Inclusion the historic control data on ASL (0.09% spontaneous incidence) did n affect the fit substantially, except for the very low dose data. lusion of the 0,0 (origin) as a data point did give significantly oser fits. The combined experiments indicate that a lifetime risk 10^{-6} for rats is obtained from a dose in the 1-2 ppb range.

Similar variation is seen with the other mathematical e ressions, such as linear or exponential equations.

Regulatory Status

The current regulatory status of vinyl chloride is summarized in Table II. The first regulatory action on VC was taken in 1973 when the Bureau of Tax, Alcohol and Firearms prohibited the use of rigid PVC as liquor containers. This was based on it being present as an adulterant, and not on any consideration of risk. The Consumer Product Safety Commission (CPSC), the Food and Drug Administration, (FDA), and the EPA all acted to ban the use of VC as an aerosol propellant thus establishing a zero risk position. The FDA proposed (FDA, 1975) to withdraw the prior sanction status of rigid PVC as a food package component because of the concern for residual VC that might migrate. The FDA has taken no further action on this proposal, and now is considering a "constituent" policy which would permit a lifetime exposure at some acceptable risk level. This risk has been proposed recently to be 10^{-6} lifetime for the gluttonous consumer. As was discussed above, the EPA required a best available technology approach which reduces the average exposure to those within 5 miles of a plant to about 0.2 ppb, by EPA estimates. OSHA established a rule in 1974 which set 1 ppm for 8 hours as the maximum permissible exposure, and also set 0.5 ppm as an action level below which most features of the regulation did not apply. These were chosen as feasible levels, and not necessarily "safe" doses (OSHA, 1974; EPA, 1976).

The EPA has established an exposure to the general population only 0.1% of that allowed in the workplace. The CPSC has required zero exposure, and the FDA has considered that approach. Depending on which method of estimation the FDA may choose, its allowable exposure could be either greater or less than those currently set by EPA and OSHA. It has been estimated that the maximum amount of VC ingested by the average European, who uses much more plastic packaging than we, is less than 2_6 g/day, (CEFIC, 1976) which would be in the order of a 10^{-5} or 10^{-6} lifetime risk by even the most conservative models.

There have been various estimates made of the cost-effectiveness of the Federal regulation for vinyl chloride. Graham and Vaupel (1981) estimated that the OSHA rule cost $7.5 million per life saved, and $490 thousand per life-year saved over the option of leaving the exposure limit at 50 ppm. Luken and Miller (1981) state that the imputed value of a life from the OSHA standard is $4 million. Morrell (1982) uses an annual cost of $20 million and an annual benefit of 0.1 life saved to derive a cost/benefit of $200 million per life for the OSHA rule. The EPA has reported (EPA, 1979) that the cost of compliance with its VC standard was $296 million through July 7, 1981, and will be an additional $470 million during the next five years, all in 1977 dollars. If the EPA estimate of up to 20 dealths per year were correct, this would be a cost of $4.7 million per life. However, as discussed here, there is no evidence that any lives have been saved by this rule.

There are many difficulties in obtaining accurate estimates of this type, and serious problems in determining the proper value to be assigned to a life. nevertheless, the doubtful nature of the claims

for any significant benefit from these rules suggests that at best, these regulations are excessively costly to society. Therefore, we must attempt to improve both our data base and our methods for interpreting and applying the data.

Discussion

What can be learned from this exercise other than the already recognized fact that various extrapolation models can yield very different results? In this case, at least, there are several points which are worth considering.

1. Vinyl chloride is no exception to the rule that human data always must be incorporated whenever possible. The epidemic of occupationally induced ASL which was feared in 1974 has not materialized, probably due to the steps that were taken in the early 1960's to reduce exposure because of the discovery of AOL. No instances of ASL from exposure to VC in the general population have been substantiated. The overprediction of occupational cases was due to the underestimation of worker exposure and overreliance on raw animal data without proper pharmacokinetic adjustment. We are not now able to extrapolate reliably between similar species and certainly not from rodents to humans, without much additional data.

2. The regulations for vinyl chloride were not based primarily on scientific data, but on socioeconomic and political decisions. This is no surprise (Crandall and Lave, 1981), but is a fact which should be acknowledged openly, along with the understanding that this position will continue to penalize good science.

3. Mathematical extrapolation models are not adequate in themselves for predictions of risks much beyond the experimental range, no matter how good the fit is to the data in the observed range. The variability of relatively small experimental groups adds to the error range. Thus, bioassays intended for quantitative risk assessment applications should be at as low doses as possible, and as large as possible, and should be interpreted very cautiously.

4. The current state of the art is such that quantitative risk assessments may be useful for determining relative risks from similarly acting carcinogens, but are not suitable for across-the-board application to all mechanisms of carcinogenesis.

   This is not to say that we should abandon efforts at developing more effective risk assessment methods. We must, however, recognize the problems inherent in blind application of mathematical models without proper assessment of the available biochemical data, or an understanding of how applicable the experimental data are to humans.

We have available to us at least as much data regarding vinyl chloride as we have for any other substance, and we still have difficulty in deriving a suitable expression for risk from a purely mathematical or statistical basis. Only when human relevance is considered can we arrive at a prediction that approximates actual experience.

The regulators are faced with a tremendously difficult task when they are presented with a few pieces of animal data which suggest the need for concern and potential regulation. We must develop a suitable program to obtain and use as much relevant data as possible to assure that rational regulations are possible. The vinyl chloride experience can help us understand the kind of data which are needed.

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FIGURE 1
GRAPHICAL REPRESENTATION OF TABLE III
LOG-PROBIT PLOT

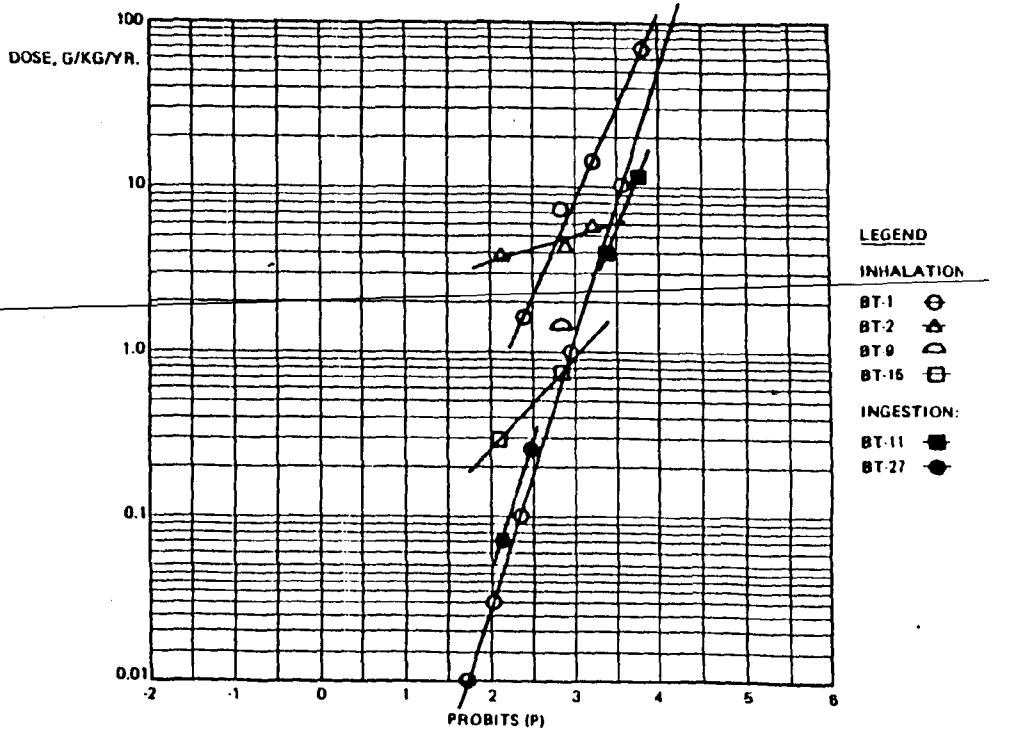

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TABLE I
SUMMARY OF
QUANTITATIVE RISK ASSESSMENTS FOR VC

STIMATE NO.	AUTHOR	BASE SPECIES	EXPOSURE FOR 10^{-6} LIFETIME RISK	COMMENTS
1	SCHNEIDERMAN, 1976	RAT	73 ppb	LOG-PROBIT
			119 ppb	LOGIT SLOPE = 3.45
			2 ppb	LOGIT SLOPE 2.3, 1-HIT
2	KUSMACK & McGAUGHY, 1976	RAT, HUMAN	14 ppb	LINEAR THROUGH ZERO
			140-1400 ppb	LOG-PROBIT
3	GEHRING, 1976	RAT, HUMAN	>1 ppm	BIOTRANSFORMAL DATA AND LINEAR OR LOG-PROBIT
4	FOOD SAFETY COUNCIL, 1980	RAT	2×10^{-6} ppb	WEIBULL
6	HEHIR, 1980	RAT, MOUSE	THRESHOLDS SEEN IN BOTH SPECIES	
7	ANDERSON, 1980	RAT, HUMAN	>1 ppm	DNA BINDING
8	EPA, 1980	RAT	4 μG/DAY	FOOD OR WATER
9	NAS, 1980	RAT	3×10^{-5} MG/KG/DAY	WATER
10	GAYLOR & KODELL, 1980	RAT	0.7 ppb	UPPER 97.5% CONFIDENCE LIMIT OF LINEAR MODEL
			0.5 ppb	ARMITAGE-DOLL MODEL
11	CRUMP & GUESS, 1980	HUMAN	0.7 μG/DAY	APPLYING WORKER DATA TO WATER, UPPER 95%
		RAT	0.5 μG/DAY	CONFIDENCE LIMITS
13	CARLBORG, 1981	RAT	2.5×10^{-5} ppb	WIEBULL
14	THIS PAPER	HUMAN	>1 ppm	NEGATIVE EPIDEMIOLOGY

TABLE II
REGULATORY STATUS OF VINYL CHLORIDE

AGENCY	CONTROLLED LEVEL	PHILOSOPHY
BATF	BANNED AS LIQUOR BOTTLE	ADULTERANT
CPSC	BANNED IN CONSUMER PRODUCTS	ZERO RISK
FDA	USE IN RIGID FOOD PACKAGING QUESTIONED	CONSIDERING ACCEPTABLE RISK
EPA	APPROXIMATELY 0.2 ppb	BEST AVAILABLE TECHNOLOGY
OSHA	1 ppm 8-HR TWO MAXIMUM 0.5 ppm ACTION LEVEL	LOWEST FEASIBLE LEVEL

TABLE III
EQUATIONS FOR CURVES FITTED TO VARIOUS SINGLE AND COMBINED MALTONI EXPERIMENTS

EXPERIMENT	LINEAR y=ax + b			LOG PROBIT P=a IN DOSE + b			CONCENTRATION AT 10^{-6} RISK, (LOG-PROBIT), ppm
	a	b	r	a	b	r	
BT-1	0.26	3.36	0.97	0.35	2.76	0.99	0.03
PLUS CONTROLS	0.27	2.47	0.97				
BT-2	3.05	-8.59	1.0	1.60	0.88	1.0	23
PLUS CONTROLS	1.52	-1.13	0.88				
BT-15	6.5	-1.06	1.0	0.69	3.46	1.0	0.34
PLUS CONTROLS	5.28	-0.30	0.95				
ALL INHALATION STUDIES (4)	0.26	3.07	0.91	0.27	2.98	0.82	0.002
PLUS CONTROLS	0.27	2.80	0.91				
ALL INGESTION STUDIES (2)	1.75	0.15	0.95	0.30	3.22	0.88	0.002
PLUS CONTROLS	1.74	0.20	0.95				
ALL STUDIES (6)	0.29	3.60	0.73	0.27	3.05	0.82	0.001
PLUS CONTROLS	0.29	3.41	0.72				
ALL STUDIES; LOW DOSES ONLY				0.51	2.53	0.75	0.42
PLUS CONTROLS	1.03	0.97	0.79	0.17	2.71	0.49	0.0002

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

16 JUN 1978

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Comparison of vinyl chloride carcinogenic risks with risks from other pollutants.

FROM: Roy E. Albert, Chariman
Carcinogen Assessment Group

TO: Ronald S. Naveen, Office of General Counsel

At your request, we have summarized preliminary risk estimates recently drafted by the Carcinogen Assessment Group and compared them with the risks from vinyl chloride.

The carcinogenic risks to vinyl chloride exposure in the ambient air near VC and PVC manufacturing plants can be compared with the risks to other air pollutants which the agency is now examining for possible regulation. Two commonly used measures of risk are the lifetime probabililty of excess cancer deaths in the population with highest exposure and the total number of excess cancer deaths in the entire exposed population. These are summarized in the attached table.

In this table the risk estimates for pollutants other than vinyl chloride are preliminary and may be modified after public review. The table shows that, after regulation, vinyl chloride is estimated to cause the lowest number of total cancer cases of all pollutants considered, and is estimated to cause individual risks to the most heavily exposed people that are about the same as typically seen with the other pollutants.

Table 1

Chemical	Lifetime Probability of Cancer Death Due to Maximum Exposure	Number Exposed	Number of Expected Cancer Deaths/Yr. In Exposure Group
Arsenic	6.83×10^{-3}	2.00×10^{2}	.20
Benzene	5.00×10^{-5}	9.98×10^{6}	7.13
Cadmium	9.40×10^{-5}	6.70×10^{4}	.09
Coke Ovens	6.04×10^{-3}	1.8×10^{3}	.16
Vinyl chloride[1/]			
Before Regulation	3.80×10^{-3}	3.4×10^{4}	1.85
After Regulation	1.90×10^{-4}	3.4×10^{4}	.09

Table 2

Chemical	Lifetime Probability of Cancer Due to Average Exposure	Total Number Exposed	Total Number of Expected Cancer Deaths/Yr in U.S. Due to Chemical in Air
Arsenic	4.37×10^{-5}	25×10^{6}	15.6
Benzene	2.45×10^{-5}	220×10^{6}	77.8
Cadmium	4.70×10^{-5}	39×10^{6}	26.2
Coke Ovens	6.98×10^{-4}	15×10^{6}	149.5
Vinyl Chloride[1/]			
Before Regulation	2.0×10^{-4}	5×10^{6}	20.0
After Regulation	1.0×10^{-5}	5×10^{6}	1.0

1/ If risk were based on the incidence of mammary tumors in the animal bioassay studies, the results would be four times higher.