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**RISK ASSESSMENT FOR VINYL CHLORIDE  
IN PERSPECTIVE**

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### 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 Ottinger, 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 (Sucin, 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<br>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.

### NOTE TO EDITORS

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### 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  $71 \times 10^{-6}$  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 procedure, including the fact that he chose for his extrapolation one point at 25 ppm from Maltoni experiment BT-15, and that this point is not in good agreement with the whole body of data. Further, he chose to use total cancer incidence in the rats, including those at zymbal glands, which have no counterpart in humans. Both Wilson and Kuzmack and McGaughy had used a factor of two times ASL to account for possible cancer at other sites. Wilson did acknowledge a mathematical error which made his results half the proper number.

Albert (1978) applied this same general procedure to other potentially carcinogenic air pollutants in the United States and calculated the expected annual cancer deaths as follows:

|                       |       |
|-----------------------|-------|
| Arsenic               | 15.6  |
| Benzene               | 77.8  |
| Cadmium               | 26.2  |
| Coke ovens            | 149.5 |
| VC (after regulation) | 1.0   |

#### 3. Gehring, 1979

Gehring, et al., (1979) applied an experimentally derived bio-transformation correction (Gehring, et al., 1978) to rat data and estimated the incidence in humans at two different exposures by means of four different extrapolation models. Their estimates at 500 and 200 ppm TWA bracket the observed experience for humans when derived from the probit and the unconstrained linear models. The linear-through-zero and one-hit models consistently overestimated the incidence. Although not considered by the authors, the linear and probit models match rather closely the total U.S. experience of occupational ASL at an assumed 1,000 ppm exposure. The linear model predicts no incidence below 99 ppb in humans. The probit model predicts a human risk of  $1.5 \times 10^{-6}$  at 1 ppm. Thus, a mechanism for adjusting for the difference in metabolism between animals and humans appears to be useful.

A limitation of the Gehring procedure is that it uses partial Maltoni data, and tests the results against the CMA epidemiology study. That study was not the "end of the experiment"; it stopped at the end of 1973, and several deaths have occurred since then. Neither did it cover the entire population, but only the employees of those plants which met certain criteria for data retention and length of operation. The Stafford (1981) data does cover the entire population and extends the history for seven years. The size of the population is not known, but a reasonable estimate, based on normal worker turnover rates and the number of plants not included in the CMA study, is certainly not less than 25,000. This would give a gross incidence of about 0.1%. Of these, the number actually exposed to substantial exposures would be about 25-30 per plant at any one time. Multiplication by 25 plants, and a factor of three for the turnover during this period, would give about 2,000 highly exposed persons, for an effective inci-

dence of just over 1%. Personal experience would indicate that, for the period prior to 1964, when all of the first exposures of the fatal 26 cases had occurred, the average exposures of this highly exposed group certainly was in excess of 1,000 ppm for the working day. Maltoni (1979) found a 1% incidence at about 1-10 ppm in rats. Calculation of the dose equivalent to a 1% incidence in rats gives 0 ppm by the linear method and 7.5 ppm from the log-probit equation for the combined Maltoni inhalation experiments. This crude and subjective estimate would then say that man is about 100 times as resistant as the rat to VC inhalation, a figure generally in agreement with other estimates (NCAB, 1979).

#### 4. Food Safety Council 1978, 1980

The Food Safety Council has recommended (FSC, 1978) the use of the gamma multi-hit model because of its flexibility in handling dose response data of varying curvilinearity at low doses. It has calculated (FSC, 1980) the maximum likely and lower 97.5% limit doses for substances at various risk levels and with different models. For VC, at  $10^{-6}$  risk, these results are as follows (based on early Maltoni data):

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

For this substance, the goodness of fit of the Weibull model (0.56) was superior to that of the multi-hit (0.32). Neither of the other two models gave acceptable fits. This was in part because of the concave shape of the curve, which included all of the high doses in the dose response data.

#### 5. Dow, 1979

A Dow Heath Team performed a relative risk estimation for several compounds (Langer, et al., 1979) which considered probable exposure, the consequence of exposure, the physical state of the substance during processing, and the current exposure standards. This resulted in a value of 480 for VC in a "closed system but with employees in the vicinity." The same procedure assigned hazard rating values to some other substances as follows: benzene, 10; phosgene, 410; hydrogen sulfide, 5; arsine, 9,700; and bis-chloromethyl ether, 69,700. In a batch operation with occasional manual handling, the hazard rating for VC increased to 9,700 by this method.

#### 6. Hehir, 1980

Hehir, et al., (1980) conducted a series of tests for the Consumer Product Safety Commission, a part of which consisted of exposing rats and mice to a series of short, high exposures, rather 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 a 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  $10^{-6}$  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 BI-1 was adjusted for the fraction of exposure, the equivalent feeding level to give the same blood concentration of VC as by inhalation (see Wilhey and Collins, 1976), and the ratio of the surface area of humans vs. rats, to produce an estimate that a lifetime risk of  $10^{-6}$  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 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  $7.1 \times 10^{-6}$  ppm for a lifetime risk of  $10^{-6}$  in rats. Their application of the Armitage-Doll multistage model gave  $5.2 \times 10^{-6}$  ppm as the dosage at  $10^{-6}$  lifetime risk compared to  $2 \times 10^{-6}$  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  $4 \times 10^{-6}$ , 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  $3.7 \times 10^{-6}$ , 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  $2.5 \times 10^{-6}$  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 sulphydryl 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  $2.7 \times 10^{-6}$  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 million persons are now supposed by EPA to be exposed to 0.2 ppb (probably a high figure), which would predict no more than 0.0003 deaths per year, or one per 3,700 years in that whole population due to VC exposure. But it also must be recognized that with approximately 20 cases per year of ASL in the general population, there can be expected from a purely statistical basis that there should be one case every two years or so among this group of 5 million plant neighbors.

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

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

#### Additional Data

All of the extrapolations reported here have used for the original Maltoni data from his experiment BT-1. He has now reported (Maltoni, 1979) three other comparable inhalation experiments on the same strain of rats, and one on another strain, in addition to two ingestion studies. The results of these experiments are shown in Figure 1, on a log-probit scale. It can be seen that they all follow a similar pattern, but that there are large variations in slope between the various data groups. Table III contains the log-probit equations calculated from some of the individual experiments, and various groups of experiments. Excellent fits are obtained for a single experiment, as would be expected from the small number of data points, but adequate fits are obtained for the group as a whole. Inclusion of the historic control data on ASL (0.09% spontaneous incidence) did not affect the fit substantially, except for the very low dose data. Inclusion of the 0,0 (origin) as a data point did give significantly poorer fits. The combined experiments indicate that a lifetime risk of  $10^{-6}$  for rats is obtained from a dose in the 1-2 ppb range.

Similar variation is seen with the other mathematical expressions, 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 26 g/day, (CEFIG, 1976) which would be in the order of a  $10^{-6}$  or  $10^{-5}$  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 deaths 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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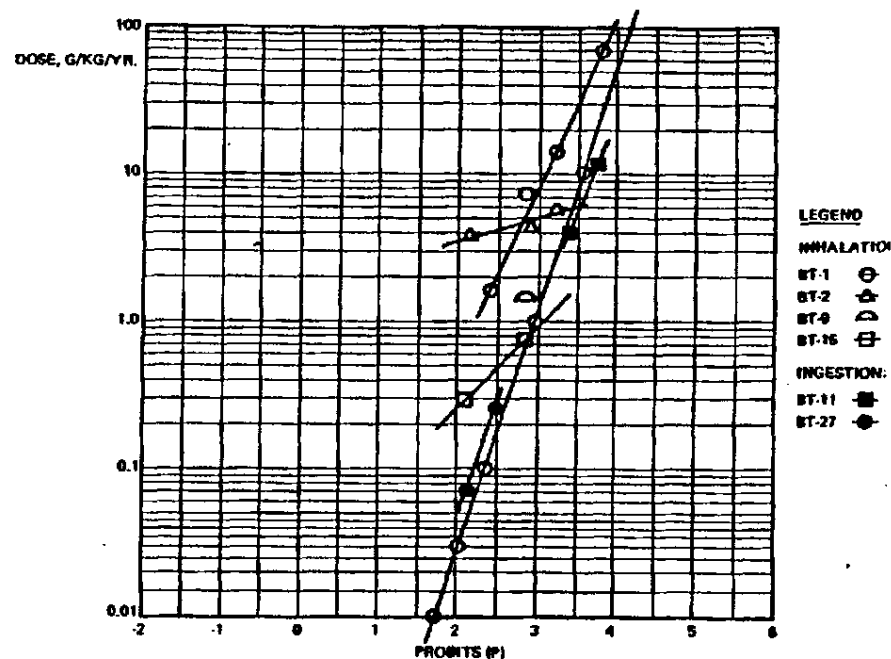
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FIGURE 1  
GRAPHICAL REPRESENTATION OF  
TABLE III  
LOG-PROBIT PLOT



**TABLE I**  
**SUMMARY OF**  
**QUANTITATIVE RISK ASSESSMENTS FOR VC**

| ESTIMATE NO. | AUTHOR                    | BASE SPECIES | EXPOSURE FOR 10 <sup>-6</sup> LIFETIME RISK | COMMENTS                                                               |
|--------------|---------------------------|--------------|---------------------------------------------|------------------------------------------------------------------------|
| 1            | SCHNEIDERMAN, 1975        | RAT          | 73 ppb<br>118 ppb<br>2 ppb                  | LOG-PROBIT<br>LOGIT SLOPE = 3.45<br>LOGIT SLOPE 2.3, 1-HIT             |
| 2            | KUSMACK & McGAUGHY, 1975  | RAT, HUMAN   | 14 ppb<br>140-1400 ppb                      | LINEAR THROUGH ZERO<br>LOG-PROBIT                                      |
| 3            | GEHRING, 1975             | RAT, HUMAN   | >1 ppm                                      | BIOTRANSFORMAL DATA AND<br>LINEAR OR LOG-PROBIT                        |
| 4            | FOOD SAFETY COUNCIL, 1980 | RAT          | 2 X 10 <sup>-6</sup> ppb                    | WEIBULL                                                                |
| 5            | HEHIR, 1980               | RAT, MOUSE   | THRESHOLDS SEEN IN<br>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 X 10 <sup>-5</sup> MG/KG/DAY              | WATER                                                                  |
| 10           | GAYLOR & KODELL, 1980     | RAT          | 0.7 ppb<br>0.5 ppb                          | UPPER 97.5% CONFIDENCE<br>LIMIT OF LINEAR MODEL<br>ARMITAGE-DOLL MODEL |
| 11           | CRUMP & GUESS, 1980       | HUMAN        | 0.7 µG/DAY                                  | APPLYING WORKER DATA TO<br>WATER, UPPER 95%<br>CONFIDENCE LIMITS       |
| 13           | CARLBORG, 1981            | RAT          | 0.5 µG/DAY<br>2.5 X 10 <sup>-6</sup> 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<br>QUESTIONED      | CONSIDERING ACCEPTABLE<br>RISK |
| EPA    | APPROXIMATELY 0.2 ppb                          | BEST AVAILABLE TECHNOLOGY      |
| OSHA   | 1 ppm 8-HR TWO MAXIMUM 0.5 ppm<br>ACTION LEVEL | LOWEST FEASIBLE LEVEL          |

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

| EXPERIMENT                  | LINEAR<br>$y = ax + b$ |       |      | LOG PROBIT<br>$P = a \ln \text{DOSE} + b$ |      |      | CONCENTRATION<br>AT $10^{-5}$ RISK,<br>(LOG-PROBIT), ppm |
|-----------------------------|------------------------|-------|------|-------------------------------------------|------|------|----------------------------------------------------------|
|                             | a                      | b     | r    | a                                         | b    | r    |                                                          |
| BT-1                        | 0.28                   | 3.35  | 0.97 | 0.35                                      | 2.75 | 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 | 0.99 |                                           |      |      |                                                          |
| BT-16                       | 5.5                    | -1.06 | 1.0  | 0.69                                      | 3.46 | 1.0  | 0.34                                                     |
| PLUS CONTROLS               | 5.26                   | -0.30 | 0.95 |                                           |      |      |                                                          |
| ALL INHALATION STUDIES (4)  | 0.26                   | 3.07  | 0.91 | 0.27                                      | 2.98 | 0.92 | 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 (8)             | 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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