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RISK ASSESSMENT OF EXPOSURE TO VINYL CHLORIDE

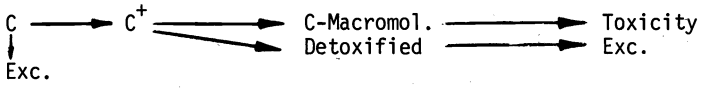
W. T. Stott and P. G. Watanabe

Dow Chemical U.S.A., Toxicology Research Laboratory, 1803 Building, Midland, MI 48640

Abstract- Carcinogenic risk estimation of human exposure to vinyl chloride (VC) was determined by utilizing laboratory animal data on the chronic bioassay of VC, VC pharmacokinetics and VC macromolecular interaction. The impact of these data upon the type of risk VC may pose to humans and the selection of appropriate mathematical models to quantitatively estimate "risk" are discussed.

The problem of estimating the carcinogenic risk of vinyl chloride (VC) exposure to humans is one that requires the integration of information derived from several areas of toxicological research. The pharmacokinetics of VC in laboratory animals and the nature of the ultimate toxic species of VC must be understood. The potential for VC to interact with critical macromolecules must be determined. Finally, the response of laboratory animals to the chronic exposure of VC as well as any human VC exposure data must be evaluated. Consideration of these three data bases on VC makes possible the application of appropriate mathematical models with which to more accurately assess the human carcinogenic risk of exposure to VC.

The understanding of the kinetics of the metabolism of chemicals *in vivo* is beneficial for the understanding of chronic bioassay results. As in the simplified example shown below, the parent compound (C) may be excreted unchanged (Exc.) or be metabolized to a more reactive molecule (C^+), which in turn may react with macromolecules (C-Macromol.), or be detoxified.



The metabolism of VC follows a similar course in the rat. It requires metabolic activation to a reactive intermediate, believed to be an epoxide, which may covalently bind critical macromolecules resulting in a toxic response. The activated VC species may also be detoxified by conjugation with glutathione and be excreted as a mercapturic acid in the animals' urine. Thus, the tumorigenic response to VC is not related to exposure to VC, but rather to its rate of metabolism. At the molecular level this is a function of the activities of activating and detoxifying enzyme systems which may vary with species, sex, environment, etc.

The differences between species in their ability to metabolize VC to its reactive intermediate is obviously of considerable importance when extrapolating from the response of VC in rodents to that in humans. The rat appears to be a good model for human response to VC both in terms of types of tumors observed and clearance of VC. Quantitative differences, however, do exist between rat and human metabolism of VC consistent with the observation by Rall (1) that the basal metabolic rate of mammals is roughly related to body surface area. Thus, the ability to activate VC is much greater in the rodents than in larger animals such as humans.

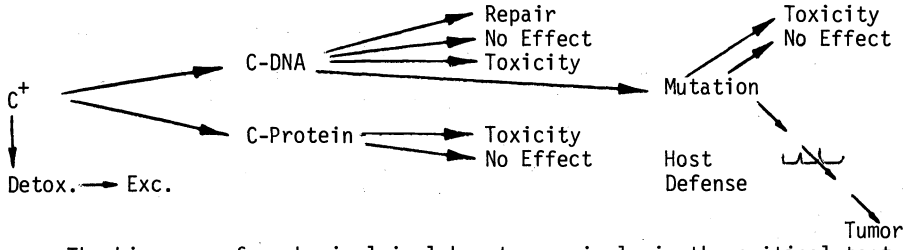
mouse >> rat >>>>> human

The fact that VC activation and detoxification are enzymatic functions means that the kinetics governing such reactions will have an impact upon any toxic manifestation of VC exposure. These enzyme systems may be "saturated" by high dosages of VC resulting in a disproportionate change in the amount of VC activated relative to dose and in changes in the routes of detoxification. For example, in the rat the ability to activate VC to a reactive metabolite has been observed to be a linear function of the dose of VC administered the animal up to about 200 ppm VC for 6 hours. Above this exposure level, there is a decrease in the activation of VC relative to dose, and the excretion pattern of metabolites changes in the rat, more being exhaled as the unmetabolized monomer and less being excreted in the urine. Such "saturation" dosages may have a great impact upon animal bioasays results which will be discussed below.

Another area of research required to accurately assess the carcinogenic potential of VC is that of VC-macromolecular interaction. According to the widely accepted somatic mutation theory of chemical carcinogenesis (2), cancer can be initiated by a mutation in

a cell genome caused by the interaction of a chemical with the DNA of that genome, ie. alkylation of the DNA. Yet, not all alkylation of DNA results in a mutation. Proteins will absorb many of the reactive molecules without observable harmful effects. Ultimately, of course, enough alkylation of cellular proteins will result in toxicity. Reactive molecules may also simply alkylate the DNA in such a way that it does not elicit a biological response, for example alkylation of the ribose or phosphate esters.

Should the reactive metabolite of a chemical alkylate DNA bases, possibly altering the genetic "code" of the cell, cellular DNA repair mechanisms exist which are capable of eliminating these bases and replacing them with normal ones, thus repairing the potentially mutagenic lesion. These repair mechanisms are in a race with cellular replication which "fixes" the lesion. If a cytotoxic dosage of a chemical is present, DNA synthesis may be increased leaving less time for repair, and the fidelity of that repair impaired, resulting in a higher mutation frequency. It should also be noted that a mutation which does occur does not necessarily "program" the cell to become cancerous. The mutation may result in some minor physical or functional change in proteins or may result in cell death. Those mutated cells which are altered in such a way as to eventually result in a tumor, still face eradication by several host defense mechanisms and environmental conditions. Thus, as diagramed below, the interaction of the reactive VC metabolite with cellular macromolecules may not always result in a mutation leading to cancer. Indeed, it appears that this may be a rare occurrence.



The bioassay of a chemical in laboratory animals is the critical test of a compound's carcinogenic potential, the biological endpoint of all the metabolic activity and macromolecular interactions discussed above. The dose-response data obtained from such animal studies usually provide information about the carcinogenicity of the compound at very high dosages administered via a convenient, rather than appropriate, route. These data still leave questions about the effects of low dosages unanswered. Thus, the extrapolation of high dose bioassay data to low dose bioassay response becomes very important in estimating the carcinogenic risk of the compound to man, and usually involves the use of mathematical modeling. Only by the intelligent application of kinetic data about a compound, and a knowledge of its probable mechanisms of carcinogenic action, can an accurate extrapolation of bioassay data to low dosage levels be made. The bioassay of VC provides an excellent example of this.

VC has been observed to cause hepatic angiosarcomas in rats and mice exposed either orally or by inhalation for prolonged periods of time (3,4).

Exposure ppm	µg VC Metabolized/day	Rats with Angiosarcoma (%)	Average Latency (wk)
10.000	5521	19	64
6,000	5403	22	70
2,500	5030	22	78
500	3413	12	81
250	2435	7	79
50	739	2	135

As shown, the incidence of angiosarcoma in the rats and the calculated amount of VC metabolized leveled off above the enzyme saturation dosage (≃ 250 ppm). The direct relationship between dose and tumor incidence observed at lower dosages of VC does not exist at high dosages. Thus, any high dose to very low dose extrapolation using these saturating doses of VC would be invalid since the metabolic fate of VC at these two levels is not the same. The 50 ppm exposure level appears to be a borderline measurable tumorigenic dose both in terms of the tumor incidence and in the latency period required for tumor development.

In an attempt to extrapolate from the high dose bioassay data to low dose exposure response, four commonly used mathematical models have been applied to the rat bioassay data by Gehring et al. (5). These were the probit %, linear %, linear % forced through the origin and the one-hit model currently in use by the Cancer Assessment Group at the National Cancer Institute. None of the four models was observed to be superior at predicting the tumor incidence in rats at high exposure concentrations. However, by making several assumptions with regard to human exposure levels, time and rates of VC absorption, and metabolism of humans relative to rats, the four models can be used to predict human risk.

At a 200 ppm VC exposure (estimated time weighted average for exposure prior to 1974). The probit % incidence model, using the extrapolation of pharmacokinetic data from rats to humans, was a reasonable predictor of the incidence of VC induced cancer observed in workers (6).

Population	Number Angiosarcoma	Probit %	Linear %	Forced Linear %	One Hit
4384	1	0.0	0	5.9	6.3
2339	0	0.8	0	10.4	11.1
946	2	1.1	0	7.2	7.6
1007	2	2.7	0	11.0	11.7
677	0	3.0	0.3	9.5	10.1
324	0	2.1	1.3	5.6	5.9
	5	10	2	50	53

As a number of those exposed workers have yet to reach the 15 to 20 years required for tumor production, another 3 to 4 angiosarcomas are expected with time. It is noteworthy that the epidemic predicted by some does not seem likely. Using the probit % model and assuming worker exposure to the OSHA standard of 1 ppm VCM (adopted in 1974), for a 35 year work time, a VC tumor risk of 15 tumors per one billion people exposed would be expected, clearly a rather minor risk.

In summary, the intelligent estimation of human risk associated with exposure to VC, or any compound, may be made only if based upon experimentally obtained data about the in vivo pharmacokinetics of metabolism, probable mechanism of tumor initiation, and appropriate bioassay of VC. The union of these data make possible the fitting of an appropriate mathematical model with which to estimate the risk at various exposure levels.

REFERENCES

1. D. P. Rall, Enviornm. Res. 2, 360-367 (1969).
2 T. Boveri, The Origin of Malignant Tumors, William and Wilkins, Baltimore (1929).
3. C. Maltoni, Ambio, 4, 18-23 (1975).
4. C. Maltoni and G. Lefemine, Ann. NY Acad. Sci., 2446, 195-224 (1975).
5. P. J. Gehring, P. G. Watanabe and C. N. Park, Toxicol. Appl. Pharmacol., 49, 15-23 (1979).
6. Equitable Environmental Health Inc., Report prepared for MCA, Washington, D.C. (1978).