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Print Schedule: Volume 53 will present the proceedings from the Workshop on Ingested Asbestos.

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Introduction

by Edward P. Radford*

As epidemiologic studies have developed in the past twenty years, it has become apparent that results from such studies quickly become significant elements in public perceptions of health effects from environmental agents. Most epidemiology is concerned with establishing in human populations risk factors contributing to morbidity or other effects on health. Because they avoid many problems associated with interpretation of animal experiments, their importance in the public domain is obvious. It follows, therefore, that where epidemiologic evidence exists relating an agent to human disease, there is a strong impetus to make use of that evidence in regulating conditions leading to exposure to the agent.

In this meeting, the Second Annual Symposium on Environmental Epidemiology, we have explored some of the limitations as well as the advantages in use of epidemiologic results for establishing standards for environmental exposure limits. Most of the program consists of case studies of particular pollutants whose effects on various human populations have been investigated recently, and which offer examples of the application of studies to standard-setting. In some instances these pollutants are of considerable public interest and involve highly controversial regulatory actions. Thus many parts of our society need to understand the degree to which epidemiologic methods are able to help define effects on human health, especially from exposure to low doses of environmental agents over long periods of time, the principal concerns of the public at large.

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Relevance of Experimental Studies to Human Risk

by F. K. Dietz,*† J. C. Ramsey* and P. G. Watanabe*

Confidence in the extrapolation of animal toxicity data to humans can be enhanced by the application of pharmacokinetic concepts integrated with chronic toxicity data and knowledge of a chemical's mechanism(s) of toxicity. Basic pharmacokinetic concepts (including dose-dependent or Michaelis-Menten kinetics) and their relationship to the risk estimation process are discussed using vinyl chloride and styrene as specific examples. Species differences in metabolic rates must be considered in order to arrive at realistic estimates of human risk to vinyl chloride-induced liver angiosarcomas utilizing vinyl chloride toxicity data observed in rats. Because small animal species generally metabolize chemicals more rapidly than larger species on a body surface area basis, small animals should be more sensitive to chemicals (such as vinyl chloride) that exert their toxicities via the metabolic formation of toxic products. Inhaled styrene is a chemical whose clearance from the blood at low exposure levels in both rats and humans follows first-order kinetics. However, at higher exposure levels, the pharmacokinetic fate of styrene in rats is dose-dependent, suggesting a saturation of styrene metabolism. These data indicate that any extrapolation of observable toxicity at elevated exposure levels in rats to anticipated responses at lower levels in either rats or humans may be invalid. An integration of the foregoing concepts provides a sound scientific basis for the use of experimental animal data to predict the risk to humans from chemical exposure.

Introduction

Chemically induced carcinogenicity is one type of toxic response that has received primary attention in recent years. The potential lethality of cancer, combined with its generally irreversible nature and long latent period are all characteristics that have placed carcinogenesis in the forefront of public concern. Many chemicals shown to be mutagenic in short-term *in vitro* studies and/or carcinogenic in long-term animal studies have consequently been considered as potential human carcinogens. This conclusion is typically based on studies of animal models performed under tightly controlled experimental conditions in which potentially interfering variables are kept to a minimum. Although a basic toxicological goal is to evaluate the risk to man associated with exposure to potentially harmful substances, interspecies variation in response may often preclude a simple extrapolation of animal toxicity to that anticipated in man. The purpose of this presentation is to review and emphasize the importance of animal pharmacokinetic studies in properly implementing animal toxicity data to predict human risk from chemical exposure.

Pharmacokinetic Concepts and Dynamics of Toxicity

Pharmacokinetics is a study of the dynamics of absorption, distribution, metabolism and excretion of a chemical within the body. Pharmacokinetic studies of a chemical as a function of administered dose often provide valuable information on how a chemical's overall biological fate may change in response to different amounts within the body. Since many toxic responses to chemical exposure are not only dependent on the amount of a chemical that reaches a target site but also on how long a sensitive site might be exposed, a comparison of the pharmacokinetic fate of a chemical between different species of

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animals can provide data about differential susceptibility relating to interspecies extrapolation of toxicity data.

A classical approach to pharmacokinetic analysis depicts the body as consisting of a system of compartments. An individual compartment generally refers to all tissues, organs, cells and/or fluids within the body for which the rate of uptake and loss of a chemical is sufficiently similar as to preclude further kinetic resolution. Gehring et al. (*1*) have provided a detailed description of pharmacokinetic compartments and their use in evaluating toxicity data, and consequently no detailed discussion will be included here. While compartments do not always have direct physiological or anatomical counterparts when analyzed kinetically, they constitute a basic tool by which quantitative expressions describing the fate of a chemical within the body can be derived.

Dose-Independent Pharmacokinetics

Over a range of selected dose levels, many chemicals exhibit first-order kinetics which can be referred to as being "linear." For these chemicals, the rates of absorption, distribution, metabolism and elimination from the body are proportional to the concentration or amount of the chemical within the body. As a consequence of this proportionality, the rate constants of all these processes are thus independent of the administered dose. In a simplified fashion, first-order kinetics may be expressed by the equation:

$$\text{rate} = -dC/dt = kC$$

in which C is the concentration of the chemical in the body at time t and k is the rate constant for the given process. As long as first-order kinetics apply and thus the rate constants for all processes responsible for a chemical's pharmacokinetic fate are independent of administered dose, tissue concentration and consequent toxicity should also be proportional to administered dose.

Dose-Dependent Pharmacokinetics

In actuality, many reactions that influence a chemical's pharmacokinetic fate are not independent of administered dose, but are instead dose-dependent. In this situation, saturable active transport systems or metabolic reactions that often play key roles in the prevention or enhancement of chemical toxicity are not adequately described by first-order kinetics. As a consequence, the administration of high dose levels, as frequently done in long-term animal bioassays, may overwhelm these processes and result in a disproportionate increase in blood and/or tissue concentration and possibly elicit a toxic response.

The rates of saturable processes are often described by Michaelis-Menten or dose-dependent kinetics according to the equation:

$$\text{rate} = -dC/dt = V_{max}C/K_m + C$$

In this equation, $-dC/dt$ is the rate of change in the concentration of the chemical's concentration at time t, V_{max} is the maximum velocity of the process and K_m is the Michaelis constant or that concentration at which the rate of the process is at a value of one-half V_{max}. There are two limiting situations to this equation. When the concentration (C) is much greater than K_m, the Michaelis-Menten equation approaches a limit of:

$$\text{rate} = -dC/dt \approx V_{max} \qquad C >> K_m$$

In this situation, the rate of the process is limited by the value V_{max}, and, as C increases, the rate of the reaction remains constant. It is in this concentration range $(C >> K_m)$ that the biological processes governed by this type of kinetic behavior have become overwhelmed and can be considered to be saturated.

Conversely, if the concentration C is much less than K_m, the rate of the processes described by the Michaelis-Menten equation can be approximated by:

$$\text{rate} = -dC/dt \approx kC \qquad C << K_m$$

where $k = V_{max}/K_m$. Under these conditions, the rate of the process remains proportional to the chemical's concentration and all of the previously described concepts for first-order kinetics regarding proportionality between blood and tissue concentration and toxicity apply.

Use of Animal Studies for Predicting Human Toxicity

Recent authors have suggested that there are at least five potential factors responsible for species variations in response to chemical exposure (2). Collectively, these factors include absorption, distribution, metabolism, site and mechanism of action and excretion of the chemical from the body. It is of interest to note that an analysis of the dynamics of many, if not all, of these factors as a function of administered dose level constitutes what has been previously described as a pharmacokinetic study.

In utilizing animal studies to predict possible human toxicity, it is important to determine if the toxicity resulting from chemical exposure is due to the parent chemical itself or rather to an

active metabolite generated via metabolic processes occurring within the animal. It is commonly accepted that metabolism can either lead to detoxification or activation, depending on the toxicological potential of the parent compound and/or its possible metabolites. Consideration of this information is important for the extrapolation of results from animal toxicity studies to man, since there may be relative species differences in the activity of enzymes responsible for chemical metabolism. As pointed out by Rall (*3*), it is often possible to estimate the relative sensitivity of different species to a chemical by using an approximation that the basal metabolic rate is roughly proportional to the body surface area. This suggests that if factors other than metabolism are ignored, a large animal species is more sensitive to a directly toxic agent than a small animal species (Table 1). In contrast, a large animal species should then be less sensitive to toxicity mediated by a metabolic activation than a smaller species (*4*). It should be emphasized, however, that for some types of metabolic activation the relative rates may not only be a simple function of body size. For example, the metabolic activation of 2-acetaminofluorene involves the formation of an active sulfate, and the species and organ sensitivity of the tumorigenicity of this agent correlates well with the level of sulfotransferase enzyme activity (*5*). Since the rat has a higher level of sulfotransferase than the mouse, it develops more tumors when exposed to an equivalent amount of 2-acetaminofluorene. In this instance, the larger animal species is more sensitive to the effects of the metabolically activated agent than the smaller species. Thus, the reliability of interspecies extrapolation depends to a large degree upon how much is known of the details of metabolism and how metabolism affects toxicity in the species of interest.

Pharmacokinetic Concepts and Risk Estimation

Many mathematical models are commonly used in extrapolating an observed carcinogenic response in animal bioassays at relatively high dose levels (*6*). While these models differ from each other by the rapidity in which a zero response is approached as the dose level approaches zero, they are similar in that they usually assume that a zero response occurs only when the dose level equals zero. Another feature common to these models is their assumption that the concentration of the carcinogenic entity is directly proportional to the dose level of the administered chemical.

Table 1. Predicted relative cancer risk from equivalent doses (mg/kg) calculated on the basis of (body weight).[a]

Species	Predicted relative cancer risk	
	Directly toxic agents	Metabolically activated agents
Man (70 kg)	1.00	1.00
Dog (20 kg)	0.66	1.52
Rabbit (3 kg)	0.35	2.85
Rat (0.5 kg)	0.18	5.58
Mouse (0.03 kg)	0.08	13.20

[a]After Rall (*3*).

This assumption applies whether the carcinogenic entity is produced via a metabolic activation of the parent chemical or whether the parent chemical itself is the primary toxicant. An important consequence of this assumption is that toxicity or carcinogenicity is also expected to be proportional to administered dose level. Recent studies of several chemicals, including vinyl chloride and styrene, illustrate how an understanding of the pharmacokinetic fate of these compounds as influenced by the magnitude of administered dose can be used to evaluate animal toxicity data in order to predict the hazard to man from exposure to these agents.

Vinyl Chloride

An example of dose-dependent pharmacokinetics that directly relates to carcinogenic risk estimation in man is that of inhaled vinyl chloride (*7, 8*). Vinyl chloride has been demonstrated to induce hepatic angiosarcomas in rats at exposure levels ranging from 10 to 10,000 ppm, with an essentially flat dose-response curve at exposure levels from 1,000 to 10,000 ppm (*9*). Numerous studies have indicated that a reactive metabolite of vinyl chloride is likely to be the carcinogenic entity for this halogenated ethylene rather than the parent compound itself (*10–15*). Other studies have shown that the bioactivation of vinyl chloride in rats is a saturable process that follows Michaelis-Menten kinetics becoming overwhelmed at high exposure levels, thereby limiting the *in vivo* production of the toxic metabolite (*7, 16–19*). As a consequence of this saturable metabolic activation, Gehring et al. (*7*) have shown that the toxicity or carcinogenicity in rats resulting from vinyl chloride exposure is not directly proportional to all exposure concentrations. Alternatively, these authors found it was possible to relate the observed carcinogenicity in rats to the amount of vinyl chloride metabolized after pharmacokinetic parameters describing the

saturable bioactivation of vinyl chloride were determined.

In accordance with these observations of the kinetic behavior of vinyl chloride in rats, Gehring et al. (*7, 8*) utilized similar pharmacokinetic concepts to estimate the amount of vinyl chloride metabolized in man. Their prediction incorporated the concepts that vinyl chloride bioactivation in man was a saturable process as observed in laboratory animals and that the metabolic process responsible for vinyl chloride metabolism in mammals was related to differences in body surface area. Using this methodology, these authors predicted that man's rate of vinyl chloride bioactivation would be much less than that observed in rats, resulting in a decreased sensitivity of man to the tumorigenic effects of vinyl chloride (*7, 8*). Recent data from other laboratories on the rate of vinyl chloride metabolism have provided additional support for this conclusion. In studies of the pharmacokinetics of vinyl chloride in different species (including man), Buchter et al. (*20, 21*) and Filser and Bolt (*22*) have confirmed that a marked species variation in vinyl chloride metabolism does indeed exist (Table 2). These investigators found that mice and rats metabolized vinyl chloride at a rate approximately 5-12 times that for man. In contrast to the results observed in these rodent species, rhesus monkeys were found to metabolize vinyl chloride at a rate that closely paralleled that seen in man. Collectively, these results are significant in that they confirm the predictions reached by Gehring et al. (*7, 8*), who used pharmacokinetic concepts to predict differences in the relative rates of vinyl chloride metabolism in rats versus man.

Styrene

Styrene is another example of a chemical whose metabolic elimination in experimental animals is dose-dependent. In an analysis of the pharmacokinetic fate of styrene in rats following a 6-hr inhalation exposure to 80, 200, 600 or 1200 ppm, Ramsey and Young (*23*) observed that there was a marked dose dependency in the elimination of styrene from the blood. Figure 1 depicts a plot of the blood styrene concentration versus time data in animals exposed to 80 or 1200 ppm for 6 hr. Other animals were left in the exposure chambers for periods of up to 24 hr in order to establish whether plateau blood levels were achieved. Note that a disproportionality exists between maximum blood concentration and exposure level. At an exposure level of 80 ppm, the maximum styrene concentration was 0.8 μg/mL, while at 1200 ppm the maximum blood concentration reached a value of 64 μg/mL. Thus, as exposure concentration increased by 15-fold, the maximum blood concentration increased over 80-fold, indicating a dose dependency in the pharmacokinetic profile of styrene. As reviewed by the original authors (*23*), these and other data indicated that the capability of laboratory animals to metabolize styrene becomes overwhelmed at exposure concentrations somewhere between 200 and 600 ppm. These results indicate that any extrapolation of animal toxicity data observed at exposure levels of 600 ppm and above to anticipated responses in animals at lower levels may be invalid.

How do these results relate to the extrapolation of styrene toxicity data in laboratory animals to that in man? Such an extrapolation can be greatly facilitated by a direct pharmacokinetic comparison of the chemical in question between both species. Accordingly, Ramsey and Young

Table 2. First-order metabolic clearance rates for vinyl chloride in man versus other species.[a]

Species	Clearances, L/hr/kg body weight
Man	2.02
Monkey	3.55
Rat	11.00
Mouse	25.60

[a]Data from Buchter et al. (*20, 21*) and Filser and Bolt (*22*).

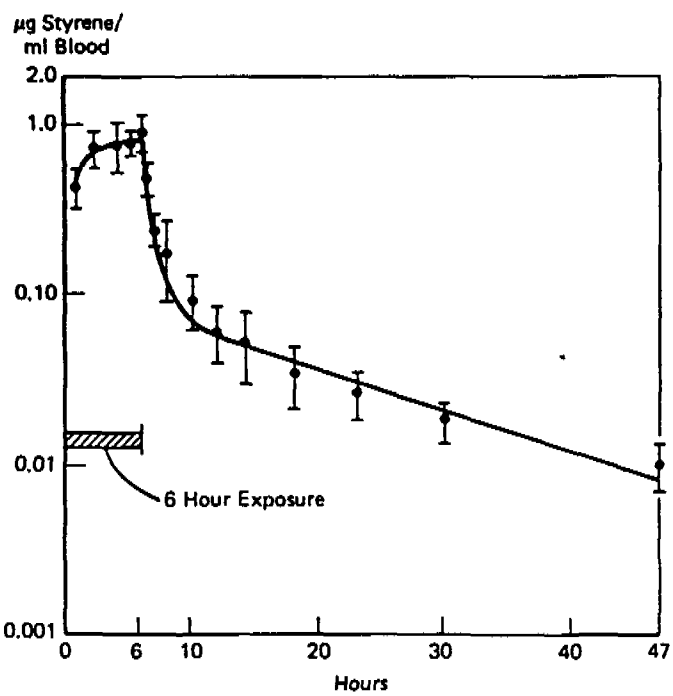

FIGURE 1. Blood styrene concentration in rats exposed to 80 or 1,200 ppm. Data from Ramsey and Young (*23*).

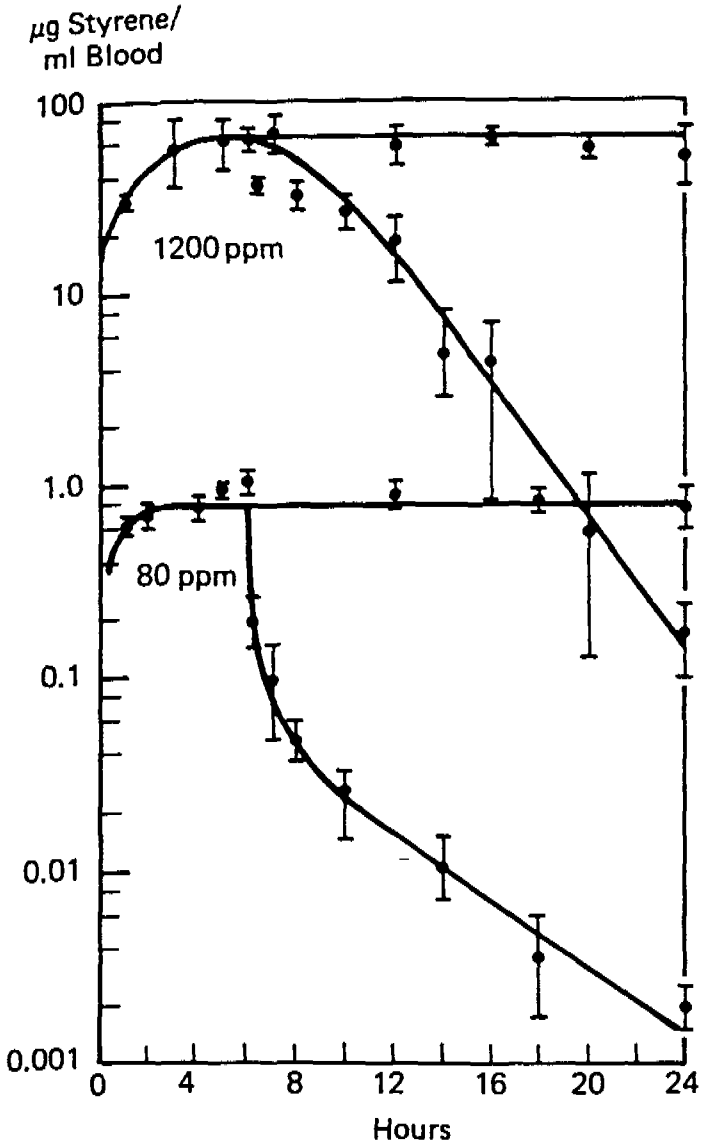

FIGURE 2. Blood styrene concentration in humans exposed to 80 ppm for 6 hr. Data from Ramsey and Young (*23*).

(*23*) conducted a pharmacokinetic study of inhaled styrene in human volunteers exposed to 80 ppm for 6 hr. Figure 2 depicts the blood styrene concentration during and after exposure in the four volunteers. Note that the blood styrene concentration rose to a maximum of 0.9 μg/mL at 6 hr and declined in a linear fashion. A comparison of these results with those of Figure 1 indicates a marked similarity between the pharmacokinetic fate of styrene in man and rats following exposure to 80 ppm. These authors concluded that this type of similarity lends confidence to the extrapolation of toxicity data observed in laboratory animals at levels below 80 ppm to that anticipated in man. In contrast, the demonstration of a saturable elimination of styrene from laboratory animals at higher exposure levels precludes the use of toxicity data obtained at high levels to predict possible risks to humans at lower exposure levels.

Conclusions

In summary, it should be noted that animal studies of pharmacokinetic behavior only represent one segment of the total data base of interrelated information required to make a rational extrapolation of toxicity data observed in laboratory animals to anticipated responses in man. Other authors have demonstrated that the risk estimation process is greatly enhanced when animal studies of pharmacokinetic behavior are integrated with observations of chronic toxicity and a knowledge of mechanisms of toxicity such as the production of active metabolites that interact with critical macromolecular sites. Collectively, an evaluation of the relationships between these parameters and toxicity in experimental animals will improve the estimation of relative degrees of risk to man associated with chemical exposure.

REFERENCES

1. Gehring, P. J., Watanabe, P. G., and Blau, G. E. In: New Concepts in Safety Evaluation, Vol. 1, Part 1 (M. A. Mehlman, R. E. Shapiro and H. Blumenthal, Eds.), Hemisphere Publishing Corp., New York, 1979, pp. 195–270.
2. Reichsman, F. P., and Calabrese, E. J. Animal extrapolation in environmental health: its theoretical basis and practical applications. Rev. Environ. Health 3: 59–78 (1979).
3. Rall, D. P. Difficulties in extrapolating the results of toxicity studies in laboratory animals to man. Environ. Res. 2: 360–367 (1969).
4. Reitz, R. H., Gehring, P. J., and Park, C. N. Carcinogenic risk estimation for chloroform: An alternative to EPA's procedures. Food Cosmet. Toxicol. 16: 511–514 (1978).
5. Miller, E. C. Carcinogenesis by aromatic amines and amides. Reported at the symposium on environmental carcinogenesis. Michigan State University, East Lansing, MI, 1978.
6. Gaylor, D. W., and Shapiro, R. E. In: New Concepts in Safety Evaluation, Volume 1, Part 2 (M. A. Mehlman, R. E. Shapiro and H. Blumenthal, Eds.), Hemisphere Publishing Corp., New York, 1979, pp. 65–87.
7. Gehring, P. J., Watanabe, P. G., and Park, C. N. Resolution of dose-response toxicity data for chemicals requiring metabolic activation: example—vinyl chloride. Toxicol. Appl. Pharmacol. 44: 581–591 (1978).
8. Gehring, P. J., Watanabe, P. G., and Park, C. N. Risk of angiosarcoma in workers exposed to vinyl chloride as predicted from studies in rats. Toxicol. Appl. Pharmacol. 49: 15–21 (1979).
9. Maltoni, C., and Lefemine, G. Carcinogenicity assays of vinyl chloride: current results. Ann. N.Y. Acad. Sci. 246: 195–224 (1975).
10. Barbin, A., Bresil, H., Croisy, A., Jacquignon, P., Malaveille, C., Montesano, R., and Bartsch, H. Liver-microsome-mediated formation of alkylating agents from vinyl bromide and vinyl chloride. Biochem. Biophys. Res. Commun. 67: 596–603 (1975).

11. Bartsch, H., Malaveille, C., and Montesano, R. Human rat and mouse liver mediated mutagenicity of vinyl chloride in salmonella typhimurium strains. Int. J. Cancer 15: 429–437 (1975).
12. Bolt, H. M., Kappus, H., Kaufmann, R., Appel, K. E., Buchter, A., and Bolt, W. Metabolism of 14C-vinyl chloride *in vitro* and *in vivo*. Inserm 52: 151–164 (1975).
13. Malaveille, C., Bartsch, H., Barbin, A., Camus, A. M., and Montesano, R. Mutagenicity of vinyl chloride, chloroethylene-oxide, chloroacetaldehyde and chloroethanol. Biochem. Biophys. Res. Commun. 63: 363–370 (1975).
14. Kappus, H., Bolt, H. M., Buchter, A., and Bolt, W. Liver microsomal uptake of (14C) vinyl chloride and transformation to protein alkylating metabolites *in vitro*. Toxicol. Appl. Pharmacol. 37: 461–471 (1976).
15. Watanabe, P. G., Zempel, J. H., Pegg, D. G., and Gehring, P. J. Hepatic Macromolecular binding following exposure to vinyl chloride. Toxicol. Appl. Pharmacol. 44: 571–579 (1978).
16. Bolt, H. M., Kappus, H., Buchter, A., and Bolt, W. Disposition of (1,2-14C) vinyl chloride in the rat. Arch. Toxicol. 35: 153–162 (1976).
17. Watanabe, P. G., Hefner, R. E., Jr., and Gehring, P. J. Vinyl chloride induced depression of hepatic non-protein sulfhydryl content and effects on bromosulphthalein (BSP) clearance in rats. Toxicology 6: 1–8 (1976).
18. Watanabe, P. G., McGowan, G. R., and Gehring, P. J. Fate of 14C-vinyl chloride after single oral administration in rats. Toxicol. Appl. Pharmacol. 36: 339–352 (1976).
19. Watanabe, P. G., McGowan, G. R., Madrid, E. O., and Gehring, P. J. Fate of ^{14}C-vinyl chloride following inhalation exposure in rats. Toxicol. Appl. Pharmacol. 37: 49–59 (1976).
20. Buchter, A., Bolt, H. M., Filser, J. G., Goergens, H. W., Laib, R. J., and Bolt, W. Pharmkokinetik und Karzinogenese von Vinylchlorid arbeitsmedizinische Risikobeurteilung. Verhandl. Deut. Gesell. Arbeitsmed. 18: 111–124 (1978).
21. Buchter, A., Filser, J. G., Peter, H., and Bolt, H. M. Pharmacokinetics of vinyl chloride in the rhesus monkey. Toxicology Letters 6: 33–36 (1980).
22. Filser, J. G., and Bolt, H. M. Pharmacokinetics of halogenated ethylenes in rats. Arch. Toxicol. 42: 123–136 (1979).
23. Ramsey, J. C., and Young, J. D. Pharmacokinetics of inhaled styrene in rats and humans. Scand. J. Work. Environ. Health 4: 84–91 (1978).

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Toxicity of Vinyl Chloride and Poly(vinyl Chloride): A Critical Review

by Joseph K. Wagoner*

In 1974, vinyl chloride (VC) was first reported in the open scientific literature to induce angiosarcoma of the liver both in humans and in animals. Additional research has now demonstrated the carcinogenicity of VC to other organs and at lower concentrations. The target organs for VC now clearly include the liver, brain and the lung, and probably the lymphohematopoietic system.

The evidence for a carcinogenic risk has been extended to jobs associated with poly(vinyl chloride) exposure. Cases of liver angiosarcoma have been reported among individuals employed in PVC fabrication facilities and an epidemiological study has demonstrated a significant association between exposure to PVC dust and the risk of lung cancer mortality. Cases of angiosarcoma of the liver also have been reported among individuals living in near proximity to vinyl chloride-poly(vinyl chloride) plants.

An association between PVC dust and pneumoconiosis also has been demonstrated. On the basis of findings, prudent control of PVC dust in the industrial setting is indicated.

Laboratory Bioassay

In 1971, 44 years after vinyl chloride was introduced into American commerce (*1*), 24 years after vinyl chloride was shown to cause cardiac arrhythmia in experimental animals (*2*), 22 years after vinyl chloride was reported to be associated with hepatic abnormalities in workers in a Russian plastic factory (*3*), 14 years after toxic angioneuropathy was noted among workers exposed to vinyl chloride below the then Russian maximum allowable concentration of 390 ppm (*4*), 11 years after the vinyl chloride production process was associated with a severe neurologic disorder in Minamata, Japan (*5*), 10 years after vinyl chloride at concentrations down to 200 ppm were reported to cause centrilobular granular degeneration of the liver (*6*) and 5 years after vinyl chloride was shown to induce acro-osteolysis in workers cleaning reactor vessels (*7*), Viola et al. (*8*) reported the induction of tumors of the skin, lung and bone in rats exposed by inhalation to 30,000 ppm of vinyl chloride.

These oncogenic findings have been interpreted by some to have elicited little response because the testing was conducted only at unrealistically high dosages bordering on the lower explosive limit of vinyl chloride (*9*). In reality, however, such was not the case. In May of 1971, Viola had presented to several U.S. companies unpublished findings of an increased incidence of tumors in rats exposed to vinyl chloride concentrations down to and including 500 ppm (*10*). Additional ongoing studies involving vinyl chloride exposures of 20,000, 10,000, 5,000, 2,000, 500 and less than 500 ppm were also described to those same companies. In like manner, Maltoni, in 1972, upon noting angiosarcoma of the liver and cancer of other sites in rats exposed by inhalation to vinyl chloride at lower concentrations, also had transmitted his findings to the Manufacturing Chemists Association in the United States and to several chemical companies in Europe (*11*). Government, labor and the independent research community were first informed of the expanding carcinogenic properties of vinyl chloride in January of 1974, when representatives of industry announced having found liver angiosarcoma in three workers who had cleaned reactor vessels as part of their employment at a single vinyl chloride polymerization facility in the United States. Almost simultaneously, findings of the induction of liver angiosarcoma in rats exposed to vinyl chloride were made public.

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The carcinogenic properties of vinyl chloride were further clarified in 1974, when Caputo et al. (*12*) reported an increasing incidence of liver angiosarcoma with an increasing dosage of vinyl chloride. Among rats exposed to vinyl chloride by inhalation, the incidence of liver angiosarcoma was 3% at 500, 5% at 1,000, 6% at 5,000, 8% at 10,000 and 12% at 20,000 ppm. Among controls not exposed to vinyl chloride, liver angiosarcoma was not found. In that same year Maltoni and Lefemine (*13*) also reported the induction of tumors in mice, hamsters and rats exposed to vinyl chloride by inhalation. The spectrum of induced tumors included angiosarcomas of the liver, adenomas and adenocarcinomas of the lung, neuroblastomas of the brain, lymphomas and carcinomas of other sites. Vinyl chloride in that study was shown to induce liver angiosarcoma in rats at 50 ppm of exposure. Keplinger et al. (*14*) in that same year also reported the induction of liver angiosarcoma in mice exposed to 50 ppm of vinyl chloride by inhalation. Subsequently, Holmberg et al. (*15*) reported the induction of hepatic and extrahepatic angiosarcoma in mice following inhalation exposure to vinyl chloride at 50 ppm. Shortly thereafter Maltoni (*16*) extended the carcinogenicity of vinyl chloride to lower levels of exposure. Vinyl chloride administered by inhalation was shown to induce tumors at a variety of sites, including liver angiosarcoma at 25 ppm and mammary carcinomas at 25, 10, 5 and 1 ppm. Recently Maltoni (*17*) reported the induction of hepatic and extrahepatic angiosarcoma at 10 ppm of vinyl chloride.

Epidemiology

Occupational Exposure: Vinyl Chloride Production or Polymerization

In 1974, the same year that the public was first informed that vinyl chloride induced liver angiosarcoma and cancers of other sites by way of experimental bioassay, epidemiological studies also were reported demonstrating an excess of cancer of multiple organs among workers occupationally exposed to vinyl chloride. Tabershaw and Gaffey (*18*) reported that cancers of the buccal cavity and pharynx, digestive tract (primarily liver angiosarcoma), respiratory tract, central nervous system (primarily brain) and the lymphatic system were excessive among workers in the United States having been employed for at least one year in plants producing and/or polymerizing vinyl chloride. Monson et al. (*19*) in that same year reported the results of a proportionate mortality analysis of 161 deceased workers having been employed at one of two plants in the United States producing and polymerizing vinyl chloride. The specific sites of cancer with the greatest excess were the liver and biliary tract, with an 11-fold excess; the brain, with a 4-fold excess; the digestive tract and the lung.

In 1975, Nicholson et al. (*20*) published a study of cancer mortality among 257 individuals occupationally exposed to vinyl chloride for at least 5 years, with the initial exposure having occurred more than 10 years in the past during employment in a U.S. plant polymerizing vinyl chloride. A 2.3-fold excess in deaths from cancer of all sites combined was demonstrated with three deaths due to hemangiosarcoma of the liver. In that same year, Ott et al. (*21*) reported the mortality experience of 549 individuals occupationally exposed to vinyl chloride–poly(vinyl chloride). Whereas no angiosarcomas of the liver were found, an excess of all malignancies combined was reported among those workers classified as having been highly exposed when contrasted with workers of all other exposure intensities. Among the nine cancer deaths in the highly exposed group of workers, four were due to lung cancer. In a discussion of the limitations of the study, the investigators noted that the majority of workers in the category "other than highly exposed" had less than one year of work experience in departments with exposure to vinyl chloride-polyvinyl chloride.

Duck et al. (*22*) in 1975 reported that a study of 2100 employees of a vinyl chloride polymerization plant in the United Kingdom revealed no excess of total or cause-specific mortality. In addition to reporting no excess of cancer mortality. The investigators reported an inverse relation between vinyl chloride exposure and cancer mortality, i.e., as the duration of exposure to vinyl chloride–poly(vinyl chloride) increased, the risk of cancer decreased. The results and conclusions of that study were adjudged by Wagoner et al. (*23*) to be spurious and due to the use of faculty analytical methodology. Upon reanalysis of the data in that study, Duck and Carter (*24*) reported an increased risk of cancer of the digestive system among workers observed 15 years or more after onset of exposure to vinyl chloride–poly(vinyl chloride).

Subsequently, Waxweiler et al. (*25*) reported the results of a retrospective study of mortality among a cohort of 1294 workers occupationally exposed to vinyl chloride in the United States. Since occupationally induced cancers often take years to become clinically manifest following exposure to carcinogens, the study was restricted to

those individuals with 5 years or more of employment in departments and jobs directly involving vinyl chloride exposure and with 10 years or more elapsed time since onset of initial exposure. Specific jobs and departments with vinyl chloride exposure were determined following a walk-through survey and review of the manufacturing process, engineering controls and air-sampling data for the plants studied. When analyses were based on the total study cohort, only two major causes of death were in excess: nonneoplastic respiratory disease (6 observed vs. 3.4 expected) and all malignant neoplasms combined (35 observed vs. 23.4 expected). The latter excess was statistically significant at $p = 0.05$. When analyses were made according to site of malignancy and latency (interval since onset of exposure), an excess cancer mortality was found for four organ systems, i.e., central nervous system, respiratory system, hepatic system and lymphatic and hematopoietic system. The excessive mortality was statistically significant for three of the four organ systems, i.e., cancer of the central nervous, the respiratory and the hepatic systems, among workers who had been observed 15 years or more since onset of exposure. During the course of the study by Waxweiler et al., an evaluation was made of the pathologic data underlying each neoplasm identified. Of the 14 cases of liver cancer identified, 11 were diagnosed as angiosarcoma. Of ten cases of brain cancer identified, nine were shown to be glioblastoma multiforme in type. Furthermore, of eight lung cancer cases histologically confirmed, all were large cell undifferentiated or adenocarcinoma in type.

Byren et al. (*26*) in 1976 also reported a statistically significant excess of liver-pancreatic and brain cancer deaths among 771 workers employed in a Swedish vinyl chloride/poly(vinyl chloride) production plant. These investigators reported that this excess appeared within the first 5 years after onset of exposure to vinyl chloride.

In 1977, von Reinl et al. (*27*) reported the results of a study of cancer mortality among 7021 males employed in the production and polymerization of vinyl chloride. When compared to the mortality experience of the West German male population, vinyl chloride–poly(vinyl chloride) exposed workers experienced an excess of cancer of multiple organs, i.e., liver, lung, brain and the lympatic and hematopoietic system. Fox and Collier (*28*) in 1977 also reported the results of the study of cancer mortality patterns among 7561 males who, at some time between 1940 and 1974, were employed at one of four plants producing poly(vinyl chloride). An excess mortality from liver cancer was shown for each group of workers whether exposure to vinyl chloride was judged to have been high, medium or low. The authors commented that, although there were no data from the study to support an excess mortality from cancers other than of the liver, the period of follow-up of the workers was too short to permit a clear evaluation of those carcinogenic effects at that time.

Epidemiological investigations have now clearly demonstrated that laboratory bioassay findings were predictive not only for the carcinogenicity of vinyl chloride, but also for several of the target organs. On the basis of these results, the IARC (*29*) in 1979 concluded "Vinyl chloride is a human carcinogen. Its target organs are the liver, brain, lung and haemo-lymphopoietic system."

Occupational Exposure: Poly(vinyl Chloride) Packing and Fabricating

Christine et al. in 1974 reported (*30*) two histopathologically confirmed cases of hepatic angiosarcoma in Connecticut among individuals who had been employed in industrial facilities that used poly(vinyl chloride). One of these individuals, a 47-year-old man, had worked for the previous 10 years as an accountant in a factory producing vinyl sheets and processing poly(vinyl chloride) resins. This individual had frequently visited the plant's production area. The second individual, a 61-year-old man, had spent 25 years in an electrical plant operating a machine that applied poly(vinyl chloride)-containing plastic to wires. In 1977, Baxter et al. (*31*), in a review of 14 cases of hepatic angiosarcoma diagnosed in Great Britain during 1963–73, noted one case who had worked on a process which used poly(vinyl chloride) as a raw material.

In 1975, Selikoff wrote to NIOSH suggesting that appropriate precautions be taken to avoid the inhalation of poly(vinyl chloride) dust, both in the packaging and transport and in its handling during the manufacture of poly(vinyl chloride) products. Selikoff based his suggestion on the results of studies by Lilis et al. (*32*) and Miller et al. (*33*) showing radiographic and pulmonary function changes among vinyl chlorides–poly(vinyl chloride) workers and on the findings of a poly(vinyl chloride) inhalation toxicologic study by Frongia et al. (*34*). This latter investigation showed that rats and guinea pigs, exposed in the same occupational setting as workers who were employed in filling sacks with poly(vinyl chloride) powder, subsequently developed alveolar reactions and septal thickening. This investigation

also showed that 7 months after their initial exposure, both species exhibited granulomatous changes, with fine granules observed intracellularly. Agarwal et al. (*35*) in 1978 demonstrated that intratracheal administration of poly(vinyl chloride) dust in rats resulted in an increase in the activity of lysomal enzymes, interstitial fibrosis and granulomatous lesions surrounded by fibroblasts, reticulin and collagen fibers. Pulmonary disorders possibly associated with exposure to poly(vinyl chloride) resins produced by the emission process might by expected, as dust samples taken by NIOSH during the bagging of poly(vinyl chloride) resin have shown concentrations ranging from less than 1 up to 19 mg/m^3, with about 90% of the particles being smaller than 2.5 μm and 100% smaller than 7 μm in diameter.

In 1978, Arnaud et al. (*36*) reported a case of pneumoconiosis in a 53-year-old man who had been exposed to poly(vinyl chloride) in the bagging area of a VC polymerization plant. This patient presented with exertional dyspnea, pulmonary function changes, and chest radiographic abnormalities. Electron microscopy of lung tissue obtained by drill biopsy showed foreign particles in the macrophages that were identical to poly(vinyl chloride) powder viewed under the electron microscope. *In vitro* incubation of poly(vinyl chloride) powder with human lung macrophages showed that the macrophages engulfed the powder to give an appearance similar to that seen *in vivo*. The authors noted that the histological lesions in this patient were identical to those recorded by Szende et al. (*37*), who diagnosed advanced pneumoconiosis in a 31-year-old man secondary to the inhalation of poly(vinyl chloride) dust. Szende et al. also reported that microscopic examination of poly(vinyl chloride) dust particles showed them to be morphologically similar to particles found in the patient's lungs.

Results of epidemiologic studies by Vertkin and Hamontov (*38*) and by Mastrangelo et al. (*39*) further support the role of poly(vinyl chloride) in the etiology of pneumoconiosis. A total of 1216 employees of a poly(vinyl chloride) production factory in Italy underwent chest X-ray examinations. Of 731 examined individuals with exposure to poly(vinyl chloride) dust, 20 were diagnosed as having pneumoconiosis. All of these individuals had worked 5 years or more in departments classified as having poly(vinyl chloride) dust pollution. No cases of pneumoconiosis were observed among the 485 examined individuals who worked in areas free of poly(vinyl chloride) dust.

The effects of vinyl chloride–poly(vinyl chloride) exposure on the respiratory system of exposed workers seem to indicate a pattern of n[redacted] neoplastic effects, a granulomatous reaction to poly(vinyl chloride) dust, with inclusion of poly(vinyl chloride) particles in macrophages and histocytes, and associated interstitial fibrosis.

The long-term carcinogenic effect, with a significant increase in lung cancer also is of concern. In 1978, Waxweiler et al. (*40*) reported the results of a study of lung cancer at a single vinyl chloride–poly(vinyl chloride) facility. One objective of this study was to determine whether there was an excess risk of lung cancer of a particular histological type at the plant. A case control study showed a clear excess of type 3 (adenocarcinoma) and type 4 (large-cell undifferentiated) lung cancers in cases occurring among plant employees as compared to other lung cancer cases from the same hospital of diagnosis, matched for age and calendar period of diagnosis. The authors noted that adenocarcinomas of the lung, accounting for a minor proportion of this excess risk, have been shown to be at most only weakly related to cigarette smoking; some studies have shown no association at all. The authors also noted that large-cell differentiated carcinoma of the lun[redacted] accounting for the vast majority of the exc[redacted] lung cancer risk, is the only major histological type that has never been related to cigarette smoking by epidemiologic study. Thus, they concluded that cigarette smoking was not a major confounding variable in the study.

A further study was made by Waxweiler et al. to test whether one or more chemicals used at the plant were responsible for the excess of lung cancer of types 3 and 4 or for the excess of only type 4. A model was specifically developed for this purpose. The sensitivity and specificity of the model was demonstrated by its confirmation of the relationship between angiosarcoma of the liver and direct vinyl chloride exposure. The authors reported that of all 19 chemicals used at the plant, poly(vinyl chloride) dust was the only chemical for which they found a statistically significant association with lung cancer mortality and specifically with large-cell undifferentiated lung cancer.

The studies mentioned above suggest that the excess lung cancer risk in the vinyl chloride–poly(vinyl chloride) industry is related to exposure to poly(vinyl chloride) dust. That the dust itself or as a carrier of residual vinyl chloride monomer is a factor in the etiology of lung can[redacted] seems biologically plausible. Poly(vinyl chloride) dust particles are known to be often in the respirable range—that is, less than 10 μm in diameter. Almost all poly(vinyl chloride) particles produced by the emulsion system, one of the systems

at the facility studied by Waxweiler et al., are in the respirable range. These particles could easily settle in the lung and conceivably by themselves cause lung cancer. However, it is known that vinyl chloride monomer becomes entrapped in poly(vinyl chloride) dust and can be released slowly over time. Thus it is also possible that poly(vinyl chloride) dust particles in the lung could slowly release vinyl chloride monomer to small adjacent areas of the tissue, prolonging the contact time of that chemical with tissue.

On the basis of these findings, one must seriously question the safety of the current OSHA standard for poly(vinyl chloride) dust, i.e., a standard which treats poly(vinyl chloride) as a nuisance dust.

Community Exposure to Vinyl Chloride

Christine et al. (*30*) reported two cases of hepatic angiosarcoma in Connecticut having a probable residential exposure to vinyl chloride. One individual with hepatic angiosarcoma lived within 2 miles of the plant producing poly(vinyl chloride)-coated wire, while the second individual lived within 0.5 miles of a plant producing vinyl sheets. Each of these two plants also had a case of hepatic angiosarcoma among its labor force. Neither of these residential cases was known to have had occupational exposure to vinyl chloride or arsenic or diagnostic exposure to thorium dioside, the only three agents known to cause hepatic angiosarcoma in humans. Baxter et al. (*31*), in 1977 reported another case of liver angiosarcoma in Great Britain who had lived for 6 years within half a mile of a plant manufacturing poly(vinyl chloride). On the basis of these observations, Brady et al. (*41*) in 1977 undertook a study in New York State of 26 confirmed cases of hepatic angiosarcoma. Controls comprised of individuals who had an internal malignant tumor other than primary liver cancer were matched with index cases on the basis of age at diagnosis, race, sex, place of residence and vital status. This study showed a statistically significant association between angiosarcoma of the liver and direct occupational or therapeutic exposure to arsenic (two cases), vinyl chloride (three cases) and thorium dioxide (two cases). In addition, this study demonstrated that of ten female cases of liver angiosarcoma (no direct occupational or therapeutic exposure to vinyl chloride, arsenic or thorium dioxide) one lived within 1700 ft of a vinyl chloride polymerizarion plant and four lived from 500 to 4500 ft of a poly(vinyl chloride) fabrication plant. In contrast, none of their matched controls lived within 1 mile of any facility polymerizing vinyl chloride or fabricating poly(vinyl chloride). These study findings are supportive of the role of indirect modes of vinyl chloride exposure in the etiology of liver angiosarcoma.

Summary

Adenomas and adenocarcinomas of the lung, angiosarcomas of the liver and of other sites, lymphomas, mammary carcinomas, neuroblastomas of the brain, in addition to various other tumors have been induced in mice, rats and hamsters exposed by inhalation to vinyl chloride. In addition vinyl chloride when administered by inhalation has been found to induce hepatic and extrahepatic angiosarcomas at concentrations as low as 10 ppm and mammary carcinomas at even lower concentrations, i.e., 5 and 1 ppm.

Several mutually confirmatory studies, using the retrospective cohort method, have shown an increased risk of liver angiosarcoma and cancer of other sites among employees of vinyl chloride polymerization facilities. The full magnitude of this site-specific cancer risk among employees of vinyl chloride polymerization plants will only be determined following full lifetime observation. Nevertheless, studies already have shown that for liver angiosarcoma the excess risk is approximately 11 to 16 times that of the general population. For brain cancer the excess risk is 4-fold.

The role of indirect modes of exposure to vinyl chloride has now been shown to be associated with an excess risk of cancer. Several cases of liver angiosarcoma have been reported among individuals living in close proximity (less than 2 miles) to facilities polymerizing vinyl chloride or fabricating poly(vinyl chloride). A recent epidemiological study has demonstrated that 50% of females with liver angiosarcoma (5/10) lived within 1 mile of such industrial facilities, whereas none of their matched control did so.

Experimental bioassay and epidemiological studies have shown a high concordance for the carcinogenicity of vinyl chloride, specifically for liver angiosarcoma. This excess of liver angiosarcoma has been shown to persist from the polymerization of vinyl chloride to the residence in near proximity to such facilities.

Both experimental and epidemiological data indicate that PVC dust is probably associated with respiratory effects, both neoplastic and nonneoplastic in nature.

REFERENCES

1. U.S. Tariff Commission. Census of Dyes and of Other Synthetic Organic Chemicals, 1927. Tariff Information

Series No. 37, U.S. Government Printing Office, Washington, DC, 1928, p. 139.
2. Oster, R. H., Carr, C. J., and Krantz, J. C. Anesthesia. Narcosis with vinyl chloride. Anesthesiology 8: 359 (1947).
3. Tribukh, S. R., Tikhomirova, V. A., and Koslov, L. A. Working conditions and measures for their sanitation in the production and utilization of vinyl chloride plastics. Gigiena Sanit. 10: 38 (1949).
4. Filatova, V. S., Balahonova, L. I., and Gronsberg, E. S. Hygienic characteristics of vinyl chloride. Gigiena Truda Prof. Zabolevaniya 2: 6 (1958).
5. Kurland, L. T., Faro, S. N., and Siedler, H. Minamata disease. World Neurology 1: 370 (1960).
6. Torkelson, T. R., Oyen, R. F., and Rowe, V. K. The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. Am. Ind. Hyg. Assoc. J. 22: 354 (1961).
7. Cordier, J. M., Fievez, C., Lefevre, M. J., and Sevrin, A. Acroosteolysis combined with skin lesions in 2 workers exposed in cleaning autoclaves. Cahiers Med. Travail. 4: 14 (1966).
8. Viola, P. L., Bigotti, A., and Caputo, A. Oncogenic response or rat skin, lungs and bones to vinyl chloride. Cancer Res. 31: 516-522 (1971).
9. Heckman, J. H. Symposium presentation, 1980.
10. Wheeler, R. N., Jr. Personal communication, 1971.
11. Maltoni, C. Predictive value of carcinogenesis bioassays. Ann. N.Y. Acad. Sci. 271: 431-443 (1976).
12. Caputo, A., Viola, P. L., and Bigotti, A. Oncogenicity of vinyl chloride at low concentrations in rats and rabbits. Int. Res. Communs. 2: 1582 (1974).
13. Maltoni, C., and Lefemine, G. Carcinogenicity bioassay of vinyl chloride: current results. Ann. N.Y. Acad. Sci. 246: 195-218 (1975).
14. Keplinger, M. L., Goode, J. W., Gordon, D. E., and Calandra, J. C. Interim results of exposure of rats, hamsters, and mice to vinyl chloride. Ann. N.Y. Acad. Sci. 246: 219-224 (1975).
15. Holmberg, B., Kronevi, T., and Winell, M. The pathology of vinyl chloride exposed mice. Acta Vet. Scand. 17: 328-342 (1976).
16. Maltoni, C. Vinyl chloride carcinogenicity: an experimental model for carcinogenesis studies. In: Origins of Human Cancer, Book A (H. H. Hiatt, J. D. Watson, and J. A. Winsten, Eds.), Cold Spring Harbor Laboratory, 1977 p. 119.
17. Maltoni, C. Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on experimental basis. NIEHS HIOSH OSHA conference to Re-evaluate Toxicity of Vinyl Chloride, Polyvinyl Chloride and Structural Analogues, Bethesda, Maryland (1980).
18. Tabershaw, I. R., and Gaffey, W. R. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J. Occup. Med. 16: 509-518 (1974).
19. Monson, R. R., Peters, J. M., and Johnson, M. N. Proportional mortality among vinyl-chloride workers. Lancet 2: 397-398 (1974).
20. Nicholson, W. J., Hammond, E. C., Seidman, H., and Selikoff, I. J. Mortality experience of a cohort of vinyl chloride-polyvinyl chloride workers. Ann. N.Y. Acad. Sci. 246: 225-230 (1975).
21. Ott, M. G., Langner, R. R., and Holder, B. B. Vinyl chloride exposure in a controlled industrial environment. a long-term mortality experience in 594 employees. Arch. Environ. Health 30: 333-339 (1975).
22. Duck, B. W., Carter, J. T., and Coombes, E. J. Mortality study of workers in a polyvinyl-chloride production plant. Lancet 2: 1197-1199 (1975).
23. Wagoner, J. K., Infante, P. F., and Saracci, R. chloride and mortality. Lancet 1: 194-195 (1976).
24. Duck, B. W., and Carter, J. T. Vinyl chloride and mortality? Lancet 2: 195 (1976).
25. Waxweiler, R. J., Stringer, W., Wagoner, J. K., Jones, J., Falk, H., and Carter, C. Neoplastic risk among workers exposed to vinyl chloride. Ann. N.Y. Acad. Sci. 271: 40-48 (1976).
26. Byren, D., Engholm, G., Englund, A., and Westerholm, P. Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. Environ. Health Perspect. 17: 167-170 (1976).
27. Reinl, W., Weber, H., and Greiser, E. Epidemiological study on mortality of VC-exposed workers in the Federal Republic of Germany. Medichem. 2 (Sept. 1977).
28. Fox, A. J., and Collier, P. F., Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Brit. J. Ind Med. 34: 1-10 (1977).
29. IARC. Evaluation of Carcinogenic Risk of Chemicals to Humans. 19. Some Monomers, Plastics, and Synthetic Elastomers, and Acrolein. IARC, Lyon, 1979, pp. 378-438.
30. Christine, B. W., Barrett, H. S., and Lloyd, D. S. Angiosarcoma of the liver—Connecticut. Morbidity and Mortality Weekly Report 23: 210 (1974).
31. Baxter, P. J., Anthony, P. P., MacSween, R. N. M., and Scheuer, P. J. Angiosarcoma of the liver in Great Britain, 1963-73. Brit. Med. J. 2: 919-921 (1977).
32. Lilis, R., Anderson, H., Nicholson, W. J., Daum, S. Fishbein, A. S., and Selikoff, I. J. Prevalence of disesase among vinyl chloride and polyvinyl chloride wo . Ann. N.Y. Acad. Sci. 246: 22-41 (1975).
33. Miller, A., Teirstein, A. S., Chuang, M., Selikoff, I. J., and Warshaw, R. Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. Ann N.Y. Acad. Sci. 246: 42-52 (1975).
34. Frongia, N., Spinazzola, A., and Bucarelli, A. Experimental lung damage from prolonged inhalation of airborne PVC dust. Med. Lav. 65: 321-342 (1974).
35. Agarwal, D. K., Kaw, J. L., Srivastava, S. P., and Seth, P. K. Some biochemical and histopathological changes induced by polyvinyl chloride dust in rat lung. Environ. Res. 16: 333-341 (1978).
36. Arnaud, A., Pommier de Santi, P., Garbe, L., Payan, H., and Charpin, J. Polyvinyl chloride pneumoconiosis. Thorax 33: 19-25 (1978).
37. Szende, B., Lapis, K., Nemes, A., and Pinter, A. Pneumoconiosis caused by the inhalation of polyvinyl chloride dust. Med. Lav. 61: 433-436 (1970).
38. Vertkin, Y. I., and Mamontov, Y. R. On the state of the bronchopulmonary system in workers engaged in the manufacture of articles made of polyvinyl chloride. Gigienz Truda Prof. Zabolevaniya, 19: 29 (1970).
39. Mastroangelo, G., Manno, M., Marier, G. Bartolucci, G. B., Gemignani, C., Saladine, G., Simonato, L., and Saia, B. Polyvinyl chloride pneumoconiosis: epidemiological study of exposed workers. J. Occup. Med. 21: 540-542 (1979).
40. Waxweiler, R. J., Smith, A. H., Tyroler, H. A., and Falk, H. An epidemiologic investigation of an excess lung cancer risk in a synthetic chemicals plant. Paper presented at International Congress on Occupational Health, D nik, Yugoslavia, 1978.
41. Brady, J. S., Likeratore, F., Harper, P., Greenwald, P., Burnett, W., Davies, J. N. P., Bishop, M., Polan, A., and Vianna, N. Angiosarcoma of the liver: an epidemiologic survey. J. Natl. Cancer Inst. 59: 1383-1385 (1977).