REGULATORY TOXICOLOGY AND PHARMACOLOGY 7, 120–127 (1987)

A Scientific Basis for the Risk Assessment of Vinyl Chloride

Developed jointly by the Members of the Committee on the Evaluation of Carcinogenic Substances, National Health Council of The Netherlands[1]

Received October 28, 1986

In July 1984 the Minister of Welfare, Public Health and Culture, representing the Dutch government, sent a request to the Health Council of The Netherlands to advise on the health risks presented by environmental exposure to several carcinogenic substances. One of these substances was vinyl chloride (VC). On the basis of a working document prepared by the National Institute of Public Health and Environmental Hygiene, a committee of the Health Council of The Netherlands prepared a report concerning a health risk assessment of VC which was published in May 1986. A short review is presented of the available data and the considerations that formed the basis for the risk assessment of the carcinogenicity of VC to humans. The advice was based mainly on human data from epidemiological studies of workers occupationally exposed to VC. The committee concludes that continuous exposure to 0.001 mg/m^3 VC corresponds to an additional cancer mortality risk of 10^{-6} per lifetime. The Dutch government considers this additional risk to the general population to be acceptable.

INTRODUCTION

Man is continuously exposed to a multitude of substances that are present in the environment in which he lives. A number of these substances possess the capability to induce malignant tumors in animals, humans, or both. Some carcinogens are naturally occurring chemicals and exposure to these can hardly be prevented. Others are man-made, emitted into the environment as a consequence of human activities, and thus exposure can, at least in principle, be reduced to an acceptable level. Reduction of the emission of carcinogens can be achieved by governmental regulation. One of the instruments for such regulation is to set upper limits for pollutants in the environ-

[1] Committee on the Evaluation of Carcinogenic Substances. G. M. H. Swaen, Department of Occupational Medicine, University of Limburg, P.O. Box 616 6200 MD Maastricht, The Netherlands (to whom correspondence should be addressed); A. E. M. de Hollander, *Secretary,* Health Council of The Netherlands, The Hague, The Netherlands; R. Kroes, *Chairman of the Committee,* National Institute of Public Health, Bilthoven, The Netherlands; L. den Engelse, Dutch Cancer Institute, Amsterdam, The Netherlands; V. J. Feron, TNO-CIVO, Toxicology and Nutrition Institute, Zeist, The Netherlands; G. J. Mulder, Department of Toxicology, University of Leiden, Leiden, The Netherlands; A. L. M. Verbeek, Department of Social Medicine, University of Nijmegen, Nijmegen, The Netherlands; H. G. Verschuuren, Dow Chemical Europe, Horgen, Switzerland; E. W. Vogel, Department of Radiation Genetics, University of Leiden, Leiden, The Netherlands; A. W. van der Wielen, Ministry of Housing, Physical Planning and Environment, The Hague, The Netherlands.

0273-2300/87 $3.00

ment that may not be exceeded. These limits are in principle based on qualitative and quantitative information about the carcinogenicity of the specific substance. A particular health risk is then defined as an acceptable risk, which is frequently given as one additional cancer death per one million lives after a lifetime of continuous exposure. This risk will further be referred to as the 10^{-6} risk level. The actual low exposure levels that result in this risk cannot be directly determined and must therefore be estimated by extrapolation. The extrapolation of tumor incidence at high exposure levels to the incidence at low exposure levels is one of the principle problems connected with carcinogenic risk assessment. Several mathematical models have been developed to describe the relationship between the level of exposure to a carcinogen and the probability of developing cancer, none of which have been verified in real life circumstances. In principle two types of data can be used in an extrapolation model for carcinogenic risk assessment:

Data on the carcinogenic response in species other than man from experiments in which animals are exposed to high levels of a carcinogen.

Data on the carcinogenic response in humans circumstantially exposed to high levels of a carcinogen, e.g., industrial epidemiologic studies.

Animal studies should be performed in a rigorously controlled environment and thus ideally are not necessarily subject to bias or confounding by extraneous influences. However, the results must be extrapolated from the animal model to man, which introduces a considerable degree of uncertainty.

Epidemiology can only study the health effects of environmental or occupational exposures as they actually occur or have occurred. Moreover, epidemiological studies are more likely to be subject to bias or confounding due to uncontrolled differences between the exposed and nonexposed groups that have not been investigated. In addition epidemiological studies generally lack precision with respect to exposure data. However, they have the advantage of being actual health effects in humans and thus could provide more relevant information for human risk assessment.

Relatively high human exposures to carcinogens may occur in the occupational environment. Epidemiological studies that evaluate the carcinogenic effects of occupational exposure to particular substances may provide the most significant human data for carcinogenic risk assessment (Cook, 1982; Day, 1985). The purpose of this article is to compare two approaches for carcinogenic risk assessment, taking exposure to vinyl chloride (VC) as the exposure of interest. Long-term health effects of occupational exposure to VC have been entensively studied; thus VC is a chemical for which a good comparison can be made between the two approaches. An extensive review on the health hazards of VC has been compiled by the Dutch National Institute of Public Health and Environmental Hygiene (1984). We will first assess the carcinogenic risk of VC on the basis of animal data. Then we will conduct a risk assessment for VC using human data collected by means of epidemiological studies of workers occupationally exposed to VC. In both types of risk assessment a linear dose–response model has been applied. A linear dose–response relationship is supported by the one-hit stochastic model for carcinogenisis, recommended by the American Food and Drug Administration (1971) and by the Dutch National Health Council (1978). The application of a linear dose–response model was also supported by the occupational mortality study conducted by Weber *et al.* (1981). In this study a subanalysis was undertaken in which the VC exposed cohort was subdivided into

TABLE 1

INCIDENCES OF ANGIOSARCOMAS IN THE EXPERIMENTS OF MALTONI *et al.* (1981) WITH SPRAGUE–DAWLEY RATS AFTER VARIOUS CONCENTRATIONS OF VC

Expt	VC concentration (ppm)	Incidence of angiosarcomas[a] (%)	Ratio of concentration to incidence
BT 1	250	8.5	29
BT 2	200	10.8	19
BT 2	150	5.0	30
BT 2	100	0.8	125
BT 1	50	3.4	15
BT 9	50	7.9	6
BT 15	25	4.2	6
BT 15	10	2.5	4

[a] Hepatic and extrahepatic angiosarcomas.

several dose groups, in terms of duration of exposure. The results of this subanalysis are indicative for the existence of a linear dose–response relationship between the duration of occupational exposure to VC and the subsequent risk of liver cancer mortality.

The pharmacokinetics of VC in animals and humans are still not understood well enough to incorporate an estimation of the "biologically effective dose," based on a pharmacokinetic model for saturable metabolism, in the dose–response extrapolation model, as was proposed by Gehring *et al.* (1978, 1979). Thus this model was not used in the risk assessment of VC.

RISK ASSESSMENT BASED ON ANIMAL DATA

VC is a procarcinogen which requires metabolic activation through the cytochrome *P*-450 system to exert genotoxic properties (Ivanetich *et al.*, 1977). Mutagenic activity of VC has been demonstrated in both *in vitro* and *in vivo* assays (Bartsch and Montesano, 1975; IARC, 1979). In several animal studies the animals exposed to VC by oral dosing developed more tumors than the control populations (Maltoni *et al.*, 1981; Feron *et al.*, 1981). There can be no doubt that VC is a carcinogen in animals. In several studies with mice and rats a clear dose–response relationship was noted between VC exposure and frequency of angiosarcomas of the liver. A series of studies with Sprague–Dawley rats, performed by Maltoni *et al.* (1981), was selected to form the scientific basis for the risk assessment based on animal data because in these studies VC was applied by means of inhalation and because the results suggested a clear dose–response relationship for angiosarcoma of the liver. The results of the experiments conducted by Maltoni with mice and rats are presented in Table 1. A linear, nonthreshold model was applied for risk extrapolation to lower dose levels.

The results of each separate dose experiment were combined by taking the arithmetic mean of the incidence per mg/m^3 of VC applied in each experiment. The arithmetic mean of the ratios was 29, which indicates that in order to increase the incidence of angiosarcoma by 1% an additional concentration 29 ppm VC must be applied,

TABLE 2

RESULTS OF SEVEN OCCUPATIONAL MORTALITY OF WORKERS WITH PAST EXPOSURE TO VC

Reference	Number of exposed workers	Total mortality		Cancer mortality		Liver cancer mortality	
		obs/exp	SMR	obs/exp	SMR	obs/exp	SMR
Tabershaw and Gaffey, 1974 (United States)	8384	352/467	0.75	79/77	1.10	7/0.5[a]	14.0
Weber *et al.*, 1981 (West Germany)	7021	414/435.7	0.95	94/90.6	1.12	12/0.09	15.2
Fox and Collier, 1977 (United Kingdom)	7717	393/521	0.75	115/127	0.91	4/1.64	2.4
Waxweiler *et al.*, 1976 (United States)	1294	136/126	1.08	35/23.5	1.49	7/0.6	11.5
Ott *et al.*, 1975 (United States)	594	89/100	0.89	20/17.9	1.12	0/0	1.0
Theriault and Allard, 1981 (Canada)	451	59/55	1.07	20/13.5	1.48	8/0.14	57.1
Nicholson and Henneberger, 1984 (United States)	257	80/85.6	0.93	28/19.7	1.42	10/0.42	23.8

[a] Estimated.

which equals 74 mg/m^3 VC. Taking the inverse of this ratio, it can be concluded that an average increase of risk of 0.000135 of angiosarcoma per animal will be the result of an increase of 1 mg/m^3 VC. In order to adapt the experimental situation to human lifetime exposure, two conversion factors were introduced. The animals in the experiment were exposed to VC during 20 hr a week. Human exposure to environmental concentrations of VC occur during 168 hr per week, giving a conversion factor of 168/20 = 8.4. A second conversion factor was necessary because the rats were not exposed for 143 weeks, the average life span of a rat, but only 52 weeks, giving a conversion factor of 143/52 = 2.75.

The additional risk of angiosarcoma per mg/m^3 VC concentration for a continuous lifetime exposure for one individual was calculated to be $0.000135 \times 8.4 \times 2.75 = 0.0031$ per mg/m^3 VC. The proposed maximum level for environmental exposure to a particular carcinogen as formulated by the committee is one additional death of cancer per one million lives, giving a lifetime environmental exposure of 0.00032 mg/m^3 VC ($10^{-6}/0.0031$). Thus the committee would consider an environmental exposure to 0.00032 mg/m^3 VC to correspond to a 10^{-6} risk level on the basis of animal data.

RISK ASSESSMENT BASED ON HUMAN DATA

The risk for humans of occupational exposure to VC in industry has been investigated by epidemiologists for groups of workers. All studies used the design of a retrospective cohort study. A group of workers exposed to VC in the past was identified and followed through time to observe the occurrence of cancer in the exposed group.

Based on national statistics an expected number of deaths from a particular disease was calculated, taking into account the age distribution, length of follow-up, and calender period. By dividing the observed number by the expected number, the standardized mortality ratio (SMR) was calculated, which is a measure of the relative risk for a particular cause of death resulting from VC exposure.

Table 2 summarizes the results of the seven largest epidemiological studies on workers exposed to VC. All studies except one indicate an excess mortality from cancer of the liver and in particular of angiosarcoma of the liver (ASL). Other types of cancer also showed a tendency to be increased in incidence, but these increases are not consistent. Total cancer mortality, however, is higher in four out of the seven studies. In order to carry out a risk assessment the results of these epidemiological studies had to be combined to obtain an overall estimate of the relative risk. Prior to combining the results, the studies indicating the highest and the lowest relative risk were omitted, because these studies were considered to be extreme results due to random variation. Three studies were regarded as unbiased estimates of the true standardized mortality ratio. Although the cohort studied by Waxweiler *et al.* (1976) was probably completely included in the study conducted by Tabershaw and Gaffey (1974), both studies were regarded as being independent estimates of the risk of liver cancer after exposure to VC. An alternative analysis after omission of the study conducted by Waxweiler *et al.* revealed similar conclusions. Because the three studies were not of the same size, a weight was given to each study according to its size, based on the standard error of the observed SMR. This weight was the expected number squared divided by the observed number, being the inverse of the variance. The overall SMR was subsequently calculated by dividing the sum of the products of the individual weight and the SMR by the total sum of the weights. The overall SMR for liver cancer mortality obtained in this manner was 13.07, meaning that workers occupationally exposed to VC experienced a 13.07-fold risk of dying of liver cancer. The overall SMR for total cancer mortality is 1.14.

VC concentrations that have occurred at the workplace have varied greatly through time. Barnes (1980) retrospectively estimated these exposures to have been approximately 1000 ppm between 1945 and 1955, between 400 and 500 ppm, from 1955 to 1965; between 300 and 400 from 1966 to 1972; 150 ppm by 1973; and 5 ppm after 1975. Based on these numbers a time-weighted average of 500 ppm for the total exposure period was applied in the risk assessment.

An important aspect of the occupational exposure to VC and its long term health effects as described in the epidemiological studies, is the average duration of exposure. In the report of the large cohort study of VC exposed workers, conducted in the United States by Tabershaw and Gaffey (1974), it was stated that the average duration of VC exposure was 8.7 years. The committee decided that for the risk assessment for the duration of exposure of all three cohorts 8.7 years would be taken. In summary, epidemiological studies of workers occupationally exposed to an average concentration of 500 ppm for an average duration of 8.7 years indicated that these workers experienced a 13-fold risk of liver cancer as compared to the general population. Total cancer mortality was 1.14 times the cancer mortality in the general population.

Extrapolation to Lifetime, Continuous Exposure

A number of steps must be taken before the risks existing for workers exposed to 500 ppm VC for a period of 8.7 years can be converted into estimated risks of lifetime,

continuous exposure to low concentrations. The first step is to convert the intermittent exposure occurring for 8 hr/workday to a continuous lifetime exposure. A workweek usually consists of 40 working hr, whereas a total week consists of 168 hr. Therefore a conversion factor of 168/40 = 4 must be applied. This means that an exposure encountered only at the workplace corresponds to one-fourth of the dose resulting from a continuous exposure to the same concentration.

The second step is the calculation of the conversion factor for the duration of the time-limited VC exposure experienced by the workers to lifetime exposure to ambient air concentrations of VC. The workers studied by epidemiological methods were exposed for an average duration of 8.7 years. Given an average lifetime of 70 years, lifetime exposure results in a 70/8.7 = 8-fold higher dose at equal concentrations. The conversion from 500 ppm during 40 hr per week, for 8.7 years ($500 \times \frac{1}{4} \times \frac{1}{8}$ ppm), leads to a lifetime exposure of 15.6 ppm. An estimated SMR of 13.07 will result from lifetime exposure to 15.6 ppm.

Extrapolation to the 10^{-6} Risk Level

Extrapolating the effects of high exposures to low concentrations can only be done if certain assumptions are made regarding the dose–response relationship. We will assume a linear dose–response relationship. This straight line is defined by two points. Having identified two points on the straight line, it is possible to express this line by means of a mathematical equation: $SMR = 1 + b \times c$ (in which c is the lifetime exposure concentration). Calculate b from the model: $SMR = 1 + b \times c$, if $c = 15.6$ and SMR = 13.07. Thus, $b = 0.774$. The dose–response relationship is $SMR = 1 + 0.774 \times c$. The next step is to express the 10^{-6} risk level in terms of an SMR. The accepted risk is expressed as one additional death by cancer per one million lives. In The Netherlands 1484 per million people die of liver cancer (CBS, 1980). One additional case would be 1485, giving an SMR of 1485/1484 = 1.00067.

By means of the above equation for the linear dose–response relationship, the concentration of VC for lifetime exposure can be calculated, resulting in this SMR of 1.00067: $SMR = 1 + b \times c$, $c = 0.0008$ ppm.

A lifetime exposure to a concentration of 0.0008 ppm = 0.002 mg/m^3 VC is expected to lead to an additional 10^{-6} risk. However, it can not be excluded that there are other cancer types related to VC exposure, or perhaps cancer unrelated to specific sites. In fact four of the seven epidemiological studies presented in Table 1 showed elevated cancer mortality.

The overall SMR of the three studies used earlier for cancer mortality is 1.14 for all types of cancer. The lifetime exposure concentration remains 15.6 ppm.

$$SMR = 1 + b \times c$$

if $c = 15.6$ and SMR = 1.4, then

$b = 0.009$, giving $SMR = 1 + 0.009 \times c$.

In The Netherlands about 250,000 per one million deaths are due to cancer (CBS, 1980). One additional death will then result in an SMR of

$$250{,}001/250{,}000 = 1.000004$$

$$SMR = 1 + 0.009 + c$$

thus, $c = 0.000004/0.009 = 0.00044$ ppm = 0.001 mg/m^3 VC. It was concluded that a lifetime exposure to 0.001 mg/m^3 VC results in an additional risk to the general population of one death per million lives.

DISCUSSION

Epidemiological data have rarely been applied in environmental risk assessment. Extrapolation on the basis of experimental data as well as epidemiological data suffers from a number of shortcomings. The main uncertainty of a risk assessment based on animal experiments is extrapolation to humans. Differences in body size, metabolism, DNA-repair mechanisms, and immunological responses can lead to differences in response to exposures to carcinogens between animals and humans. As pointed out by many researchers on many occasions, the linear, nonthreshold dose–response model is likely to be an oversimplification of the complex process of carcinogenesis. However, no ideal model incorporating relevant biological mechanisms is yet available, or will be in the near future. Therefore a simple model of a conservative nature was considered to be most appropriate for environmental carcinogen risk assessment of VC.

The main uncertainty of a risk assessment based on human data is the lack of exact information with respect to the actual past exposures. Application of a linear extrapolation to these two different types of data resulted in two different environmental exposure limits, being 0.00032 mg/m^3 VC based on the experimental data and 0.001 mg/m^3 VC based on human data, which differ only by a factor of 3. Because of the existence of extensive human data the committee decided to base its risk assessment on human data. Conseqently, the Dutch Government was advised to take 0.001 mg/m^3 VC as an exposure corresponding to an additional risk of one death per million individals exposed for a lifetime as the scientific basis for the development of air quality standards.

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