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To: The Vinyl Institute Health, Safety & Environment Committee
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The attached article "Vinyl Chloride: An Assessment of the Risk of Occupational Exposure" (Fd. Chem. Toxic, Vol. 25, No. 2, 1987) is for your information and files.

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MNS/pmb
attachment

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Review Section

VINYL CHLORIDE: AN ASSESSMENT OF THE RISK OF OCCUPATIONAL EXPOSURE*

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Introduction

Vinyl chloride monomer (VCM), more properly named monochlorethane, is a colourless gas normally handled under pressure as a liquid which boils at −14°C at normal pressure. Discovered around 1835, VCM's commercialization did not begin until the 1930s and did not reach high volume until after 1945. Present manufacture is around 12×10^6 tonnes per annum, nearly all of which is used to make the polymer polyvinyl chloride (PVC).

Until the 1960s, VCM was regarded as a material of low human toxicity and the main concerns were related to the compound's narcotic effect. Indeed there are many reports of employees exposed to VCM monomer in polymer plants becoming dizzy and unconscious. Because VCM was considered to be relatively innocuous, it had a threshold limit value (TLV) of 500 ppm, 8-hr time-weighted average [TWA) for many years (ACGIH, 1974; Lester *et al.* 1963; Torkelson *et al.* 1961). Measurements of employee exposure were infrequent, since most measurement and warning systems were designed to ensure that plant atmospheres were beyond the explosive limits, fire and explosion being the main hazards of VCM. Retrospective estimates (Barnes, 1976) of typical TWA personal exposures (in ppm) for polymerization workers have been cited as: 1000 in 1945–1955, 400–500 in 1955–1960, 300–400 in 1960–1970, 150 in mid-1973 and 5 in 1975. However in some jobs, particularly in the cleaning of the autoclaves in which VCM is polymerized to PVC, very-much higher exposures, in thousands of ppm, were undoubtedly experienced for short/medium periods, since in some plants operators became faint and unconscious from time to time.

The first clear indication of chronic health problems associated with VCM arose in the 1960s in men who entered VCM polymerization autoclaves to remove build-up of polymer from the walls. Some of these men developed acro-osteolysis (AOL; Cook *et al.* 1971; Harris & Adams, 1967; Suciu *et al.* 1963). Modification of working practices led to a reduction in the incidence of AOL cases in autoclave cleaners. Although AOL is occasionally seen in people not exposed to VCM (Meyerson & Meier, 1972; Wilson *et al.* 1967) it is a rare disease. In the late 1960s, studies in rats involving exposure to high concentrations of VCM for long periods (Viola, 1969) failed to produce AOL but showed an increase in the incidence of tumours at various sites.

Further studies (Maltoni *et al.* 1980 & 1981; Maltoni & Rondinella, 1980) showed the rare tumour angiosarcoma of the liver (ASL) in exposed rats, and confirmed VCM as an animal carcinogen. Three ASL cases in employees at a PVC polymerization plant (Creech & Johnson, 1974) confirmed VCM as a human carcinogen. Other known aetiological agents for ASL in man were thorium dioxide, arsenic and, possibly, anabolic steroids (Maltoni *et al.* 1980).

Since 1974, the health hazards of VCM have been the subject of many investigations, scientific papers, seminars and other presentations (Conference to Reevaluate the Toxicity of Vinyl Chloride Monomer, Poly(vinyl Chloride) and Structural Analogs, 1981; Gauvain, 1976; IARC Working Group, 1979; Selikoff, 1975; Szadkowski & Lehnert, 1982; US DHEW, 1980). The plethora of information (and misinformation) now available suggests that an objective historical case study of VCM would be of value.

Experimental and human data

Experimental studies

The principal effect seen in the acute and subacute studies is anaesthesia, which occurs at relatively high

*A longer version of this paper has been published in *Toxicological Risk Assessment*, edited by D. B. Clayson, D. Krewski and I. Munro and published by CRC Press, Inc., Boca Raton, FL (1985).

Abbreviations: AOL = acro-osteolysis; ASL = angiosarcoma of the liver; PVC = polyvinyl chloride; TLV = threshold limit value; TWA = time-weighted average; VCM = vinyl chloride monomer.

Table 1. Lowest concentrations or doses at which a significant excess of various tumour types was observed in rat carcinogenicity studies

Tumour	Concn (ppm)	Dose (mg/kg)
Forestomach papilloma	30,000	
Zymbal-gland carcinoma	10,000	
Neuroblastoma	10,000	
Nephroblastoma	250 (female)	
	100 (male)	
Liver angiosarcoma	200	50 (male)
	50	16.65 (female)
Mammary-gland adenocarcinoma	5 (female)	

Data from Maltoni *et al.* (1981).

doses (7–10%) in both animals and man. The doses responsible for acute toxicity are about 1000-fold higher than the minimum dose for carcinogenicity and there is frequently no sign of overt organ toxicity prior to the development of the carcinogenic response.

VCM is mutagenic in a variety of test systems including *Salmonella typhimurium* (Rannug *et al.* 1976), Saccharomyces (Loprieno *et al.* 1977) and Drosophila (Verburgt & Vogel, 1977), usually with some form of mammalian microsomal metabolizing system to convert VCM into its active metabolites, chloroethylene oxide and chloroacetaldehyde. The data on the mutagenicity of VCM provide useful qualitative information on its mode of action and metabolism, but are not suitable for the quantitative estimation of risk to man.

The most useful experimental data are derived from long-term animal carcinogenicity studies. An extensive series of 17 studies (Maltoni *et al.* 1981) gives a useful database for risk assessment. Other studies (Feron *et al.* 1981; Lee *et al.* 1978) tend to confirm the findings of Maltoni.

Carcinogenic effects were observed in mice, rats, and hamsters. A complication in the selection of these data for risk assessment is the variety of tumour types observed (Table 1). Some of these occurred at very high exposure levels, but mammary adenocarcinoma in females and ASL in both sexes of both rats and mice occurred at 50 ppm or less, exposures similar to those believed to have occurred on manufacturing plants (Barnes, 1976).

Epidemiological studies

Several major epidemiological studies on workers exposed to VCM have been reported (Table 2). The main organs that have been associated with higher incidences of cancer in workers exposed to VCM are the liver, lung and brain. Increases in the standardized mortality ratios of cancers in the buccal cavity and pharynx, of lymphomas and of cancers of the lymphatic and cardiovascular systems have been reported in one or two studies. The analysis of cancer of the respiratory system is often confounded by smoking, making quantitative analysis of the contribution of VCM difficult. The excess of liver cancers is due to an excess of ASL in many of the studies.

An analysis of the statistical power of various studies for association between VCM exposure and cancer of the lung, liver and brain (Beaumont & Breslow, 1981) concluded that the results for liver were consistent with an aetiological role for VCM. For brain cancer, where three out of five studies had statistically significant findings, the results were more variable, positive findings occurring in the studies with the greatest statistical power. The most reasonable interpretation was that the data were consistent with a causal association between VCM exposure and an excess of brain cancer. Infante (1981), in reaching the same conclusion, points out that the relative risk for brain cancer is much lower than that for liver cancer. Only two out of eight studies on lung cancer (Beaumont & Breslow, 1981) yielded statistically significant results and, because studies with a high power were negative, a causal association was considered unlikely.

ASL is the most suitable endpoint for analysis of the risk of exposure to VCM for a number of reasons. It is a rare cancer in unexposed populations, making attribution to VCM exposure on the basis of work history a reasonable approach. ASL occurs in both animals and humans exposed to VCM and it is unlikely that any other carcinogenic effect of VCM will be found to occur at lower exposures than the lowest exposures that induce ASL. For these reasons, most work on the quantitative risk assessment of chronic exposure to VCM has used ASL as the endpoint to study.

Case register

The availability of data from a comprehensive case register of ASL cases with a history of occupational exposure to VCM provides an opportunity to identify risk factors for the induction of ASL.

Persons potentially exposed to vinyl chloride

Current manufacture and use of VCM and PVC results in the potential exposure of four groups of the population. The highest exposure category covers the workers involved in the manufacture of VCM, its polymerization to PVC and certain other industrial uses of VCM. Within this group, certain occupations, particularly autoclave cleaning, involve higher potential exposure than others, although all groups would now be expected to have exposures complying with hygiene standards of 1–5 ppm.

The next category covers those exposed as a result of using the PVC. Workers in the compounding and fabrication of PVC products are exposed to residual VCM released from PVC on heating (but PVC does not decompose to VCM when heated). In general the exposure levels for these workers are very low in comparison to those for PVC polymerization workers (from 10 to 100 times lower).

Consumers who eat food and drink beverages that have been packed in PVC may ingest unreacted VCM

which has migrated into the food or beverage. Since 1974, the amount of VCM in PVC has been reduced to less than 1 mg/kg with the result that the maximum human daily intake of VCM in food and drink is 0.1 μg/day (Ministry of Agriculture, Fisheries & Food, 1978).

The fourth group with potential exposure to VCM are those who live in the vicinity of VCM or PVC manufacturing or fabricating factories. The levels in ambient air around a factory are very low (in the parts per 10^9 range) but much larger population groups, which include all age groups, are involved.

For the workers in VCM manufacture and PVC polymerization and fabrication, the route of exposure is by inhalation. Much of the animal carcinogenicity data are based on inhalation exposure and the human epidemiology is predominantly of populations exposed occupationally by inhalation. Thus an assessment of the risk factors and the quantitative risk of inhalation exposure is the main objective. For the consumer exposed to VCM via food and beverages the route is by ingestion. Relatively few experimental studies have used oral administration and only one study used a comparable exposure pattern (Feron *et al.* 1981). Similarly there are no specific epidemiological data on oral ingestion. Risk assessment for exposure via the oral route must rely on the existing animal data and on extrapolation from epidemiological and experimental studies of inhalation exposure.

Risk assessment from experimental animal data

Assumptions

In carrying out a risk assessment on the basis of animal data, a number of assumptions have to be made. The first of these relates to the overall dosimetry. Experimental animals are exposed to concentrations of vinyl chloride or dosed with amounts of vinyl chloride that allow an estimate of the amount to which they have been exposed. It is possible to calculate a correction factor for these quantities so that they are applicable to man. However, rats and mice live for relatively short periods of time (up to 2 years) during which they develop cancers of a type similar to those seen in man. The latent period for the same tumours in man may be between 20 and 40 years. It is therefore assumed that the lifetime of man is equivalent to the lifetime of an experimental animal species even though the chronological time is substantially different.

Strictly speaking, mathematical extrapolation of risk on the basis of experimental animal data provides an estimate of the risk at low doses to the experimental animal under consideration. A variety of factors, particularly inherent biological susceptibility and differences in metabolism, render the extrapolation of the data from animals directly to man subject to numerous errors. It is at this point that scientific judgement is required to decide whether these data are applicable to the human situation.

Metabolism

In rats, VCM has been shown to be metabolized extensively, producing a range of excretion products. After administration by gavage or inhalation, part of the dose is exhaled unchanged and the remainder is excreted or retained in the carcass. A general scheme

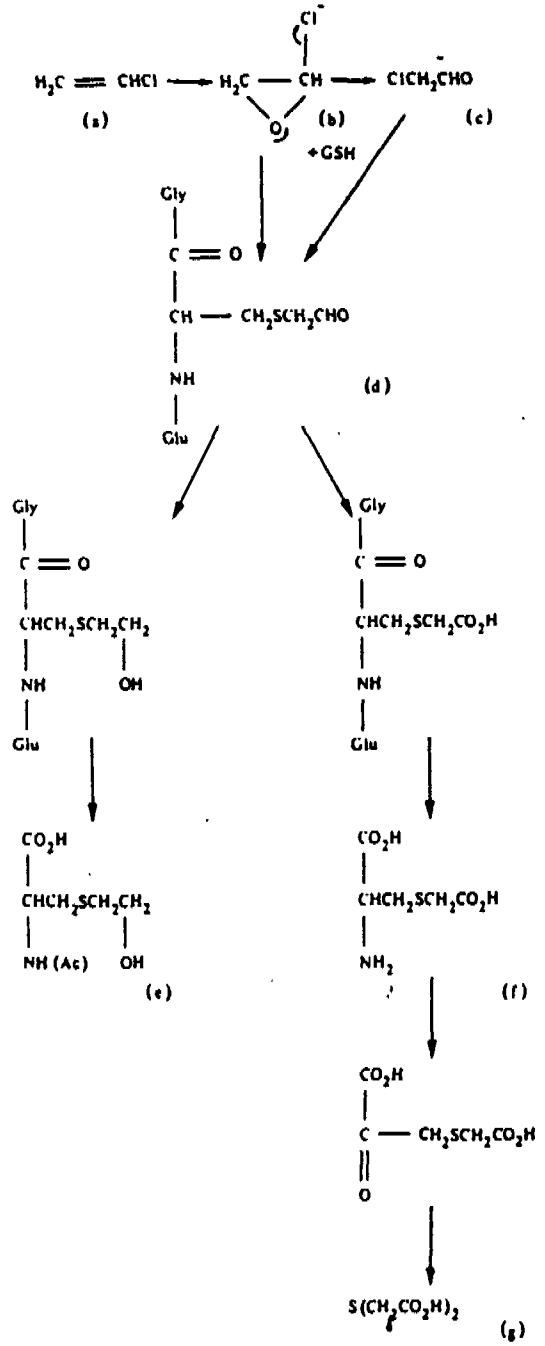

Fig. 1. Scheme showing the metabolism of vinyl chloride monomer (VCM) in rats to *S*-containing metabolites. VCM (a) is converted to chloroethylene oxide (b) which is transformed spontaneously to chloroacetaldehyde (c). These two metabolites are mutagenic and hence are considered to be the proximate carcinogens. The urinary excretion products *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (e) *S*-(carboxymethyl)-cysteine (*f*) and thiodiglycollic acid (*g*) are derived from these mutagenic metabolites via (d). Gly and Glu are the glycine and glutamate residues of glutathione. [After Green & Hathway (1977)].

Table 2. Epidemiological studies of cancer associated with exposure to vinyl chloride monomer

Reference	No. in study* (% follow up)	Sites (or tumours) with changes in SMR		
		Increase	No increase	Comments
Monson *et al.* (1974)	?	Brain Lung Liver, including ASL		
Tabershaw & Gaffey (1974)	8384 (85%)	Buccal cavity and pharynx Respiratory system Unknown site Lymphoma Angiosarcoma		Significant SMR not significant but increases with exposure and time
			Genital Digestive organs Urinary tract Leukaemia	
Duck *et al.* (1975)	2120	None		Some criticism of conduct of study
Nicholson *et al.* (1975)	257 (99%)	ASL		
Ott *et al.* (1975)	594 (99%)	All tumours?		Arsenicals involved
Byren *et al.* (1976)	771 (97%)	Liver/pancreas		Significant increase (2 ASL)
		Cerebral?		Increase not significant
		Cardiovascular		
ORC (1976)	10,173 (95%)	Digestive tract		PMR study
Reinl & Weber, 1976; Reinl *et al.* 1978; Weber *et al.* 1981	11,028 (90%)	Malignant liver Lymphatic system GI tract	Brain	Related to duration of exposure
Waxweiler *et al.* (1976)	1151	Brain Respiratory tract Lymphatic system ASL		Mixed exposure, not VCM related
Fox & Collier (1977)	7409 (99%)	Primary liver ASL		Not significant Significant
			Stomach Brain Lymphatic and haemopoietic system	
Fretzel-Beyme *et al.* (1978)	1618 (95%)	Colon/stomach Prostatic hyperplasia		
Bertazzi *et al.* (1979)	5441 (86%)	All tumours		
Buffler *et al.* (1979)	464 (100%)	Respiratory system		
Chiazze & Ference (1981)	3847	Digestive system		PMR study of female and male fabricators
Chiazze *et al.* (1980)			Breast	Increase in PMR not confirmed by case-controlled study
Beaumont & Breslow (1981)		Liver Brain	Respiratory tract	Review of nine studies

Cooper (1981)	10,173 (95%)	Brain			Follow up of Tabershaw and Gaffey's study. No increase in incidence of brain cancer with increase in exposure	
				Buccal cavity and pharynx		
				Respiratory tract		
				Digestive system		
				Brain		
				Lung		
Theriault & Allard (1981)	1310 (97%)	Liver		Liver	No ASL	
Filatova *et al.* (1982)	3232 (100%)	Lymphatic and haemopoietic systems				
Theriault (1982)	1310 (97%)	Digestive system (liver)		Lung	Lung SMR = 42.6	

ASL = Angiosarcoma of the liver SMR = Standardized mortality rate PMR = Proportional mortality rate

*With percentage follow-up in brackets.

of VCM metabolism in rats is given in Fig. 1. On the basis of this scheme, the highly reactive intermediates in the metabolic process (particularly chloroethylene oxide) react with cellular macromolecules, including DNA to produce the critical lesions leading to mutation or the induction of cancer.

Studies on the quantitative aspect of VCM metabolism have shown that there is a dose dependency in the rate of metabolism. After administration of ^{14}C-labelled VCM by gavage at doses between 0.5 and 100 mg/kg to Wistar rats, the amount of ^{14}C excreted in the urine and faeces and retained in the carcass was estimated over 72 hours (Watanabe & Gehring, 1976). As the dose of VCM was increased, the proportion exhaled increased and that excreted in the urine and faeces decreased (Fig. 2). The proportion retained in the carcass also decreased. The same general trend occurred after administration by inhalation, although the magnitude of the differences in retention and excretion was less (Watanabe & Gehring, 1976).

Studies of the amount of non-volatile material retained in the carcasses of rats exposed to various levels of ^{14}C-labelled VCM for 6 hours demonstrated that the metabolism of VCM appeared to be in accordance with Michaelis–Menten kinetics (Gehring *et al.* 1978). The constants for maximum velocity of metabolism (V_m in μg metabolized/6 hr) and the Michaelis constant (K_m in μg VCM/litre air) according to the formula:

$$V = \frac{V_m S}{K_m + S}$$

(where V = velocity of metabolism in μg/6 hr and S = concentration of VCM being inhaled) were $V_m = 8558\ \mu$g metabolized/6 hr and $K_m = 860\ \mu$g VCM/litre air. Thus there was a considerable change in the ratio of administered dose to metabolized dose as the exposure concentration increased (Table 3). At the higher doses a smaller proportion of VCM was metabolized than at low doses.

Review of earlier calculations of risk

There have been a number of attempts to calculate the risk of ASL development on the basis of extrapolation from experimental data. These have been reviewed by Barr (1982) and an adaptation of his data is presented in Table 4.

The introduction of biotransformation data into the estimation of risk increased the level of exposure calculated to cause a 10^{-6} lifetime risk, from parts per billion to in excess of one part per million. A further refinement of the technique using DNA binding as the measure of dosimetry (Anderson *et al.* 1980) provided a similar estimate of the exposure.

A variety of mathematical models can be used for extrapolating below the experimental dose range, and it is not possible to select from amongst these mathematical models on the basis of goodness of fit to experimental data. Attempts to do so have shown that most of the models fit the data equally well (Gehring *et al.* 1979). It is equally difficult to select amongst the models on the basis of the assumed mechanism of action of VCM. Thus a comparison of the lifetime risks calculated using the Armitage–Doll

Table 3. Vinyl chloride dose and incidence of hepatic angiosarcoma in Sprague–Dawley rats exposed on 5 days/wk for 52 wk*

Concn (ppm)	Amount metabolized		Angiosarcoma incidence (%)			Expmt no.
	μg/4 hr	μg (total)	Male	Female	Mean	
30,000	5647	1.47×10^6	16.6	43.3	30.0	BT 6†
10,000	5521	1.44×10^6	10.0	13.3	11.7	BT 1
6000	5403	1.41×10^6	10.3	33.3	22.0	BT 1
2500	5030	1.3×10^6	20.0	23.3	21.7	BT 1
500	3413	8.8×10^5	0	20.0	10.0	BT 1
250	2435	6.3×10^5	3.4	6.7	5.1	BT 1
200	2129	5.5×10^5	11.7	8.3	10.0	BT 2
150	1761	4.6×10^5	1.7	8.3	5.0	BT 2
100	1309	3.4×10^5	0	1.7	0.8	BT 2
50	739	1.9×10^5	1.1	7.2	4.2	BR 1, 9
25	395	1.0×10^5	1.7	6.7	4.2	BT 15
10	169	4.4×10^4	0	1.7	0.8	BT 15
5	84	2.2×10^4	0	0	0	BT 15
1	17	4.4×10^3	0	0	0	BT 15
0	0	0	0	0	0	BT 1, 2, 9, 15

*After Maltoni *et al.* (1981).
†Experiment BT 6 ended after only 68 wk, while the rest were all approximately 140 wk; therefore the percentage of tumours in BT 6 is probably low relative to the rest because of the short latency period available.

multistage model by the Food Safety Council (1980) and by Gaylor & Kodell (1980) showed that for the same 10^{-6} lifetime risk, the Food Safety Council estimated the dose as 2×10^{-2} ppm whereas Gaylor & Kodell estimated the dose as 5×10^{-4} ppm. The difference between these two estimates was due to alternative assumptions on the value of the expansion of the exponential term used.

In general, calculations based on the amount of material metabolized or on human data have produced exposure values of about 1 ppm for a 10^{-6} lifetime risk. All the other studies have produced exposure values in the ppb range. A large variable appears to be the selection of the mathematical model applied to the experimental data.

In the following section two models are used to calculate the exposure for a 10^{-6} risk from a variety of experimental animal data applying the correction for metabolism used by Gehring *et al.* (1979).

Calculation of exposure for 10^{-6} risk

A summary of the crude ASL incidence rates for inhalation studies in Sprague–Dawley rats is given in Table 3. Similar data for Wistar rats exposed by

Table 4. Summary of quantitative risk assessments for vinyl chloride monomer*

References	Species	Exposure for 10^{-6} lifetime risk (ppb†)	Comments
		By inhalation	
Schneiderman *et al.* (1975)	Rat	73	Probit (slope = 1, Mantel)
		119	Logit (slope = 3.45)
		2	Logit (slope = 2.3, one-hit)
Kuzmack & McGaughy (1975)	Rat, man	14	Linear through zero
		140–1400	Log-probit
Gehring *et al.* (1979)	Rat, man	>1000	Biotransformation data included
			Linear or log-probit
	Rat	<10–>1000	Depends on mathematical model used
Food Safety Council (1980)	Rat	20	One-hit
		20	Armitage–Doll
		2.1×10^{-4}	Weibull
		3.9×10^{-7}	Multi-hit
Anderson *et al.* (1980)	Rat, man	>1000	DNA binding used for dosimetry
Gaylor & Kodell (1980)	Rat	0.7	Upper 97.5% confidence limit of linear model
		0.5	Armitage–Doll
Carlborg (1981)	Rat	2.5×10^{-5}	Weibull
Barr (1982)	Man	>100	Derived from Barr's negative epidemiology
This paper (Table 9)	Rat	0.025–9.16	Log-probit
	Mouse	2×10^{-13}	
	Man	0.63–90	Log-probit including biotransformation data for man
	Rat	2×10^{-3}–2×10^{-8}	Weibull
	Mouse	6×10^{-43}	
	Man	0.067–8.14	Weibull including biotransformation for man
		By ingestion	
EPA (1980)	Rat	4 μg/day	Food or water
NAS (1980)	Rat	3×10^{-3} mg/kg/day	Water
Crump & Guess (1980)	Man	0.7 μg/day	Applying worker data to water
	Rat	0.5 μg/day	Upper 95% confidence limits

*After Barr (1982).
†Except where stated otherwise.

inhalation (Table 5) for rats exposed orally (Table 6) and for mice exposed by inhalation (Table 7) are also presented. Data from experiments with various exposure periods of short duration are given in Table 8. For calculating the amounts of the dose metabolized in rats in the inhalation experiments, the constants calculated (Gehring *et al.* 1978) have been applied. For Wistar rats, the K_m and V_m values derived for Sprague–Dawley rats have been used. These estimates of metabolized dose have been included in the tables.

For the experiment in which VCM was given by gavage, the data from Fig. 2 were used to estimate the amount of VCM exhaled unchanged. As the $t_{1/2}$ for exhalation of VCM was 14 minutes, these data based on a 72-hour period give a good estimate of the fraction of VCM exhaled in the 24 hours between doses. It has been assumed that the VCM not exhaled was metabolized, an assumption similar to the one used for estimating metabolized dose in the inhalation experiments. Green & Hathway (1975 & 1977) showed that VCM administered by gavage to Wistar rats was exhaled and metabolized in a similar manner to that in the Sprague–Dawley rats, and the V_m and K_m values derived for Sprague–Dawley rats have been used. In the experiments by Feron *et al.* (1981), who used Wistar rats, the same assumptions about V_m and K_m have been made. The quantity of VCM administered has been dealt with as if it had been administered by gavage.

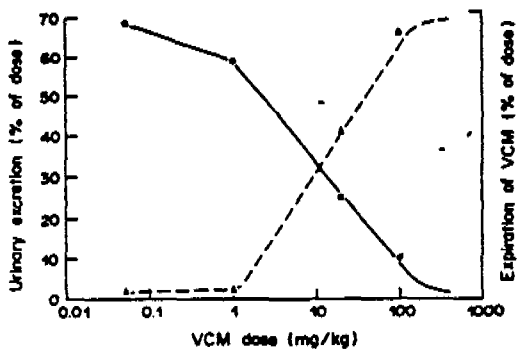

Fig. 2. Summary of dose-dependent urinary and pulmonary excretion of vinyl chloride monomer (VCM). Urinary excretion (●) represents metabolites of VCM, while pulmonary elimination (▲) is unchanged VCM. [After Watanabe & Gehring (1976)].

For mice, the data have been combined in Table 7. The estimation of the dose metabolized in mice has been calculated using values for V_m that have been adjusted on the basis that, for a chemical requiring metabolism to its active form, the quantity metabolized will be proportional to the body surface area and must be expressed in terms of metabolized dose/kg body mass. This technique has also been used by Gehring *et al.* (1978) for estimating the dose metabolized by man.

Table 5. Vinyl chloride dose and incidence of hepatic angiosarcoma in male Wistar rats exposed on 5 days/wk for 52 wk

Concn (ppm)	Amount metabolized		Angiosarcoma incidence (%)	Expmt no.
	μg/4 hr	μg (total)		
10,000	5521	1.4×10^6	29.6	BT 7
6000	5403	1.4×10^6	11.5	BT 7
2500	5030	1.3×10^6	12.0	BT 7
500	3413	8.8×10^5	10.7	BT 7
250	2435	6.3×10^5	3.7	BT 7
50	739	1.9×10^5	0	BT 7
1	17	4.4×10^3	0	BT 17
0	0	0	0	BT 7, 17

Table 6. Vinyl chloride (VCM) dose and incidence of hepatic angiosarcoma in rats given VCM by gavage or ingestion

Dose (mg/kg)	Amount exhaled* (% of dose)	Amount metabolized		Angiosarcoma incidence (%)			Expmt no.
		μg/dose†	μg (total)	Male	Female	Mean	
50‡	50	6250	1.6×10^6	20	22.5	21.2	BT 11
16.65	35	2705	7.0×10^5	10	15.1	12.5	BT 11
3.33	10	750	2.0×10^5	0	0	0	BT 11
1.0	2	3245	7.26×10^4	1.3	2.7	2.0	BT 27§
0.3	1.7	74	2.16×10^4	0	1.4	0.7	BT 27
0.03	1.4	7.4	2.16×10^3	0	0	0	BT 27
0	—	0	0	0	0	0	BT 11, 27
300‖	80	15,000	6.2×10^6	49	53	51	Feron *et al.* (1981)
14.1¶	32	2390	1.65×10^6	49	16	32	
5.0	16.5	1040	7.25×10^5	10	4	7	
1.7	2	420	2.9×10^5	0	0	0	
0	69	0	0	0	0	0	

*Calculated from data derived from Watanabe & Gehring (1976) presented in Fig. 2.
†Assuming a 250-g rat.
‡Sprague–Dawley rats dosed by gavage with VCM in corn oil 5 times/wk for 52 wk.
§BT27 dosed for 59 wk.
‖Wistar rats used as controls by Feron *et al.* (1981) and dosed for 83 wk.
¶Wistar rats receiving a diet containing VCM dissolved in PVC.

Table 7. Vinyl chloride dose and incidence of hepatic angiosarcoma in mice

Concn (ppm)	Amount metabolized		Angiosarcoma incidence (%)			Expmt no.
	μg/4 hr	μg (total)	Male	Female	Mean	
10,000	11,245	1.7×10^6	3.8	30	17.8	BT 4*
6000	11,007	1.7×10^6	6.7	36.7	21.7	BT 4
2500	10,246	1.5×10^6	20.7	33.3	27.1	BT 4
1000	8699	3.4×10^6	39.4	50.0	44.7	Lee *et al.*†
500	6952	1.0×10^6	20.0	26.7	23.3	BT 4
250	4959	7.4×10^6	30.0	30.0	30.0	BT 4
250	4959	7.4×10^6	24.0	47.0	36.5	Lee *et al.*†
50	1506	2.2×10^5	3.3	0	1.7	BT 4
1	1506	5.9×10^5	10.3	0	5.2	Lee *et al.*†
0	0	0	0	0	0	BT 4 & Lee *et al.*

*Swiss mice, 81-wk experiment, dosed for 30 wk.
†CD, mice, 52-wk experiment, 6 hr/day exposure (Lee *et al.* 1978). These results have not been included in the calculations for Table 9 because the experimental design incorporated interim kills.

Thus:

$$V_m \text{ (mouse)} = V_m \text{ (rat)} \times \frac{0.011\ m^2}{0.045\ m^2}$$

$$= 5706\ \mu g/4\ hr \times \frac{0.011}{0.045}$$

$$= 1395\ \mu g/4\ hr$$

The values of 0.045 m^2 and 0.011 m^2 are the body surface area of a rat and a mouse, respectively. Since toxicity is a function of the concentration of the toxic metabolite in the tissue, the amount transformed must be normalized for mass to estimate an equivalent response. Thus V_m must be adjusted on the basis of the body weights of a rat (0.25 kg) and a mouse (0.03 kg) by dividing by 0.03/0.25 = 0.12.

The V_m for the mouse on a mass-equivalent basis is therefore:

$$\frac{1395}{0.12} = 11625\ \mu g/4\ hr$$

This value of V_m has been used in calculating the total amount of VCM metabolized (Table 7).

From the variety of models (or mathematical extrapolation techniques) used for low-dose risk extrapolation (Table 4), an arbitrary choice of models has been made to test the robustness of the extrapolation from the different animal studies.

A log-probit analysis of the dose that would be expected to produce a lifetime risk of ASL of 10^{-4} is presented in Table 9. This calculation can be carried out on the basis of the concentration inhaled, the daily dose metabolized or the total quantity metabolized during the whole experiment. There is a wide variation in the estimated dose depending on the database used for the calculation. The largest variation between doses derived from the rat experiments is 360-fold (0.025 ppb *v.* 9.1 ppb) when exposure in ppb is considered, but this decreases to 100-fold for other estimates of dose. The results from mice are substantially lower when expressed in ppb (2×10^{-15} ppb) but the difference is less for other expressions of dose.

Similar calculations of the dose expected to give a 10^{-6} lifetime risk of ASL have been based on a Weibull analysis (Table 9). This is a more 'conservative' mathematical model and the estimates of dose are accordingly lower. The variation in estimates of dose is, if anything, larger than that observed with the log-probit analysis (for example, a 10^{-5} difference between the S values derived from Wistar and Sprague–Dawley rats). The doses for mice are so much lower than those calculated for rats or man that the assumptions used in their calculation must be suspect.

A further calculation to derive the human dose likely to produce a risk of 10^{-6} is given in Table 9 (S calculated for man). These calculations are based on a V_m for man of 1675 μg/8 hr based on corrections for body surface area and mass. The values are substan-

Table 8. Vinyl chloride (VCM) dose and hepatic angiosarcoma incidence in Sprague–Dawley rats exposed to VCM by inhalation

Concn (ppm)	Schedule†	No. of doses	Amount metabolized‡		Angiosarcoma incidence (%)			Expmt no.
			μg/4 hr	μg (total)	Male	Female	Mean	
10,000	I	260	5521	1.4×10^6	10	13.3	11.7	BT 1
10,000	II	85	5521	4.7×10^5	0	0	0	BT 3
10,000	III	25	5521	1.4×10^5	1.7	0	0.8	BT 10
10,000	IV	100	1379	1.4×10^5	1.7	0	0.8	BT 10
10,000	V	25	5521	1.4×10^5	0	1.7	0.8	BT 10
6000	I	260	5403	1.4×10^6	10.3	33.3	22.0	BT 1
6000	II	85	5403	4.6×10^5	0	3.3	1.7	BT 3
6000	III	25	5403	1.4×10^5	0	0	0	BT 10
6000	IV	100	1350	1.4×10^5	3.4	1.7	2.5	BT 10
6000	V	25	5403	1.4×10^5	0	1.7	0.8	BT 10

*After Maltoni *et al.* (1981).
†Schedules: I—4 hr/day, 5 days/wk for 52 wk; II—4 hr/day, 5 days/wk for 17 wk; III—4 hr/day, 5 days/wk for 5 wk; IV—1 hr/day, 4 days/wk for 25 wk; V—4 hr/day, 1 day/wk for 25 wk.
‡Amount metabolized (v) in 4 hour derived from the formula: $V\ (\mu g/hr) = V_m \times S/K_m + S$ where V_m is 4/6 of the 6 hr value.

Table 9. Quantitative risk estimations derived from available animal carcinogenicity data and expressed as the amount or concentration of vinyl chloride calculated to give a lifetime risk of ASL of 10^{-4} either on the basis of log-probit analysis or a Weibull distribution

Table no.	Experimental data	Exposure for rodents (S ppb*)	Amount metabolized in 6 hr by rodents (V μg/6 hr)	Total amount metabolized by rodents (TM mg)	Exposure (ppb) calculated from V (S calculated for man)†
			Log-probit analysis‡		
4	S–D rats, inhalation	0.025	1.23	0.305	0.63
5	Wistar rats, male only, inhalation	9.16	159	39.3	90
6	Rats, ingestion—Wistar	3×10^{-3} mg/kg	0.69 mg/dose	2.27	
	—S–D	9×10^{-4} mg/kg	2.19 mg/dose	0.2	—
	—both§	6×10^{-4} mg/kg	1.70 mg/dose	0.88	
7‖	Mice, inhalation	2×10^{-15}	0.60	0.0063	0.03
4, 5	Wistar and S–D rats combined, inhalation	0.038	1.41	0.35	0.72
8	S–D rats, short-term inhalation	—	0.004	2.86	—
			Weibull distribution‡		
4	S–D rats, inhalation	2×10^{-8}	0.013	0.0032	0.067
5	Wistar rats, male only, inhalation	2×10^{-3}	15.7	3.68	8.14
6	Rats, ingestion—Wistar	9×10^{-14} mg/kg	3×10^{-6} mg/dose	0.0002	
	—S–D	4×10^{-6} mg/kg	0.33 mg/dose	0.003	
	—both§	2×10^{-6} mg/kg	0.005 mg/dose	0.0015	
7‖	Mice, inhalation	6×10^{-43}	2×10^{-5}	2×10^{-9}	1×10^{-3}
4, 5	Wistar and S–D rats combined, inhalation	6×10^{-8}	0.0172	0.0042	0.009
8	S–D rats, short-term inhalation	—	3×10^{-6}	0.19	

ASL = Angiosarcoma of the liver S–D = Sprague–Dawley

*Except where stated otherwise.
†Exposure calculated from V (in column 3) using the formula: $S = V \times 860/1675 - V$, where V_m for man is 1675 μg/8 hr.
‡Estimated using maximum likelihood.
§Wistar and S–D rats combined.
‖Study BT 4 only.

tially higher than those calculated for the rat and mouse and there is still a range of over 100-fold in the estimates derived from the different rodent experiments. When this amount of variability occurs in the extrapolation of the risk of low-dose exposure to VCM based solely on different experiments in the same species, the reliability and hence the utility of these procedures is open to question.

The general relationship between the dose administered and the incidence of angiosarcomas derived from 52-week exposure does not apply to exposures of shorter duration (Table 8). In all experiments a total metabolized dose in excess of $5 \times 10^5 \mu g$ was required to produce an incidence of angiosarcoma in excess of 1–2%. This relationship was seen in both rats and mice and in experiments in which VCM was administered by gavage or by inhalation. In long-term inhalation studies, a total metabolized dose of $5 \times 10^5 \mu g$ is equivalent to about 200 ppm administered over 52 weeks and represents a practical threshold for this series of experiments.

In conclusion there is a wide variation in the estimates of dose for a 10^{-6} lifetime risk. This variation is due to the type of mathematical model that is applied, to the assumptions that are made and to the particular experiment that is used to provide data for the extrapolation. A high level of confidence cannot be placed on low-dose extrapolations when variables that would not be expected to alter the expression of risk have a profound effect on the estimated risk. In addition, the interspecies extrapolation from experimental animals to man is largely intuitive. It is clear that estimates of risk should take into account all available data, including epidemiology, to provide a degree of reliability.

Risk assessment from human studies

Register of ASL cases

Since 1974, lists of reported ASL cases attributable to VCM exposure in the VCM/PVC industry have been kept by NIOSH (Spirtas & Kaminski, 1978), by IARC and by the VCM Committee of the Association of Plastics Manufacturers in Europe (APME). Details of 99 cases in the APME register at the end of 1982 have been analysed by country and by manufacturing company and plant. The cases have been recorded from all major VCM/PVC manufacturing countries (Table 10), but the incidence has not necessarily been in proportion to the PVC production capacity now or prior to 1962. In the absence of data on the number of workers employed, production capacity is the only available indication of the numbers of people potentially exposed.

The majority of the ASL cases are PVC autoclave cleaners or men who have worked in or around autoclaves. There are ASL cases among men who manufactured VCM and a few cases were involved both with monomer and with polymer production. Only one case suffered from both acro-osteolysis and ASL. The ASL cases tended to occur in larger numbers in some plants than in others (Table 11). Of the total of 39 ASL cases recorded in North America, 34 have occurred at four PVC plants, while over 40

Table 11. Clustering of ASL cases in individual PVC plants

Plant* no.	Country		No. of ASL cases
	Western Europe		
1	West Germany		10
2	West Germany		4
3	West Germany		2
4	West Germany		2
1	France		5
2	France		5
3	France		2
1	UK		5
2	UK		2
1	Sweden		5
		Total...	42
	North America		
1	Canada		10
1	USA		11
2	USA		9
3	USA		4
		Total...	34
	Rest of World		
1	Japan		2
1	Yugoslavia		4
1	Czechoslovakia		2
		Total...	8

*For the purposes of this case study, it is not necessary to identify the precise ownership and location of these plants.

Table 10. Distribution of ASL cases by country

Country	No. of ASL cases	PVC production nameplate capacity (kilotonnes/yr) 1952	1962	1972
USA	29	193	704	2090
West Germany.	21	22	260	1155
France	14	11	176	627
Canada	10	5	22	88
UK	7	27	177	502
Sweden	5	3	20	105
Yugoslavia	4	3	8	60
Italy	3	9	212	778
Czechoslovakia	2	1	25	48
Japan	2	12	384	1699
Belgium	1	3	25	195
Norway	1	2	20	65
Total...	99			
Western Europe	52	82	951	3950
North America	39	198	726	2178
Rest of World	8	51	709	3334
Total...	99	331	2386	9462

ASL = Angiosarcoma of the liver

Table 12. ASL case numbers by year of death and geographical location (excluding IT01*)

Year of death	ASL cases† in: Western Europe	North America	Rest of world	Key publications
1955		C1		
6				
7		C2		
8				
9				
1960				
1		US8		
2		C3		
3				
4		US5	Cz2	
5				
6				
7	F1			
8		C4, C5, US4, US7, US10		
9	G1	US12, US16		
1970	Sw1	US11		Viola
1	G2	C6, US2		
2	N1, Sw2, UK1, It2	C7		
3	G3‡	C8, US1, US3, US23	Y1, Y2, Cz1	Maltoni
4	G4, G5, UK3	C9, US13		Creech & Johnson
5	F2, F3, G6, G7, G8, It3	US6, US9, US18, US26	Jap1	
6	B1, F4, F5, F6, F7, Sw3	US19, US20, US22	Jap2, Y3	
7	F8, F9, G10, G11, G12, Sw4	C10, US21, US24§		
8	F10, F11, G9, G13, G15, G16, G17	US27, US28	Y4	
9	F12, F13, UK4, UK5, G18			
1980	UK6, UK7, G19, Sw5, G20, G21	US17, US29, US30, US32		
1	It4, F14, UK8, G22			
2				
Total...	52	38‖	8	

ASL = Angiosarcoma of the liver

*Italian case 01 was not a typical ASL; his primary tumour was probably of the pericardium. This man was engaged in extrusion of PVC sacks.

†B = Belgium, G = W. Germany; Sw = Sweden; C = Canada; It = Italy; UK = United Kingdom; Cz = Czechoslovakia; Jap = Japan; Y = Yugoslavia; F = France; N = Norway; US = USA. Thus G9 = case no. 9 in West Germany. Cases UK2, G14, US14, US15 and US25 were shown not to be associated with VCM exposure and hence withdrawn from the list.

‡Aerosol can filler.

§Cholangiosarcoma.

‖Does not include US31 (still alive).

North American PVC plants have not recorded an ASL case so far.

The average latent period between starting work in an occupation involving VCM exposure and death from ASL for the 99 cases is 21.9 years (in France, Sweden and the USA between 24 and 25 years, in Germany about 18 years). It is still too early to predict whether the annual number of ASL cases amongst VCM workers has reached a peak. ASL cases appeared earlier in North America than in Western Europe and while the occurrence is tending to decrease in North America (Table 12), it is still high in Western Europe.

On the basis of the data in this case register, it is possible to draw certain conclusions about risk factors associated with ASL. The large number of ASL cases in some factories and the absence of ASL cases in others of similar age indicates that variations in manufacturing practices between factories may be the cause. These variations may reflect both differences in the types of job carried out by individual workers and differences in engineering practices. The bulk of the cases have occurred, however, in highly exposed autoclave cleaners, with relatively few in other PVC or VCM production jobs. So far no well-authenticated cases have occurred in PVC compounding or fabrication where many more people have been exposed but to a much lower dose.

Prediction of future ASL cases as a consequence of pre-1974 exposure

The causal relationship between VCM and ASL is proved beyond doubt by the specificity of the tumour, the high relative incidence of that tumour in highly exposed workers, the consistency of the excess in different parts of the world, the time relationship between exposure and diagnosis and the dose-response relationship. An intensive analysis of the pre-1974 cohorts should establish the dose-response curve for ASL after VCM exposure and predict the likely outcome for the future.

It will be impossible to collect a complete data set on which to calculate risks of ASL for the whole world, but within a single company there may be closer definition of the cohort, the number of cases and the pattern of exposure. Using these data and averaging across the worldwide population exposed to VCM, it is possible to calculate the future incidence of ASL using relatively crude assumptions which can only be tested in time when the prediction can be judged against the final outcome.

Table 13. ASL case numbers by year of first exposure and geographical location (excluding IT01*)

Year of first exposure	ASL cases† in:			Key events
	Western Europe	North America	Rest of world	
1939		US24‡		
40				
1	Fr11	C3, US27		
2		US13, US29		
3	Fr14	C2, US19		
4	UK1	C1, C5, US5, US7, US28		
5	Sw2	C4, US3, US9		
6	Fr1, Fr3, Sw4	C7, C9, US8, US11, US21, US31§		
7	Sw3	C6, US22, US26		
8	Fr9	US1		
9	Fr12, Fr4	US12		
1950	Fr7, N1, UK8	US16	Y2, Cz2	
1	Sw1, UK5	US10, US32		
2	G3	US4		
3	G15, It3	C10	Jap1, Y1	
4	G7, G8, UK4, G19	US18	Y3	
5	G11, G16, G18	US2, US17, US20		
6	Fr10, G1			
7	Fr8, G4, It2, G2		Cz1	
8	Fr6, B1	US23	Jap2, Y4	
9	Fr2, It4			
1960	G5, G13			
1	G9, G10, G12, G17, G20, G22	C8		
2	G6, UK6, G21	US6		
3	Fr13, UK7			
4	Sw5	US30		
5	Fr5			
6	UK3			
7				
8				
9				
1970				Viola
1				
2				
3				Maltoni
Total...	52	39	8	

ASL = Angiosarcoma of the liver

*It01 is not consistent with other ASL cases; the primary tumour may have been of the pericardium. The man extruded PVC sacks.

†For explanatory key, see Table 12.

‡Cholangiosarcoma.

§US31 is still alive.

‖Aerosol can filler.

The data required are:

(1) Annual populations of employees classified by age;
(2) Annual exposure estimates for each person in (1);
(3) An exposure–response latency model for ASL induced by VCM.

The data under item (1) are available in the UK as a result of the data extracted from the relevant occupational records (Fox & Collier, 1977). Exposure data for item (2) are more difficult to obtain, but can be gleaned from the records that are used to define the occupational population. The problem of occupation changing, which occurred frequently, has been dealt with by using the principal employment category or the highest exposed employment category. The estimation of time-weighted average exposures for the least exposed employees is straightforward, as the exposures were essentially continuous and constant, but for autoclave cleaners, maintenance workers and laboratory workers, exposures could vary from zero to near narcotic levels. In the calculations described below, it has been possible to avoid using the exposure data directly by relying on the similarity in exposure levels in differing locations. The exposure/response/latency data indicated under item (3) can be derived from established cases.

The key data for these procedures are the set of cases worldwide, together with the descriptive data (Tables 12–14). It has been possible to calculate an incidence rate for each latency period for each exposure level for each age group (on the basis of the UK data and assuming that it is representative of the worldwide population) and to use these rates to derive a simple model of dose-response latency that can be applied to the population data. The broad conclusions are that most cases have a latency of about 20 years and cases will continue to occur for the next 10 years.

In the calculation used to estimate the future number of ASL cases (Table 15) an assumption has been made that when exposures were reduced to low levels, the future risk of ASL became negligible. Two dates at which the negligible risk levels were attained have been selected: 1964, when levels were reduced to hundreds of ppm and 1974 when the levels were reduced to below 10 ppm following the discovery of

Table 14. Annual incidence of ASL cases (date of death) by geographical area

Year	No. of ASL cases dying in: Western Europe	North America	Rest of world	Annual total	Cumulative total	Key events
1955		1		1	1	
7		1		1	2	
1961		1		1	3	
2		1		1	4	
4		1	1	2	6	
7	1			1	7	
8		5		5	12	
9	1	2		3	15	
1970	1	1		2	17	Viola
1	1	2		3	20	
2	4	1		5	25	
3	1	4	3	8	33	Maltoni
4	3	2		5	38	Goodrich
5	6	4	1	11	49	
6	6	3	2	11	60	
7	6	3		9	69	
8	7	2	1	10	79	
9	5			5	84	
1980	6	4		10	94	
1	4	*		4	98	
2†	0	0	0	0		
Total...	52‡	38*	8	98*	98*	

ASL = Angiosarcoma of the liver

*Does not include US31 (still alive in 1982).

†At time of compilation.

‡Includes G03 (aerosol can filler) but omits It01 (bag extruder).

the association between ASL and VCM exposure. A hypothetical exposed population of 100,000 has been used, but this is unimportant (see (a) below). An estimate of the age distribution within the hypothetical 'total' exposed population of 100,000 has been based on UK data (Fox & Collier, 1977). For persons already exposed during the whole of the various latent periods, the numbers with a latency of 30 years or more form only a small proportion of the total. The numbers of persons at risk in the future are calculated by advancing time in 5-year periods taking account of the age-dependent death rates in the population at large. Death rates for an intermediate year for the male population of England and Wales have been used in this calculation and the future cases (column 10) have been obtained by multiplication. The incidence figures for long latent periods (>25 years) are unreliable or non-existent but those for latencies of 15–25 years are fairly constant and values of 0.5 and 0.8 cases/1000 persons have been used for all latency periods over 15 years to calculate the expected number of cases for the 1964 and 1974 assumptions.

The calculation is unrealistic in many respects but the simplifications are unlikely to affect the estimate of future cases by more than a small factor. For example:

(a) The population size used for the calculation is probably larger than the exposed population, but the calculation depends on the ratio of "person-years to come" and "person-years experienced" and this ratio is the same for any population size.

(b) Exposure level has been ignored. The calculations are based on the overall risk to the cohort and although the incidence figures for sub-cohorts could be higher, the estimate of future cases will change very little. Similarly duration of exposure has been ignored.

Table 15. Hypothetical calculation of future ASL cases using two different assumptions about the date at which the levels became free of risk

Latency (yr)	Cases to date	Calculations assuming no risk after 1964: Persons at risk to date	5-yr incidence	Future persons at risk	Future cases	Calculations assuming no risk after 1974: Persons at risk to date	5-yr incidence	Future persons at risk	Future cases
1–5	0	100,000	0.00	0	0	100,000	0.00	0	0
6–10	1	98,250	0.01	0	0	94,500	0.01	3750	0
11–15	11	95,500	0.12	0	0	78,000	0.14	17,500	2
16–20	28	84,750	0.33	6750	2	46,500	0.60	45,000	27
21–25	28	61,400	0.46	24,550	11	28,750	0.97	57,200	57
26–30	18	36,750	0.49	41,750	20	18,750	0.96	59,750	57
31–35	6	21,250	0.28	48,100	13	10,850	0.55	58,500	32
36–40	6	6750	0.89	51,750	46	3500	1.71	55,000	94
41–45	0	600	?	45,750	?	310	?	46,350	?
46–50	0	0	?	34,500	?	0	?	34,500	?
51–	0	0	?	47,600	?	0	?	47,600	?
16–			0.50	300,750	150		0.80	403,900	323

For details of the assumptions and methods see text (pp. 197 & 198).

(c) The UK is not typical of the worldwide growth in the exposed population.
(d) No account has been taken of plant improvements occurring prior to 1964 and hence fewer cases may occur in, for example, the 1980–2000 period than are estimated from the 1940–1980 experience.

An assumption that the risk of ASL ceased in 1964 rather than in 1974 results in a considerable reduction in the estimate of future cases. For either assumption, the number of new cases observed annually should soon begin to decline and the rate of decline will indicate which assumption is nearer to the truth.

There have been two other predictions of the number of cases of ASL likely to result from previous exposure to VCM. Nicholson *et al.* (1984) suggest that there will be a further 1500 cases of ASL, while Forman *et al.* (1986) conclude that a further 150–200 deaths might be expected over the next 30 years. Our estimates rely on a more sophisticated model than the latter estimate and on a larger data set than the former. Nevertheless, the conclusions of Forman *et al.* (1986) are similar to ours. Only the experience of the next few years will show which is the best estimate.

Summary and conclusions

There is little doubt that exposure to high levels of VCM as a consequence of occupation can result in an increased incidence of ASL. A review of 20 epidemiological studies involving about 45,000 workers occupationally exposed to VCM showed that neoplasms of the liver showed an increase in incidence in the majority of studies. For brain cancer the association between exposure to VCM and an increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and haemopoietic system, buccal cavity and pharynx, cardiovascular system and colon/stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies. In view of the increased incidence of breast neoplasms in rodents exposed to VCM, the studies of Chaizze *et al.* (1980), who did not confirm these findings in humans, are of importance.

The register of ASL cases now contains records of 99 persons with confirmed ASL and occupational exposure to VCM. The average latent period between first exposure to VCM and death from ASL is 21.9 years. The majority of cases occurred in autoclave workers, who are recognized as having been exposed to extremely high levels. Although precise estimates of exposure are not available for the periods of most interest, the pattern of cases roughly suggests that extremely high exposures were necessary for the induction of ASL. For example, ASL cases tended to occur in larger numbers in some plants than in others, a finding that can be explained most easily by differences in exposure patterns.

There is an extensive series of animal studies on the carcinogenicity of VCM. Some of these precede the epidemiological studies confirming the association between VCM exposure and ASL in man. ASL and neoplasms of a number of other organs have been induced in laboratory rodents by VCM. Estimation of the exposure levels likely to cause a lifetime risk of ASL of 10^{-6} on the basis of these data give extremely low levels (down to 3.9×10^{-7} ppb) which appear to be unrealistic estimates for man. Part of the reason for this is that laboratory studies have shown that VCM is metabolized in the liver (and elsewhere in the body) to the reactive metabolites chloroethylene oxide and chloroacetaldehyde. The rate of conversion is limited at high levels of exposure giving inaccurate estimates of the slope of the dose-response relationship. It has not been possible to estimate the rate of conversion in man, and hence extrapolation of these low-risk dose estimates is conjectural. The second part of the problem of extrapolation at low risk is the selection of the most suitable mathematical model for extrapolation. Using Maltoni's data from rats (Maltoni *et al.* 1981), there is a substantial range (up to 10^8) of low-risk dose estimates, depending on the mathematical model and the assumptions used in applying the models. Using the same (probit and log-dose) model and different sub-sets of experimental data, a large range of estimates is again obtained, even after correction for the non-linear kinetics of metabolism at high dose (which reduces this range to about 10^2). Larger differences are obtained with calculations using the Weibull analysis as a basis of low-dose estimation, suggesting that this is a problem with the use of mathematical models rather than one associated with the log-probit analysis. Although there was considerable variability in the dose-response relationship in the different experiments reported, in all cases a total metabolized dose of 5×10^5 μg (equivalent to inhalation of 200 ppm) was required to produce an elevation in ASL incidence. This dose represents a practical threshold in rodents. At this stage in their development, mathematical models for low-risk dose estimates are not sufficiently reliable or reproducible to engender confidence in their use.

Using negative epidemiological studies of populations living in the vicinity of VCM production facilities, an estimate of the dose for a 10^{-4} lifetime risk in man may be made (Barr, 1982). The value (100 ppb) is similar to the highest estimates derived from animal data and taking biotransformation data into account, is substantially larger than the lowest estimates, which are up to 10^{10} lower (3.9×10^{-7} ppb using a multi-hit model). The higher estimates are compatible with occupational experience and suggest that the current hygiene standard of around 1 ppm is sufficiently low to protect the health of VCM/PVC workers. The estimates also give a considerable safety factor for the general public consuming PVC-packed food and drink or living near VCM/PVC facilities.

It has been possible to provide a crude estimate of the number of cases of ASL that may occur in the future from exposure to VCM prior to 1974. Using the age structure of employees in one company, the total number of cases of ASL reported to date and the mortality pattern expected from a normal population, the possible future number of ASL cases has been estimated as in the region of 150–300.

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