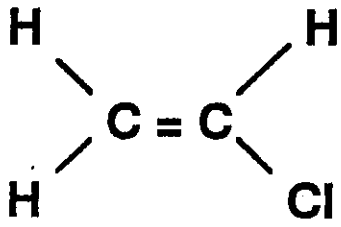
TECHNICAL SUPPORT DOCUMENT

PART C

PROPOSED IDENTIFICATION OF



VINYL CHLORIDE

AS A TOXIC AIR CONTAMINANT

OCTOBER 1990

State of California
Air Resources Board
Stationary Source Division

This report has been reviewed by the staff of the California Air Resources Board and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Air Resources Board, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

PART C

STAFF RESPONSES TO PUBLIC COMMENTS ON THE VINYL CHLORIDE REPORT

Prepared by the Staffs of the Air Resources Board
and the Department of Health Services

October 1990

PART C

TABLE OF CONTENTS

I. COMMENTS RECEIVED

DRAFT

The Goodyear Tire & Rubber Company

Akron, Ohio 44316-0001

CORPORATE ENGINEERING

September 1, 1989

Air Resources Board
Toxic Air Contaminant Identification Branch
P.O. Box 2815
Sacramento, California 95812
ATTN: Vinyl Chloride
Mr. Robert Barham, Chief

Dear Mr Barham:

The following comments are offered in response to the "Report to the Air Resources Board on Vinyl Chloride - Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant".

Clarification is requested concerning the relationship between the California ambient air quality standard for vinyl chloride - 10 ppb, as it was discussed in the report, the level of concentration of vinyl chloride which poses "no significant risk" to the population - 0.3 micrograms/day and the interaction of these two values in the regulation of toxic air contaminants.

In the sampling and determination of the concentration of vinyl chloride, the use of analytical techniques comparable to and as reliable as the method outlined in the report should be permitted.

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An adequate review of the medical studies of the effect of exposure to vinyl chloride can not be satisfactorily completed before the end of the first comment period. Therefore, a request is being made for an extension of the initial comment period.

If you have questions, please call the writer at 216-796-2698.

Sincerely,

C A See

C A See
Environmental Engineer
Corp Environmental Engineering

CAS:cas

BFGoodrich

DRAFT

The BFGoodrich Company
3925 Embassy Parkway
Akron, Ohio 44313

September 6, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Vinyl Chloride
P.O. Box 2815
Sacramento, CA 95812

Comments on Technical Support Document:
Proposed Identification of Vinyl
Chloride as a Toxic Air Contaminant
Part A and Part B Reports

Dear Mr. Barham:

The BFGoodrich Company welcomes this opportunity to comment on the above-captioned documents and we would like to commend CARB for accurately assembling and summarizing the extensive data describing vinyl chloride's uses, emissions, physical properties and exposure in California.

We have only two comments for your consideration. First, the primary deficiency of the CARB document on identifying VCM as an air toxic from landfills is that it fails to note these important epidemiology studies:

1) Doll, Sir R., (1988) "Effects of Exposure to Vinyl Chloride: An Assessment of the Evidence", Scandinavian Journal of Work, Environment, and Health, 14(2):61-78.

DRAFT

2) Wu, W.; Steenland, K.; Brown, D.; Wells, V.; Jones, J.; Schulte, P. and Halperin, W. "Cohort and Case-Control Analyses of Workers Exposed to Vinyl Chloride — An Update". NIOSH Report Draft, October, 1988.

3) Wong, O.; Whorton, M.D.; Ragland, D.; Klassen, C.; Samuels, D. and Chaxton, K. "Final Report — An Update of an Epidemiology Study of Vinyl Chloride Workers, 1942-1982". Prepared for Chemical Manufacturer's Association, October 17, 1986.

The second area of concern with the CARB document is more an issue of semantics; nevertheless, we offer it for your consideration. The PART A Report at pages A-1, A-17 and A-27 accurately states the following facts, but we would like to see clarifying phrases added or sentences reordered as described below.

Page A-1 to A-2

* PVC is fabricated for use in several products of which many are used by the construction industry. In California, the identified sources of vinyl chloride emissions are landfills, PVC production and fabrication facilities, and sewage treatment plants, not PVC fabricated products for consumer or construction industry use.

Page A-17 to A-18

* Plastic Materials and Consumer Products. Plastic products made of PVC and other vinyl chloride polymers are ubiquitous in most homes. Because vinyl chloride monomer can remain in the PVC resin for an extended period of time, an indirect source of indoor vinyl chloride emissions may come from the release of unreacted vinyl chloride monomer from these plastic products. However, emissions of unreacted vinyl chloride monomer have been substantially reduced due to improvements in monomer stripping technology (Wheeler, 1987). Thus, consumer products made of PVC resins no longer contain elevated residual levels of vinyl chloride monomer and, therefore, are not expected to be an important contributor of indoor levels of vinyl chloride.

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In the past, residual vinyl chloride concentrations in PVC resins at the time of shipment, were as high as 2000 ppm. Curently, PVC resins contain about 10 ppm residual vinyl chloride at the time of shipment and may lose vinyl chloride at a rate of 20 to 50 percent per month during storage. In addition, most of the vinyl chloride will vaporize and escape during the high temperature processes in which PVC resins are melted and made into final products.

Page A-27

Landfill Emissions. Emissions of vinyl chloride from landfills mainly occur by two mechanisms: 1) direct vinyl chloride emission from disposed wastes which contain vinyl chloride (i.e., chlorinated organic compounds); and and the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons.

It is hoped that by making the previously described suggested changes, the readers of Report A will more readily understand that the major source of VCM emissions in California in landfills is from chlorinated organic waste disposal, not from the disposal of PVC fabricated consumer and construction industry products.

Thank you for the opportunity to comment on the Part A and B Reports. Please feel free to call me at (216) 374-2962 should you have any questions on our proposed additions to these documents.

Sincerely,

Kathleen E. Stimler

Kathleen E. Stimler
Manager, Government Relations

6661W

The Vinyl Institute

A Division of The Society of The Plastics Industry, Inc.

September 8, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Vinyl Chloride
1102 Q Street
Sacramento, California 95812

Re: Draft Report on Vinyl Chloride

Dear Mr. Barham

On August 29th, the Vinyl Institute* received the preliminary draft report on vinyl chloride dated July 1989 being prepared by the California Air Resources Board (CARB). There has been, therefore, a limited amount of time for our membership to thoroughly review the documents prior to the comment deadline.

Nevertheless, after reviewing the document, there are at least two areas of discussion that are inadequately treated in the California Air Resources Board (CARB) document. Therefore, most of the comments will be spent on those two areas. They are the pharmacokinetic knowledge of vinyl chloride in the risk assessment approach and a total inadequate treatment of the large number of epidemiology studies in the published literature. These are very concisely dismissed by the Department of Health Services (DHS) as being unacceptable to be used in the risk assessment process for regulatory purposes.

* The Vinyl Institute is an operating division of the Society of the Plastics Industry, Inc. Its members include Air Products and Chemicals, Borden Chemicals & Plastics, Certain-Teed Corporation, Dow Chemical USA, BFGoodrich Company, Georgia Gulf Corporation, Occidental Chemical Corporation, PPG Industries, Shintech Inc., and Vista Chemical Company. Together, these companies account for more than 80% of the domestic production of both vinyl chloride and polyvinyl chloride.

Wayne Interchange Plaza II • 155 Route 46 West • Wayne, NJ 07470 • (201) 890-9299

Point One: Pharmacokinetic Information. There are several publications in the literature not cited in the DHS document, that address the incorporation of pharmacokinetics in low dose risk estimation for chemical carcinogenesis. One such article was published as far back as 1980 in Toxicology and Applied Pharmacology, authored by Anderson, Hoel and Kaplan. That document demonstrates how to incorporate the pharmacokinetic information on vinyl chloride into a risk assessment approach for low dose risk estimation. There are numerous other publications on the pharmacokinetics of vinyl chloride as well. Another such document, published in 1981 in the Archives of Toxicology authored by Bolt, Filser and Buchter, demonstrates significant information that is relevant when extrapolating low level carcinogenic risk estimates from the existing data base. The DHS document fails to incorporate any of the established pharmacokinetic information in its treatment of theoretical risk for vinyl chloride.

A number of studies indicate that probably a reactive metabolite, not vinyl chloride per se is responsible for its toxicity. Although some inhaled vinyl chloride is excreted unchanged, depending on dose, a varying amount is metabolized. The metabolism of vinyl chloride has been the subject of numerous studies and it is currently thought that vinyl chloride is metabolized by epoxidation with subsequent production of chloroacetaldehyde. The further oxidation and conjugation with glutathione are responsible for the metabolites found in the urine. Gehring, et al. analyzed the metabolic and carcinogenic data from man and laboratory animals, and used several models to predict the incidence in man from the animal data. They found that all models over-predicted the risk to man unless corrections were made for the varying rates of metabolism and for the surface area differences of the different species.

Point Two: Epidemiology. There have been many published epidemiological investigations of occupational workers exposed to vinyl chloride at a variety of occupational exposure levels. Vinyl chloride may, in fact, be one of the most epidemiologically-studied industrial chemicals in the literature. To dismiss that data and relegate it only for comparative purposes to animal data is unacceptable. DHS demonstrates a bias towards the utilization of animal experiments as a priority over human evidence in their approach to risk assessment. This results in a dramatic overestimate of likely human risk at the low environmental levels being addressed by the document. The DHS goes on to state that risk extrapolations based on the human data yield results they judge to be comparable. The practical aspect of responding to an order of magnitude or two in risk assessment can often be dramatic, therefore risk estimates that yield order of magnitude different estimates of risk are extremely important. When adequate or substantial human evidence exists, that data should be given preferential treatment in the risk assessment process.

Many of the epidemiology studies that have been in the published literature have been updated in the past year or two. One example is the study Update of Vinyl Chloride Mortality authored by Dahar, et al. which was updated as recently as 1988 and further demonstrated a decreasing cancer incidence rate in workers as the latency period has been expanded substantially. The person years in this one particular study has been expanded from only approximately 4,000 person years to over 17,000 person years, thus a substantial increase in sensitivity of the study, as only one example. The Chemical Manufacturers Association (CMA) Vinyl Chloride Panel-sponsored epidemiology study was updated as recently as 1986. It is a very comprehensive epidemiology study consisting of a cohort of over 10,000 workers employed at 37 different plants belonging to 17 different companies. That study identified at that time, over 1,536 deaths. These are only several examples of many epidemiology studies published on vinyl chloride and DHS's approach to dismiss human epidemiology evidence in their risk assessment is inadequate.

Many of the human epidemiological studies point out a statistically-significant association between an increase in lung, liver and brain cancer and exposure to vinyl chloride. For brain cancer, three out of five studies demonstrate statistically-significant findings, although the results were somewhat variable. Positive findings occurred in studies with the greatest statistical power. Most reasonable interpretation of the data is consistent with the causal association of vinyl chloride exposure and an excess of brain cancer, however, the relative risk calculation for brain cancer is much lower than that for liver cancer. Only two out of eight studies on lung cancer yield statistically-significant results, and because studies with the higher power were negative, a causal association is unlikely. It is for these reasons, therefore, that the incidence rate on the angiosarcoma is the most suitable end-point for analysis of risk of exposure to vinyl chloride for a number of reasons:

1. Vinyl chloride angiosarcoma is a rare cancer in unexposed populations, thereby making the utilization of angiosarcoma as a demonstration of vinyl chloride exposure on the basis of work history truly a reasonable approach.

2. Angiosarcoma has been demonstrated to occur both in animals and humans when exposed to vinyl chloride.

3. It is therefore demonstrated unlikely that any other carcinogenic result from vinyl chloride would incur lower exposures than those lowest exposures that would induce angiosarcoma. Recent publications entitled Vinyl Chloride, An Assessment of the Risk of Occupational Exposure, was published in 1987 in the Fundamentals of Chemical Toxicology Journal, Volume 25, pages 187 to 202, 1987, authored by

Purchase, et al. A very extensive evaluation of the available information at that time is included in this article, and a very comprehensive examination of risk assessment approaches to vinyl chloride is examined. We believe that this document demonstrates a much more studied and scientifically defensible approach to assessing risk of exposure to vinyl chloride.

In summary, there are at least twenty epidemiological studies which involve over 45,000 workers who have occupationally been exposed to vinyl chloride. To dismiss this body of epidemiological study in favor of basing risk assessment on animal data is questionable at best. In the paper by Purchase, et al., information that is precisely the issue being addressed by DHS is present. In addition, an epidemiological study of populations living in the vicinity of VCM production facilities had been conducted previously. This study, Barr, et al. 1982, suggests that 100 ppb represented the estimated dose representing a 1x10-6 lifetime risk in man. That value is similar to the highest estimates derived from the animal data when taking biotransformation data into account. The studies discussed in the paragraphs above, will be forwarded under separate cover.

Finally, the Vinyl Institute is extremely interested in reviewing the revised draft document before it is forwarded to the Scientific Review Panel. Please add our organization to your distribution list. Materials should be forwarded to:

Meredith N. Scheck
Assistant Director
The Vinyl Institute
155 Route 46 West
Wayne, New Jersey 07470

Thank you for your attention to this matter.

Sincerely yours,

Meredith N. Scheck

Meredith N. Scheck
Assistant Director

MNS/pmb
cc: Mr. Richard Forey
Substance Evaluation Section
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

The Vinyl Institute

A Division of The Society of The Plastics Industry, Inc.

September 12, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
P.o. Box 2815
Sacramento, California 95812

Re: Draft Report on Vinyl Chloride

Dear Mr. Barham:

The enclosed article was referenced in comments submitted on September 8th by The Vinyl Institute on the Air Resources Board's Draft Report on Vinyl Chloride. I would appreciate it if this report is appended to those comments.

Sincerely yours,

Meredith N. Scheck
Assistant Director

MNS/pmb

enc.:
I.F.H. Purchase, J. Stafford and G. M. Paddle, "Vinyl Chloride: An Assessment of the Risk of Occupational Exposure", Fundamentals of Chemical Toxicology Journal, Vol. 25, No. 2, pp. 87-202 (1987).

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1 Ele Vinyl Chloride - Risk Assessment

Fd Chem-Toxic Vol 25, No 2, pp 187-202, 1987
Printed in Great Britain

0278-6915/87 $3.00 + 0.00

DRAFT

Review Section

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

I. F. H. PURCHASE
Central Toxicology Laboratory

J. STAFFORD
Plastics and Petrochemicals Division

and

G. M. PADDLE
Central Medical Group, Imperial Chemical Industries plc, Alderley Park, Macclesfield, Cheshire, England

(*Received* 14 *December* 1983; *revisions received* 13 *January* 1986)

Introduction

Vinyl chloride monomer (VCM), more properly named monochloroethane, 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 carcinogenesis 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

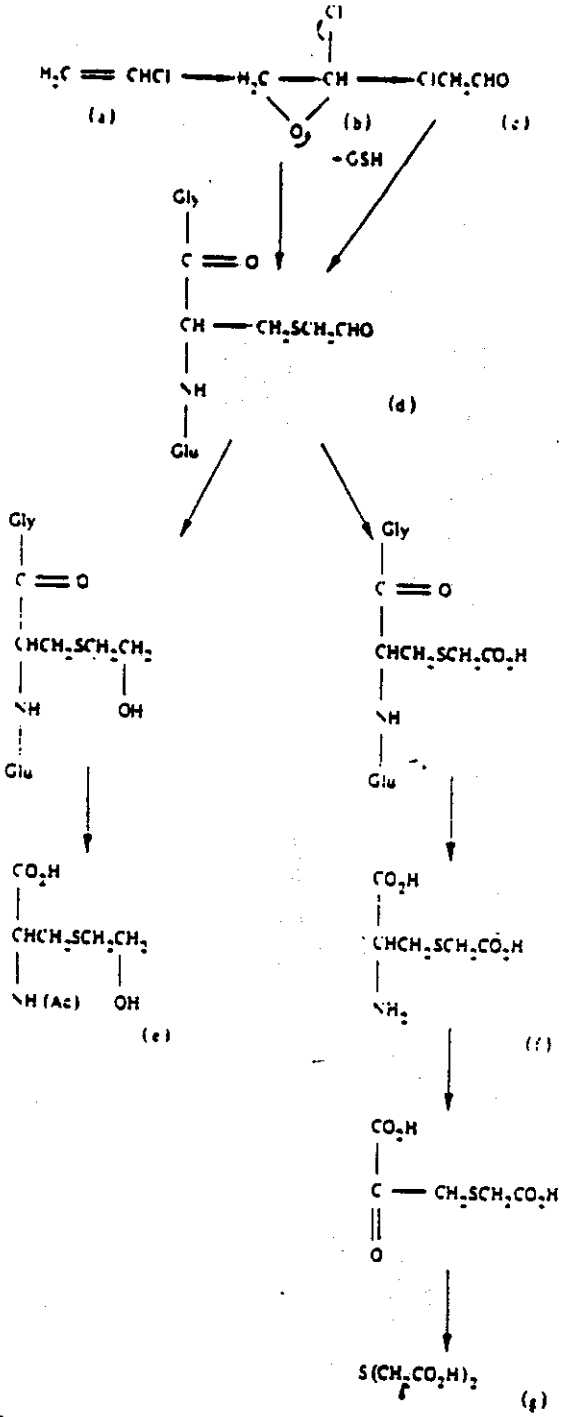

Fig. 1. Scheme showing the metabolism of vinyl chloride monomer (VCM) in rats to *S*-containing metabolites. VCM (a) is converted to chloroethylene oxide (b) which is transformed spontaneously to chloroacetaldehyde (c). These two metabolites are mutagenic and hence are considered to be the proximate 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)	7	Brain Lung Liver, including ASL Buccal cavity and pharynx Respiratory system Unknown site Lymphoma Angiosarcoma		
Tabershaw & Gaffey (1974)	8384 (85%)			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		Arsenicals involved
Ott *et al.* (1975)	594 (99%)	All tumours?		Significant increase (2 ASL)
Byren *et al.* (1976)	771 (97%)	Liver/pancreas		Increase not significant
		Cerebral?		
		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		Related to duration of exposure
Waxweiler *et al.* (1976)	1151	Brain Respiratory tract Lymphatic system ASL	Brain	Mixed exposure, not VCM related
Fox & Collier (1977)	7489 (99%)	Primary liver ASL		Not significant Significant
			Stomach Brain Lymphatic and haemopoietic system	
Fritzel-Reyme *et al.* (1978)	1618 (95%)	Colon/stomach Prostatic hyperplasia		
Bertazzi *et al.* (1979)	5441 (86%)	All tumours		
Baillie *et al.* (1979)	464 (100%)	Respiratory system		
Chiazze & Fetcenc (1981)	3847	Digestive system		
Chiazze *et al.* (1980)				PMR study of female and male fabricators
			Breast	Increase in PMR not confirmed by case-controlled study
Beaumont & Breslow (1981)		Liver Brain	Respiratory tract	Review of nine studies

Cooper (1981)	10,171 (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			
Filatova *et al.* (1982)	3212 (100%)	Lymphatic and haemopoietic systems			
			Liver		No ASL
Theriault (1982)	1310 (97%)	Digestive system (liver)			
			Lung	Lung SMR = 424	

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 $K_m = 560\ \mu$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 angiosarcomas in Sprague–Dawley rats exposed for on 5 days wk for 52 wk*

Concn (ppm)	Amount metabolized†		Angiosarcoma incidence (%)			Experiment 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*

Reference	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)
Kuzmack & McGaughy (1975)	Rat, man	2	Logit (slope = 2.3, one-hit)
		14	Linear through zero
Gehring *et al.* (1979)	Rat, man	140–1400	Log-probit
		> 1000	Biotransformation data included
Food Safety Council (1980)	Rat	< 10–> 1000	Linear or log-probit
	Rat		Depends on mathematical model used
		20	One-hit
		20	Armitage–Doll
		2.1×10^{-4}	Weibull
		3.9×10^{-3}	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^{-3}	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^{-6}	Weibull
	Mouse	6×10^{-43}	
	Man	0.067–6.14	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.

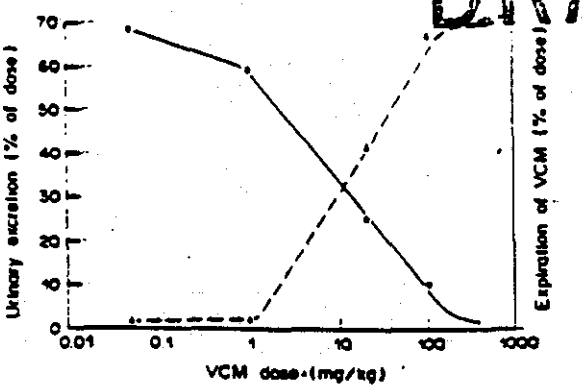

Fig. 2. Summary of dose-dependent urinary and pulmonary excretion of vinyl chloride monomer (VCM). Urinary excretion (●) represents metabolites of VCM, while pulmonary elimination (▲) is unchanged VCM. [After Watanabe & Gehring (1976)].

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: µg 4 hr	Amount metabolized: µg (total)	Angiosarcoma incidence (%)	Expmt no.
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	6.8×10^5	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: µg dose†	Amount metabolized: µg (total)	Angiosarcoma incidence (%): Male	Female	Mean	Expmt no.
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 3. Vinyl chloride dose and incidence of hepatic angiosarcoma in mice

Concn (ppm)	Amount metabolized: µg/4 hr	µg (total)	Angiosarcoma incidence (%): Male	Female	Mean	Expmt no
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	7.4×10^5	30.0	30.0	30.0	BT 4
250	4959	7.4×10^5	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 c. 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^{-4} 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^{-4} 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‡: µg/4 hr	µg (total)	Angiosarcoma incidence (%): Male	Female	Mean	Expmt no.
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	1.21	0.305	0.61
5	Wistar rats, male only, inhalation	9.16	159	39.1	90
6	Rats, ingestion – Wistar	3×10^{-5} 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^{-03}	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^{-6}	0.011	0.0032	0.067
5	Wistar rats, male only, inhalation	2×10^{-4}	15.7	3.68	8.14
6	Rats, ingestion – Wistar	9×10^{-10} mg/kg	3×10^{-6} mg/dose	0.0002	
	– S D	4×10^{-6} mg/kg	0.11 mg/dose	0.003	
	– both§	2×10^{-6} mg/kg	0.005 mg/dose	0.0015	
7‖	Mice, inhalation	6×10^{-05}	2×10^{-3}	2×10^{-9}	1×10^{-3}
4, 5	Wistar and S D rats combined, inhalation	6×10^{-6}	0.0172	0.0042	0.009
8	S D rats, short-term inhalation	—	3×10^{-4}	0.19	

ASL = Angiosarcoma of the liver S D = Sprague Dawley

*Except where stated otherwise.

†Exposure calculated from V (in column 4) using the formula: S = V × 860/1675 · V_m, where V_m for man is 1675 μg/8 hr.

‡Estimated using maximum likelihood.

§Wistar and S D rats combined

‖Study 01 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 5×10^5 μg 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 5×10^5 μg 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^{-4} 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	Ca2	
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: Western Europe	North America	Rest of world	Key events
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, Ca2	
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		Ca1	
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				Mahoni
Total...	32	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	Mahour Goodrich
4	3	2		5	38	
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 In01 (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 & 196).

(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 10^6) 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^{-6} 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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STATEWIDE AIR POLLUTION RESEARCH CENTER

RIVERSIDE, CALIFORNIA 92521-0312

July 20, 1989

Dr. Richard Corey
Toxic Air Contaminant Identification Branch
California Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, CA 95812

Dear Dr. Corey:

As promised in our telephone conversation of June 10, 1989, I enclose comments concerning the atmospheric chemistry of vinyl chloride, trichloroethene and tetrachloroethene (perchloroethene). I hope that these comments are of use to you.

Yours sincerely,

Roger Atkinson

Roger Atkinson
Research Chemist

DRAFT

Comments Concerning the Atmospheric Chemistry of Vinyl Chloride

Roger Atkinson

A. Vinyl Chloride.

OH Radical Reaction.

In addition to the flash photolysis-resonance fluorescence data of Perry et al., Liu and coworkers (A. Liu, W. A. Mulac and C. D. Jonah, J. Phys. Chem., 93, 4092-4094, 1989) have used a pulsed radiolysis-resonance absorption method to determine absolute rate constants for the gas-phase reaction of the OH radical with vinyl chloride over the temperature range 313-1173 K in the presence of 1 atmosphere of argon diluent. The rate constants obtained by Liu et al. over the temperature range common to the Liu et al. and Perry et al. studies (313-423 K) are in good agreement with those of Perry and coworkers.

A product study of the gas-phase reaction of the OH radical with vinyl chloride, in the presence of NO_x, has recently been carried out by Tuazon et al. (E. C. Tuazon, R. Atkinson, S. M. Aschmann, M. A. Goodman and A. M. Winer, Int. J. Chem. Kinet., 20, 241-265, 1988) using long pathlength Fourier transform infrared (FT-IR) absorption spectroscopy to monitor the reactants and products in irradiated ethyl nitrite - NO - vinyl chloride - air mixtures in the presence and absence of ethane (used to scavenge any chlorine atoms produced from the OH radical reaction). The major products observed were formaldehyde (HCHO) and formyl chloride (HC(O)Cl), with the measured yields (corrected for secondary reactions of these products with the OH radical) being 0.96 and 0.83, respectively, in the presence of ethane and 0.89 and 0.80, respectively, in the absence of ethane. These product yield data show that HCHO plus HC(O)Cl account for essentially all of the vinyl chloride reacted, and that Cl atom production in this OH radical reaction with vinyl chloride is minor, at most. These data then agree with the reaction sequence shown on page A-46 of the vinyl chloride document.

DRAFT

Comments: - page 2

NO_3 Radical Reaction.

A rate constant for the gas-phase reaction of the NO_3 radical with vinyl chloride has recently been obtained, using a relative rate technique (R. Atkinson, S. M. Aschmann and M. A. Goodman, Int. J. Chem. Kinet., 19, 299-307, 1987). Combining the measured rate constant ratio at 298 ± 2 K of $k(NO_3 + \text{vinyl chloride})/k(NO_3 + \text{ethene}) = 2.08 \pm 0.09$ with the room temperature rate constant for the reaction of the NO_3 radical with ethene of 2.1×10^{-16} cm^3 $molecule^{-1}$ s^{-1} (R. Atkinson, S. M. Aschmann and J. N. Pitts, Jr., J. Phys. Chem., 92, 3454-3457, 1988) leads to a rate constant of

$$k(NO_3 + \text{vinyl chloride}) = 4.4 \times 10^{-16} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$$

at 298 ± 2 K.

Lifetime.

As noted, the lifetime of vinyl chloride in the troposphere is calculated by combining the measured rate constants for the gas-phase reactions with OH and NO_3 radicals and O_3 (and other gas-phase loss processes, if applicable) with measured or estimated ambient concentrations of OH and NO_3 radicals and O_3. Few, if any, reliable real-time measurements of ambient tropospheric OH radical concentrations exist to date. The most reliable global tropospheric OH radical concentration value is that derived from the ambient tropospheric concentrations and emission inventory of methylchloroform, leading to an annually and diurnally averaged global tropospheric concentration of 7.7×10^5 molecule cm^{-3} (Prinn et al., 1987). For the NO_3 radical, the measured lower tropospheric concentrations over continental areas range from <1 part-per-trillion (ppt) up to 430 ppt (see R. Atkinson, A. M. Winer and J. N. Pitts, Jr., Atmos. Environ., 20, 331-339, 1986). An average value of 10 ppt (2.4×10^8 molecule cm^{-3}) seems reasonable, with the recognition that this concentration is uncertain at any given time by a factor of ± 10.

With these ambient OH and NO_3 radical concentrations, the calculated lifetimes of vinyl chloride with respect to reaction with OH and NO_3 radicals are then 2.3 days and 220 days, respectively. Since the lifetimes of vinyl chloride with respect to reaction with O_3 is (Table IV-2) ~50 days (using the rate data of Zhang et al. and Gay et al.), the OH radical reaction appears to be the dominant tropospheric loss process for vinyl chloride.

II. AIR RESOURCES BOARD STAFF RESPONSES TO COMMENTS ON PART A

DRAFT

A. Comments from the Goodyear Tire & Rubber Company

1. Comment: Clarification is requested concerning the relationship between the California 10 ppb ambient air quality standard for vinyl chloride and the 0.3 ug/day concentration of vinyl chloride which poses no significant risk to the population.

   Response: This comment is addressed in Part C, III. Department of Health Services Responses to Comments on Part B.

2. Comment: In the sampling and determination of the concentration of vinyl chloride, the use of analytical techniques comparable to, and as reliable as, the method outlined in the report should be permitted.

   Response: The ARB did not intend to imply that the sampling and analysis techniques described in the preliminary draft report on vinyl chloride should be the only method used by facilities testing for vinyl chloride.

B. Comments from the B.F. Goodrich Company

1. Comment: On page A-1 and A-2, the report should clarify that polyvinyl chloride (PVC) products used by consumers and the construction industry are not sources of vinyl chloride.

   Response: Page A-2 of the second draft report states that finished commercial PVC products are not expected to be significant sources of vinyl chloride due to current processing and shipping procedures. ARB staff can not conclude that these products have absolutely no vinyl chloride associated with them.

2. Comment: On page A-17 and A-18, the report should emphasize that consumer products of PVC no longer contain elevated residual levels of vinyl chloride monomer and are not expected to be important contributors to indoor levels of vinyl chloride.

   Response: The last sentence on page A-17 of the preliminary draft report states: "Thus, consumer products made of PVC resins no longer contain elevated levels of vinyl chloride monomer and, therefore, are not expected to be an important contributor of indoor levels of vinyl chloride."

3. Comment: On page A-27 the ninth line from the top, the report should insert "i.e., chlorinated organic compounds" after, "which contain vinyl chloride".

   Response: The preliminary draft report states: "Emissions of vinyl chloride from landfills mainly occur by two mechanisms: 1) direct vinyl chloride emissions from disposed wastes which

contain vinyl chloride; and 2) the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons." The "chlorinated organic compounds" referred to in the comment are addressed by the second mechanism.

C. Comments from Dr. Roger Atkinson of the Statewide Air Pollution Research Center at the University of California, Riverside:

1. Comment: The report (page A-44) should indicate that the results of the study of Liu and coworkers (A. Liu, W.A. Muloc, and C.D. Jonah, Journal of Physical Chemistry, 93, pp. 4092-4094, 1989) which determined absolute rate constants for the gas-phase reaction of the hydroxyl radical with vinyl chloride over the temperature range of 313 to 423° K agree with those of Perry and coworkers.

   Response: The second draft of the report reflects this additional information on page A-41.

2. Comment: The report (page A-44) should include the most reliable estimated average hydroxyl radical concentration of 7.7×10^5 molecules cm^{-3} derived by Prinn and coworkers (Prinn et al., 1987) through the use of the ambient tropospheric concentration and emission inventory of methyl chloroform.

   Response: This additional information is included on page A-41 in the second draft of the report.

3. Comment: The report (page A-46) should indicate that a study by Tuazon and coworkers (E.C. Tuazon, R. Atkinson, S.M. Aschmann, M.A. Goodman, and A.M. Winer, International Journal of Chemical Kinetics, 20, pp. 241-265, 1988) confirmed the study by Pitts and coworkers (Pitts et al., 1984) which demonstrated that the reaction of one molecule of vinyl chloride with hydroxyl radicals yields one molecule of formyl chloride.

   Response: This additional information is included on pages A-42 and A-43 in the second draft of the report.

4. Comment: The report (page A-47) should include new data (R. Atkinson, S.M. Aschmann and M.A. Goodman, International Journal of Chemical Kinetics, 19, pp. 299-307, 1987 and R. Atkinson, S.M. Aschmann and J.N. Pitts, Jr., Journal of Physical Chemistry, 92, pp. 3454-3457, 1988) concerning the rate constant of the gas-phase reaction of vinyl chloride and the nitrate radical.

   Response: This new data is included on pages A-43 and A-44 in the second draft of the report.

III. DEPARTMENT OF HEALTH SERVICES RESPONSES TO COMMENTS ON PART B

DRAFT

Response to Comments: Vinyl Institute

I. General comment

Comment: "There are at least two areas of discussion that are inadequataly treated.....They are the pharmacokinetic knowledge of vinyl chloride in the risk assessment approach and a total inadequate treatment of the large number of studies in the published literature." (sic)

Response: DHS staff note the usefulness of the commenter's general suggestions advocating more explicit consideration of the pharmacokinetic model and of the epidemiological data in the quantitative risk assessment. Therefore, in the revised document, DHS staff have described quantitatively the Michaelis-Menten kinetic model, as developed by Gehring et al. (1978), which the commenters specifically mention. The model has been included in the risk analysis of the major epidemiological study and in the quantitative analysis of the animal studies.

II. Specific comments

A. Concerning the assertion that the risk assessment does not adequately treat pharmacokinetic knowledge of vinyl chloride:

1. Comment: The DHS risk assessment did not cite several pharmacokinetically oriented studies. One such study was Anderson et al. (1980). Another was Bolt et al. (1981).

Response: DHS considered both the references that the commenter mentioned. The original DHS risk assessment cited one of these two references, as well as many other references on pharmacokinetics. See pages 2-1 through 2-17, and especially page 2-4, where Bolt et al. (1981) is cited. The original public announcement listed the Anderson et al. (1980) paper, but the DHS risk assessment did not cite that reference because the original DHS risk assessment did not use the pharmacokinetic approach in the quantitative modelling of risk predictions. That reference obtained a multistage risk estimate in the lower end of the range of risks, consistent with the DHS calculations for the early Maltoni data that Anderson et al. used. The revised risk assessment now cites Anderson et al. (1980).

2. Comment: "The DHS document fails to incorporate any of the established pharmacokinetic information in its treatment of theoretical risk for vinyl chloride."

Response: The revised document now includes a pharmacokinetic model in the quantitative prediction of risk. The original version of the document included on pages 8-1 and 8-6 a summary of the implications of the pharmacokinetic information and concluded that the pharmacokinetic analysis is not quantitatively necessary (for laboratory rodents) because of sufficient bioassay data at exposures below the saturation concentration for rats. This view is consistent with an independent analysis of Krewski et al.

(1987). They reported that when basing the quantitative risk analysis for rats on doses below 200-500 ppm, which is within the linear range of dose-response, there is virtually no difference between unit risks obtained using administered dose and delivered dose, as obtained in a pharmacokinetic model. The revised analysis did find a greater difference, and the revised version of the document performs the analysis using a pharmacokinetic model.

3. Comment: A reactive metabolite is probably responsible for VC toxicity.

Response: DHS agrees. The original vinyl chloride risk assessment document stated at page 8-1, "the oncogenicity of vinyl chloride appears to be due to one or more reactive metabolites, rather than the parent molecule". Also, the first sentence in Chapter 2, Metabolism and Pharmacokinetics, stated, "Experimental evidence has suggested that vinyl chloride must undergo transformation to a reactive metabolite(s) by the liver to be toxic."

4. Comment: "It is currently thought that VC is metabolized by epoxidation with subsequent production of chloroacetaldehyde. The further oxidation and conjugation with glutathione are responsible for the metabolites found in the urine."

Response: The risk assessment mentioned both the epoxidation process and the conjugation with glutathione -- on pages 2-1 and 2-13 respectively. Both also appeared in the IARC diagram, which is Fig. 2.1.

5. Comment: Gehring found that several models overpredicted the risk to man unless corrected for varying rates of metabolism and for surface area differences of the different species.

Response: In 1978 Gehring et al. used pharmacokinetics in fitting a probit model to observed cancer rates in the rat bioassay. Those authors then went on to use surface area scaling on the assumed rate of metabolism to extrapolate the results from rats to compare to a human risk measurement, derived from an occupational study (Fox and Collier, 1977). In 1979 Gehring et al. used the same pharmacokinetics in fitting four models to observed cancer rates in the rat bioassay. Those authors then went on to extrapolate all four results from rats to compare to an occupational risk study that was then recently completed by Equitable Environmental Health (EEH, 1978). The comparison by Gehring et al. considered the probit prediction to be in satisfactory agreement with the new human measurement without any scaling of risk by surface area. Of the remaining three models, the authors reported one as being too low and the other two as being too high. A follow up study of the occupational group (Wong et al., 1986; see comment B-2 below) subsequently indicated much higher rates of human liver angiosarcoma than had the earlier study. These last two occupational studies (EEH, 1978 and Wong et al., 1986) remain unpublished.

B. Concerning the assertion that the risk assessment does not adequately treat the large number of epidemiology studies in the published literature:

DRAFT

1. Comment: To dismiss the large number of epidemiology studies and to relegate them only to comparisons with animals is unacceptable. "DHS demonstrates a bias towards the utilization of animal experiments as a priority over human evidence in their approach to risk assessment. This results in a dramatic overestimate of likely human risk at the low environmental levels being addressed by the document." The DHS judges that risk extrapolations based on the human data are comparable to those of the animal predictions, yet differences of an order of magnitude or two in risk assessment can often have a dramatic practical effect. "When adequate or substantial human evidence exists, that data should be given preferential treatment in the risk assessment process."

Response: The original document pointed out at pages 1-4, 7-55, 8-7, B-2 and B-3 that the epidemiological data are important to consider in the risk assessment but mostly are not sufficient to construct reliable dose-response functions. One of the main reasons for this limitation is the inability of the occupational studies to account for the effects of sex, tumor site and age of exposure, all of which are found to be important in the animal carcinogenicity results. Also, there are large uncertainties of exposure in the occupational studies. The original document did make the comparative statement that, taking all the limitations of the occupational studies into account, "the human risk estimates are consistent with those obtained for laboratory animals." (page 1-4). See also page 8-10. Using suggestions of the commenter about pharmacokinetics, DHS has revised the estimate of lifetime unit risk for all cancers to be 4.5×10^{-5} ppb^{-1}, based on an occupational study by Waxweiler et al. (1976). This estimate is only a factor of four less than the best animal predictions. Such a result represents reasonable consistency, considering that the occupational results may not take proper account of the greater sensitivity found in females, the greater risk to children, and the inability of the human studies to detect any, except relatively large increases, in any specific type of tumor. The DHS has revised the document to include the two most reliable human results, both from the Waxweiler et al. (1976) study, which do now overlap the narrowed range of risk for animals.

2. Comment: Two updated epidemiology studies, one of over 10,000 workers, are cited in support of the commenter's position that "DHS's approach to dismiss human epidemiology evidence in their risk assessment is inadequate."

Response: The original document reviewed epidemiology studies on pages 7-31 through 7-55 and developed quantitative analyses in Appendices B and C. The document cited both the studies mentioned by the commenter. The first is the paper of Daher et al. (1988), which is cited at page 7-46. This paper, which is less than two pages in length, continues to follow the same 593 Dow employees as did the study of Ott et al. (1975). The number of persons in the study is still too small to expect to detect any effect. The second study mentioned by the commenter is the epidemiological follow up for the Chemical Manufacturers Association (CMA), which was summarized in the Tables B-1 and B-2 of the original document. This study recorded 359 cancer deaths. The SMR for liver and biliary cancer was very large, .641, and the SMR for brain cancer, 180, was statistically significant. On page B-10 that study

was also cited as providing some evidence against a relationship between lung cancer and vinyl chloride exposure. This work for the CMA was listed in the original bibliography by the corporate author, Environmental Health Associates (1986). The risk assessment has been revised to use a consistent means of referencing this unpublished work as Wong et al. (1986). DHS staff has not put much weight on this work because it does not appear to be proceeding to the peer reviewed literature and it is problematic to relate most of the studies to exposure.

3. Comment: Liver angiosarcoma "is the most suitable end-point for analysis of risk of exposure to vinyl chloride."
   (a) The "most reasonable interpretation of the data is consistent with the causal association of vinyl chloride and an excess of brain cancer; however, the relative risk calculation for brain cancer is much lower than that for liver cancer."
   (b) "Only two out of eight studies on lung cancer yield statistically-significant results, and because studies with the higher power were negative, a causal association is unlikely." (sic)
   (c) "Vinyl chloride angiosarcoma is a rare cancer in unexposed populations, thereby making the utilization of angiosarcoma as a demonstration of vinyl chloride exposure on the basis of work history truly a reasonable approach."
   (d) "Angiosarcoma has been demonstrated to occur both in animals and humans when exposed to vinyl chloride."

Response: Liver angiosarcoma plays a major role in the current risk assessment, for the reasons given by the commenter. Nevertheless, other sensitive indicators of carcinogenesis, such as breast cancer observed in rodents and several cancers in humans are also considered.

4. Comment: A recent paper by Purchase et al. (1987) "demonstrates a much more studied and scientifically defensible approach to assessing risk of exposure to vinyl chloride."

Response: The approach of Purchase et al. is not defensible by current standards of risk assessment in the U.S. The models that they use in their risk assessment to interpret animal data have become of marginal importance compared to the multistage (or single stage) model, which has more biological plausibility and also provides more stable estimates of confidence limits on risk. Expressing their results as dose producing one-in-a-million risk, they use the marginal models to produce an excessively large range of dose, with the highest dose being 10^{10} the lowest dose. The higher doses are said to be consistent with the occupational experience, but there is no support for that statement in spite of a lengthy analysis of data on liver angiosarcoma in vinyl chloride workers in several countries prior to 1982. The only dose that the paper derives from the human studies is from a sketchy environmental effects analysis of Barr (1982). See the next item.

5. Comment: Barr (1982) conducted an analysis of liver angiosarcoma cases that could be located among populations inferred to be living in the vicinity of VCM production facilities. The results suggest that "100 ppb represented the

estimated dose representing a 1 x 10^{-6} lifetime risk in man. That value is similar to the highest estimate derived from the animal data when taking biotransformation into account."

Response: The risk assessment did not cite the study of Barr (1982) with its brief analysis of liver angiosarcoma because that analysis is so unsubstantial epidemiologically and the work remains unpublished in the peer-reviewed literature. As a counter to Barr's brief analysis, a well considered recent assessment by the Committee on the Evaluation of Carcinogenic Substances, National Health Council of the Netherlands (1987), published in the scientific literature, has found carcinogenic risk based on published occupational studies to be one in a million per ppb, which was about the same as found in the original DHS risk assessment, 2.1 x 10^{-6}/ppb, before revising the model to take account of the pharmacokinetics of vinyl chloride.

Response to Comments: The Goodyear Tire and Rubber Company

Comment: "Clarification is requested concerning the relationship between the California ambient air quality standard for vinyl chloride - 10 ppb, as it was discussed in the report, the level of concentration of vinyl chloride which poses "no significant risk" to the population - 0.3 micrograms/day and the interaction of these two values in the regulation of toxic air contaminants." (sic)

Response: As pointed out at page A-1 of the risk assessment document, the Air Resources Board in 1978 adopted 10 ppb as the ambient air quality standard for vinyl chloride in California. That standard is not to be exceeded in air within the jurisdiction of the Air Resources Board.

The rate of intake of vinyl chloride which poses "no significant risk" under Health and Safety Code 25249.10 is 0.3 μg/day. DHS determined that intake rate to ensure that the estimated lifetime risk of cancer from intake of vinyl chloride by all routes is less than 10^{-5} or one chance in a hundred thousand, taking the carcinogenic potency of vinyl chloride to be 2.3/(mg/kg-day) in accordance with the U.S. EPA (1984) assessment based on a diet study. For exposure by inhalation alone that EPA potency is equivalent to a unit risk of 7×10^{-4} ppb^{-1} vinyl chloride for a 70kg human breathing 20 m^3/day with 40% absorption. Thus, the potency used to calculate the current intake rate for no significant risk corresponds to a unit risk that is above the range of unit risks for inhalation in the revised risk assessment document. See Figure 8.1 of the revised document for more information.

The quantitative relationship of the 0.3 μg/day intake rate to the 10 ppb air quality standard is obtained by converting the 10 ppb (26 $\mu g/m^3$) to its equivalent intake rate of 210 μg/day for a human breathing 20 m^3/day with 40% absorption. Thus, the air quality standard, which was set at the detection limit at the time of adoption (1978), is 690 times greater than the existing DHS determination of intake rate posing "no significant risk."

Response to Comments: The B.F. Goodrich Company

Comment: The "primary deficiency of the CARB document on identifying VCM as an air toxic from landfills is that it fails to note these important epidemiology studies:

1. Doll, Sir R., (1988) "Effects of Exposure to Vinyl Chloride: an Assessment of the Evidence", Scandinavian Journal of Work, Environment, and Health, 14(2):61-78.

2. Wu, W.; Steenland, K.; Brown, D.; Wells, V.; Jones, J.; Schulte, P. and Halperin, W. "Cohort and Case-Control Analyses of Workers Exposed to Vinyl Chloride - an Update". NIOSH Report Draft, October, 1988.

3. Wong, O.; Whorton, M.D.; Ragland, D.; Klassen, C.; Samuels, D. and Chaxton, K. "Final Report - An Update of an Epidemiology Study of Vinyl Chloride Workers, 1942-1982". Prepared for Chemical Manufacturer's Association, October 17, 1986."

Response: Reference to Doll's recent review of cancer mortality in occupational studies is a useful addition to the risk assessment, and it has been included in the revised document.

The Wu et al. study has recently been published in the Journal of Occupational Medicine 31(6) 518-523 (1989). That study provides useful additional information on following up the worker outcomes for one of the four plants of the Waxweiler (1976) study of vinyl chloride workers. DHS staff has included a discussion of this recent work in the revision.

The Wong et al study, an industry-wide compilation, remains unpublished. Nevertheless, the original version of the risk assessment did cite it by authors in Tables B-1 and B-2, and by corporate authorship, Environmental Health Associates, in the list of references. The revision uses a consistent method to site this work (Wong et al., 1986).

IV. LANDFILL GAS TESTING PROGRAM UPDATE

IV. LANDFILL GAS TESTING PROGRAM UPDATE

Landfill Gas Testing Program data on page A-31 of the preliminary draft report were amended on page A-29 of the second draft to include test results through December 1989.

V. AIR RESOURCES BOARD STAFF LETTER TO THE GOODYEAR TIRE AND RUBBER COMPANY REGARDING THE REQUEST FOR AN EXTENSION OF THE FIRST COMMENT PERIOD

ATE OF CALIFORNIA
AIR RESOURCES BOARD
[illegible] STREET
[illegible] BOX [illegible]
SACRAMENTO CA 95812

George Deukmejian, Governo

DRAFT

September 29, 1989

C.A. See
Corporate Environmental Engineering
Department 1100
Goodyear Tire & Rubber Company
1144 East Market Street
Akron, Ohio 44316-0001

Dear Ms. See:

Thank you for your response to the draft report Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant. Your comments will be considered and addressed in Part C of the second draft of the report.

The second draft of the report will be mailed to you and other members of the public for final review. It will include Parts A, B, and C of the report as well as an executive summary which summarizes Parts A and B. A 20-day comment period will be given for your review. During this comment period, only comments on the executive summary and any revisions made to the report will be accepted. All of the comments received and our responses will then be incorporated as an addendum to Part C. The final draft report, including Part C, will then be submitted to the Scientific Review Panel for its review.

The Scientific Review Panel has requested that all public comments be directed to the Air Resources Board within the time spans allotted for the two comment periods. In accordance with this process, we are unable to extend the first comment period as you requested.

If you have any questions, please call me at (916) 322-7072.

Sincerely,

Robert Barham, Chief
Toxic Air Contaminant
Identification Branch

DRAFT

The Goodyear Tire & Rubber Company

Akron, Ohio 44316-0001

CORPORATE ENGINEERING

September 1, 1989

Air Resources Board
Toxic Air Contaminant Identification Branch
P.O. Box 2815
Sacramento, California 95812
ATTN: Vinyl Chloride
Mr. Robert Barham, Chief

Dear Mr Barham:

The following comments are offered in response to the "Report to the Air Resources Board on Vinyl Chloride - Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant".

Clarification is requested concerning the relationship between the California ambient air quality standard for vinyl chloride - 10 ppb, as it was discussed in the report, the level of concentration of vinyl chloride which poses "no significant risk" to the population - 0.3 micrograms/day and the interaction of these two values in the regulation of toxic air contaminants.

In the sampling and determination of the concentration of vinyl chloride, the use of analytical techniques comparable to and as reliable as the method outlined in the report should be permitted.

DRAFT

An adequate review of the medical studies of the effect of exposure to vinyl chloride can not be satisfactorily completed before the end of the first comment period. Therefore, a request is being made for an extension of the initial comment period.

If you have questions, please call the writer at 216-796-2698.

Sincerely,

C A See

C A See
Environmental Engineer
Corp Environmental Engineering

CAS:cas

I. PART C ADDENDUM COMMENTS RECEIVED

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION IX
215 Fremont Street
San Francisco, CA 94105

June 8, 1990

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Vinyl Chloride
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma,

Thank you for the opportunity to comment on the Air Resources Board's technical support document entitled "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant" dated May 1990. Please incorporate the comments listed below into the the final report. Also, the Environmental Protection Agency's risk assessment group is conducting a detailed review of the report. Any additional comments resulting from this review will be delivered by June 22 of this month. Ms. Barbara Cook of your office assured me that these additional comments will be addressed by the Scientific Review Panel.

Please note that the Operating Industries, Incorporated (OII) landfill is currently a federally listed Superfund site. As part of the Remedial Investigation at the site, EPA is conducting a 12-month ambient air quality study at the OII landfill. Twenty-four hour air samples are being collected every eighth day at nine permanently located stations (including 2 background stations) near the landfill. The detection limit for vinyl chloride for this study is 0.30 parts per billion. Meteorological data is also being collected for this study. The results of this study will be used to support EPA's risk assessment for the OII landfill.

Please include the following paragraph in the Executive Summary:

> The Operating Industries, Incorporated (OII) landfill is currently a federally listed Superfund site. Subsequent to the Air Resources Board's vinyl chloride sampling during 1987, the Environmental Protection Agency (EPA) has implemented more stringent landfill gas control measures. EPA has also selected a remedy for landfill gas control that is expected to substantially reduce landfill gas emissions from the OII landfill. It is fully anticipated that these control measures will substantially lower the levels of vinyl chloride in the ambient air in the vicinity of the OII landfill.

Thank you for the opportunity to comment.

Sincerely,

for Sheller Swanson
Roy Herzig,
Environmental Engineer

000044

Waste Management of North America, Inc.
Government Affairs
925 L Street, Suite 970
Sacramento, California 95814
916/448-4675
Fax: 916/448-2475

June 11, 1990

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
AIR RESOURCES BOARD
P.O. Box 2815
Sacramento, CA 95812

ATTENTION: Vinyl Chloride

SUBJECT: PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT BY THE CALIFORNIA AIR RESOURCES BOARD (ARB)

Thank you for the opportunity to provide comment on the ARB's proposal to identify vinyl chloride as a toxic air contaminant. Waste management of North America (WMNA) is a comprehensive waste management services company owning and operating, among other things, landfills and waste hauling companies in the State of California. In addition, Chemical Waste Management, Inc. (CWM) provides comprehensive hazardous waste management services including hazardous waste collection, transportation, treatment, and disposal in California.

Both WMNA and CWM are supportive of your efforts to identify vinyl chloride as a toxic air contaminant. Indeed, identification of this compound as a toxic air contaminant is mandated by state law by virtue of the fact that it is identified as a hazardous air pollutant pursuant to federal law. However, we are concerned about the bases for identification that are contained in your staff report in two primary areas:

1. Presence of vinyl chloride in the atmosphere and the inference that landfills in California are the principle source of this proposed toxic air contaminant, and

2. The degree of public health risk that is posed by vinyl chloride.

LANDFILLS AS A SOURCE OF VINYL CHLORIDE

On page A-23, the second paragraph states, "Based on the emission estimates for two landfills in California (BKK and OII), landfills are the largest identified source category of vinyl chloride emissions in the state. The information necessary to estimate vinyl chloride emissions for the hundreds of other landfills in California is not available." Other references to landfills being the largest source of vinyl chloride emissions are made elsewhere throughout the report. It is erroneous to assume that these two landfills are representative of all landfills. Both BKK and OII are landfills that are currently included on the state superfund list of hazardous substance release sites. Both of these sites are reported to have accepted significant quantities of waste vinyl chloride during their operating life.

In fact, contrary to the statement made above, significant information DOES exist that landfills are NOT a significant source. The Air SWAT programs mandated by Health and Safety Code Section 41805.5 show that waste management units operated by WMNA are not a significant source of vinyl chloride emissions. Unfortunately the ARB's report makes only passing reference to the Air SWAT data. Even this passing reference indicates that, while the presence of vinyl chloride has been detected in some landfills, the concentrations and amounts are vastly lower that those represented by BKK and OII. Rather than attribute vinyl chloride emissions to landfills, the report would be more accurate in attributing such emissions to superfund sites that once received vinyl chloride waste for disposal.

Attached to this letter I have included summary tables of the Air SWAT results for six of the landfills owned and operated by WMNA. This data shows that, while vinyl chloride is detectable at low to very low levels within the landfills themselves it is, with only minor exception, virtually undetectable in surface samples and in downwind ambient air samples. Finalization of the rulemaking for vinyl chloride as a toxic air contaminant should be delayed until this recent and very critical information can be properly incorporated into the report. In fact, section 39660(f) of the Health and Safety Code mandates that DHS and the ARB give priority to the evaluation and regulation of substances as air toxic contaminants based on a variety of factors including amount or potential amount of emissions and ambient concentrations in the community. To proceed with identification of vinyl chloride as a toxic air contaminant while identifying landfills as the largest source of emissions based on two unrepresentative sites would be

a disservice to the waste management industry and contrary to state law. This is made even more true by not using readily available Air SWAT data which provides a much more accurate indication of the true contribution of waste management units to emissions of vinyl chloride.

PUBLIC HEALTH RISK OF VINYL CHLORIDE

While we do believe that it is ultimately appropriate to regulate vinyl chloride as an air toxic contaminant, we are concerned that the unit risk factor that you have attributed to this compound is overly conservative. I have also attached to this letter a copy of a brief paper on Carcinogenic Risks from Landfill Emissions dated June 6, 1988. This paper was submitted in comment on a preliminary draft document circulated by EPA in March, 1988, "Air Emissions from Municipal Solid Waste Landfills--Background Information for Proposed Standards and Guidelines". This information provides a much more realistic assessment of the health risks posed by municipal landfills not only from the standpoint of vinyl chloride but a number of other compounds as well. In summary this brief paper, based on an assessment of the cumulative impact of all landfill emissions, concludes, "Using a dispersion model for area emissions, we find that for persons spending their whole lives 100 m from the edge of such a landfill the lifetime risk is about 20×10^{-6}, while even for persons staying permanently at the edge of the landfill the lifetime risk is only 50×10^{-6}."

In addition, I have attached some specific comments prepared by Dave Dolan, Waste Management Inc. toxicologist, listing specific concerns we have pertaining to the risk assessment information contained in the ARB's Technical Support Document for Vinyl Chloride. The report Mr. Dolan cites in his second item (U.S. EPA, 1985) is entitled, "Techniques for the Assessment of the Carcinogenic Risk to the U.S. Population due to Exposure from Selected Volatile Organic Compounds from Drinking Water via the Ingestion, Inhalation, and Dermal Routes".

RECOMMENDATION

Due to the fact that the ARB knows that the Air SWAT data is now available to assess the impact of vinyl chloride, identification of vinyl chloride as an air toxic contaminant should more properly be delayed until this information can be included in the report to provide a realistic assessment of landfills as a very limited source of risk to adjacent communities.

Thank you for the opportunity to comment on your draft Technical Support Document. If you have any questions or concerns pertaining to these comments, please do not hesitate to contact me.

Sincerely,

Charles A. White, Manager
Regulatory Affairs

CAW:fal
Attachments
cc: Dave Dolan
Sara Broadbent
Sue Briggum

TABLE 2-1
SUMMARY OF ALTAMONT ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air (Net Downwind Increase Compared with Upwind Concentration) 24-Hour Continuous
	Landfill Gas	Integrated Surface Sample	
Primary Target Monitoring Compound			
Vinyl Chloride	3,000	3.0	0.0
Supplemental Target Monitoring Compounds			
Benzene	<500	<2.0	--
Ethylene Dibromide	<50	<0.5	--
Ethylene Dichloride	32	<0.2	--
Methylene Chloride	21,000(a)	<1.0	--
Perchloroethylene	5,400	0.8(b)	--
Carbon Tetrachloride	<5	<0.2	--
Methyl Chloroform	210	0.5(c)	--
Trichloroethylene	8,600	0.9(d)	--
Chloroform	430	<0.8	--
Methane	480,000,000	3,000	--

Note: ppbv = parts per billion by volume.

(a) This result is potentially due to limitations of the analytical methods specified by the ARB in the Testing Guidelines (i.e., a non-Calderon constituent may coelute with methylene chloride).
(b) Altamont integrated surface sample value of 0.8 ppbv for perchloroethylene is similar to the ARB background value of 0.6 ppbv for the Bay Area Region (1985 data) in which Altamont is located.
(c) Altamont integrated surface sample value of 0.5 ppbv for methyl chloroform is nearly identical to the laboratory detection limit (<0.5 ppb), and is well below the ARB background value of approximately 2.1 ppbv for the Bay Area Region (1985 data) in which Altamont is located.
(d) Altamont integrated surface sample value of 0.9 ppbv for trichloroethylene is similar to the ARB background value of approximately 0.5 ppbv for the Bay Area Region (1985 data) in which Altamont is located.

TABLE 2-1
SUMMARY OF LANCASTER ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air (Net Downwind Increase Compared with Upwind Concentrations)	
	Landfill Gas(c)	Integrated Surface Sample	24-Hour Continuous(c)	Directionally Controlled(c)
Primary Target Monitoring Compound				
Vinyl Chloride	4,629	<2.0	0.2(b)	0.0
Supplemental Target Monitoring Compounds				
Benzene	571	<2.0	0.0	0.0
Ethylene Dibromide	<1	<0.5	0.0	0.0
Ethylene Dichloride	<20	<0.2	0.0	0.0
Methylene Chloride	2,094	<1.0	4.0(b)	2.3(b)
Perchloroethylene	578	0.4(a)	0.2 (b)	0.0
Carbon Tetrachloride	<5	0.8	4.8 (b)	0.7(b)
Methyl Chloroform	824	<0.5	0.9(b)	3.7(b)
Trichloroethylene	442	<0.6	0.0	0.0
Chloroform	40	<0.8	0.0	0.0
Methane	62,000,000	10,000	-	-

Note: ppbv = parts per billion by volume.

(a) Lancaster integrated surface sample value of 0.4 ppbv for perchloroethylene is similar to the ARB background value of 0.2 ppbv for the Southwest Desert Region in which Lancaster is located (see Table 2-2).
(b) These downwind ambient increments are greater than expected considering the low concentrations for the integrated surface samples and landfill gas samples. However, these downwind increments are less than 5 ppbv, which corresponds to inherent data uncertainties with ASWAT ambient air data associated with limitations of the analytical methods specified by the ARB in the Testing Guidelines.
(c) Based on composite data which includes all samples.

TABLE 2-1
SUMMARY OF DAVIS STREET ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient
	Landfill Gas	Integrated Surface Sample	24-Hour Ambient Air (Net Downwind Increase Compared with Upwind Concentration)(a)
Vinyl Chloride	<500	<2.0	0.0
Benzene	<500	<2.0	0.0
Ethylene Dibromide	<1	<0.5	0.0
Ethylene Dichloride	<20	<0.2	0.0
Methylene Chloride	<60	8(b)	0.0
Perchloroethylene	<10	<0.2	0.0
Carbon Tetrachloride	<5	<0.2	0.0
Methyl Chloroform	<10	1.1(c)	0.4(d)
Trichloroethylene	<10	<0.6	0.0
Chloroform	<2	<0.8	0.0
Methane	530,000,000	<2000	

Note: ppbv = parts per billion by volume.

(a) Based on composite data for all sampling days.
(b) Davis Street integrated surface sample value is higher than expected considering the nondetection of this constituent in the landfill gas sample. The reported value may have been affected by ambient background levels, which may exceed 10 ppbv in the Bay Area (see Table 2-2), and/or limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines, which may result in data uncertainties of approximately 5 ppbv.
(c) Davis Street integrated surface sample value of 1.1 ppbv is higher than expected considering the nondetection of this constituent in the landfill gas sample. The reported value is similar to the background value of 1.4 ppbv based on BAAQMD data for San Leandro. (See Table 2-2.)
(d) This downwind concentration increment may be due to limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines, which may result in data uncertainties of approximately 5 ppbv. The results presented above do not include the primary sampler results, which have a contamination bias of approximately 4 ppbv.

TABLE 5-1
SUMMARY OF DURHAM ROAD ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air (Net Downwind Increase Compared to Upwind Concentration)
	Landfill Gas	Integrated Surface Sample	24-Hour Continuous
Primary Target Monitoring Compound			
Vinyl Chloride	3,000	<2.0	0.0
Supplemental Target Monitoring Compounds			
Benzene	1,000	<2.0	--
Ethylene Dibromide	<1	<0.5	--
Ethylene Dichloride	<20	0.2	--
Methylene Chloride	7,500	<1.0	--
Perchloroethylene	5,200	0.3(a)	--
Carbon Tetrachloride	<5	<0.2	--
Methyl Chloroform	300	1.3(b)	--
Trichloroethylene	2,000	<0.6	--
Chloroform	260	<0.8	--
Methane	520,000,000	<2,000	--

Note: ppbv = parts per billion by volume.

(a) Durham Road integrated surface sample value of 0.3 ppbv for perchloroethylene is similar to the ARB background value of 0.6 ppbv for the Bay Area Region (1985 data), in which Durham Road is located.

(b) Durham Road integrated surface sample value of 1.3 ppbv for methyl chloroform is similar to the ARB background value of approximately 2.1 ppbv for the Bay Area Region (1985 data), in which Durham Road is located.

TABLE 2-1
SUMMARY OF BRADLEY ASWAT RESULTS (ppbv)

	Gas Characterization(c)		Ambient Air (Net Downwind Increase Compared with Upwind Concentrations)(c)	
	Landfill Gas	Integrated Surface Sample	24-Hour Continuous	Directionally Controlled
Primary Target Monitoring Compound				
Vinyl Chloride	33,625(a)	2.5	0.2	0.0
Supplemental Target Monitoring Compounds				
Benzene	900	1.5	0.1	0.3
Ethylene Dibromide	<3	<0.5	0.0	0.0
Ethylene Dichloride	<30	<0.2	0.0	0.0
Methylene Chloride	2570	<1.0	0.0	1.3
Perchloroethylene	375	0.4	<0.1	0.1
Carbon Tetrachloride	<5	0.2	<0.1	0.0
Methyl Chloroform	<10	7.5(b)	0.8	0.0
Trichloroethylene	1435	<0.6	0.0	0.0
Chloroform	<4	<0.8	0.3	0.6
Methane	500,000,000	<5,000	—	—

Notes: 1. ppbv = parts per billion by volume.
2. The landfill gas samples were collected in December 1987/August 1988, integrated surface samples in May 1988/August 1988, and ambient samples in May 1988.

(a) Based on composite data, which include all downwind samples.
(b) This result may have been affected by sample matrix interferences, coelution of constituents with similar GC retention times, and other inherent limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines. Ambient air concentration results confirm that Bradley Landfill gas emissions for this constituent do not affect offsite air quality.
(c) Value is similar to the ARB range of background values (1.11 - 7.07) for the South Coast Region.

TABLE 2-1
SUMMARY OF KIRBY CANYON ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air
	Landfill Gas	Emission Screening	24-Hour Continuous Downwind[a]
Vinyl Chloride	41,000[b]	---	<2.0
Benzene	2,500	---	<2.0
Ethylene Dibromide	<1	---	<0.5
Ethylene Dichloride	<20	---	<0.2
Methylene Chloride	59,000[b]	---	<1.0
Perchloroethylene	2,100	---	0.7[c]
Carbon Tetrachloride	<5	---	<0.2
Methyl Chloroform	190	---	1.0[d]
Trichloroethylene	2,200	---	<0.6
Chloroform	2,000	---	<0.8
Methane	2,600,000	<50,000	---

Note: ppbv = parts per billion by volume.

(a) One sample day with two collocated samplers.
(b) These results may have been affected by sample matrix interferences, co-elution of constituents with similar GC retention times, and other inherent limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines. Ambient air concentration results confirm that Kirby Canyon Landfill gas emissions for these constituents do not affect offsite air quality (in fact, they were not detected in the ambient samples).
(c) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, this concentration of 0.7 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.5-0.8 ppbv mean with 1.6 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.
(d) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, the concentration of 1.0 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.6-4.1 ppbv mean with 47.3 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.

TABLE 2-2
COMPARISON OF KIRBY CANYON AMBIENT AIR RESULTS (ppbv) (BASED ON THE 24-HOUR CONTINUOUS DOWNWIND STATION) AND AVAILABLE REGIONAL DATA

	Mean			Maximum		Number of Observations	
	Kirby Canyon	S.F. Bay Area[a]	San Jose[b]	Kirby Canyon[c]	S.F. Bay Area[a]	Kirby Canyon[d]	S.F. Bay Area[a]
Vinyl Chloride	<2.0	(c)	(c)	<2.0	(c)	2	(c)
Benzene	<2.0	1.8-3.2	4.4	<2.0	15.6	2	91
Ethylene Dibromide	<0.5	0-0.01	(c)	<0.5	0.1	2	82
Ethylene Dichloride	<0.2	0.05-0.07	(c)	<0.2	0.3	2	84
Methylene Chloride	<1.0	0.7-4.3	2.6	<1.0	11.9	2	82
Perchloroethylene	0.7[e]	0.5-0.8	0.5	1.3	1.6	2	84
Carbon Tetrachloride	<0.2	0.2	0.1	0.2	0.5	2	83
Methyl Chloroform	1.0[f]	0.6-4.1	1.8	1.2	47.3	2	83
Trichloroethylene	<0.6	0.3-0.7	0.3	<0.6	1.0	2	43
Chloroform	<0.8	0.03-0.05	0.05	<0.8	0.1	2	84

Note: ppbv = parts per billion by volume.

(a) Based on available ARB data for the San Francisco Bay Area (California Toxic Air Quality Data - Summary of 1985 Toxic Air Quality Data, Preliminary).
(b) Based on available 1986 BAAQMD data for San Jose (Toxic Air Monitoring Summary, 1986-1987, Board of Directors Meeting, September 2, 1987).
(c) Information not available for this report.
(d) One sample day with two collocated samplers.
(e) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, this concentration of 0.7 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.5-0.8 ppbv mean with 1.6 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.
(f) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, the concentration of 1.0 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.6-4.1 ppbv mean with 47.3 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.

ATTACHMENT 3[2]

DATE: June 11, 1990

FROM: Chuck White

TO: David Dolan DD

RE: Comments on the Air Resources Board's "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant"

I have reviewed Part B of the Air Resources Board's "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant". The ARB is to complimented for the thoroughness of this report. There are, however, several issues that deserve some attention. Given the short amount of time available for this memo, please excuse its terseness.

First, why bother using the linearized multistage model under the pretense that it is a true mechanistic model (which it is not), when a simple linear regression usually yields nearly identical estimates of q_1^* (r^2 = 0.98)(Personnel conversation with Curtis Travis, Oak Ridge National Laboratory)?

Second, the discussion of uncertainty in the quantitative risk estimates is given short shrift. Although the uncertainties or absence of exposure data in the occupational cohort studies is mentioned, there is no discussion of the conservatism built into the risk estimates by the selection of data for extrapolation, and the extrapolation assumptions, and the effects their underlying assumptions may have on the risk estimates. For instance, the use of the most sensitive sex/strain/species instead of the average may alter risk estimates by "several orders of magnitude." (U.S. EPA, 1985) Similarly, the issues the extrapolation of rodent potency estimates to humans, particularly on the basis of surface area, and the use of upper 95th percentile estimates of carcinogenic potency instead of the MLE, may alter potency estimates by an order of magnitude, or more. (U.S. EPA, 1985)

Third, it is perplexing that the Krewski et al. (1987) chapter is referenced, yet the 36-fold lower carcinogenic potency factor they derive is omitted from the brief discussion. Some discussion on the merits and limitations of the Krewski et al. analysis is necessary.

Fourth, the ARB cites the concordance of the potency estimate derived from the Drew et al. (1983) study and the Maltoni et al. (1984) experiments. It is unclear whether the Maltoni experiments were conducted in his medieval castle/laboratory where the mycobacterium infection is endemic, or in some other facility. (Personnel conversation with E.E. McConnell, National Toxicology Program) In the U.S., mycobacterium infections in test animals would likely violate GLPs, and serve as grounds for invalidating a study.

Fifth, the recommended use of a potency factor derived from animal instead of the human occupational study of Waxweiler et al. (1976) is not robust, given that the human data already represents an upper-bound estimate in the target species of concern (i.e., humans). The additional rationale that the selection of the highest animal estimate is justified by the limited evidence of an effect by age at first exposure (Drew et al., 1983) suggests that perhaps the ARB should consider using a true mechanistic model, perhaps one based upon the MVK model paradigm, as the basis of its potency determinations.

cc: Jim McHenry

5/32.3

ATTACHMENT 2

Carcinogenic Risks from Landfill Emissions.

Addendum to

Comments on a Preliminary Draft Document circulated by the EPA in March, 1988:

Air Emissions from Municipal Solid Waste Landfills--
Background Information for Proposed Standards and Guidelines

by

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Produced at the request of

The National Air Pollution Control Techniques Advisory Committee to the EPA

and

Waste Management Inc.

June 6, 1988

CONTENTS

An estimate of carcinogenic risks from landfill emissions.

Introduction

On May 18, 1988, we presented testimony to the National Air Pollution Control Techniques Advisory Committee to the EPA on the risk assessment aspects of a Preliminary Draft Document, "Air Emissions from Municipal Solid Waste Landfills -- Background Information for Proposed Standards and Guidelines." The gist of that testimony was that the carcinogenic risks predicted by the Draft Document were incorrect. The analysis that follows is our attempt to derive such risks more correctly. In particular, we derive estimates of "average" and "worst-case" risks of cancer that could be attributed to volatile organic compounds that may be emitted from municipal solid waste landfills. The estimates are all "standard" in the sense that they are deliberate overestimates, predicated upon "no-threshold" models for all chemical carcinogens of interest. It is our toxicologic opinion that many of the chemicals of interest here are in fact likely to contain thresholds in their dose-response curves for carcinogenesis, such that the very low-level exposures involved carry with them no excess risk of cancer to humans. Nonetheless, we have not "taken credit" for this probability, but instead modeled all compounds as if they carry excess risks of cancer at all non-zero levels of exposure.

1. Data summary

Table 1.1 summarizes measurements of landfill gases collected at 8 municipal landfills, labelled A to H. All these measurements are given in ppm by volume, and include entrained air (the amount of which can be estimated from the nitrogen and oxygen content of the gas). The landfills labelled B, C, G and H were used in the past for co-disposal of municipal waste and hazardous waste, although this practice has now ceased. This former practice of co-disposal is likely to have led to emissions of larger quantities of chemicals of interest than would have occured from the disposal of municipal solid waste alone.

Table 1.2 shows the average concentrations of components of the emitted gases from each landfill. These averages may be compared with the values given in the EPA Draft Document, Table 3.9. Despite the differing data sources, the average concentrations are very similar. In this data, carbon tetrachloride was never detected, whereas the EPA data has an average concentration of 0.0115 ppmV. Also, the average concentration of 1,1-dichloroethene (vinylidene chloride) is a factor 10 lower here than in the EPA data. In both cases, the concentrations were very low even in the EPA data.

Also shown in Table 1.2 are the molecular weights of all the measured components, together with upper bound estimates of "unit risk" for the known carcinogens. These estimates were taken directly from the Carcinogen Assessment Group (CAG) assessments where they have made such estimates. Otherwise they come from CAG estimates for "potency" of a compound, and assume that a human breathes 20 m^3/day of air, and that 100% of a compound is absorbed. At this breathing rate, if a material is present at 1 ug/m^3 in air, a person will inhale 20 ug/day or 3.33×10^{-4} mg/kg-day for a 60 kg person. For a compound with potency P mg/kg-day, this results in a unit risk (risk from 1 ug/m^3 of air) of 3.33×10^{-4} P. The estimates in Table 1.2 generally agree

with those in the EPA Draft Document, except for carbon tetrachloride, where we take the upper end of a suggested range (EPA uses an average of the range); vinyl chloride, where a more recent estimate by the CAG (which we use) has raised the carcinogenic potency estimate by a large factor; and vinylidene chloride, where our estimate is again substantially higher than that of the EPA Draft Document.

Using the molecular weights of the components, together with the unit risks, we can define an average unit risk for the "as measured" average landfill gas. This is obtained by finding the weighted average unit risk for all components, where the weighting factor is the product of molecular weight and volumetric concentration for each component. The result obtained is 1.6×10^{-9} per ug/m^3 for the landfill gas including entrained air, and approximately 1.9×10^{-9} per ug/m^3 after correction for entrained air. We do not use this average, since it is preferable to compute risk estimates on a landfill by landfill case, taking into account the differing concentrations and emission rates at each landfill.

The unit cancer risks estimated by the EPA in Table 2-4 of the Draft Document suffer from major deficiencies. The first two "scenarios" cannot be justified at all. Averaging together the unit risks of the various carcinogens found in landfill gas could only be justified if there were equal emission rates (by mass) of those carcinogens, but it is clear that this is incorrect. Furthermore, the Draft Document includes one carcinogen (Table 2-3, ethylene dichloride) which was apparently never found in their samples of landfill gas (Table 3-9, although it is listed twice in Table 3-8). The "scenario 1" estimate appears to ignore measurements of non-methane VOCs which indicate that the major components (certainly more than 75%) are simple alkanes (especially ethane and propane). Furthermore, it is unclear what is meant in this document by non-methane VOCs. Since these are

TABLE 1.1 (contd.)
Average Concentrations (ppmV)

SITE	E	F	G	H
Carbon tetrachloride	nd	nd	nd	nd
Chlorobenzene	4.3E-01	nd	nd	2.1E+01
Chloroethane	9.1E-02	7.0E-01	3.8E-01	nd
Chloroform	nd	2.5E+00	nd	nd
Chloromethane	1.2E+00	1.1E+01	3.6E+00	6.2E-01
Dibromochloromethane	nd	nd	nd	nd
1,1-Dichloroethane	7.6E-01	2.0E-01	1.6E+00	2.8E-01
1,2-Dichloroethane	nd	nd	nd	nd
1,1-Dichloroethene	nd	nd	nd	nd
t-1,2-Dichloroethene	1.1E-01	nd	nd	nd
1,2-Dichloropropane	2.2E-01	nd	nd	nd
c-1,2-Dichloropropene	nd	nd	nd	nd
t-1,3-Dichloropropene	nd	nd	nd	nd
Methylene chloride	3.2E+00	9.2E+00	1.4E+01	3.4E-01
1,1,2,2-Tetrachloroethane	1.1E-01	nd	nd	nd
Tetrachloroethene	6.9E+00	3.8E+00	1.2E+01	1.4E+00
1,1,1-Trichloroethane	2.0E-01	nd	1.7E-01	nd
1,1,2-Trichloroethane	nd	nd	nd	nd
Trichloroethene	4.1E+00	6.0E-01	2.9E+00	nd
Trichlorofluoromethane	4.4E-01	2.0E-01	7.6E+00	1.3E-01
Vinyl Chloride	5.3E+00	3.1E+00	2.6E+00	4.2E+00
1,2-Dichlorobenzene	nd	nd	nd	nd
1,3-Dichlorobenzene	nd	nd	nd	nd
1,4-Dichlorobenzene	nd	nd	nd	2.0E+00
Chlorodifluoromethane	6.9E-01	6.0E-01	4.0E-01	4.7E-01
Dichlorodifluoromethane	nd	nd	nd	nd
Dichlorofluoromethane	4.6E-01	8.0E-01	2.0E+00	nd
Methane	4.7E+05	5.1E+05	3.7E+05	5.1E+05
Ethane	9.5E+02	7.6E+02	5.0E+02	1.6E+03
Propane	1.1E+01	5.6E+01	1.5E+01	2.5E+01
n-Butane	nd	1.7E+01	2.8E+00	nd
n-Pentane	4.1E+00	5.5E+00	2.9E+00	1.5E+00
n-Hexane	6.1E+00	6.4E+00	6.9E+00	4.0E+00
Acrylonitrile	nd	nd	nd	nd
Benzene	2.7E+00	2.0E+00	2.0E+00	7.2E+00
Toluene	1.2E+02	5.8E+01	1.4E+02	5.2E+01
Ethylbenzene	2.4E+01	1.4E+01	2.3E+01	2.7E+01
Total Xylenes	7.2E+01	3.4E+01	8.4E+01	7.1E+01
TNMHC (as C6)	9.7E+02	9.9E+02	1.0E+03	1.3E+03
Carbon dioxide	3.8E+05	3.7E+05	3.0E+05	3.1E+05
Oxygen	1.7E+04	1.1E+04	6.5E+04	1.8E+04
Nitrogen	1.4E+05	1.1E+05	2.6E+05	1.6E+05

TABLE 1.2
Average concentration over sites, and unit risks

	Average conc. ppmV	Mol. weight	unit risk	potency	weighted unit risk
Carbon tetrachloride	nd	1.5E+02	4.3E-05	1.3E-01	
Chlorobenzene	2.7E+00	1.1E+02			
Chloroethane	3.3E-01	6.5E+01			
Chloroform	3.1E-01	1.5E+02	2.3E-05		3.9E-11
Chloromethane	4.3E+00	5.0E+01			
Dibromochloromethane	nd	2.1E+02			
1,1-Dichloroethane	2.5E+00	9.9E+01			
1,2-Dichloroethane	2.8E-02	9.9E+01	3.0E-05	9.1E-02	3.0E-12
1,1-Dichloroethene	9.8E-02	9.7E+01	3.9E-04	1.2E+00	1.3E-10
t-1,2-Dichloroethene	2.4E-01	9.7E+01			
1,2-Dichloropropane	5.1E-02	1.1E+02			
c-1,2-Dichloropropene	nd	1.1E+02			
t-1,3-Dichloropropene	nd	1.1E+02			
Methylene chloride	2.7E+01	8.5E+01	4.7E-07		3.8E-11
1,1,2,2-Tetrachloroethane	1.4E-02	1.7E+02	6.7E-05	2.0E-01	5.5E-12
Tetrachloroethene	1.4E+01	1.7E+02	9.5E-07		8.1E-11
1,1,1-Trichloroethane	1.7E-01	1.3E+02	1.9E-05	5.7E-02	1.5E-11
1,1,2-Trichloroethane	nd	1.3E+02			
Trichloroethene	5.0E+00	1.3E+02	1.7E-06		4.0E-11
Trichlorofluoromethane	1.4E+00	1.4E+02			
Vinyl Chloride	5.7E+00	6.2E+01	9.8E-05	2.9E-01	1.2E-09
1,2-Dichlorobenzene	nd	1.5E+02			
1,3-Dichlorobenzene	nd	1.5E+02			
1,4-Dichlorobenzene	2.5E-01	1.5E+02			
Chlorodifluoromethane	1.3E+00	8.6E+01			
Dichlorodifluoromethane	9.4E-02	1.2E+02			
Dichlorofluoromethane	4.4E+00	1.0E+02			
Methane	4.7E+05	1.6E+01			
Ethane	7.7E+02	3.0E+01			
Propane	2.4E+01	4.4E+01			
n-Butane	3.8E+00	5.8E+01			
n-Pentane	3.1E+00	7.2E+01			
n-Hexane	7.3E+00	8.6E+01			
Acrylonitrile	nd	5.3E+01	8.0E-05	2.4E-01	
Benzene	2.9E+00	7.8E+01	8.0E-06		6.4E-11
Toluene	7.6E+01	9.2E+01			
Ethylbenzene	1.5E+01	1.1E+02			
Total Xylenes	4.4E+01	1.1E+02			
TNMHC (as C6)	8.3E+02				
Carbon dioxide	3.6E+05	4.4E+01			
Oxygen	2.8E+04	3.2E+01			
Nitrogen	1.5E+05	2.8E+01			

2. Methodology

2.1 Emission rates

Table 1.1 gives the concentrations of various gases measured in collected gases at various landfills. Also available for each landfill is the rate at which these gases are released. Taking the product of total emission rate for landfill gas with these concentrations gives the volumetric emission rate for each gas. This volumetric emission rate may be converted to a mass emission rate by using the gas density, which we approximate by assuming all the gases behave perfectly. For the 8 landfills considered here, the average volumetric emission rate is 2.7×10^6 cfd per landfill, from an average amount of refuse in place of 5.4×10^6 tons per landfill. This is about 50% higher than assumed in the EPA Draft Document for wet landfills.

From the mass emission rate, we may use air dispersion modelling to estimate the expected long term average concentrations of each component of the landfill gas at various positions off-site. The product of those concentrations (in ug/m^3) and the upper bound unit risk estimate (measured in units of m^3/ug) gives an upper bound estimate to lifetime risk. The net effect of all the landfill gas can thus be obtained from the sum over all components of the product of mass emission rate and unit risk for each components. Table 2.1.1 shows this product (in units of m^3/s) for all detected components of the landfill gases which have unit risks defined. Also shown are the sums of products for each landfill.

TABLE 2.1.1
Mass emission rate x unit risk (m^3/s)

SITE	A	B	C	D
Chloroform	0	0	0	0
1,2-Dichloroethane	0	3.5E-03	0	3.8E-03
1,1-Dichloroethene	4.3E-02	5.2E-02	0	2.6E-01
Methylene chloride	3.8E-04	4.5E-02	1.2E-02	2.9E-02
1,1,2,2-Tetrachloroethane	0	0	0	0
Tetrachloroethene	5.4E-03	1.8E-02	5.8E-02	1.4E-01
1,1,1-Trichloroethane	2.0E-03	1.6E-03	4.7E-03	2.8E-02
Trichloroethene	2.4E-03	2.3E-02	3.3E-02	4.9E-02
Vinyl Chloride	1.5E-01	6.4E-01	2.7E+00	3.3E-01
Benzene	8.8E-03	5.2E-03	5.0E-02	4.0E-02
Total	2.2E-01	7.9E-01	2.8E+00	8.8E-01

SITE	E	F	G	H
Chloroform	0	1.7E-01	0	0
1,2-Dichloroethane	0	0	0	0
1,1-Dichloroethene	0	0	0	0
Methylene chloride	4.6E-03	7.0E-03	3.7E-02	1.3E-03
1,1,2,2-Tetrachloroethane	4.5E-02	0	0	0
Tetrachloroethene	4.0E-02	1.1E-02	1.2E-01	2.2E-02
1,1,1-Trichloroethane	1.9E-02	0	2.8E-02	0
Trichloroethene	3.3E-02	2.6E-03	4.3E-02	0
Vinyl Chloride	1.2E+00	3.6E-01	1.1E+00	2.6E+00
Benzene	6.1E-02	2.4E-02	8.2E-02	4.5E-01
Total	1.4E+00	5.8E-01	1.4E+00	3.1E+00

Average total 1.4E+00

The average total for all the landfills is 1.4 m^3/s, and the maximum is 3.1 m^3/s for landfill H (which was used in the past for co-disposal). In every case, the vinyl chloride present contributes the majority of the risk.

2.2 Nationwide average risk

To make an estimate of the nationwide average risk from landfill gas now requires a scale-up, together with some dispersion modelling. The landfills discussed in the previous sections have an average amount of refuse in place of 5.4 million tons, which is 1/900 of the total estimated refuse in place in municipal landfills in the U.S. (EPA Draft Document, page 3-1). The land area of the contiguous U.S. is about 7.84×10^6 km^2, so that the U.S. land area per average landfill is about 8.7×10^9 m^2, corresponding to a radius of about 52 km.

As a first approximation, the effects of landfills on the U.S can thus be obtained by finding the average effects of a single landfill on a radius of about 50 km around it. This approximation would be correct if (1) landfills were uniformly distributed over the U.S.; (2) the population were evenly distributed; and (3) no landfill had any effect beyond 50 km. It is plausible that the third of these is correct, since the chlorinated VOCs which contribute to carcinogenic risk are relatively short-lived (vinyl chloride, for example, has a half-life in air estimated at 1.5 - 1.8 days). The first two are clearly incorrect, but will be compensated by the overestimation of risks to those close to landfills (see below).

For an average landfill, we have an emission rate x carcinogenic unit risk of 1.4 m^3/s. Using the standard gaussian plume model, the average concentration obtained from this over the radial range 0.1 to 50 km corresponds to a lifetime risk of 1.6×10^{-8}. This assumes a uniform wind rose, a wind speed of 3 m/s, and a simple averaging over 7 wind stability classes (A, B, C, Dday,

Dnight. E, F), and emission height of 1 m, and a receptor height of 1.5 m. This averaging procedure has been found to give estimates within 20% of those obtained using the ISC model in particular cases with observed wind rose and stability class data, provided the average wind speed is used. The assumed average wind speed of 3 m/s (6.7 mph) is a reasonable estimate, probably a little low (resulting in an overestimate of risk) for most of the U.S. For 67 cities in the 50 contiguous states, just 3 report average windspeeds less than 6.7 mph.

The minimum distance used for this averaging, 100 m, corresponds to an estimate of the minimum distance from the center of a landfill at which people can be expected to be living. If landfill gas is collected at some landfill, it may be collected together at any point over the landfill. However, if it is collected it will be flared, so that there is negligible exposure of anybody to it. If it is not collected, then the emissions will take place over the whole landfill, and so the nearest person to the landfill may be closer than 100 m. In that case, however, the dispersion modelling performed above is a substantial overestimate for estimating exposures close to the landfill (within distances similar to the dimensions of the landfill). This is dealt with below for the worst case estimate.

The estimate of average effect, a lifetime risk of 1.6×10^{-3}, corresponds to an annual cancer incidence of 0.05 in the United States. Considering the differing methodologies, this agrees well with the EPA Draft Document estimate of 0.11 (Scenario 3, the only one which can be given any credence). However, the differences noted above, especially the dominant effect of vinyl chloride in these estimates, suggests that the EPA Draft Document is considerably in error. Insufficient data is given in the Draft Document to locate where such error may have arisen, but one likely place is in the Effects Model. The technique described of locating population centers relative to landfills is prone to lead to substantial

overestimates of exposure if a small error is made in the location of a population close to a landfill. The average exposure may then be dominated by those estimated for nearby populations.

2.3 Worst case risk estimates

The worst case risk estimate will be for those persons living near to a landfill. As mentioned above, however, the dispersion modelling used for the nationwide average (both here and in the EPA Draft Document) will give very misleading results close in. If landfill gas is collected together into a single vent, that gas will be flared. The worst case exposure estimate will correspond to a landfill with no collection system, in which case the emissions will take place from over the whole surface area of the landfill. The concentrations from such area emissions are considerably lower than those from a vent pipe emitting the same total quantity of gas, at equal distances from the edge of the area or the vent pipe.

To make an estimate of the worst case emissions, consider the landfill labelled M above (Table 1.1). This was previously used for co-disposal of hazardous waste as well as municipal waste. The total emission rate x unit risk for this landfill is 3.1 m^3/s, and it contains 12.6 million tons of refuse. The worst case will occur with maximum emissions per unit area of landfill, so we will assume waste piled to a height of 100 feet and with an average density of 1 ton/cu. yd. (double that assumed in the EPA Draft Document). The emission rate x unit risk per unit area for this landfill is then 8.2×10^{-6} m/s, and the landfill covers an area of about 3.2×10^6 m^2, corresponding to a diameter of about 640 m.

Using a dispersion model for area emissions, we find that for a person spending their whole lives 100 m from the edge of such a landfill the lifetime risk is about 20×10^{-6}, while even for a person staying permanently at the edge of the landfill the lifetime risk is only 50×10^{-6}.

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48674

1803 BUILDING
July 3, 1990

Ms. Barbara Cook
Project Manager
California Air Resources Board
1102 Q Street
Sacramento, CA 95814

Dear Ms. Cook:

Attached are our comments on the unit risk derivation presented in the May, 1990 Draft Technical Support Document, Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant.

We appreciate your accepting our comments, which have been submitted to promote the best possible science in the performance of health risk assessments.

Pleased call on us should you require additional information.

Sincerely,

Neil C. Hawkins, Sc.D.
Senior Research Risk Analyst
Health and Environmental Sciences
1803 Building
(517) 636-8237

kal

Attachments

COMMENT: DRAFT TECHNICAL SUPPORT DOCUMENT, MAY, 1990, "PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT"

Derivation of a unit risk for Vinyl Chloride (CAS 75-01-4)

VCM is clearly a rat and human carcinogen, causing liver angiosarcoma in both species and zymbal gland tumors in rats. Thus, for regulatory purposes, there is interest in deriving a quantitative estimate of a level of no significant risk. There are two general approaches to this problem. One approach has been the use of safety factors or uncertainty factors applied to no-observed-effect-levels (NOEL's) in animals to derive a safe level in humans. The other general approach, which has been used more recently by regulatory agencies, has been the use of quantitative risk assessment to estimate levels of risk for any given exposure. The risk assessment process involves a number of decision points for which there is no scientific consensus as to the correct approach. These areas of uncertainty, including the presence or absence of thresholds, the shape of the dose response model, and animal to man conversion factors, have been resolved within the agencies through the use of policy decisions as to a default methodology. The default methodology is conservative in nature, so as to protect public health. However, the State of California Cancer Risk Assessment Guidelines as well as EPA and OSTP guidelines on the use of risk assessment clearly state that the default methodology should not be used when other data are available. In particular, epidemiology data and pharmacokinetic information should be incorporated into risk assessment when the appropriate data are available. The DHS unit risk for vinyl chloride of 20 x 10(-5) per ppb, as cited in the CARB Draft Technical Document (CARB, 1990), does not utilize the available pharmacokinetic or epidemiological information.

Pharmacokinetic Information

Pharmacokinetic (PK) information can be used in two ways to augment risk assessments for vinyl chloride. PK data have been used to demonstrate and explain nonlinear behavior at both the high dose and low dose portions of the dose-response curve. The bioassay data of Maltoni (1979) clearly indicated a plateau in the dose-response curve at high doses. This phenomenon can be explained by the use of a Michaelis-Menton function to calculate metabolite concentrations, as suggested by Watanabe *et al.* (1976), and implemented by Gehring *et al.* (1978), Crump (1982) and USEPA (1987). However, this methodology only explains the high-dose results in the animal bioassay rather than addressing the problem of low-dose extrapolation. Low-dose risk assessments utilizing PK data have been discussed by Gehring *et al.* (1979) and Anderson *et al.* (1980).

Purchase *et al.* (1980) reviewed risk assessments for VCM and showed that, among the linear models used, risk estimates varied from the current DHS value, (equivalent to a unit risk of 20 x 10(-5) per ppb), upwards (less risk) at least a factor of 100-fold. The different values derived from animal models vary primarily on the basis of whether or not pharmacokinetic information has been utilized in the assessment. In evaluating the use of pharmacokinetic data, Anderson *et al.* (1980) conclude that: "Based on the present understanding of the mechanism of carcinogenesis, we believe this to be a more rational approach to the low-dose extrapolation problem."

Gehring *et al.* (1979) fit a number of extrapolation models to the metabolized dose of VCM, and showed that risk estimates derived without consideration of low-dose metabolite formation potentially overestimate risk by at least an order of magnitude. For example, the one-hit model applied to metabolized dose predicts a risk of 189 per million at 1 ppm for an occupational exposure (Gehring, 1979). By comparison, use of nominal dose (air concentration), predicts upper bound "risks" of 37,000 per million using the unit risk of 20 x 10(-5) per ppb. Other viable dose response models predict much lower risk.

Not withstanding the fact that the health criteria represent one aspect of many inputs considered in the standard setting process, we submit it is essential to base any proposed regulation on the most complete information possible. For this reason we believe that risk assessments for vinyl chloride should include PK data, or preferably, the use of actual human data.

Risk assessments derived from epidemiology data

In the early 1970's, vinyl chloride was reported to cause a rare form of cancer, angiosarcoma of the liver, among workers who had been exposed at extremely high levels for many years in polyvinyl chloride (PVC) polymerization plants. Since this discovery, there have been approximately 50 angiosarcoma of the liver deaths reported throughout the United States and Canada which have been associated with previous vinyl chloride exposure. Eighty percent of these deaths occurred in four PVC plants where exposures to vinyl chloride were known to have been over 500 ppm in the 1950's and 1960's. Today, there are strict emission limitations under the NESHAP regulation, and the OSHA regulated 8-hour time weighted average for vinyl chloride is 1 ppm. It is particularly noteworthy that there has never been a reported death from angiosarcoma of the liver among Louisiana chemical workers who have worked with vinyl chloride.

Vinyl chloride has not been shown to cause cancer at any other anatomical site in humans. Epidemiologic studies conducted in the 1970's suggested that there may be an association with brain and lung cancer, however, recent updates of these studies have reported either no association, or associations only at a much lower statistical level of significance.

A world-recognized expert in epidemiology, Sir Richard Doll, recently reviewed the existing vinyl chloride literature as it pertains to cancer in humans. He concluded that vinyl chloride is a known occupational carcinogen (only for angiosarcoma of the liver) which is due to high occupational exposure levels which have not existed since this association was reported in the early 1970's. According to Doll, the risk for cancer in communities surrounding vinyl chloride production plants from environmental emissions in today's tightly controlled and well-regulated environment "must be negligible." (Doll, 1988)

Generally, risk assessments utilize animal data as the basis for quantification of risk. Human epidemiology data often do not have sufficiently precise exposure estimates or sufficiently well-defined populations to be of quantitative value. Human results are clearly preferred, when available, however, and should be included in any risk assessment review. In the case of VCM there are at least three assessments of sufficient precision which utilize the human database to estimate risk. In one analysis (Barr, 1982), negative epidemiological studies of people living near VCM production facilities have been used to estimate human potency. Barr estimates that 100 ppb is the approximate lifetime dose corresponding to a human risk of 10(-6). Purchase *et al.* (1987) note that Barr's estimate is similar to the highest estimates of 10(-6) dose levels derived from animal data and are orders of magnitude higher than the conservative dose estimates which do not take into account low dose PK. This result is consistent with other observations that humans may be less sensitive than animals to the carcinogenic effects of VCM.

Gehring *et al.* (1979) compared the results of an epidemiological study of approximately 10,000 occupationally exposed workers to the values predicted by four different mathematical models derived from animal data. They conclude that the observed human results are inconsistent with the two linear non-threshold models used, and are consistent with both the probit model and a linear threshold model. The latter two models predict 10^{-6} risk levels at occupational exposure levels in excess of 1 ppm.

These analyses by no means prove the validity of the two models and undoubtedly numerous other models would fit and give quite different results for predicting the ambient level corresponding to a 10^{-6} risk level. However, these analyses do show that human epidemiology data can be used to derive risk estimates for VCM exposures and that the models indicate that the linear non-threshold models are conservative by a substantial margin. This is to be expected in light of the well known conservativeness of the models. U.S. EPA, for instance, when presenting risks estimates describes them as upper bounds and notes that: **"the true value of the risk is unknown and may be as low as zero"** (Federal Register, 1986).

In an analysis of alternative modeling assumptions for animal to human extrapolation, Elizabeth Anderson, (1984) as head of the U.S. EPA Cancer

Assessment Group found that alternative plausible modeling assumptions would lead to risk estimates that were 15-fold to 10,000-fold lower than the standard LMS procedure. Thus it is essential to use the available human data to place some perspective on the results predicted solely from animal data.

In an independent review of VCM, the National Health Council of the Netherlands (1987) derived ambient exposure levels corresponding to risk levels of 10(-6) in humans. Their estimates were derived from both animal data and from epidemiological human data. While noting that the estimates did not differ greatly, they expressed a preference for the human data and reported a value of 1 μg/cubic meter as corresponding to a risk of 10(-6). This value is approximately 80 times higher than the exposure level derived using the DHS unit risk of 20 x 10(-5) per ppb.

The over prediction of the models can be further demonstrated for VCM by comparing predictions of risk utilizing the DHS unit risk with human exposure scenarios. To make this comparison, Table 1 shows the "risk" predicted from the DHS model for a number of occupational exposure situations. The relevance of the specific exposure scenarios are also discussed below.

The specific exposure scenarios used in Table 1 were based upon a retrospective study (Barnes, 1976), in which past typical VCM exposures in PVC plants were estimated as: 1000 ppm in 1945-1955, 400-500 ppm in 1955-1960, 300-400 ppm in 1960-1970, 150 ppm in mid-1973 and considerably lower afterwards. Considering the latency of carcinogenesis in general, and for VCM in particular, tumor incidence rates noted in the 1980's reflect exposures from the 1960's.

It can be seen from Table 1 that incidence rates predicted from the linear animal model are completely incompatible with that observed in actual human studies. For example, in the study examined by Gehring (1970) there were only 5 observed cases in 9677 workers. This is approximately three orders of magnitude less than that which would be predicted by the DHS model.

Thus, there are a number of assessments based upon human epidemiological data which would indicate that linear models utilizing animal data overpredict risk by at least one to two orders of magnitude. In the interests of assuring that any proposed regulation is supported by as comprehensive a review of the available health data as possible, we submit these assessments should be incorporated into any risk assessments which will be used for regulatory control. This is particularly important in view of the fact that they are based upon human data rather than on laboratory animal results.

It can be seen from the above analysis that standard risk assessment methodology and the use of reported literature results lead to orders of magnitude over-estimates of the predicted risk from emissions of VCM from

existing facilities. We recommend that these inconsistencies in the risk estimates be resolved if they are to be used as the basis for any proposed regulation.

TABLE 1. "RISK" PREDICTED FROM LMS MODEL
(using unit risk of 20×10^{-5} per ppb)

Occupational Exposure Scenario	Upper Bound on "Risk" (Cases Per 10,000)
400 ppm 30 years	9999
400 ppm 20 years	9995
300 ppm 30 years	9998
300 ppm 20 years	9964
200 ppm 30 years	9960
200 ppm 20 years	9770
100 ppm 30 years	9400
100 ppm 10 years	6090
100 ppm 5 years	3750

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II. PART C ADDENDUM
AIR RESOURCES BOARD STAFF RESPONSES TO COMMENTS ON PART A

A. COMMENT FROM THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

1. Comment: Please include the following paragraph in the Executive Summary:
"The Operating Industries, Incorporated (OII) landfill is currently a federally listed Superfund site. Subsequent to the Air Resources Board's sampling during 1987, the Environmental Protection Agency (EPA) has implemented more stringent landfill gas control measures. EPA has also selected a remedy for landfill gas control that is expected to substantially reduce landfill gas emissions from the OII landfill. It is fully anticipated that these control measures will substantially lower the levels of vinyl chloride in the ambient air in the vicinity of the OII landfill."

Response: The paragraph (corrected to indicate that OII sampling was performed by the South Coast Air Quality Management District during 1986) appears in the revised Executive Summary.

B. COMMENTS FROM WASTE MANAGEMENT OF NORTH AMERICA, INC.

1. Comment: It is erroneous to assume that BKK and OII landfills are representative of all landfills since both of these sites accepted significant quantities of vinyl chloride waste during operation.

Response: Landfill records of whether or not vinyl chloride waste was accepted may not be a reliable means of predicting the potential for vinyl chloride emissions. For decades, vinyl chloride waste (as well as other halogenated industrial waste which can form vinyl chloride) was disposed in some Class II as well as Class I landfills. In addition, Class III landfills accept disposed consumer products containing chlorinated compounds which can form vinyl chloride. Also, incomplete recording of vinyl chloride waste disposal and illegal vinyl chloride waste dumping have occurred to an unknown extent. However, a statement has been added to the report indicating that the vinyl chloride emissions measured at BKK and OII may not be typical of all landfills.

2. Comment: Significant information exists that landfills are not significant sources of vinyl chloride emissions. For example, data from the Air Solid Waste Assessment Testing Program (Landfill Gas Testing Program) mandated by Section 41805.5 of the California Health and Safety Code show that six waste management units operated by Waste Management of North America (WMNA), Inc. are not significant sources of vinyl chloride emissions.

Response: After considering the data available on potential sources of vinyl chloride emissions, the staff of the Air

Resources Board (ARB) concluded that landfills are a potential major source. Modeled estimates of vinyl chloride emissions for just BKK and OII landfills were far greater than emissions estimates for publicly-owned treatment works (POTWs) and polyvinyl chloride (PVC) fabrication and production facilities:

Source	Emissions (tons/year)	Inventory Year
BKK Landfill	44-197	1987
OII Landfill	4-61	1986
POTWs	1.7	1985
PVC fabrication	0.75	1982
PVC production	<0.5	1988

Although BKK and OII landfills may not be typical, one cannot rule out the possibility of elevated vinyl chloride emissions from other California landfills using preliminary Landfill Gas Testing Program data. The preliminary data show that vinyl chloride was detected at or above the detection limit in the internal landfill gas at 160 out of 340 landfills tested. Also, vinyl chloride was detected at or above the detection limit in the ambient air near 24 out of 251 landfills tested. However, because landfills vary in the amount and composition of wastes accepted as well as disposal methods used, estimating total statewide vinyl chloride emissions from landfills is not possible at this time. Therefore, the staff report has been revised to indicate that landfills are a potential major source-category.

3. Comment: Section 39660 (f) of the California Health and Safety Code mandates that the Department of Health Services (DHS) and the ARB give priority to the evaluation of a substance's amount or potential amount of emissions and ambient concentrations in the community. To proceed with identification of vinyl chloride as a toxic air contaminant (TAC) while identifying landfills as the largest source of emissions based on two unrepresentative sites (BKK and OII landfills) would be a disservice to the waste management industry and contrary to the law.

Response: In the revised vinyl chloride report, based on available data, the staff of the ARB conclude that landfills are a potential major identified source-category of vinyl chloride emissions. The staff further conclude that sufficient overall data are available to proceed with the identification of vinyl chloride as a TAC as provided in the statutes. Furthermore, vinyl chloride, as a federally designated hazardous air pollutant, must be identified as a TAC pursuant to Health and Safety Code Section 39655. Also, please see the responses to comments 1 and 2.

4. Comment: Waste Management of North America, Inc. recommends that identification of vinyl chloride be delayed until Landfill Gas Testing Program data are included in the report.

Response: Preliminary Landfill Gas Testing Program data have been included at appropriate places in the revised vinyl chloride report. In addition, a table of Landfill Gas Testing Program data has been provided in Appendix VI.

III. PART C ADDENDUM
DEPARTMENT OF HEALTH SERVICES RESPONSES TO COMMENTS ON PART B

RESPONSE TO COMMENTS:

WASTE MANAGEMENT OF NORTH AMERICA, INC.

June 11, 1990

PUBLIC HEALTH RISK OF VINYL CHLORIDE

COMMENT: "While we do believe that it is ultimately appropriate to regulate vinyl chloride as a toxic air contaminant, we are concerned that the unit risk factor that you have attributed to this compound is overly conservative."

RESPONSE: The DHS document of May, 1990, provides estimates of unit risk that use data, assumptions and methods that are highly defensible, based on standard procedures utilized by DHS and EPA. The analysis uses animal and human data. Dose rates to tissue have been obtained from a pharmacokinetic model. The range of unit risks does not include some of mouse data which is up to 2.5 times above the top of the range in the risk assessment, as indicated in the text at page 8-8. The best estimate of unit risk for regulatory purposes is the top of the tightly clustered -- less than 10-fold -- range, containing numerous results, including human results. The two top points include liver angiosarcoma in the female rat, this tumor being one of the most distinctively linked to vinyl chloride exposure in both rats and humans. DHS staff conclude that this choice is not overly conservative.

COMMENT: "I have also attached to this letter a copy of a brief paper on Carcinogenic Risks from Landfill Emissions dated June 6, 1988. . . . This information provides a much more realistic assessment of the health risks posed by municipal landfills not only from the standpoint of vinyl chloride but a number of

other compounds as well. In summary this brief paper, based on an assessment of the cumulative impact of all landfill emissions, concludes, 'Using a dispersion model for area emissions, we find that for persons spending their whole lives 100 m from the edge of such a landfill the lifetime risk is about 20×10^{-6}, while even for persons staying permanently at the edge of the landfill the lifetime risk is only 50×10^{-6}.'"

RESPONSE: The cited paper, which was an addendum to comments to EPA and not a journal article, was produced at the request of Waste Management Inc. and of The National Air Pollution Control Techniques Advisory Committee to the EPA. This response will focus on the unit risk estimate utilized in the document and not on site-specific factors such as emission rates, source areas and meteorology. The cited paper uses for vinyl chloride a unit risk of 22×10^{-5} ppb^{-1}, expressed as 9.8×10^{-5} $(\mu g/m^3)^{-1}$ in their Table 1.2. This risk estimate is essentially equivalent to the DHS best estimate of 20×10^{-5} ppb^{-1} for unit risk. Therefore, DHS is recommending essentially the same unit risk as is the basis for the calculation of risk for landfills that is advocated by the commenter.

The cited paper refers to EPA (1985b) as the source for that unit risk, but DHS staff, after obtaining and reviewing that document, calculate that the unit risk corresponding to the EPA's (1985a) potency of 2.95×10^{-1} $(mg/kg\text{-}day)^{-1}$ is 11×10^{-5} ppb^{-1}, using EPA's own assumption of 50% absorption, which the cited paper's authors evidently did not use. The reason for that EPA unit risk being 55% of the DHS best estimate stems from the EPA analysis combining male and female rats, giving a lower risk than the DHS use of females, the sex with the higher risk in this case. For comparative purposes the EPA 1985b unit risk has now been included in the document at page 8-13 and in Figure 8-1.

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SPECIFIC DOLAN COMMENTS

COMMENT: "First, why bother using the linearized multistage model under the pretense that it is a true mechanistic model (which it is not), when a simple linear regression usually yields nearly identical estimates of q_1^* ($r^2 = 0.98$) (Personnel conversation with Curtis Travis, Oak Ridge National Laboratory)?"

RESPONSE: The linearized multistage model affords an efficient unified approach to determining carcinogenic potencies of most substances for which there are enough data to determine the potency. Once the appropriate computer software and a knowledge of its use have been acquired, the model is quite convenient to use. This model accommodates pharmacokinetic conversion of dose rate and can account for a wide range of test results in a way that allows extrapolation that is frequently in accord with available knowledge of mechanisms. In contrast, the simple linear regression becomes inappropriate at high doses in many animal experiments. Even in the case of vinyl chloride, the multistage model indicates an improved fit to the data by including a quadratic term. Thus, a simple linear model would introduce some bias into the low dose extrapolation.

COMMENT: "Second, the discussion of uncertainty in the quantitative risk estimates is given short shrift. Although the uncertainties or absence of exposure data in the occupational cohort studies is mentioned, there is no discussion of the conservatism built into the risk estimates by the selection of data for extrapolation, and the extrapolation assumptions, and the effects their underlying assumptions may have on the risk estimates. For instance, the use of the most sensitive sex/strain/species instead of the average may alter risk estimates by 'several orders of magnitude.' (U.S. EPA, 1985). Similarly, the

issues of the extrapolation of rodent potency estimates to humans, particularly on the basis of surface area, and the use of upper 95th percentile estimates of carcinogenic potency instead of the MLE, may alter potency estimates by an order of magnitude, or more. (U.S. EPA, 1985)."

RESPONSE: DHS staff do not agree that there is unjustified conservatism built into the risk estimates. DHS used procedures that are standard for EPA and DHS, taking account of the pharmacokinetics of vinyl chloride. The DHS risk assessment did not use the most sensitive species and strain. Some of the mouse data resulted in unit risks up to 2.5 times higher than actually used in the risk assessment. The assessment does use data for the more sensitive sex in order to protect women as well as men because female rats had a 3-fold higher risk than male rats. The assessment does use the 95th percentile estimates, clearly identifying them by UCL throughout the document. The analysis uses these estimates in the risk assessment only when the ratio of UCL to MLE is less than 3, specifically avoiding the possibility of that ratio being "an order of magnitude, or more", as found in other circumstances by EPA (1984a).

In order to expand the discussion of uncertainties, DHS staff have added a brief paragraph to the document at page 8-13 as follows:

"All these estimates are subject to substantial uncertainties as have been discussed in the scientific literature (DHS, 1986, and EPA, 1984a). The available information does not suggest that there is a threshold for vinyl chloride's carcinogenic effect, though this remains uncertain. The multistage model is the best choice based on the plausible mechanism of vinyl chloride carcinogenicity. Nevertheless, our incomplete understanding of cancer makes this choice subject to uncertainty. Furthermore, the present approach uses other assumptions that are

designed to be somewhat health protective in the absence of precise knowledge. One of the most important of these is the extrapolation from humans to animals on the basis of surface area in accordance with DHS guidelines (1985). This approach may overpredict or underpredict human risk.

COMMENT: "Third, it is perplexing that the Krewski et al. (1987) chapter is referenced, yet the 36-fold lower carcinogenic potency factor they derive is omitted from the brief discussion. Some discussion on the merits and limitations of the Krewski et al. analysis is necessary."

RESPONSE: The Krewski et al. (1987) result of 0.0058 ppm^{-1} is based on virtually all the relevant female liver angiosarcoma data of Maltoni et al. (1984) and is unadjusted for lifetime exposure. When adjusted for lifetime exposure the unit risk is 9.7×10^{-5} ppb^{-1}. On this basis, the unit risk of Krewski et al, rather than being 36-fold lower, is actually 45% higher than the result from the analysis (BT-9, 15) which corresponds most closely in the document, 6.7 x 10-5 ppb^{-1}. This is among the highest rodent risks in the assessment. Because of the rather good agreement despite the differing analyses, adding a discussion of the merits and limitations is inappropriate for this document.

COMMENT: "Fourth, the ARB cites the concordance of the potency estimate derived from the Drew et al. (1983) study and the Maltoni et al. (1984) experiments. It is unclear whether the Maltoni experiments were conducted in his medieval castle/laboratory where the mycobacterium infection is endemic, or in some other facility. (Personnel conversation with E.E. McConnell, National Toxicology Program). In the U.S., mycobacterium infections in test animals would likely violate GLPs, and serve as grounds for invalidating a study."

RESPONSE: Both EPA and IARC have relied on the Maltoni et al. data for their assessments. DHS knows of no documentation that casts serious doubt on the validity of these data. The concordance of the Maltoni data is not only with Drew et al. but also with Bi et al.

COMMENT: "Fifth, the recommended use of a potency factor derived from animal instead of the human occupational study of Waxweiler et al. (1976) is not robust, given that the human data already represents an upper-bound estimate in the target species of concern (i.e., humans). The additional rationale that the selection of the highest animal estimate is justified by the limited evidence of an effect by age at first exposure (Drew et al., 1983) suggests that perhaps the ARB should consider using a true mechanistic model, perhaps one based upon the MVK model paradigm, as the basis of its potency determinations."

RESPONSE: The human data in itself does not represent an upper bound in humans because (1) that data does not include a lifetime exposure, and there is evidence of greater sensitivity of the young and (2) the human data that is sufficient for the risk assessment includes almost no females. As to the remainder of the comment, the DHS staff note that the MVK model does have the potential to be more closely linked to the biological observations of cell proliferation than the multistage model. When the necessary data are available and the mathematical analysis is adequately established, then an analysis related to the MVK model is worth consideration.

RESPONSE TO COMMENTS:
THE DOW CHEMICAL COMPANY
July 3, 1990

Derivation of a Unit Risk for Vinyl Chloride

COMMENT: "VCM is clearly a rat and human carcinogen ...". In order to address cancer concerns, regulatory agencies have recently used "quantitative risk assessment to estimate levels of risk for any given exposure." In order to resolve uncertainties in this process, agencies have developed default assumptions which are "conservative in nature so as to protect public health." California and federal guidelines "clearly state that the default methodology should not be used when other data are available. ... The DHS unit risk for vinyl chloride of 20×10^{-5} per ppb ... does not utilize the available pharmacokinetic or epidemiological information."

RESPONSE:. The DHS staff disagree with the assertion that the current DHS risk coefficient does not utilize the available phamacokinetic or epidemiological information. DHS staff, in response to comments on the first draft document, did specifically incorporate the available pharmacokinetic and epidemiological information into the analysis that produced the estimates of unit risk. All the DHS calculations of unit risk in the document under review directly use the available pharmacokinetic information. In addition, the risk assessment specifically shows how the best estimate of upper confidence limit (UCL) for unit risk, 20×10^{-5} per ppb, cited in the comment above, is consistent with human occupational data when adjusted from males in that workforce to females who would be exposed in the general population.

Pharmacokinetic Information

COMMENT: "Pharmacokinetic (PK) information can be used in two ways to augment risk assessments for vinyl chloride. PK data have been used to demonstrate and explain nonlinear behavior at both the high dose and low dose portions of the dose-responses curve." The Michaelis-Menton "methodology explains only the high-dose results. Low-dose risk assessments utilizing PK data have been discussed by Gehring et al. (1979) and Anderson et al. (1980)."

RESPONSE: Contrary to the implication of the comment, Gehring et al. (1979) and Anderson et al (1980) used the Michaelis-Menton methodology to incorporate PK data at all doses, high and low, in essentially the same way as the DHS document. The low dose extrapolations in those two studies differed from the DHS document in that they explored extrapolation not only by the single stage model, as did the DHS document, but also by the log-probit model. DHS staff consider the log-probit model to be inappropriate based on the data that became available after these articles were published and the apparent mechanism of carcinogenesis.

COMMENT: "Purchase et al. (1980) reviewed risk assessment for VCM and showed that, among the linear models used, risk estimates varied from the current DHS value, (equivalent to a unit risk of 20×10^{-5} per ppb), upwards (less risk) at least a factor of 100-fold. The different values derived from animal models vary primarily on the basis of whether or not pharmacokinetic information has been utilized in the assessment. In evaluating the use of

pharmacokinetic data, Anderson et al. (1980) conclude that: "Based on the present understanding of the mechanism of carcinogenesis, we believe this to be a more rational approach to the low-dose extrapolation problem."

RESPONSE: Contrary to the comment, Purchase et al. (1987) do not make clear comparisons among linear models, nor do they make clear comparisons between those models that use pharmacokinetic adjustment and those that do not. The work of Anderson et al. (1980), does clearly account for the role of the pharmacokinetic adjustment and the role of the carcinogenesis model. Anderson et al. (1980) found that for the multistage model, which extrapolates linearly to zero exposure, "incorporating the pharmacokinetics has only a moderate effect on the low-dose estimates." Table 1 in that work shows that the effect of incorporating Gehring's simple pharmacokinetics into the multistage model is to increase - - by either or 4- or 26-fold, depending on the specific choice of rat data - - the extrapolations of risk estimates to low dose. The more appropriate choice of rat data, eliminating the two highest and therefore most saturated exposures, corresponds to the 4-fold increase.

DHS staff agree with the Anderson et al. statement about the rationality of the pharmacokinetic approach, provided appropriate data are available.

COMMENT: "Gehring et al. (1979) fit a number of extrapolation models to the metabolized dose of VCM, and showed that risk estimates derived without consideration of low-dose metabolite formation potentially overestimate risk by at least an order of magnitude. For example, the one-hit model applied to metabolized dose predicts a risk of 189 per million at 1 ppm for an occupational exposure (Gehring, 1979). By comparison, use of nominal dose (air concentration), predicts upper bound "risks" of 37,000 per million using the unit risk of 20×10^{-5} per ppb. Other viable dose response models predict much lower risk."

RESPONSE: Gehring et al. in their 1979 article did not derive any estimates of risk without using their model for low-dose metabolite formation. The four models in that article use the metabolized dose at all dose levels. In that article the authors did characterize the results of their models C (linear forced through the origin) and D (one-hit) as overpredicting the number of liver angiosarcomas reported in the Equitable Environmental Health (1978) study. However, a follow up study (Wong et al., 1986) of those worker populations showed a marked increase in incidence of deaths attributable to liver and biliary cancer. Neither of these papers on workers has appeared in the peer-reviewed literature, making acceptance of either of their epidemiological results problematic.

All the DHS estimates of risk use a metabolized exposure that is essentially equivalent to the metabolized dose of Gehring et al. (1978, 1979) at low exposures. For the 1 ppm occupational example in Gehring et al (1979), their assumptions of 40 hr/wk for 35 years does not give a risk of 37,000 per million for the DHS unit risk of 20×10^{-5} per ppb but gives 22,000 per million. This risk is 126-fold greater than the Gehring et al. result of 189 per million, not because of differences in analysis of the data but because of three different choices in applying the results of the rat analysis to the human. In the one-hit analysis for the rat the result of Gehring et al. (1979) is a unit risk of 1.1×10^{-5} per ppb, when adjusted to lifetime exposure. This result is actually somewhat greater than that of the nearest analysis in the DHS document, for BT-1,2, giving an MLE of $q1 = 0.8 \times 10^{-5}$ per

ppb. The sources of the higher risk estimate for DHS are (1) the use of later Maltoni et al.(1984) data, BT-9,15 for the best estimate rather than the earlier Maltoni and Lefemine (1975) data used by Gehring et al.(1978), resulting in a 3.2-fold increase, (2) the use of the 95% upper confidence level on risk rather than the mean regression estimate (similar to maximum likelihood estimate), resulting in a 2.3-fold increase , and (3) the use of DHS standard scaling of humans to animals by body weight to the two-thirds power rather than the Gehring et al. ad hoc scaling that has never been accepted, resulting in a 17.7-fold increase. The result of multiplying all these increases together is an overall 130-fold increase.

COMMENT: "Not withstanding the fact that the health criteria represent one aspect of many inputs considered in the standard setting process, we submit it is essential to base any proposed regulation on the most complete information possible. For this reason we believe that risk assessments for vinyl chloride should include PK data, or preferably, the use of actual human data."

RESPONSE: DHS staff agree and have used both in the risk assessment.

Risk Assessments Derived from Epidemiology Data

COMMENT: After introductory remarks concerning vinyl chloride in the workplace, the commenter asserts, "It is particularly noteworthy that there has never been reported death from angiosarcoma of the liver among Louisiana chemical workers who have worked with vinyl chloride."

RESPONSE: It is difficult to respond to the comment about Louisiana chemical workers without specific reference to surveillance programs and exposure estimates.

COMMENT: "Vinyl chloride has not been shown to cause cancer at any other anatomical site in humans. Epidemiologic studies conducted in the 1970's suggested that there may be an association with brain and lung cancer, however, recent updates of these studies have reported either no association, or associations only at a much lower statistical level of significance."

A world-recognized expert in epidemiology, Sir Richard Doll, recently reviewed the existing vinyl chloride literature as it pertains to cancer in humans. He concluded that vinyl chloride is a known occupational carcinogen (only for angiosarcoma of the liver) which is due to high occupational exposure levels which have not existed since this association was reported in the early 1970's.

RESPONSE: In his review article Doll (1988), cited in the next comment, discusses this issue at length. He concludes in a manner contrary to that of the comment. "It is, however, still difficult to decide whether vinyl chloride produces small risks of cancer, compared to those due to nonoccupational causes, at sites other than the liver, and, if so, whether, in total, these risks might cause almost as many deathes as angiosarcoma of the liver."

COMMENT: "According to Doll, the risk for cancer in communities surrounding vinyl chloride production plants from environmental emissions in today's tightly controlled and well-regulated environment "must be negligible." (Doll, 1988)."

RESPONSE: Doll (1988) did not estimate unit risks or any other numerical measure of the relationship between exposure and response. He did not specify numerically what he or his reference considers to be a negligible risk outside a vinyl chloride plant. Also, he does not consider other environmental exposures such as landfill sites. So his remark is difficult to apply to the present assessment.

COMMENT: "Generally, risk assessments utilize animal data as the basis for qualification of risk. Human epidemiology data often do not have sufficiently precise exposure estimates or sufficiently well-defined populations to be of quantitative value. Human results are clearly preferred, when available, however, and should be included in any risk assessment review. In the case of VCM there are at least three assessments of sufficient precision which utilize the human database to estimate risk. In one analysis (Barr, 1982), negative epidemiological studies of people living near VCM production facilities have been used to estimate human potency."

RESPONSE: The previous response to comments from the Vinyl Institute pointed out that the Barr (1982) analysis is too unsubstantial epidemiologically to be considered in this risk assessment.

COMMENT: "Barr estimates that 100 ppb is the approximate lifetime dose corresponding to a human risk of 10^{-6}. Purchase et al. (1987) note that Barr's estimate is similar to the highest estimates of 10^{-6} dose levels derived from animal data and are orders of magnitude higher than the conservative dose estimates which do not take into account low dose PK. This result is consistent with other observations that humans may be less sensitive than animals to the carcinogenic effects of VCM."

RESPONSE: Contrary to the comment, Barr, in his Table 1 and consistent with his text, found that the lifetime exposure for 10^{-6} risk was greater than 1 ppm, not 100 ppb, which was a mischaracterization appearing in the Table 4 of Purchase et al. (1987). The present DHS document gives 0.5 ppb as the lower confidence limit on lifetime exposure for 10^{-6} risk. Barr offers no rationale for using the weak data he selected from a 1975 EPA report in order to calculate his epidemiological estimate. These data do not appear to be appropriate for that purpose, and such inappropriate use of data would account for disagreement with the DHS value by orders of magnitude.

Also contrary to the comment, Purchase et al. (1987) do not specifically comment on Barr's estimate in their text. As stated in the response above, Purchase et al. do not present clear comparisons of effects of pharmacokinetics or of the results of using different basic forms of models for carcinogenesis. Finally, the commenter has offered no supported observations to show "that humans may be less sensitive than animals to the carcinogenic effects of VCM."

COMMENT: "Gehring et al. (1979) compared the results of an epidemiological study of approximately 10,000 occupationally exposed workers to the values predicted by four different mathematical models derived from animal data. They conclude that the observed human results are <u>inconsistent</u> with the two linear non-threshold models used, and are <u>consistent</u> with both the probit model and a linear threshold model. The latter two models predict 10^{-6} risk levels at <u>occupational</u> exposure levels in excess of 1 ppm."

RESPONSE: As pointed out in the response above and in the previous response to comments of the Vinyl Institute, the comparisons that Gehring et al. (1979) made are now out of date because of a follow up study of Wong et al. (1986), which found much higher rates of liver cancer incidence in vinyl chloride workers than in the data used by Gehring et al.

COMMENT: "These analyses by no means prove the validity of the two models and undoubtedly numerous other models would fit and give quite different results for predicting the ambient level corresponding to a 10^{-6} risk level. However, these analyses do show that human epidemiology data can be used to derive risk estimates for VCM exposures and that the models indicate that the linear non-threshold models are conservative by a substantial margin. This is to be expected in light of the well known conservativeness of the models. U.S. EPA, for instance, when presenting risks estimates describes them as upper bounds and notes that: "the true value of the risk is unknown and may be as low as zero" (Federal Register, 1986)."

RESPONSE: The DHS document does use human epidemiology data in the risk assessment. The DHS staff does not agree that the linear nonthreshold models extrapolate conservatively by a substantial margin, relative to actual incidence of cancer. Certainly, such models extrapolate conservatively compared to the log-probit model (Gehring et al. 1979: Model A), but that model is not in accord with present understanding of mechanisms of carcinogenesis applicable to vinyl chloride, whereas the linearized multistage model is in accord with such understanding and therefore most likely to extrapolate to low exposures accurately rather than being overly conservative. The feature of the unit risks that is health protective and might be characterized as in the conservative direction is the use of the 95% upper confidence limit (UCL) in order to provide adequate protection in the great bulk of cases. Any model with sufficient data can incorporate this feature. EPA does call such estimates "upper bounds," a term that is now commonly used for UCL although that usage is not in accord with the strict mathematical definition. The true risk is very unlikely to be exactly zero; so the quote from EPA, though possible as a point of logic, does not appear to enhance the readers perspective, particularly in cases of the maximally exposed individual.

COMMENT: "In an analysis of alternative modeling assumptions for animal to human extrapolation, Elizabeth Anderson, (1984) as head of the U.S. EPA Cancer Assessment Group found that alternative plausible modeling assumptions would lead to risk estimates that were 15-fold to 10,000-fold lower than the standard LMS procedure. Thus it is essential to use the available human data to place some perspective on the results predicted solely from animal data."

RESPONSE: The main issue in this comment is the question of what is considered plausible. If an extreme curve-fitting model such as the log-probit is compared against the more mechanism oriented linearized multistage model, then many-fold lower risks will be obtained for the log-probit.

COMMENT: "In an independent review of VCM, the National Health Council of the Netherlands (1987) derived ambient exposure levels corresponding to risk levels of 10^{-6} in humans. Their estimates were derived from both animal data and from epidemiological human data. While noting that the estimates did not

differ greatly, they expressed a preference for the human data and reported a value of 1 μg/cubic meter as corresponding to a risk of 10^{-6}. This value is approximately 80 times higher than the exposure level derived using the DHS unit risk of 20 x 10^{-5} per ppb."

RESPONSE: As pointed out in the DHS document at page 8-5, the Netherlands council obtained 1.2 x 10^{-6} per ppb for the unit risk of mortality due to liver cancer and 2.5 x 10^{-6} per ppb for all cancer. "Both these results were based on estimated atmospheric exposure. When those results are modified to take account the pharmacokinetics and to provide 95% upper confidence limits, the results are close to the present results." The DHS adjustment of the council's worker exposure of 500 ppm is 115 ppm, requiring a 4.3-fold adjustment upwards of their unit risks to account for pharmacokinetics. The council's average unit risk needs to be multiplied by about 2.3 to estimate the corresponding UCL value. The unit risks resulting from both multiplications are 10-fold greater, or 1.2 x 10^{-5} and 2.5 x 10^{-5} per ppb. These values are about half the corresponding epidemiology estimates in the document, based on the data of Waxweiler et al. (1976), which was one of the studies used by the Netherlands council for data on mortality due to cancer in vinyl chloride workers.

COMMENT: The over prediction of the models can be further demonstrated for VCM by comparing predictions of risk utilizing the DHS unit risk with human exposure scenarios. To make this comparison, Table 1 shows the "risk" predicted from the DHS model for a number of occupational exposure situations.

"It can be seen from Table 1 that incidence rates predicted from the linear animal model are completely incompatible with that observed in actual human studies. For example, in the study examined by Gehring (1970) there were only 5 observed cases in 9677 workers. This is approximately three orders of magnitude less than that which would be predicted by the DHS model.

Thus, there are a number of assessments based upon human epidemiological data which would indicate that linear models utilizing animal data overpredict risk by at least one to two orders of magnitude. In the interests of assuring that any proposed regulation is supported by as comprehensive a review of the available health data as possible, we submit these assessments should be incorporated into any risk assessments which will be used for regulatory control. This is particularly important in view of the fact that they are based upon human data rather than on laboratory animal results.

It can be seen from the above analysis that standard risk assessment methodology and the use of reported literature results lead to orders of magnitude over-estimates of the predicted risk from emissions of VCM from existing facilities. We recommend that these inconsistencies in the risk estiamtes be resolved if they are to be used as the basis for any proposed regulation."

RESPONSE: The incompatibility of predicted and observed incidence rates, as derived in the comments, arises because of the commenter's errors in making the predictions and the citation of incidence data that are not current and that do not permit adequate estimates of exposure. Thus, the commenter has made no sustainable case for overprediction or inconsistency of risk estimates in the document.