VCM-MCA

Dr. Joyner

06-C-0055-00

s/m. Kusnetz

MAY 23 1975

MEDICAL DIRECTOR

five times a week for two weeks and (b) 50 ppm for 100 exposures, one hour each, five times a week for twenty weeks. We were invited to make formal application to visit with them in either an open or closed meeting to discuss details of their experiments.

4. Standards in Other Countries

Attached is Dr. Brookman's transmittal of information on the status of regulations throughout the world.

5. Articles Received from the International Agency for Research on Cancer, 150 Cours Albert Thomas, 69008 Lyon, FRANCE (IARC)

(a) Epidemiological Studies, Report No. 75/001 of January, 1975.

(b) Oncogenicity of Vinyl Chloride at Low Concentrations in Rats and Rabbits by A. Caputo, et al.

(c) Item No. 250 citing research on vinyl chloride from IARC's most recent Information Bulletin (No. 4, November 1974) on the Survey of Chemicals Being Tested for Carcinogenicity.

(d) First pages which include summaries, of two articles on mutagenicity of vinyl chloride.

6. Attached also are title pages, indicating where copies may be obtained, for: a) "The Determination of Vinyl Chloride, A Plant Manual" (92 pages) published by the Chemical Industries Association Limited and (b) "Guidelines for Carcinogen Bioassay in Small Rodents" (65 pages) published by the National Cancer Institute.

Sincerely,

Milton Freifeld
Project Manager

MF/etv

Attachments

SCC
5-0173

APR 4 1975

Firestone Plastics Company

DIVISION OF THE FIRESTONE TIRE & RUBBER COMPANY

HARVEY S. FIRESTONE · FOUNDER

GENERAL OFFICES
P. O. BOX 699
POTTSTOWN, PENNSYLVANIA 19464

POTTSTOWN, PENNSYLVANIA

April 1, 1975

Mr. Milton Freifeld
Project Manager
Manufacturing Chemists Association
1825 Connecticut Avenue, N. W.
Washington, D. C. 20009

Dear Milt:

The reason I did not send you the summary of VCM regulations I promised is due to the fact that action in the various countries throughout the world continues to change on a regular basis.

However, I have attached information that we were able to obtain in early November 1974 that we believe to be accurate of that date.

If you have any questions, please call.

Cordially,

R. S. Brookman, Manager
Research, Development
and Technical Service

RSB:djs
Attachment
cc: Mr. R. A. Park

SCC
5-0174

JAPAN

No angiosarcoma deaths reported to date. Three non-VCM deaths by angiosarcoma are recorded. It is estimated that ten deaths (non-VCM related) have occurred in Japan during the last twenty years.

The equivalent of the Japanese Dept. of Labor feels that chromosome abnormalities may be a problem, based on conversations with Dr. Selikoff of Mt. Sinai School of Medicine.

A VCM standard may be set at about 10 ppm (no TWA). Japan uses the term MAC (maximum atmospheric concentration) since there are only two closed (in) plants in Japan. A maximum of 1 ppm may be established. New drafts (of standards) such as above must be approved by all other interested agencies in Japan, i.e., Marine Labor force, DOT, etc. It usually takes about six months for this to occur.

Currently MITI requested 300 ppm maximum VCM in low molecular weight resins; less than 100 ppm maximum VCM (high molecular weight resins). Work has been started to lower residual VCM in their resins.

STANDARDS CURRENTLY IN EFFECT:

United Kingdom:	50 ppm maximum; 25 TWA (based on agreement among government, PVC associations, labor).
West Germany:	1973 standard was 100 ppm maximum. 1974 standard was under chemical substances, Category B (cancer through animal test).
Netherlands:	1973 standard was 200 ppm. 1974 standard was 50 ppm average; 100 ppm maximum. Now standard is 25 ppm average; 50 ppm maximum. Soon to be issued is 10 ppm average; 25 ppm maximum for 15 minutes. (Labor feels this is too mild.)
France:	No government regulation. Producers use as standard 100 ppm maximum; 50 ppm normal. 1975 standard is 50 ppm maximum; 25 ppm normal. France usually disagrees with USA.
Belgium:	No government regulation. 25 ppm TWA; 50 ppm "action level".
Sweden:	1974 standard was 25 ppm TWA; 50 ppm maximum. 1975 will follow OSHA standard. Will scrap old plant and build new one.
Norway:	October 10, 1974 - Working on new standard. Plant currently shutdown until a decision is made.
Finland:	Same as Sweden.
Italy:	Not regulated but active producers use 50/25 (TWA).

SCC 5-0175

Most Scandinavian countries will follow OSHA due to the strong labor union

IARC Internal Technical Report

No. 75/001

REPORT OF A WORKING GROUP ON EPIDEMIOLOGICAL STUDIES ON VINYL CHLORIDE EXPOSED PEOPLE

Lyon, 8-9 January 1975

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R E P O R T

1. INTRODUCTION

The meeting on vinyl chloride (VC), convened by the IARC in June 1974, recommended that the IARC coordinate the various epidemiological studies being conducted in different countries on the oncological hazards associated with VC exposure. The present meeting, following a small working group held in September 1974, constitutes a first step in the development of such coordination.

The agenda for the meeting fell into three parts: (1) a consideration in general terms of the types of study that needed to be done and the principles underlying their design; (2) a review of the studies currently under way in the light of the principles so established; and (3) a discussion of how the coordination of such studies could be implemented. It was recognized that there was a need to generalize from the experience gained from VC towards the establishment of more speedy and efficient information retrieval systems for the early detection of industrial and environmental hazards.

2. CASES OF ANGIOSARCOMA OF THE LIVER IN VC MONOMER (VCM) EXPOSED WORKERS

The list of VC-related cases of angiosarcoma of the liver compiled in June 1974 (IARC Internal Technical Report No. 74/005*) was up-dated (see Table I). A total of 35 cases has been recorded so far, of which 29 were polymerization workers, two polyvinyl chloride (PVC) fabrication workers and two workers exposed to VCM. In addition, one case occurred in a worker employed in the insulation of electrical wires with PVC material and one was an accountant employed in a firm which made vinyl sheets and processed PVC resins. Since the meeting, eight additional cases have been reported to occur among the polymerization workers of a factory in Canada (Lloyd, personal communication). Three cases occurred in workers exposed to VC for a period as short as three to six years. The shortest latency period observed was six to eight years.

The observation in the USA of two cases of angiosarcoma of the liver in persons with no occupational exposure to VC but who had lived for many years

*The statement on page 20, line 9 of this report is incorrect and should read ".....the liver is in the order of 0.014" (and not 0.0014) "cases per 100,000".

within a few miles of PVC-utilizing factories, raises the possibility that exposure of the general population to VC might occasionally be sufficient to cause angiosarcoma of the liver.

3. REQUIREMENTS FOR EPIDEMIOLOGICAL STUDIES ON VINYL CHLORIDE

A document suggesting a series of requirements for epidemiological studies of VC risk was presented to the meeting for consideration. Subsequent discussion demonstrated the difficulty of going beyond a general outline of minimal requirements. A summary of this discussion is given below:

3.1 Establishing a cohort of those occupationally exposed to VC

The feasibility of including in the study cohort all those ever employed in a factory producing VC was debated. It was pointed out that the VC plant itself was often part of a much larger factory, and that to include the entire factory would increase costs substantially. Furthermore, contract workers, for whom no records were usually available, were often used for the dirtier jobs. Nevertheless, in some countries complete lists of workers could be obtained. The only criterion which seemed generally acceptable was that inclusion of a worker in a cohort should be independent of events subsequent to exposure to VC.

It was stressed that cohorts need to be established now for long-term prospective follow-up. It was recognized that failure of risk to become apparent after ten years does not preclude the emergence of such a risk, perhaps at a different target organ, many years later.

3.2 Studies of residential exposure

Although some studies are planned, it was concluded that for evaluation of carcinogenicity, such studies were a cumbersome way of obtaining information alternatively obtainable by case-control or case-history studies.

3.3 Exposure

The difficulty of establishing retrospectively an individual's history of exposure in a quantitative sense was recognized, a circumstance which emphasised the need to have careful monitoring of all manufacturing processes *ab initio*. Nevertheless, in any one plant, one would expect to be able to establish a

scale of exposure such as +, ++, +++. Even the same work station might imply quite different exposure levels in different plants; for example, an autoclave cleaner might be full-time in one plant, but only intermittently so occupied in another. Furthermore, for most work stations one would expect exposure to have fallen appreciably over the last 20 years, and exposure in more recent plants was likely to be less for any given work station than in older ones.

3.4 Confounding variables

There was agreement that retrospective information on a variety of confounding factors was often unreliable, and it was pointless to collect this for an entire cohort. Such information might be obtained on a case-control basis as cases arose, when emphasis could be placed on accuracy.

3.5 Size of the cohort

The minimum period between first exposure and tumour development is in the order of ten years. In the cohorts followed, there must thus be a sufficient number first exposed more than ten years ago for definite conclusions on risk to be made. Nothing is gained by swelling a cohort with those exposed for a short period except for the purpose of a prospective study (see Section 3.1). The problem of pooling data from several studies is discussed in Section 4.

3.6 Follow-up of cohorts

An attempt was made to put a level on the acceptable losses during the follow-up. The level of the losses depends mainly on the resources used for this purpose. Further, losses to follow-up are often greatest among those exposed earliest, i.e. the group of most interest. In the rubber industry study in the UK, 97% success has been achieved, and it was pointed out that there was a higher proportion of deaths in the last few per cent traced. Similarly, an Italian study of a cohort of about 3,000 workers traced 92%, the earliest entry date to the cohort being as far back as 1935. This cohort was, however, from a small area with little emigration. A figure of 90% was tentatively proposed as the minimum acceptable, provided that the proportion lost to follow-up was the same in both exposure groups. The quality of information must also be satisfactory.

3.7 Case control studies

There was a suggestion that for both angiosarcomas of the liver and brain tumours (see Table II) case control studies were needed to define the level of risk over wider classes of exposure.

4. PRESENT STATUS OF EPIDEMIOLOGICAL STUDIES

A summary of the epidemiological studies discussed at the meeting is given in Table II. In addition to these studies, mention was made of other studies in the USA, conducted at the Mount Sinai Hospital, the University of Louisville and the Boston School of Public Health. There was a suggestion from the Mount Sinai work that an increased risk of hepatocellular carcinoma, in addition to liver angiosarcoma, might also be associated with exposure to VC.

Preliminary data from the National Center for Disease Control, USA, show an excess of brain and lung tumours among workers employed in two PVC polymerization plants (see Table III). It was stressed that these figures are subject to revision when follow-up is complete.

5. PERMISSIBLE EXPOSURE LIMIT IN SOME COUNTRIES

In the USA a permissible level of 1 ppm (averaged over any 8 hour period) and a ceiling of 5 ppm (averaged over any period not exceeding 15 minutes) has been in effect from 1 January 1975 and applied to the manufacture, reaction, packaging, repackaging, storage, handling and use of VC and PVC. The same permissible level was established in Sweden, and from January 1976 this level has to be achieved without respirators. This is considered feasible. A VC code of practice was established in the UK, which limits exposure to a time-weighted average of 25 ppm and a ceiling of 50 ppm for a maximum of 15 minutes. In the Federal Republic of Germany a permissible level of 100 ppm in factories was effective up to 1974 and a new standard is expected by mid-1975. Similarly, new permissible levels of exposure to VC are expected in other countries.

6. DISCUSSION

6.1 Centralizing of results

In the discussion attention was turned first to the value of unifying the

results of the many different studies. The two main obstacles to unification of the results are the lack of comparability of exposure levels among the different studies and the differences in quality of the data, both in terms of the losses to follow-up and the quality of the available diagnoses. Differences in the base-line incidence of most tumours were also raised.

It was pointed out that a combined analysis could certainly take account of differences in exposure levels and base-line incidence figures, as one attempts to combine the comparisons rather than the absolute figures. No statistical methodology, however, can combine a good and a bad study in a sensible way. Nevertheless, there was considerable support for some attempt at centralizing the data. To this end, the IARC will shortly be circularizing proposals for the centralization of the data from the different studies, to invite comments and to determine the extent of willingness to cooperate.

6.2 Register of angiosarcomas of the liver

Both the USA and the UK have established review panels of pathologists and country-wide registers of angiosarcomas of the liver. The idea of IARC setting up a corresponding international register, and a further review panel, was discussed in view of a possible duplication of effort. However, there was some support for establishing a pathology review panel, with the World Health Organization Cancer Unit, and a register of liver angiosarcomas operating in parallel with UK and USA bodies.

7. VINYL CHLORIDE AS A PROTOTYPE FOR FUTURE COLLABORATIVE STUDIES ON OCCUPATIONAL CANCER

The carcinogenicity of VC was detected in experimental animals some four years before it was found to be carcinogenic in humans. The meeting expressed a strong feeling that if priorities for investigation, based on known biological activity in the laboratory and on the extent of human exposure, could be assigned to suspect chemicals, and international collaborative studies initiated accordingly, then carcinogenic dangers might be identified and eliminated more quickly. As an example, the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man have now considered 196 chemicals. Of these, 17 were found carcinogenic to man and 92 could be clearly seen as definitely

carcinogenic in some animal species. A number of these 92 are widely present in the human environment.

It was stressed that the IARC Monographs are among the tools necessary to produce a list of chemicals on which to choose priorities for epidemiological studies. This priority list should be short enough to encourage some action. International collaboration for such studies offers the advantage of reviewing world-wide patterns of use and production as well as experimental data to decide on the most suitable areas for investigating a particular compound. It was decided that the next meeting would not be limited to the consideration of VC studies, but treat the wider issue of selecting compounds for immediate epidemiological investigation, and attempting to identify populations on which these studies could be performed, as well as suggesting better ways to carry out primary prevention by preventing exposures to chemicals for which a carcinogenic activity could be strongly suggested.

The validity of tissue-mediated mutagenicity assays in determining the biological hazards of chemicals was discussed and data were presented on the mutagenicity of vinyledene chloride (*2*) and reports in the Soviet literature suggesting a carcinogenic risk of 2-chlorobutadiene for man were mentioned (*3, 4*).

8. RESPONSIBILITY OF INDUSTRY FOR FOLLOWING THE HEALTH OF ITS WORKERS

The difficulty and expense of mounting *ad hoc* studies for each new suspected compound could be reduced if an appropriate system of records of exposure and medical status were developed for the workers in industry, and if this system could be readily linked to national vital statistics, whether records of death or, preferably, cancer morbidity. Linking to the national records is essential for tracing past employees. Both Imperial Chemical Industries Ltd. and The British Petroleum Company Ltd. in the UK, and Ugine Kuhlmann in France, are developing systems of individual records, which are linkable to the national registers of deaths. It was recommended that the IARC lend its support to the establishment of such systems, and stress the desirability that industry assume responsibility for the follow-up of the health of its workers, even when they have ceased employment. It was also recommended

that the IARC take steps to ensure that the record systems developed are compatible between industries, and that they can perform the tasks required of them. This approach should be complementary to the points stressed in Section 7, aiming at the identification of carcinogenic chemicals before human exposure occurs.

9. NEXT MEETING

It was agreed that a further meeting would be particularly useful if it included the content of Sections 7 and 8 above in its agenda. Dr L. Goerke, of the Bundesministerium des Innern, Bonn, offered support for the meeting to be held in the Federal Republic of Germany.

REFERENCES

1. Wagoner, T. Statement before the Subcommittee on the Environment of the US Senate Commerce Committee, 21 August 1974.

2. Malaveille, C., Barbin, A., Brésil, H., Montesano, R. and Bartsch, H. The effect of drugs on metabolism and *in vitro* mutagenicity of vinyl chloride (VC) and vinyledene chloride (VDC). Proc. Meeting European Soc. Toxicol., Montpellier, 1975 (in press).

3. Khachatryan, E.A. The role of chloroprene in the process of skin neoplasm formation. Gig. Tr. Prof. Zabol., 18, 54, 1972.

4. Khachatryan, E.A. The occurrence of lung cancer among people working with chloroprene. Problems in Oncology, 18, 85, 1972.

TABLE I

CASES OF ANGIOSARCOMA OF THE LIVER AMONG WORKERS EXPOSED TO VC OR PVC (January 1975)

Case No.	Country	Date of diagnosis	Age at diagnosis	Years from first exposure to diagnosis	Total years of exposure	Occupation
1	USA	February 1974	45	12	12	Polymerization worker
2	USA	May 1970	36	14	13	" "
3	USA	June 1952	43	15	15	" "
4	USA	August 1961	41	15	15	" "
5	USA	May 1968	55	17	17	" "
6	USA	May 1969	50	20	15	" "
7	USA	April 1964	52	20	18	" "
8	USA	March 1973	49	22	16	" "
9	USA	March 1970	61	23	23	" "
10	USA	1968	45	24	18	" "
11	USA	December 1973	58	28	28	" "
12	USA	March 1974	43	19	17	" "
13	USA	May 1974	53	30	30	" "
14	USA	March 1969	41	19	4	" "
15	USA	October 1974	43	19	19	" "
16	USA	June 1973	60	36		Insulation of electrical wire with PVC plastic
17	USA	July 1972	47	10	10	Accountant in a plant making PVC fabric
18	UK	December 1972	71	26	20	Polymerization worker
19	UK	1974	37	8	3½	" "

TABLE I (Cont'd)

Case No.	Country	Date of diagnosis	Age at diagnosis	Years from first exposure to diagnosis	Total years of exposure	Occupation
20	UK	February 1970	55	24	11	Pouring PVC oil mixture onto fabric bases
21	Norway	December 1971	56	22	21	Polymerization worker
22	Sweden	February 1970	43	19	18	" "
23	Sweden	May 1972	61	27	23	Production of VCM
24	FRG	1971	40	14	12	Polymerization worker
25	FRG	September 1968	38	12	12	" "
26	FRG	1974	44	17	17	" "
27	FRG	July 1974	49	17	11	" "
28	FRG	1975	43	13	12	" "
29	FRG	March 1973	43	21	21	Filling pesticide cans with VC as propellant
30	France	February 1967	43	19	19	Polymerization worker
31	Italy	December 1972	43	15	6	" "
32	Italy	April 1971	36	6	3	Production of PVC bags
33	Romania	1970[a]	27	11	5½	Polymerization worker
34	Czech.	No data available				" "
35	Czech.	"	"	"		" "
36-43	Canada	"	"	"		" "

[a] A diagnosis of hepatocarcinoma associated with cholangiosarcoma was made.

TAB II

EPIDEMIOLOGICAL STUDIES ON VINYL CHLORIDE

			For short studies					
Country	Institute & principal investigators	Type of study	Size of cohort	Minimum length of exposure needed for inclusion in cohort	Type of exposure	Quantitative information on exposure	Present state of study	Remarks
Italy	Clinica del Lavoro, University of Milan Drs Foa & Bertazzi	Cohort study of industrially-exposed people	c. 5,000	6 months	VC-PVC production & PVC fabrication	Low exposure used to be 100 ppm with values going up to 2,000 ppm in polymerization plants. Levels now stated to be c. 25 ppm	Data collection has started	For 1 of the 3 factories in the study, work is nearly complete. The factory began operations in 1964. 700 workers have been exposed to VC; of these, 400 are still exposed, 200 are still employed but not in a VC plant, and 100 have either retired or changed jobs. 4 deaths have been ascertained. Follow-up of 90% is considered unlikely.
Italy	CNR Laboratory of Clinical Physiology & CNR Laboratory of Mutagenesis & Differentiation Dr Sarracci	Cohort study of industrially-exposed workers	c. 150	-	VCM production plant	-	In preparation	Only of value in conjunction with other studies, due to small size
		Morbidity, including congenital malformation, among population living near factory	30,000		Residence near a VC production plant	Levels of 2-5 ppm have been recorded in the atmosphere near the factory	In preparation	
FRG	Der Staatlicher Gewerbearzt, Duesseldorf Drs Reiss & Weber	Analysis of causes of death among 239 deaths reported among workers exposed to VC	-	-	Employment in VC or PVC plant	-	Under way	
FRG	BASF Drs Thiess & Frentzel-Beyme	Cohort study of industrially-exposed workers	1197	-	VC production & polymerization		466 of cohort have been traced so far	Production began in 1940
FRG	General information							There are 7-10 VC or PVC manufacturing plants and the present number of employees is approx. as follows: 2,100 in the production of VCM, 12,000 in PVC production and 45-50,000 in the processing of PVC. It was estimated that the total number of people who have been exposed to VC and PVC since 1940 is 35,000 in VC-PVC production and 120,000 in the processing of PVC. It was reported that among 30,000 autopsies performed at the Dept. of Pathology in Duesseldorf over a period of 10 years, 6 cases [3 females & 3 males] of angiosarcoma of the liver were observed. The age distribution of these cases or of the 30,000 autopsied cases were not available at the meeting.
USA	Center for Disease Control Reported by Dr Heath	Cohort study of industrially-exposed workers	5,000	-	VC polymerization		The results of a subset of the study are presented in Table III	The results were presented from 2 of the 4 factories in the study for workers employed for 5 or more years with first exposure more than 15 years ago. Follow-up about 80% complete so far. An excess of brain tumours and a suggestion of an excess of lung tumours were the outstanding features (see Table III)
		Nationwide register of angiosarcomas					Some 250 cases have been reported. Degree of exposure to VC, if any, to be determined. Slides to be sent, if possible, to pathology review committee	
		Medical screening of VC-PVC workers, PVC fabricating workers & rubber workers					Data being analysed	
UK	Employment Medical Advisory Service, in conjunction with HM Factory Inspectorate, with the assistance of the Trades Union Congress, Confederation of British Industry, Registrar General & the Royal College of Pathologists. Presented by Drs Gauvain & Baxter	Retrospective mortality & cancer registration study of PVC manufacturers	6-8,000		VC manufacture, PVC processors, VC polymerization		Under way	Similar prospective studies are being planned. All workers since 1948
		Case control study of angiosarcoma of the liver, from cases obtained from the Registrar General during the period 1963-73			Exposure to VC will be ascertained for liver angiosarcoma cases & matched controls		16 "probable" & 15 "possible" cases so far identified	Where possible, slides will be reviewed by a panel of pathologists

TABLE II (Cont'd.)

Country	Institute & principal investigators	Type of study	for cohort studies: Size of cohort	Minimum length of exposure needed for inclusion in cohort	Type of exposure	Quantitative information on exposure	Present state of study	Remarks
UK	British Rubber Manufacturing Assoc. Dr Parkes	Retrospective/prospective study of industrially-exposed workers	25-30,000		PVC fabricating industries	Levels of 25-30 ppm sometimes found in high speed PVB blending. Level 2-5 ppm found in stockrooms	Factories identified, work underway	
UK	British Petroleum Dr Duck	Cohort study of industrially-exposed workers at one factory	713	1 year	VC polymerisation	-	Completed	All workers traced. 37 deaths.
			1,100		Other workers at factory			57 deaths, all traced. 24/96 deaths due to cancer. No unusual features.
Sweden	Dr Englund	Industrially-exposed cohort	771		VC-PVC production. Exposure started in 1945		Nearly complete	Possible pitfall noted, of confusion among primary and secondary liver tumours and tumours of pancreas, in Cancer Registry & National Bureau of Statistics
Sweden	National Board of Occupational Safety & Health Dr Westerholm	Industrially-exposed cohort	1,000, born before 1939. To be extended to 3,000	2 months	PVC fabricating industries	-	Underway	Exposure started in 1945
France	Introduced by Dr Maugha	Cohort study of industrially-exposed workers	2,000, to be increased	-	VC polymerisation	-	Underway	An impression of an excess of cancers. Difficulty in assessing past exposure and in tracing workers who left industry long ago
		Register of angiosarcomas of liver	-	-	-	-	In preparation	-
The Netherlands	Shell International Petroleum Co. Dr de Rooy	Cohort study of industrially-exposed workers	400	-	VC or PVC production	-	Stated to be completed.	87 of the 400 had left employment. All had been traced. 1 death discovered due to myelofibrosis, which was considered surprisingly low

T A B L E III

PRELIMINARY ANALYSIS IN TWO VC POLYMERIZATION PLANTS CONCERNING WORKERS EMPLOYED 5 OR MORE YEARS AND WITH 80% FOLLOW-UP (REF. 1). EXPECTED AND OBSERVED DEATHS FROM VARIOUS CANCER CAUSES (1950-1973)

Years since onset of exposure in the selected departments	Person years at risk	All cancer		Liver cancer		Brain cancer		Respiratory system cancer		Lymphoma and Leukaemia		Residual cancer	
		Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs
10 - 14.9		4.91	6	.12	0	.22	0	1.50	3	.61	1	2.46	2
15 - 19.9		6.30	11	.17	3*	.25	1	2.08	3	.67	2	3.13	2
20 - 24.9		5.81	11	.15	3*	.20	2*	1.99	4	.55	1	2.92	2
> 25		2.72	3	.07	0	.06	1	.92	0	.24	0	1.43	1
TOTAL	9731	19.74	31*	.51	6*	.73	4*	6.49	10	2.07	4	9.94	7
Standard Mortality Ratio		157		1,176		548		154		193		70	

* Significant at $p < 0.05$

MUTAGENICITY OF VINYL CHLORIDE, CHLOROETHYLENEOXIDE, CHLOROACETALDEHYDE AND CHLOROETHANOL

C. Malaveille, H. Bartsch*, A. Barbin, A.M. Camus, R. Montesano, International Agency for Research on Cancer, Unit of Chemical Carcinogenesis, 69008 Lyon, France; and

A. Croisy and P. Jacquignon, CNRS, 91190 Gif-sur-Yvette, France.

Received January 28,1975

SUMMARY: Exposure of *S. typhimurium* strains TA 1530, TA 1535 and G-46 to vinyl chloride increased the number of *his*$^+$ rev./plate 16, 12 or 5 times over the spontaneous mutation rate. The mutagenic response for TA 1530 strain was enhanced 7, 4 or 5-fold when fortified S-9 liver fractions from humans, rats or mice were added. In TA 1530 strain, chloroacetic acid showed only toxic effects, while chloroacetaldehyde, chloroethanol and chloroethyleneoxide caused a mutagenic response. The latter compound was shown to be a strong alkylating agent.

VCM is extensively used for the production of polyvinyl chloride, other plastic material, and as a propellant for aerosols. The systemic action of this carcinogen in rats [1, 2, 3], mice[2] and humans [4-7], following exposure to VCM, as well as its low chemical reactivity, suggest that the biological effects are dependent upon its metabolic activation. In these studies, we are reporting the mutagenicity of VCM and/or its presumed metabolites in *S. typhimurium* strains, mediated by liver fractions of rat, mouse and human origin.

MATERIAL AND METHODS

Chemicals: VCM (purity 99.9%) was generously provided by Rhône-Progil, Lyon, France. Chloroacetaldehyde (50% aqueous solution), and chloroacetic acid (m.p. 61-63°) (Merck-Schuchardt, Fed. Rep. of Germany), alcohol dehydrogenase (200 U/mg) (Boehringer Mannheim, Fed. Rep. of Germany) were obtained from the sources indicated. All other commercial products were of the purest grade available. The structure and purity

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Abbreviations: VCM, vinyl chloride monomer; PB, phenobarbitone; S-9 9,000 x *g* tissue supernatant; GLC, gas liquid chromatography.

Int. J. Cancer: 15, 429-437 (1975)

HUMAN, RAT AND MOUSE LIVER-MEDIATED MUTAGENICITY OF VINYL CHLORIDE IN *S. TYPHIMURIUM* STRAINS

by

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Exposure of S. typhimurium *strains TA 1530, TA 1535 and G-46 to vinyl chloride increased the number of His+ revertants/plate 16, 12 or 5 times over the spontaneous mutation rate. After 6 h of exposure to vinyl chloride, the mutagenic response for TA 1530 strain was enhanced 7-, 4- or 5-fold when fortified postmitochondrial liver fractions from humans, rats or mice were added. The enzyme-mediated vinyl chloride mutagenicity was dependent on an NADPH generating system and the enzyme activity was localized in a liver microsomal fraction; 9,000 × g liver supernatant was three times more active than microsomes, while liver cytosol or alcohol dehydrogenase did not affect the mutagenicity. Phenobarbitone pretreatment of rats and mice increased the mutagenic response by up to 15-40% as compared to untreated controls. The relative mutagenic activities of VCM, taking the value from mouse liver as 100, for TA 1530 strain mediated by 9,000 × g tissue fractions were: rat liver, 80; mouse and rat kidney, 20 and 16; mouse and rat lung, less than 7; human liver (from four biopsy specimens), 170, 64, 70 and 46. Chloroacetaldehyde and chloroacetic acid, a urinary metabolite of VCM, showed toxic effects, while chloroethanol was weakly mutagenic for TA 1530 strain.*

Vinyl chloride monomer (VCM) is extensively used for the production of polyvinyl chloride and other plastic material, and also as a propellant for aerosols. Carcinogenicity in rats, when exposed to 30,000 ppm VCM in air, was first reported by Viola *et al.* (1971). Subsequently, Maltoni and Lefemine (1974) showed that angiosarcomas of the liver, as well as other tumours, were induced in rats and mice exposed to various doses of VCM by inhalation. Recently, cases of angiosarcoma of the liver have been found in workers exposed to VCM during the polymerization process and a causal relationship between VCM exposure and this type of tumour in man has been established (Creech and Johnson, 1974; Heath *et al.*, 1974; Lee and Harry, 1974; IARC, 1974). The systemic action of this carcinogen and its low chemical reactivity suggest that the biological effects of VCM are dependent upon its metabolic activation. In these studies, we report the mutagenicity of VCM and its presumed metabolites in *S. typhimurium* strains, mediated by liver and other tissue fractions of rat, mouse and human origin.

MATERIAL AND METHODS

Chemicals

VCM (purity 99.9%) was generously provided by Rhône-Progil, Lyons, France, contaminated with ethanol (30 ppm), water (20 ppm), methylchloride (<20 ppm) and non-volatile substances

Received: October 16, 1974.

ONCOGENICITY OF VINYL CHLORIDE AT LOW CONCENTRATIONS IN RATS AND RABBITS

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Paper received: 10th May, 1974; amended 22nd July, 1974.

In the past four years we have demonstrated (1,2) that rats exposed to a flow of air containing 30 000 p.p.m. (part per million) of vinyl chloride develop cutaneous tumors in 70% of cases, lung carcinomas in 20% of cases and, less frequently, osteochondromas.

Table 1. Oncogenicity of vinyl chloride in rats as function of the dose. The tumors appeared between 8 and 13 months of treatment.

VC concentration (p.p.m.)	Histotypes	Tumors/animals under treatment	%	P*
20 000	Skin squamous cell carcinoma	67/150	45	
20 000	Lung adenocarcinoma	21/150	14	
20 000	Liver angiosarcoma	18/150	12	<0.0005
20 000	Liver cholangioma	13/150	9	
20 000	Small intestine adenocarcinoma	7/150	5	
10 000	Skin squamous cell carcinoma	34/200	17	
10 000	Lung adenocarcinoma	14/200	7	
10 000	Lung alveolar carcinoma	2/200	1	<0.0005
10 000	Mediastinic reticulosarcoma	8/200	4	
10 000	Liver angiosarcoma	16/200	8	
5000	Skin squamous cell carcinoma	20/200	10	
5000	Lung adenocarcinoma	4/200	2	<0.0005
5000	Liver angiosarcoma	12/200	6	
5000	Peritoneal angiosarcoma	2/200	1	
2000	Skin acanthoma	6/200	3	
2000	Liver angiosarcoma	10/200	5	
2000	Small intestine adenocarcinoma	6/200	3	<0.005
2000	Lung adenocarcinoma	8/200	4	
500	Skin squamous carcinoma	3/150	4	<0.01
500	Liver angiosarcoma	4/150	3	
50	–	0/200	–	
Control†	–	0/200	–	

* χ^2 test versus control.

† The animals not exposed to VC, were kept under the same conditions for 13 mths.

Table 2. Oncogenic effect of vinyl chloride in rabbits. The tumors appeared between 9 and 15 months of exposure.

VC concentration (p.p.m.)	Histotypes	Tumors/animals under treatment	%	P*
10 000	Skin acanthoma	12/40	30	<0.0005
10 000	Lung adenocarcinoma	6/40	15	
Control†	–	0/20	–	

* χ^2 test versus control.

† The animals not exposed to VC, were kept under the same conditions for 15 mths.

In order to ascertain the degree of oncogenicity of vinyl chloride, experiments have been performed in which rats inhaled lower doses of this chemical. 1100 animals (3 month old Wistar Ar IRE male or female albino rats) were exposed for 4 hours a day, 5 days a week for 12 months to a flow of air containing 20 000, 10 000, 5000, 2000, 500 or 50 p.p.m. of vinyl chloride. With exception of the animals in the group exposed to the lowest dose (50 p.p.m.) all other experimental animals developed a high percentage of tumors. As reported in table 1, the neoplasms originated in different tissues and organs, with prevalence of the liver. It is worth emphasizing that even using lower concentrations, it was possible to confirm the oncogenicity of vinyl chloride which, under the experimental conditions employed, is to be considered a very hazardous compound and one of the most powerful carcinogens.

In a limited number of experiments utilizing other types of animals the appearance of tumors similar to those described in the rats was observed. These data, collected in table 2, indicate in particular that the rabbit, which is not very susceptible to chemical carcinogens, displays high sensitivity to vinyl chloride. Even in this case, at the concentration of 10 000 p.p.m., the histotypes reflect those obtained in the rats.

We can conclude that the carcinogenic effect of vinyl chloride has been clearly confirmed by the present results, which also indicate that almost all tissues and organs are sensitive to this carcinogen.

1. Viola, P.L. (1970) Proc. 10th International Cancer Congress, Houston, abstract 29
2. Viola, P.L., Bigotti, A. and Caputo, A. (1971) *Cancer Research*, 31, 516

INFORMATION ON CARCINOGENICITY TESIS UNDERTAKEN

Nome of Substance Synonyms)	Species (Strain)	Exposure	Stage of Experiment	Principal Investigators	Country Town Institute (See Index)
550. Vinyl chloride (CAS Reg. No.: 75-01-4; Chlorethene; Chlorethylene; Choroethene; Chloroethylene; Ethylene monochloride; VC; VCM)	Rat (Wistar)	p.o. in drinking water	planned	see under Institute	UK Carshalton (a)
551. Vitamin A palmitate (CAS Reg. No.: 7488-89-3)	Mouse (CBA & [AxIF]F_1	s.c.	pathological examination to be carried out	Flaks, A.	UK Leeds (a)

THE DETERMINATION OF VINYL CHLORIDE,

A PLANT MANUAL

ANALYTICAL METHODS REQUIRED FOR THE CONTROL OF VINYL CHLORIDE CONCENTRATIONS IN AND AROUND MANUFACTURING AND PROCESS PLANTS

Compiled by specialists convened by
the Vinyl Chloride Committee of the
Chemical Industries Association Ltd.
and edited by
W. Thain, M.A., B.Sc., M.Inst.P.

Published by

Chemical Industries Association Ltd.,
Alembic House, 93 Albert Embankment,
London, SE1 7TU.

December 1974 - First Edition