DOW CHEMICAL U.S.A.

MIDLAND, MICHIGAN 48640

November 8, 1979

RECEIVED
NOV 13 1979
Environmental Affairs

Z. G. Bell, PPG Industries
T. J. Benya, Ethyl Corporation
W. D. Harris, Uniroyal, Inc.
G. K. Hatfield, Diamond Shamrock
M. N. Johnson, M.D., The B. F. Goodrich Company
C. D. Kary, Shell Chemical Company
J. W. Lawrence, SPI
J. T. Seawell, CMA
W. M. Smith, Air Products & Chemicals, Inc.
R. N. Wheeler, Union Carbide Corp.

cc: J. M. Norris

CPSC VINYL CHLORIDE STUDY IN RATS AND MICE

Jessie Norris of our company has made an assessment showing some very obvious deficiencies in the Edgewood Arsenal Study on VCM. Since we hope to discuss this briefly as part of our already crowded Research Coordinators Agenda, November 28, I'm enclosing a copy of Mrs. Norris' review.

Please don't distribute it any further at this time. The ultimate disposition of the review will in part depend upon our November 28 discussion.

T. R. Torkelson
Chairman, CMA
Vinyl Chloride Research Coordinator

Attachment

clm

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

2040 Dow Center
October 23, 1979

T. R. Torkelson
H&ES Operations
1603 Building

cc: K. L. Burgess, 2040
P. J. Gehring, 1803
F. D. Hoerger, 2030
R. J. Kociba, 1803
B. A. Schwetz, 1803
L. M. Thomka, 2040

cc H A Farber / L K Story
CMA Vinyl Research
Coordinators
Joe Scewell CMA
John Lawrence EPI

CPSC - VINYL CHLORIDE STUDIES IN RATS AND MICE

The draft report of the research project sponsored by the Consumer Product Safety Commission (CPSC) under an inter-agency agreement with Chemical Systems Laboratory (formerly Edgewood Arsenal) was reviewed previously and deficiencies in the reporting of the studies were noted. Since the draft report contained hand-written tables, a detailed written critique was delayed until a copy of the recently completed final report was obtained.

The final report contains the same deficiencies as did the draft report. For the purpose of demonstrating that the report is deficient because of discrepancies and errors, the following discussion has been limited to those studies involving the single exposure of mice and rats and repeated exposure of mice to vinyl chloride. Specifically, the report contains discrepancies both in the reporting of the numbers of animals per group that were placed on the various studies relative to the numbers evaluated.

Further discrepancies were noted in the numbers of animals observed with tumors in various tables and the months in which the studies were terminated were incorrectly reported.

Data in the report indicate that both the ICR and A/J mice had a relatively high background incidence of pulmonary adenomas. The ICR mice also either had a chronic pneumonic condition or developed pneumonitis during the study. The marked body weight loss in these mice, both the vinyl chloride exposed and controls, during the 28th and 42nd weeks of the study suggests that external factors may have been contributory to the pneumonic condition. Except for the male ICR mice in the group exposed to 50,000 ppm vinyl chloride, the incidence of pneumonitis is roughly proportional to the incidence of pulmonary adenomas. However, since the handling/housing of the control mice relative to exposed mice is not reported, and since no statement is made as to whether medications were administered, the significance of the apparent association can not be concluded.

As an aid to the reader, facsimiles of the various tables and figures referenced in this communication and the respective page number in the report have been included in the discussion section (below).

DISCUSSION

Single Exposure Data

A. ICR Mice

Regarding the data reported on a single inhalation exposure of ICR mice to 0, 50, 500, 5000 or 50,000 ppm vinyl chloride:

1) *There are discrepancies in the numbers of mice supposedly placed on study and the numbers of mice accounted for in the report. The numbers of mice on study are given in Table 1, page 8 of the report and Appendix Table I, page 23 (below).*

TABLE 1. VINYL CHLORIDE STUDIES

Experimental Group*	PPM	DAYS (1 hr/day)	SUMMARY (ppm-hrs)	SPECIES/NUMBER EXPOSED		RESULTS
A	50,000	1	50,000	ICR Mice Fischer Rats	180 178	33% adenomas negative
C	500	49	24,500	Sprague-Dawley/ Wistar Rats	49	eosinophilic changes
A	5,000	1	5,000	ICR Mice Fischer Rats	180 180	16.8% adenomas negative
B	500	10	5,000	AJ Mice Fischer Rats	180 180	74% adenomas negative
B	50	100	5,000	AJ Mice Fischer Rats	179 180	41% adenomas negative
C	50	49	2,450	Sprague-Dawley/ Wistar	47	Eosinophilic changes
A	500	1	500	ICR Mice Fischer Rats	180 190	like controls negative
A	50	1	50	ICR Mice Fischer Rats	180 180	like controls negative
				TOTAL EXPOSED	2263	
				TOTAL CONTROL	776	
				COMBINED TOTAL	3039	

*A - 170 ICR Mice (82 male and 88 female) and 171 Fischer Rats (92 male and 79 female) served as control animals for the single exposure (50,000; 5,000; 500; 50 PPM) studies.

B - 190 AJ Mice (89 male and 101 female) and 200 Fischer Rats (100 male and 100 female) served as control animals for the multiple exposure (10 X 500 PPM and 100 X 50 PPM) studies.

C - 45 Sprague-Dawley/Wistar (20 male and 25 female) served as control animals for the multigeneration reproduction study.

APPENDIX

Table I. Single Exposure Schedule of Animals To VCM

Species	Sex	Dose	Exposure date 1st	2nd	Exposure group size(s)	Age at time of exposure
		ppm				weeks
Fischer Rat	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		85	17
		50000	3/25/75		90	18
	F	50		3/4/75	90	15
		500		3/11/75	100	16
		5000		3/18/75	95	17
		50000		3/25/75	88	18
ICR Mouse	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		90	17
		50000	3/25/75		90	18
	F	50		3/4/75	90	15
		500		3/11/75	90	16
		5000		3/18/75	90	17
		50000		3/25/75	90	18
Rat	M	Neg/Cont.			92	15-18
	F	Neg/Cont/			79	15-18
Mouse	M	Neg/Cont.			82	15-18
	F	Neg/Cont.			88	15-18

The numbers reported in the above tables and pertinent to this comment are summarized in the following tabulation:

Concentration -ppm-	# Mice on Study		
	Male	Female	Total
0	82	88	170
50	90	90	180
500	90	90	180
5000	90	90	180
50,000	90	90	180

The numbers of animals, however, that were evaluated for liver/lung changes, including those sacrificed after the 8th month and 18th month (final) sacrifices and all those animals dying spontaneously which should account for all animals placed on the study, are given in Appendix Table IV, page 43 (below).

Table IV. Over-all Summary Incidence of Non-neoplastic Changes and Histologically-Proven Neoplasms within The Liver and Lungs of ICR Swiss Mice Exposed to Vinyl Chloride.

Single Inhalation Exposure

		Incidence of Response									
	Exposure	Control		Vinyl Chloride							
	Dose Level (PPM)	0		50,000		5,000		500		50	
	Sex of Animals	M	F	M	F	M	F	M	F	M	F
*Tissue/Response	Animals Per Group*	62	77	74	82	76	82	72	75	91	90
Liver	Number Evaluated	50	75	63	78	68	76	67	72	64	68
- hepatic cell necrosis		2	10	3	5	5	7	4	5	2	3
- hepatic cell vacuolation (lipidosis)		2	11		4	2	12	3	5	1	4
- hepatic cell hypertrophy		1		2	3		8	4	13	1	
- hepatic cell hyperplasia						4	4				
- angiectasis					1		4				
- sinusoidal reticulosis					5						
- hepatic cell adenoma		2		1			1			2	
- hepatic cell carcinoma		2		4	1	6	1	9		2	
- hemangioma									2		1
- hemangiosarcoma		1				1					
Lung	Number Evaluated	50	70	61	76	65	78	66	73	71	68
- pneumonitis		1	6	21	10	13	17	19	15	4	7
- bronchio-alveolar adenoma		4	8	31	14	14	10	8	10	8	6
- bronchio-alveolar carcinoma				1	2	1			1		

* Total includes animals from scheduled sacrificed (8 and 18 month periods) and spontaneous deaths.

The pertinent data from the aforementioned table indicating the number of animals evaluated are summarized in the following tabulation.

Concentration -ppm-	# Mice Evaluated-Liver (Lung)		
	Male	Female	Total
0	50(50)	75(70)	125(120)
50	64(71)	68(68)	132(139)
500	67(66)	72(73)	139(139)
5000	68(65)	76(78)	144(143)
50,000	63(61)	78(76)	141(137)

The numbers of animals not accounted for can be estimated by using the data on the greatest numbers of animals evaluated for liver or lung responses as noted above.

The following tabulation shows the difference between the numbers of animals that are indicated in the report to have been placed on the study and the number of animals evaluated for liver and/or lung changes e.g., for male controls: Table 1 states 82 ICR mice were placed on study, the maximum number evaluated were 50; 82-50 = 32.

Concentration -ppm-	Numbers of Mice on Study (Table 1 and Appendix Table II) Minus Numbers Accounted for on Appendix Table IV		
	Male	Female	Total
0	32	13	45
50	19	22	41
500	23	17	40
5000	22	12	34
50,000	27	12	39

The fact that the numbers of mice evaluated for liver changes, as noted above, are not the same as those evaluated for lung changes is inexplicable.

Furthermore, if one assumes the discrepancies in the numbers of animals per group on the study as given in Appendix Table IV, and those actually examined could feasibly reflect the

incidence of autolysis among expired animals, the incidence was 10.5% overall and, in specific groups, namely, control males and 50 ppm males as high as 19 to 21% respectively e.g., number of control male mice: 62 per group, maximum number evaluated for either liver or lung changes = 50, 12 of the 62 in the group are not accounted for or 19%.

Further discrepancies are noted in the numbers of animals placed on study as given in Appendix Table II (page 24),

APPENDIX

Table II Exposure Schedule for Animals Exposed Repeatedly to VCM

Species	Sex	Dose	Exposure periods	Exposure dates		Exposure Group size(s)		Age	
				From	To	Start	End	Start	End
		ppm	days					wks	
Fischer Rat	M	50	100	8/27/75	1/26/76	90	86	21	41
		500	10	7/7/75	7/18/75	90	90	14	16
	F	50	100	8/27/75	1/26/76	90	87	21	41
		500	10	7/7/75	7/18/75	90	90	14	16
A/J Mouse	M	50	100	7/7/75	7/18/75	90	87	15	35
		500	10	8/27/75	1/26/76	90	90	8	10
	F	50	100	7/7/75	7/18/75	90	88	15	35
		500	10	8/27/75	1/26/76	90	90	8	10
Fischer Rat	M	Neg. control	100(c)	-		50	50	21	41
			10(c)	-		50	50	14	16
	F	Neg. control	100(c)	-		50	47	21	41
			10(c)	-		50	50	14	16
A/J Mouse	M	Neg. control	100(c)	-		40	39	15	35
			10(c)	-		50	50	8	10
	F	Neg. control	100(c)	-		50	50	15	35
			10(c)	-		50	50	8	10

NOTE: (c) control for corresponding dose above.

and the numbers of animals evaluated for responses in liver and/or lung changes (Appendix Table IV) as well as the number of animals per group given on Appendix Table IV.

2) *There are discrepancies in the incidences of histologically-proven neoplasms in liver and lung tissue of ICR mice.*

Discrepancies have been noted in the data given in Appendix Table VI (page 45) below, and the incidences as given in Appendix Table IV, for the same periods.

Table VI. Incidence of Histologically-Proven Neoplasms Within Tissues From ICR Mice Exposed to Vinyl Chloride Monomer (Single Inhalation Exposure)

Sacrifice Period	Organ Tissue	50,000 ppm			5,000 ppm			500 ppm			50 ppm			0 ppm (Control)		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Scheduled	Lung	4	1	5	1	1	2	2	2	2	2	2	2	2	2	2
8 months	Liver	0	0	0	1	0	1	1	0	1	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Others	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Totals	4	1	5	2	1	3	1	0	1	0	0	0	0	0	0
18 months	Lung	5	6	11	3	7	10	4	12	16	1	4	5	1	4	5
	Liver	2	3	5	2	0	2	1	1	2	0	1	1	1	2	3
	Kidney	0	0	0	0	1	1	0	3	3	0	2	2	0	0	0
	Stomach	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0
	Others	0	8	8	0	5	5	0	7	7	0	7	7	0	1	1
	Totals	7	14	24	5	13	18	5	24	29	2	14	16	2	12	14
Spontaneous Deaths	Lung	2	0	2	0	1	1	0	1	1	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
0-6 mon	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Others	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
	Totals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7-12 mon	Lung	2	3	5	3	1	4	1	1	2	2	2	4	0	0	0
	Liver	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	1	2	3	1	2	3	1	1	2	2	1	3	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
	Others	1	4	5	0	1	1	2	4	6	1	10	11	0	1	1
	Totals	5	11	16	4	5	9	4	8	14	4	15	19	0	1	1
13-18 mon	Lung	12	15	18	12	5	17	5	2	7	5	5	10	4	3	11
	Liver	5	5	10	5	5	10	8	4	12	4	2	6	5	2	12
	Kidney	4	0	4	1	3	4	1	2	3	3	1	4	1	5	6
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Others	2	11	13	4	14	18	5	6	11	2	10	12	3	10	14
	Total	33	32	65	22	27	49	19	14	33	9	18	27	14	41	55

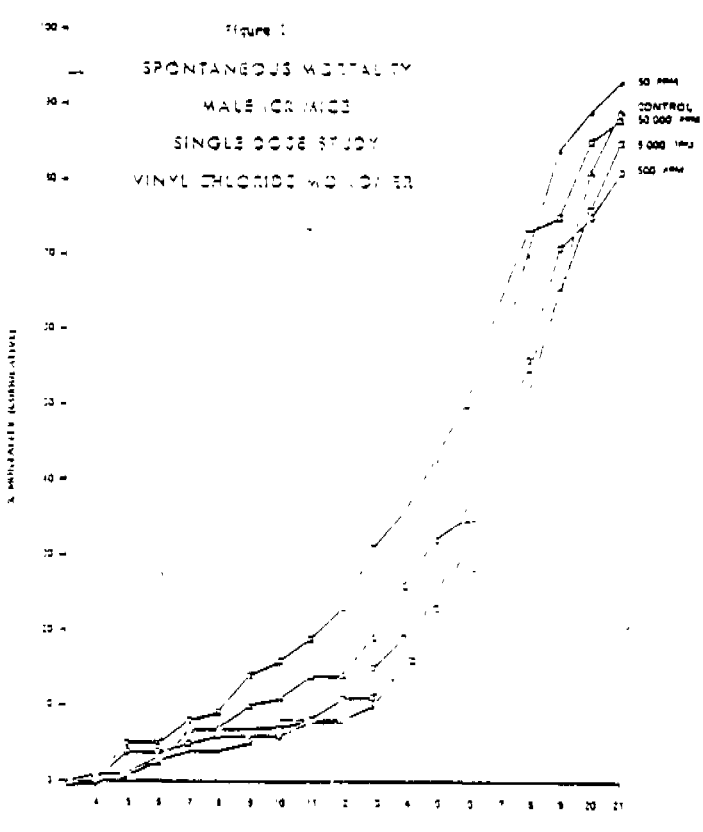
These discrepancies are summarized in the following tabulation:

Concentration -ppm-	Incidence of Liver (Lung) Neoplasms					
	Table VI			Table IV		
	Male	Female	Total	Male	Female	Total
0	6(5)	9(16)	15(21)	5(4)	0(8)	5(12)
50	5(8)	3(11)	8(19)	4(8)	1(6)	5(14)
500	12(10)	7(17)	19(27)	9(8)	2(11)	11(19)
5000	8(19)	5(15)	13(34)	7(15)	2(10)	9(25)
50,000	7(34)	10(26)	17(60)	5(32)	1(16)	6(48)

3) The data base for the results of the single inhalation study in ICR mice as reported in Table 1 (page 8) is in error. As reported it is implied that the percentages of adenomas were found in 130 mice per dose level when in fact the percentages were calculated on fewer animals (see page 5 of report):

Concentration -ppm-	# Animals On Study (Table 1)	Reported % Adenomas (Page 5)	# Animals Evaluated (Page 5)
50	180	"like controls"	139
500	180	"like controls"	139
5000	180	16.8%	143
50,000	180	33.0%	137

4) *The statement (page 5) is made that there were no consistent or dose-related differences between control and exposed mice in death rate, toxic signs or gains in weight. However, the vinyl chloride exposed male ICR mice, which according to the data on Appendix Table IV suffered from a higher incidence of pneumonitis than did the females or any of the A/J mice or Fischer rats on study, showed significantly earlier mortality than the females ICR mice (Appendix Figures I and II, pages 26 and 27 (below)), and unexplained weight losses between the 27th and 42nd weeks of the study (Appendix Figure X, page 35 (below)).*



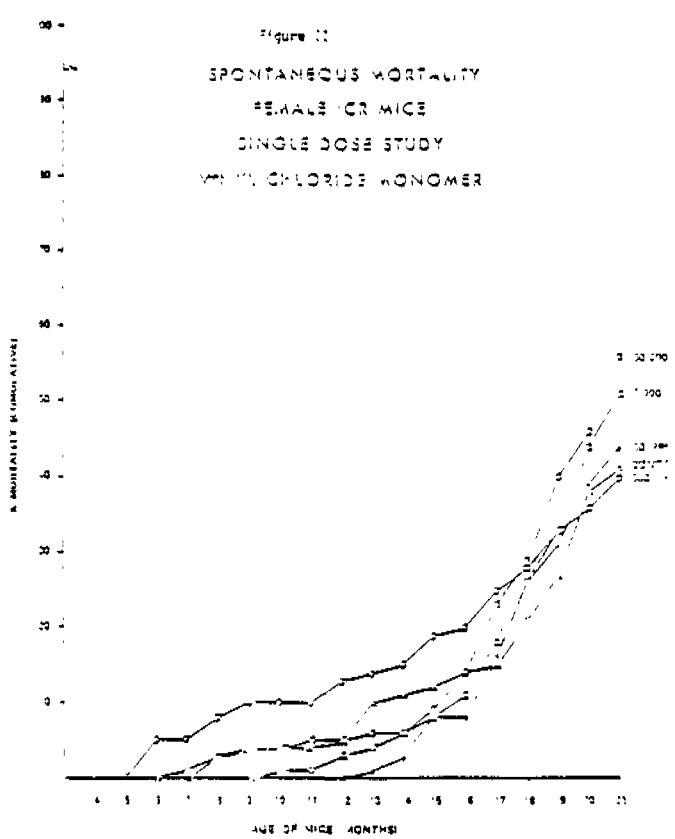
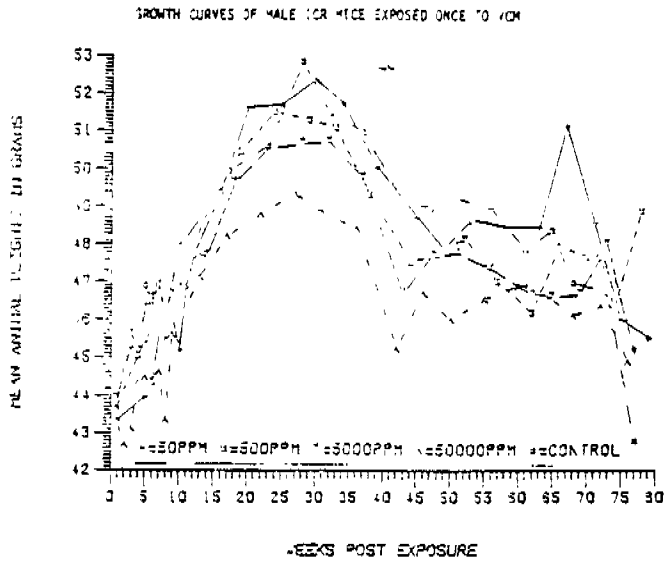


Figure 1



Except for the data on male ICR mice exposed to 50,000 ppm vinyl chloride, the incidence of pulmonary adenomas in ICR mice is roughly proportional to the incidence of pneumonitis. The following tabulation summarizes these data:

Concentration -ppm-	Pneumonitis				Adenomas			
	Male		Female		Male		Female	
	#	%	#	%	#	%	#	%
0	1/50	2.0	6/70	8.6	4/50	8.0	8/70	11.
50	4/71	5.6	7/68	10.3	8/71	11.3	6/68	8.
500	19/66	28.8	15/73	20.5	8/66	12.1	10/73	13.
5000	13/65	20.0	17/78	21.8	14/65	21.5	10/78	12.
50,000	21/61	34.4	10/76	13.2	31/61	50.8	14/76	18

The weight losses which occurred in the male ICR mice are summarized below:

Concentration -ppm-	Body Weight[1] (Grams) 20th Week	42nd Week	Difference (Grams)
0	52.8	48.2	-4.6
50	52.0	49.5	-2.5
500	51.3	49.5	-1.8
5000	50.6	47.2	-3.4
50,000	49.2	45.3	-3.9

[1] Approximated from Appendix Figure X. Quality of figure exceedingly poor.

The weight losses were never regained during the remainder of the study. Furthermore, during and following this period of significant weight loss, and in particular between the 12th and 16th months, the mortality of the male mice in each group including the controls increased significantly when compared to the females for which the maximum increase in mortality was less than 10% during the same period of time. The incidence of mortality among male mice at each dose level during this period is summarized in the following tabulation:

Concentration -ppm-	Mortality Male Mice 12th Month	16th Month	Increase
0	~13%	~35%	22%
50	~ 8.5%	~35%	26.5%
500	~ 8.5%	~30%	21.5%
5000	~11%	~30%	19.0%
50,000	~23%	~50%	27.0%

Since there is insufficient data e.g. water/food consumption, time of appearance of the pneumonitis etc. from which to form a hypothesis as to the cause of the body weight losses and increased mortality it can not be ruled out that the effects were caused by external factors.

The time of the final sacrifice was reported on page 2 of the report to be at the 18th month, however, Appendix Figures I and II, show data up through the 21st month!

B. Fischer 344 Rats

Regarding the single inhalation exposure of Fischer 344 rats, the statement is made on page 7 of the report that "except for aggravation of latent pulmonary changes, particularly bronchopneumonia, changes attributable to VCM were not apparent in any of the tissues evaluated at 8, 16 or 24 months from Fischer 344 rats exposed to concentrations of 50, 500, 5000, or 50,000 ppm". Nowhere else in this report are the "latent pulmonary changes" addressed. It must be assumed that either the incidence among animals dying spontaneously were not included in order to make the above claim or the statement is in error. The data on the incidence of bronchopneumonia presented in Appendix Table XI, page 50 (below) includes the animals dying spontaneously. Furthermore, the data in Appendix Table XI do not support the conclusion that the pneumonia is attributable to VCM exposure except for the male rats at 50,000 ppm since the incidence of bronchopneumonia in control animals was significantly higher or as high as the incidences in the treated animals.

Table XI. Over-all Summary Incidence of Non-neoplastic Changes within The Lungs of Fischer Rats Exposed To Vinyl Chloride.

Single Inhalation Exposure

		Incidence of Response									
	Exposure	Control		Vinyl chloride							
	Dose Level (PPM)	0		50,000		5,000		500		50	
	Sex of Animal	M	F	M	F	M	F	M	F	M	F
Tissue/Response	Animals Per Group*	99	74	96	87	83	93	87	100	90	91
Lung	Number Evaluated	85	57	80	77	80	87	85	95	80	74
- Bronchopneumonia		26	10	45	13	13	10	15	3	28	3
	% Incidence	30.6	14.9	56.2	16.9	16.3	11.5	17.6	3	35.0	4.1

* Total includes animals from scheduled sacrifice (8, 16, and 24 month periods) and spontaneous deaths.

Furthermore, discrepancies are apparent in the numbers of rats on the study as given on Table 1, page 8 and Appendix Tables I and XI, numbers of animals per group (pages 23 and 50, respectively), and the numbers evaluated as indicated on Appendix Table XI (page 50). The animals placed on the study but not evaluated are not accounted for in the report.

TABLE 1. VINYL CHLORIDE STUDIES

Experimental Group*	PPM	DAYS (1 hr/day)	SUMMARY (man-hours)	SPECIES/NUMBER EXPOSED		RESULTS
A	50,000	1	50,000	ICR Mice Fischer Rats	180 178	33% adenomas negative
C	500	49	24,500	Sprague-Dawley/ Wistar Rats	49	ostiomyelitic changes
A	5,000	1	5,000	ICR Mice Fischer Rats	180 180	16.8% adenomas negative
B	500	10	5,000	AJ Mice Fischer Rats	190 180	74% adenomas negative
A	50	100	5,000	AJ Mice Fischer Rats	179 180	41% adenomas negative
C	50	49	2,450	Sprague-Dawley/ Wistar	47	Eosinophilic changes
A	500	1	500	ICR Mice Fischer Rats	180 190	like controls negative
A	50	1	50	ICR Mice Fischer Rats	180 180	like controls negative
				TOTAL EXPOSED	2263	
				TOTAL CONTROL	776	
				COMBINED TOTAL	3039	

*A - 170 ICR Mice (82 male and 88 female) and 179 Fischer Rats (92 male and 79 female) served as control animals for the single exposure (50,000; 5,000; 500; 50 PPM) studies.

B - 190 AJ Mice (89 male and 101 female) and 200 Fischer Rats (100 male and 100 female) served as control animals for the multiple exposure (10 X 500 PPM and 100 X 50 PPM) studies.

C - 45 Sprague-Dawley/Wistar (20 male and 25 female) served as control animals for the multigeneration reproduction study.

APPENDIX

Table I Single Exposure Schedule of Animals in VCM

Species	Sex	Dose PPM	Exposure date AM	PM	Exposure group size(s)	Age at time of exposure weeks
Fischer Rat	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		85	17
		50000	3/25/75		90	18
	F	50	3/4/75		90	15
		500	3/11/75		100	16
		5000	3/18/75		95	17
		50000	3/25/75		88	18
ICR Mouse	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		90	17
		50000	3/25/75		90	18
	F	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		90	17
		50000	3/25/75		90	18
Rat	M	Neg/Cont			92	15-18
	F	Neg/Cont/			79	15-18
Mouse	M	Neg/Cont			82	15-18
	F	Neg/Cont.			88	15-18

Table II Over-all Summary Incidence of Non-neoplastic Changes Within The Lungs of Fischer Rats Exposed to Vinyl Chloride

Single Inhalation Exposure

		Incidence of Response								
	Exposure	Control		Vinyl chloride						
	Dose Level (PPM)	0		50,000		5,000		500		50
	Sex of Animal	M	F	M	F	M	F	M	F	M
Tissue/Response	Animals Per Group*	89	74	86	87	83	93	87	100	90
Lung	Number Evaluated	45	67	80	77	80	87	85	95	80
- bronchopneumonia		26	10	45	13	13	10	15	3	24
	% Incidence	30.6	14.9	56.2	16.9	16.3	11.5	17.6	3	35.0

* Total includes animals from scheduled sacrifice (6, 16, and 24 month periods) and spontaneous deaths.

SL 095559

The pertinent data from the above tables are summarized in the following tabulation:

Concentration -ppm-	Keepers of Fischer Rats								
	On Study						Evaluated[1]		
	Table 1 & Appendix Table I[2]			Appendix Table VI			Appendix Table XI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0	92	79	171	89	74	163	85	67	152
50	90	90	180	86	87	173	80	77	157
500	90	90	180	83	93	176	80	87	167
5000	90	90	180	87	100	187	85	95	180
50,200	90	90	180	90	91	181	80	74	154

[1] Includes animals from scheduled sacrifices and spontaneous deaths.

[2] Data on control animals on Table 1 and Appendix Table I do not agree with data on Appendix Table II.

Repeated Exposure Data

A. A/J Mice

Regarding the data reported on one hundred (100) or ten (10) inhalation exposures of A/J mice to 50 ppm or 500 ppm, respectively of vinyl chloride:

1) *There are discrepancies in the numbers of mice supposedly placed on these studies and the numbers of mice accounted for in the report in Table 1, page 3 of the report and Appendix Table II, page 23 (below):*

TABLE 1 VINYL CHLORIDE STUDIES

Experimental Group*	ppm	DAYS (hr/day)	CUMULATIVE (man-hrs)	SPECIES/NUMBER EXPOSED		RESULTS
A	50,000	1	50,000	ICR Mice Fischer Rats	180 178	33% adenomas negative
C	500	49	24,500	Sprague-Dawley/ Wistar Rats	19	Mesothelial changes
A	5,000	1	5,000	ICR Mice Fischer Rats	180 180	16.8% adenomas negative
B	500	10	5,000	AJ Mice Fischer Rats	80 180	74% adenomas negative
B	50	100	5,000	AJ Mice Fischer Rats	179 180	41% adenomas negative
C	50	49	2,450	Sprague-Dawley/ Wistar	17	Mesothelial changes
A	500	1	500	ICR Mice Fischer Rats	180 180	like controls negative
A	50	1	50	ICR Mice Fischer Rats	80 180	like controls negative
				TOTAL EXPOSED	1251	
				TOTAL CONTROL	788	
				COMBINED TOTAL	7039	

*A - 170 ICR Mice (82 male and 88 female) and 179 Fischer Rats (92 male and 79 female) served as control animals for the single exposure (50,000; 5,000; 500; 50 PPM) studies

B - 190 AJ Mice (109 male and 101 female) and 200 Fischer Rats (100 male and 100 female) served as control animals for the multiple exposure (10 & 500 PPM and 100 & 50 PPM) studies.

C - 15 Sprague-Dawley/Wistar (20 male and 25 female) served as control animals for the multigeneration reproduction study.

APPENDIX

Table II Exposure Schedule for Animals Exposed Repeatedly to VCM

Species	Sex	Dose	Exposure periods	Exposure Dates		Exposure Group Size(s)		Age	
				From	To	Start	End	Start	End
		ppm	days					days	
Fischer Rat	M	50	100	3/27/75	1/26/76	20	46	21	41
		500	10	7/7/75	7/18/75	20	20	14	18
	F	50	100	3/27/75	1/26/76	20	37	21	41
		500	10	7/7/75	7/18/75	20	20	14	18
A/J Mouse	M	50	100	7/7/75	7/18/75	20	37	19	35
		500	10	3/27/75	1/26/76	20	20	3	10
	F	50	100	7/7/75	7/13/75	20	48	5	35
		500	10	3/27/75	1/26/76	20	20	3	10
Fischer Rat	M	Neg	100(c)	-		50	50	21	41
		control	10(c)	-		50	50	14	18
	F	Neg	100(c)	-		50	47	21	41
		control	10(c)	-		50	50	14	18
A/J Mouse	M	Neg	100(c)	-		10	19	19	35
		control	10(c)	-		50	50	3	10
	F	Neg	100(c)	-		50	50	19	35
		control	10(c)	-		50	50	3	10

NOTE (c) control for corresponding dose above

The numbers reported in the above tables and pertinent to this comment are summarized in the following tabulation:

Exposure		# Mice on Study		
ppm	# Days	Male	Female	Total
0	-	89(1) 40(2) 50(3)	101(1) 50(2) 50(3)	190(1) 90(2) 100(3)
50	100	90	90	180
500	10	90	90	180

(1) Table 1 common controls for both exposure groups.
(2) Appendix Table II control for 100 day exposure group.
(3) Appendix Table II control for 10 day exposure group.

The numbers of animals, however, that were evaluated for liver/lung changes, including those sacrificed after the 8th, 16th and 18th month (final) sacrifices and all those animals dying spontaneously which should account for all animals placed on the study are given in Appendix Tables VII and VIII pages 46 and 47, respectively (below).

Table VII Overall Summary Incidence of Non-neoplastic Changes and Histologically-Proven Neoplasms Within The Liver and Lungs of CJ Mice Exposed to Vinyl Chloride (Multiple Inhalation Exposure)

		Incidence of Response			
	Exposure	Control		Vinyl Chloride	
	Dose Level (PPM)	0		500	
	Hours/ Exposure	0 x 1		0 x 1	
	Sex of Animal	M	F	M	F
Tissue/Response	Animals Per Group*	46	48	78	92
Liver	Number Evaluated	45	48	78	92
- hepatic cell necrosis		4	6	6	13
- lymphoid cell infiltrate		1		1	
- hepatic cell fibrosis		2		2	
- neutrophil infiltrate		2			1
- bile duct hyperplasia		1			
- granulomatous foci				1	
- sinusoidal reticulosis				1	
- hepatocyst					1
- amyloidosis				1	
- angiectasis					1
- hepatic cell adenoma		1			
- cholangiocarcinoma				1	
		11	5	13	6
Lung	Number Evaluated	43	47	76	90
- edema					1
- pneumonitis			2		
- bronchio-alveolar hyperplasia		2	1		2
- bronchio-alveolar adenoma		15	16	56	68
- bronchio-alveolar carcinoma		1	3	12	10
		17	22	58	31

* Total includes animals from scheduled sacrifices 8, 16, 20 month controls and spontaneous deaths

Table VIII. Overall Summary Incidence of Non-Neoplastic Changes and Histologically-Proven Neoplasms within The Lungs of All Mice Exposed to Vinyl Chloride.

Multiple Inhalation Exposure

Tissue/Response	Treatment	Incidence of Response			
		Control		Vinyl Chloride	
	Dose Level (PPM)	0		50	
	Hours Exposure	30 x		100 x	
	Sex of Animal	M	F	M	F
	Animals Per Group*	39	47	81	83
Lung	Number Evaluated	39	45	77	81
- Edema		2			
- Congestion		4	1	1	
- Focal Hemorrhage		2		2	
- Inflammation		5	3	4	5
- Bronchio-alveolar Hyperplasia			3		3
- Osseous Metaplasia					1
- Bronchio-alveolar Adenoma		11	18	27	38
- Bronchio-alveolar Carcinoma		2		3	4
- Reticulum Cell Sarcoma					1
		11	18	30	43

* Total includes animals from scheduled sacrifice (8, 16, 20 month periods) and spontaneous deaths.

The pertinent data from the above tables indicating the number of animals evaluated are summarized in the following tabulation:

Exposure		# Mice Evaluated-Liver (Lungs)		
ppm	# Days	Male	Female	Total
0	-	45(43)	48(47)	93(90)
500	10	78(76)	89(90)	167(166)
0	-	N.A.(39)	N.A.(45)	N.A.(84)
50	100	N.A.(77)	N.A.(81)	N.A.(158)

N.A. - not available.

The fact that the numbers of mice evaluated for liver changes in the control and 500 ppm groups are not the same as those evaluated for lung changes within these groups or why data on the liver in the 50 ppm groups are omitted is inexplicable. The numbers of animals not accounted for can be estimated by using the data on the greatest numbers of animals evaluated for liver or lung responses (Appendix Tables VII and VIII).

The following tabulation shows the difference between the numbers of animals that are indicated in the report to have been placed on the study and the number of animals evaluated for liver and/or lung changes e.g., for male controls: Appendix Table II states that 90 A/J mice were placed on the 10 day study, the maximum number evaluated for either liver or lung changes (Appendix Table VII) was 78, 90-78 = 12 male mice not accounted for.

Exposure		# Male (Female) Mice on Study		Maximum # Male (Female) Mice Evaluated		# Male (Female) Mice on Study (Appendix Table II) Minus # Mice Accounted For Appendix Tables VII or VIII)
ppm	# days	Table	Appendix Table II	Appendix Table VII	Appendix Table VIII	
0	-	89(101) [1]	40(50) [2]		39(45) [2]	1(5) [2] Totals 6 [2]
			50(50) [3]	45(48) [3]		5(2) [3] 5 [3]
500	10	"	90/90)	78(90)		12(0) 12
50	100	"	90(90)		77(81)	13(9) 22

[1] Common controls to be used for both exposure groups. Report indicates common controls were divided between exposure groups

[2] # Control mice for 100 day exposure

[3] # Control mice for 10 day exposure

*Only total number of mice given 180

Furthermore, there is an additional discrepancy on Appendix Tables VII and VIII regarding the numbers of animals listed per group and the numbers of animals actually evaluated.

2) *There are discrepancies in the incidence of histologically-proven neoplasms in liver and/or lung tissue of A/J mice as given in Appendix Table X, page 49 (below), with the incidences given in Appendix Tables VII and VIII.*

Table X. Incidence of Histologically-Proven Neoplasms Within Tissues From AJ Mice Exposed to Vinyl Chloride Monomer (Multiple Inhalation Exposure)

Sacrifice Period	Organ Tissue	Scheduled Sacrifice and Spontaneous Deaths											
		50 ppm x 100			Control			500 ppm x 100			Control		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
Scheduled	Lung	1	1	2	2	1	3	5	5	12	0	0	0
8 Months	Liver	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Others	0	0	0	0	0	0	0	0	0	0	0	0
	Totals	1	1	2	0	1	1	5	5	12	0	0	0
16 Months	Lung	4	5	9	2	3	5	9	8	17	1	1	2
	Liver	5	0	5	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	1	1	0	0	0	0	0	0	0	0	0
	Others	2	1	0	0	1	0	5	0	5	0	0	0
	Totals	10	5	15	2	3	5	14	8	22	1	1	2
20 Months	Lung	14	28	44	10	11	21	35	40	55	14	17	31
	Liver	2	3	5	2	0	2	0	0	0	1	2	3
	Kidney	0	1	1	1	0	1	1	0	1	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Others	1	10	11	5	0	5	1	1	2	2	4	6
	Totals	19	44	63	18	11	27	34	41	70	17	21	38
Spontaneous Deaths	Lung	0	0	0	0	0	0	0	1	1	0	0	0
	Liver	0	2	0	0	0	0	0	0	0	0	0	0
0-6 Months	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Others	0	0	0	0	0	0	0	1	1	0	0	0
	Totals	0	0	0	0	0	0	0	1	1	0	0	0
7-12 Month	Lung	2	1	3	0	0	0	1	0	1	0	0	0
	Liver	2	0	2	0	0	0	0	0	0	0	0	0
	Kidney	1	0	1	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Others	3	2	5	0	0	0	1	1	2	0	0	0
	Totals	3	3	11	0	0	0	2	1	3	0	0	0
13-20 Months	Lung	13	10	23	2	3	5	29	23	51	3	1	4
	Liver	2	3	5	0	1	1	2	0	2	0	1	1
	Kidney	4	0	4	0	0	0	0	0	0	2	1	3
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Others	4	7	11	1	1	2	5	5	10	1	1	2
	Total	23	20	43	3	5	8	36	27	63	2	3	5

The extent of the discrepancies are summarized in the following tabulation:

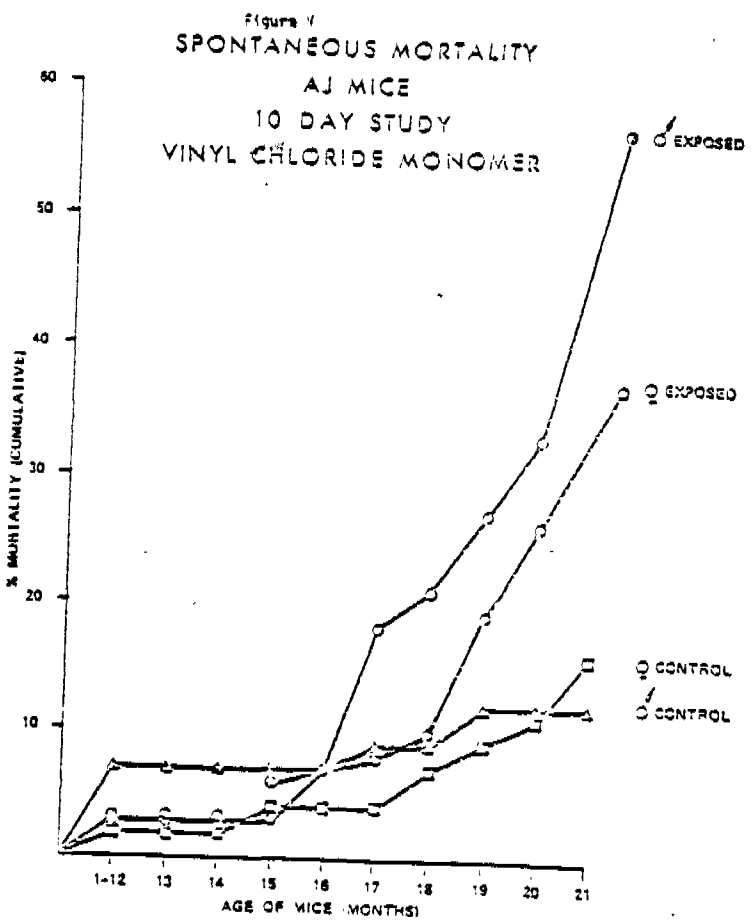
Exposure		Incidence of Liver (Lung) Neoplasms					
		Table X			Tables VII or VIII		
ppm	# Days	Male	Female	Total	Male	Female	Total
0	-	1(15)	1(19)	2(34)	1(15)	0(18)	1(33)
500	10	2(69)	0(78)	2(147)	1(68)	0(78)	1(147)
0	-	2(14)	1(18)	3(32)	N.A.(13)	N.A.(18)	N.A.(31)
50	100	12(36)	6(45)	18(81)	N.A.(30)	N.A.(43)	N.A.(73)

3) The results of the repeated inhalation studies in A/J mice as reported on Table 1 of the report erroneously imply that the following percentage of adenomas were found in the stated numbers of animals on study when in fact the percentage was calculated on fewer animals (page 6). Furthermore, the incidences are not reported for the control animals in Table 1 of the report. The errors/omissions in the reported incidence are summarized below:

Exposure		# Animals on Study (Table 1)	Reported % Adenomas	# Animals Evaluated (Page 6)
ppm	# Days			
0	-	190[1]	34.5	84
500	10	180	44.1	158
0	-	190[1]	34.4	90
50	100	180	74.7	166

[1] Controls used for both studies.

4) *The statement is made on page 5 of the report that there were no remarkable signs of toxicity in the animals repeatedly exposed to vinyl chloride. However, the cumulative spontaneous mortality among mice exposed to 500 ppm for a 10 day period (Appendix Figure V, page 30) is higher in exposed animals after the 17-19th month when compared to control animals.*



An additional error has been made on the time of the termination of the study. Data on the A/J mice for 10 days to 500 ppm or to 100 days to 50 ppm are given up to the 21 or 23 months (Appendix Figures V and VII). However, the final sacrifice is reported to have occurred at the 20th month (see page 3)!

Jessie M. Norris

Jessie M. Norris
Associate Scientist
Chemicals and Plastics Regulations
Health and Environmental Sciences

jan