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## The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals

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Groups of laboratory animals were exposed repeatedly for up to six months to either 500, 200, 100 or 50 ppm vinyl chloride in air. Detectable changes occurred at all but the lowest concentration. The results are discussed and handling precautions suggested.

### Introduction

VINYL chloride ( $\text{CH}_2=\text{CHCl}$ ) is a chemical of great industrial importance. It is used in the preparation of polyvinyl chloride resin, as a copolymer in saran and other plastics, as a chemical intermediate and as a solvent. Because of the flammability of vinyl chloride, it has been generally assumed that the greatest hazard associated with vinyl chloride is that due to its flammability rather than its toxicity.<sup>1</sup>

The toxicity of vinyl chloride has been reviewed by von Oettingen<sup>2</sup> and more recently by Mastromatteo *et al.*<sup>3</sup> von Oettingen concluded that the gas was anesthetic in high concentrations and that considerable interest had been shown in the use of vinyl chloride as a surgical anesthetic. However, its effect on the circulatory system has discouraged exploitation of this property. No doubt the hazard from flammability has also hindered this use. Only limited repeated exposures which were reported by Schaumann<sup>4</sup> were discussed by von Oettingen. These repeated exposures indicated little or no chronic effects even from anesthetic concentrations.

Mastromatteo *et al.*<sup>3</sup> also discussed the published data and reported the results of single exposures of mice, rats and guinea pigs which confirmed the low acute toxicity of vinyl chloride. Mastromatteo reported that only two human fatalities due to vinyl chloride had been reported.

It can be concluded from the published toxicological data that anesthesia is the only significant effect of acute exposure. Sufficient repeated exposures have not been reported to draw conclusions about chronic toxicity. The Threshold Limit Value of 500 ppm suggested by the American Conference of Governmental Industrial Hygienists (ACGIH)<sup>5</sup> is reported by Smyth<sup>6</sup> to be based on single animal exposures and human experience.

The following report summarizes the results of repeated exposures of laboratory animals to either 500, 200, 100 or 50 ppm of vinyl chloride. The significance of the results is discussed and recommendations for a threshold limit value are made.

### Experimental Procedures

#### Materials Tested

Vinyl chloride,  $\text{CH}_2=\text{CHCl}$ , is a colorless gas. It has a boiling point of  $-13.35^\circ\text{C}$  ( $+7.93^\circ\text{F}$ ) and a freezing point of  $-154^\circ\text{C}$  ( $-244.82^\circ\text{F}$ ). The material polymerizes readily and hence is sometimes inhibited with phenol or tertiary butylcatechol. Vinyl chloride is very flammable, its flashpoint being  $-78^\circ\text{C}$  ( $-108^\circ\text{F}$ ). The explosive limits are from 4% to 22% by volume. It has little odor although high concentrations may smell faintly sweet.

A single, uninhibited sample was used in these studies. It was shown by mass spectrographic analysis to be essentially pure  $\text{CH}_2=\text{CHCl}$ , air being the only impurity detected in gas phase samples.

#### Source and Feeding of Animals

The rats and rabbits used in this study were obtained from the stock colony of this laboratory, the guinea pigs were obtained from a commercial grower<sup>7</sup> and the dogs were purebred beagles obtained from a local kennel. The rats and dogs were fed Purina Laboratory Chow<sup>8</sup> or Famo Laboratory Ration.<sup>9</sup> The rabbits and guinea pigs received Famo Rabbit Breeder Ration. The guinea pig diet was supplemented with carrots.

#### Experimental Protocol

The experiments were conducted in three phases. In the first phase, groups of 10 male

and 10 female rats were exposed seven hours per day five days per week to 500 ppm for 4.5 months. Exposures were given in a 160-liter chamber previously described.<sup>10</sup> Mortality and growth records were kept. Final organ weights were obtained and tissues were saved for microscopic examination. Five male and five female rats served as unexposed controls.

The second phase consisted of repeated 7-hour daily exposures of 20-24 male and 24 female rats, ten male and eight female guinea pigs, three male and three female rabbits and one male and one female dog to either 200 ppm or 100 ppm of vinyl chloride. These animals and two groups of controls were carefully selected and matched on the basis of age, condition and weight. The first group of controls received no exposure and served as unexposed controls. The second group received repeated daily 7-hour exposures to room air in a chamber similar to the one used for exposures to the chemical. This group is referred to as the air-exposed control group. In addition to the animals receiving 7-hour daily exposures, eight separate groups of five male rats each were exposed to either 200 or 100 ppm for 4, 2, 1 or 0.5 hours per day.

The procedures and equipment used were basically the same as reported previously.<sup>11</sup> Growth and mortality records were kept on all groups. The livers of the dogs were biopsied prior to exposure and after 3½ months of exposure, hence the liver of each dog served as its own control. Pre-exposure and terminal hematological determinations were made on all dogs and terminal determinations on representative groups of rats. Urine samples were collected from the dogs and representative groups of rats. At the termination of the experiment, part of the rats were starved overnight and then these and all the guinea pigs and rabbits were killed by decapitation on the day after their last exposure. The dogs were killed by exsanguination after anesthesia with thiopental, sodium (Pentothal, Abbott). Samples of blood were taken of representative groups of animals for determination of alkaline phosphatase, serum-urea-nitrogen (SUN), serum-glutamic-pyruvic-transaminase (SGPT), and serum-glutamic-oxalacetic-transaminase (SGOT). The organs were weighed and tissues fixed for histopathological examination. The rats which were not killed the day after exposures were stopped were pastured for eight weeks and then sacrificed in the previously described manner.

The third phase of this experiment consisted of repeated daily 7-hour exposures of 24 male and 24 female rats, 12 male and 12 female guinea pigs, 3 male and 3 female rabbits and one male

and one female dog to 50 ppm vinyl chloride. Equal matched groups served as unexposed and air-exposed controls. Three additional groups of 10 male rats each were exposed for 4, 2 or 1 hour per day to 50 ppm.

The procedures followed were essentially the same as used for exposures to 200 and 100 ppm except that hematological examinations were made on the dogs after three months and liver biopsies were made only prior to exposure. Urine was collected from the rabbits as well as the rats and dogs. The rats which were not sacrificed at the end of the exposures were pastured for six weeks and then sacrificed.

#### *Equipment Used*

The exposure equipment used has been described previously.<sup>11</sup> However, in order to gain additional data about the results of repeated short daily exposures, it was necessary to devise a method of introducing additional groups of rats. This was done without opening the doors of the chamber by dropping the rats through chutes made of 3.25-inch stainless steel tubing. These chutes were closed with a rubber stopper except during the brief time it took to insert the rats. The chutes, which were sloped at a 45° angle, ended in covered, screened cages inside the chamber. The additional groups were started 3, 5, 6 and 6.5 hours after the 7-hour exposures started. Since all animals were removed after the 7-hour exposure was completed, this routine resulted in exposures lasting 4, 2, 1 or 0.5 hours.

The vinyl chloride was metered from a saran plastic bag which served as a reservoir for the gas. Metering of the gas was done by Dual Syringe Pumps.<sup>12</sup> Total air flow through the chambers was measured by means of calibrated flow meters.

#### *Analysis of the Chamber Atmospheres*

Analyses of the air were made by direct combustion of a known volume of air in a heated quartz tube. The resulting chloride was trapped in 1% sodium formate—1% sodium carbonate solution and subsequently titrated by a micro-Volhard technique. The results of the individual analyses were within 15% of the theoretical concentrations during the exposures to 200, 100 and 50 ppm. The average concentrations recovered were 197, 100.5 and 48.7 ppm respectively.

#### *Results of Repeated Exposures*

##### *Exposure to 500 ppm Vinyl Chloride*

The rats exposed repeatedly at 500 ppm for 4.5 months, grew normally and no changes were

TABLE I  
Summary of Terminal Average Body and Organ Weights of Male Rats Receiving Repeated Exposures to Vinyl Chloride 5 Days per Week

| Concentration in ppm      | Months on Exposure | Duration of Daily Exposure, hours | Ratio of Survival | Final Average Body Weight, g | Organ Weights, g/100 g Body Weight |       |                   |        |        |        |
|---------------------------|--------------------|-----------------------------------|-------------------|------------------------------|------------------------------------|-------|-------------------|--------|--------|--------|
|                           |                    |                                   |                   |                              | Lung                               | Heart | Liver             | Kidney | Spleen | Testes |
| Unexposed control.....    | 0                  | 0                                 | 4/5               | 304                          | 0.54                               | 0.33  | 2.52              | 0.71   | 0.15   | 0.89   |
| 200                       | 4.5                | 7                                 | 7/10              | 312                          | 0.56                               | 0.33  | 3.00 <sup>a</sup> | 0.73   | 0.17   | 0.95   |
| Unexposed control.....    | 0                  | 0                                 | 11/12             | 343                          | 0.53                               | 0.32  | 2.46              | 0.69   | 0.14   | 0.80   |
| Air exposed control.....  | 6                  | 7                                 | 10/12             | 366                          | 0.52                               | 0.32  | 2.53              | 0.70   | 0.15   | 0.78   |
| 200                       | 6                  | 7                                 | 9/12              | 341                          | 0.52                               | 0.32  | 2.85 <sup>b</sup> | 0.68   | 0.17   | 0.94   |
| 200                       | 6                  | 4                                 | 4/5               | 349                          | 0.47                               | 0.29  | 2.86 <sup>c</sup> | 0.64   | 0.16   | 0.85   |
| 200                       | 6                  | 2                                 | 4/5               | 341                          | 0.56                               | 0.30  | 2.82 <sup>d</sup> | 0.64   | 0.16   | 0.89   |
| 200                       | 6                  | 1                                 | 3/5               | 350                          | 0.48                               | 0.28  | 2.46              | 0.61   | 0.13   | 0.78   |
| 200                       | 6                  | 0.5                               | 4/5               | 339                          | 0.51                               | 0.29  | 2.38              | 0.67   | 0.14   | 0.95   |
| 100                       | 6                  | 7                                 | 7/12              | 363                          | 0.51                               | 0.29  | 2.61 <sup>e</sup> | 0.63   | 0.15   | 0.85   |
| 100                       | 6                  | 4                                 | 3/5               | 380                          | 0.51                               | 0.28  | 2.63              | 0.65   | 0.15   | 0.74   |
| 100                       | 6                  | 2                                 | 4/5               | 331                          | 0.53                               | 0.31  | 2.64              | 0.67   | 0.16   | 0.93   |
| 100                       | 6                  | 1                                 | 3/5               | 357                          | 0.49                               | 0.28  | 2.52              | 0.64   | 0.15   | 0.78   |
| 100                       | 6                  | 0.5                               | 5/5               | 363                          | 0.46                               | 0.30  | 2.42              | 0.64   | 0.16   | 0.78   |
| Unexposed* control.....   | 0                  | 0                                 | 10/12             | 354                          | 0.49                               | 0.31  | 2.43              | 0.64   | 0.14   | 0.84   |
| Air exposed* control..... | 6                  | 7                                 | 8/12              | 393                          | 0.59                               | 0.30  | 2.41              | 0.63   | 0.15   | 0.78   |
| 200*                      | 6                  | 7                                 | 8/8               | 388                          | 0.47                               | 0.29  | 2.59 <sup>f</sup> | 0.64   | 0.15   | 0.71   |
| 100*                      | 6                  | 7                                 | 6/7               | 376                          | 0.47                               | 0.31  | 2.53 <sup>g</sup> | 0.66   | 0.14   | 0.78   |

\* Pastured for 8 weeks after exposures ceased.

(a)  $P = 0.001$

(b)  $P = <0.001$

(c)  $P = 0.07$

(d)  $P = 0.1$

(e)  $P = 0.02$

(f)  $P = 0.12$

apparent grossly at autopsy. Microscopically their livers showed increased central lobular granular degeneration and the kidneys showed interstitial and tubular changes. The average weight increase of the livers of the male rats was statistically significant ( $P = 0.001$ ), Table I. The average weight of the livers of the female rats was above that of the controls but not statistically significant, Table II. SUN, SGPT, S-GOT, and alkaline phosphatase determinations were within normal limits (Table III).

#### Exposure to 200 ppm Vinyl Chloride

All groups exposed seven hours per day 138-144 times in 204 days were normal in appearance, mortality and growth. Hematological, SUN, S-GOT, SGPT and alkaline phosphatase values (Table III) and the results of the urinalysis were within normal limits. Gross pathology was normal in all species. Micropathology was normal in the rats, guinea pigs and dogs, however, adverse effects were noted in the livers of

rabbits of both sexes. In the male rabbits this was characterized by central lobular granular degeneration and necrosis with some foamy vacuolation. In the female rabbits the changes noted were central lobular granular degeneration and necrosis with periportal cellular infiltration. All organ weights were normal except for the livers of the male and female rats which were increased significantly after repeated daily 7-hour exposures (Tables I, II, IV, V, VI, and VII). In the males this increase was still apparent eight weeks after exposure ceased, although the liver weights appeared to be decreasing and returning to normal.

The male rats exposed to 200 ppm of vinyl chloride for either four or two hours per day for six months had elevated average liver weights (Table I). However, the small size of the experimental groups made the finding statistically insignificant ( $P = 0.07$  and  $0.1$ ). The groups exposed for either 1 or 0.5 hours per day were entirely normal.

TABLE II  
Summary of Average Body and Organ Weights of  
Female Rats Receiving Repeated 7-Hour Ex-  
posures to Vinyl Chloride 5 Days per Week

| Concentration<br>in ppm  | Months on<br>Exposure | Ratio of<br>Survival | Final Average<br>Body Weight,<br>g | Organ Weights,<br>g/100 g Body<br>Weight |       |                   |                   |        |
|--------------------------|-----------------------|----------------------|------------------------------------|------------------------------------------|-------|-------------------|-------------------|--------|
|                          |                       |                      |                                    | Lung                                     | Heart | Liver             | Kidney            | Spleen |
| Unexposed con-<br>trol   | 0                     | 5/8                  | 194                                | 0.82                                     | 0.41  | 3.06              | 0.80              | 0.19   |
| 500                      | 4.5                   | 9/10                 | 195                                | 0.68                                     | 0.38  | 3.22 <sup>a</sup> | 0.81              | 0.20   |
| Unexposed con-<br>trol   | 0                     | 10/12                | 202                                | 0.65                                     | 0.38  | 2.92              | 0.82              | 0.17   |
| Air exposed<br>control   | 6                     | 9/12                 | 223                                | 0.66                                     | 0.39  | 2.99              | 0.81              | 0.18   |
| 200                      | 6                     | 10/12                | 208                                | 0.63                                     | 0.38  | 3.39 <sup>b</sup> | 0.84              | 0.18   |
| 100                      | 6                     | 11/12                | 221                                | 0.69                                     | 0.39  | 3.35 <sup>a</sup> | 0.79              | 0.20   |
| Unexposed*<br>control    | 0                     | 8/12                 | 225                                | 0.61                                     | 0.37  | 2.67              | 0.82              | 0.18   |
| Air exposed*<br>control  | 6                     | 9/12                 | 240                                | 0.58                                     | 0.37  | 2.97              | 0.83              | 0.18   |
| 200*                     | 6                     | 12/12                | 233                                | 0.61                                     | 0.38  | 3.06              | 0.81              | 0.20   |
| 100*                     | 6                     | 12/12                | 235                                | 0.63                                     | 0.40  | 3.17              | 0.83              | 0.21   |
| Unexposed con-<br>trol   | 0                     | 11/12                | 211                                | 0.56                                     | 0.39  | 3.02              | 0.83              | 0.20   |
| Air exposed<br>control   | 6                     | 12/12                | 202                                | 0.59                                     | 0.38  | 2.93              | 0.84              | 0.20   |
| 50                       | 6                     | 9/12                 | 206                                | 0.61                                     | 0.37  | 3.02              | 0.84              | 0.20   |
| Unexposed**<br>control   | 0                     | 11/12                | 195                                | 0.66                                     | 0.40  | 2.68              | 0.91              | 0.22   |
| Air exposed<br>control** | 6                     | 9/12                 | 221                                | 0.63                                     | 0.40  | 3.01              | 0.87              | 0.19   |
| 50**                     | 6                     | 11/12                | 233                                | 0.63                                     | 0.38  | 2.63              | 0.82 <sup>c</sup> | 0.20   |

\* Fastured for 8 weeks after exposures ceased.

\*\* Fastured for 6 weeks after exposures ceased.

(a)  $P = 0.17$

(b)  $P = 0.03$

(c)  $P = 0.01$

(d)  $P = 0.06$

#### Exposure to 100 ppm Vinyl Chloride

All species exposed to 100 ppm of vinyl chloride, seven hours per day, 138-144 times in 204 days, were judged normal on the basis of the following criteria: appearance, mortality, growth, hematological examination, SUN, SGOT, S-GPT, alkaline phosphatase determination, urinalysis and gross and microscopic examination of tissue. However, slight increases were found in

the average weights of the livers of male and female rats (Tables I and II). Although not significant statistically, an increase was also seen in the average weight of the livers of the male rats exposed to 100 ppm for either four or two hours per day. The groups exposed for either 1.0 or 0.5 hour per day were entirely normal.

#### Exposures to 50 ppm Vinyl Chloride

The increase in weight of the rat livers, the only significant finding in animals exposed to 100 ppm, did not occur in rats exposed repeatedly to 50 ppm of vinyl chloride, 130 times in 189 days. All groups of animals were judged normal in all other respects. See Tables II, V, VI, VII, VIII and IX. A statistically significant decrease in kidney weight which was seen in the female rats (Table II) was considered to be an artifact since it was not seen at higher concentrations.

#### Discussion

Repeated exposure to vinyl chloride at concentrations considerably below the level that has been considered safe for human exposure has been shown to have an effect on the liver and kidney of laboratory animals. Histopathological changes and increased liver weights in male and female rats were noted after repeated exposure at 500 ppm. Repeated exposure at 200 ppm for six months resulted in an increase in the average weight of the livers of male and female rats and micropathological changes in the livers of the male and female rabbits. The only effect noted after repeated daily 7-hour exposures to 100 ppm for six months was a slight increase in the average weight of the rat livers. Repeated 7-hour exposures to 50 ppm for six months had no effect on any species studied. Hence, the highest concentration without detectable effect on any species was 50 ppm.

It is interesting to speculate on the apparent discrepancy between the effects observed at 100 ppm in this experiment and the lack of reported injury in humans using a threshold limit of 500 ppm. Several factors may be contributory. First, the effects noted in animals at 500 ppm were only slight to moderate; growth, mortality, and general appearance were unaffected. Hence, it is possible that if humans were exposed repeatedly at 500 ppm slight injury might occur but due to the lack of subjective symptoms the injury would escape detection. Secondly, the injury was apparently reversible. The liver weights of both male and female rats which had shown definite increases after exposures at 200 and 100 ppm were normal or approaching normal after 6-8 weeks of recovery (Tables I, II and VIII).

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TABLE III  
Summary of Average Biochemical Values Determined for Animals Receiving Repeated Exposures to Vinyl Chloride 5 Days per Week

| Species and Dog No. | Sex | Concentration in ppm | Months on Exposure | Duration of Daily Exposure, hours | Number of Animals | Alkaline Phosphatase King-Armstrong Units | Blood Urea Nitrogen, mg/100 ml | SGPT SGOT          |    |
|---------------------|-----|----------------------|--------------------|-----------------------------------|-------------------|-------------------------------------------|--------------------------------|--------------------|----|
|                     |     |                      |                    |                                   |                   |                                           |                                | Sigma-Frankel Unit |    |
| Dog #101.....       | M   | Unexposed control    | 0                  | 0                                 | 1                 | 12.2                                      | 24                             | 18                 | 43 |
| #113.....           |     | Air exposed control  | 6                  | 7                                 | 1                 | 4.1                                       | 19                             | 19                 | 17 |
| #41.....            |     | 200                  | 6                  | 7                                 | 1                 | 8.6                                       | 11                             | 18                 | 48 |
| #98.....            |     | 100                  | 6                  | 7                                 | 1                 | 4.3                                       | 16                             | 21                 | 19 |
| Dog #106.....       | F   | Unexposed control    | 0                  | 0                                 | 1                 | 5.1                                       | 11                             | 10                 | 26 |
| #107.....           |     | Air exposed control  | 6                  | 7                                 | 1                 | 7.1                                       | 20                             | 14                 | 17 |
| #103.....           |     | 200                  | 6                  | 7                                 | 1                 | 7.9                                       | 14                             | 16                 | 26 |
| #110.....           |     | 100                  | 6                  | 7                                 | 1                 | 5.6                                       | 10                             | 10                 | 14 |
| Rat.....            | M   | Unexposed control    | 0                  | 0                                 | 5                 | 32.9*                                     | 20.6*                          | 30                 |    |
|                     |     | 500                  | 4.5                | 7                                 | 4                 | 18.9                                      | 13.8                           | 35                 |    |
|                     |     | 200                  | 6                  | 7                                 | 5                 | 17.7                                      | 16.2                           | 36                 |    |
|                     |     | 200                  | 6                  | 4                                 | 4                 | 18.4                                      | 16.2                           | 32                 |    |
|                     |     | 200                  | 6                  | 1                                 | 3                 | 20.2                                      | 17.7                           | 42                 |    |
|                     |     | 100                  | 6                  | 7                                 | 4                 | 19.4                                      | 15.0                           | 27                 |    |
|                     |     | 100                  | 6                  | 4                                 | 3                 | 14.7                                      | 16.3                           | 36                 |    |
|                     |     | 100                  | 6                  | 1                                 | 3                 | 19.0                                      | 15.3                           | 30                 |    |
| Rat.....            | F   | Unexposed control    | 0                  | 0                                 | 4                 | 12.1                                      | 20.5                           | 38                 |    |
|                     |     | 500                  | 6                  | 7                                 | 3                 | 16.1                                      | 22.3                           | 26                 |    |
|                     |     | 200                  | 6                  | 7                                 | 5                 | 13.6                                      | 22.2                           | 21                 |    |
|                     |     | 100                  | 6                  | 7                                 | 6                 | 9.8                                       | 22.8                           | 23                 |    |
| Rabbit.....         | M   | Control              | 6                  | 0                                 | 5                 | 4.0                                       | 26                             | 36                 |    |
|                     |     | 200                  | 6                  | 7                                 | 3                 | 5.3                                       | 21                             | 23                 |    |
|                     |     | 100                  | 6                  | 7                                 | 2                 | 5.9                                       | 26                             | 26                 |    |
| Rabbit.....         | F   | Control              | 6                  | 0                                 | 6                 | 4.9                                       | 33                             | 38                 |    |
|                     |     | 200                  | 6                  | 7                                 | 2                 | 5.6                                       | 27                             | 36                 |    |
|                     |     | 100                  | 6                  | 7                                 | 3                 | 4.0                                       | 26                             | 35                 |    |

\* Because of two unusually high individual values in this group these average values are elevated and do not correspond with the values obtained on similar control groups in our laboratory. Normal control values are in the same ranges as those of the experimental groups listed in this table.

TABLE IV  
Summary of Average Hematological Values for Animals Receiving Repeated 7-Hour Exposures to Vinyl Chloride

| Species or Dog # | Sex | Concentration in ppm | Months on Experiment | No. of Animals | Hemoglobin g/100 g | Hematocrit | WBC $\times 10^6$ | Neutrophils | Lymphocytes | Monocytes | Eosinophils |
|------------------|-----|----------------------|----------------------|----------------|--------------------|------------|-------------------|-------------|-------------|-----------|-------------|
| Rat.....         | M   | Air exposed control  | 6                    | 4              | 14.5               | 51         | 15.8              | 26.5        | 71.2        | 1.5       | 0.8         |
| Rat.....         | M   | 200                  | 6                    | 5              | 14.4               | 50         | 16.7              | 18          | 77.8        | 0.2       | 3           |
| Rat.....         | F   | Air exposed control  | 6                    | 4              | 14.0               | 49.8       | 13.8              | 22.8        | 74.5        | 0.2       | 2.8         |
| Rat.....         | F   | 200                  | 6                    | 5              | 13.6               | 47.4       | 12.6              | 24.6        | 70.2        | 1.0       | 4           |
| Dog #101.....    | M   | Unexposed control    | 0                    | 1              | —                  | —          | —                 | —           | —           | —         | —           |
| Dog #101.....    | M   | Unexposed control    | 6                    | 1              | 15                 | 53         | 14.2              | 46          | 51          | 0         | 3           |
| Dog #113.....    | M   | Air exposed control  | 0                    | 1              | 14.5               | 50         | 13.5              | 61          | 23          | 5         | 11          |
| Dog #113.....    | M   | Air exposed control  | 6                    | 1              | 14.5               | 52         | 13.2              | 58          | 34          | 4         | 4           |
| Dog #111.....    | M   | 200                  | 0                    | 1              | 13                 | 47         | 16.2              | 56          | 38          | 3         | 13          |
| Dog #111.....    | M   | 200                  | 6                    | 1              | 16.5               | 58         | 15.8              | 56          | 41          | 2         | 1           |
| Dog #98.....     | M   | 100                  | 0                    | 1              | 15.5               | 52         | 19.8              | 46          | 46          | 4         | 4           |
| Dog #98.....     | M   | 100                  | 6                    | 1              | 16                 | 54         | 18.6              | 61          | 39          | 0         | 0           |
| Dog #106.....    | F   | Unexposed control    | 0                    | 1              | 14.5               | 51         | 21.8              | 42          | 37          | 3         | 18          |
| Dog #106.....    | F   | Unexposed control    | 6                    | 1              | 15.5               | 54         | 19.5              | 54          | 41          | 1         | 4           |
| Dog #107.....    | F   | Air exposed control  | 0                    | 1              | 15                 | 53         | 14.4              | 55          | 33          | 4         | 8           |
| Dog #107.....    | F   | Air exposed control  | 6                    | 1              | 16                 | 57         | 11.7              | 66          | 33          | 4         | 7           |
| Dog #103.....    | F   | 200                  | 0                    | 1              | 14                 | 50         | 17.5              | 44          | 48          | 3         | 5           |
| Dog #103.....    | F   | 200                  | 6                    | 1              | 16                 | 54         | 17.3              | 48          | 51          | 0         | 3           |
| Dog #110.....    | F   | 100                  | 0                    | 1              | 12.5               | 44         | 16.3              | 61          | 37          | 2         | 0           |
| Dog #110.....    | F   | 100                  | 6                    | 1              | 15.5               | 54         | 14.4              | 49          | 50          | 1         | 0           |

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TABLE V  
Summary of Terminal Average Body and Organ Weights of Guinea Pigs Receiving Repeated Daily 7-Hour Exposures to Vinyl Chloride 5 Days per Week for 6 Months

| Sex | Concentration in ppm | Ratio of Survival | Final Average Body Weight, g | Organ Weights, g/100 g Body Weight |       |                   |        |        |        |
|-----|----------------------|-------------------|------------------------------|------------------------------------|-------|-------------------|--------|--------|--------|
|     |                      |                   |                              | Lung                               | Heart | Liver             | Kidney | Spleen | Testes |
| M   | Unexposed control    | 8/10              | 927                          | 0.64                               | 0.28  | 3.32              | 0.70   | 0.18   | 0.48   |
| M   | Air exposed control  | 5/10              | 1030                         | 0.52                               | 0.28  | 3.36              | 0.61   | 0.10   | 0.48   |
| M   | 200                  | 7/10              | 1044                         | 0.53                               | 0.27  | 3.01              | 0.60   | 0.09   | 0.44   |
| M   | 100                  | 7/10              | 1089                         | 0.52                               | 0.25  | 2.79 <sup>a</sup> | 0.58   | 0.11   | 0.47   |
| M   | Unexposed control    | 8/12              | 918                          | 0.60                               | 0.29  | 3.24              | 0.68   | 0.12   | 0.52   |
| M   | Air exposed control  | 11/12             | 938                          | 0.61                               | 0.27  | 3.31              | 0.64   | 0.12   | 0.50   |
| M   | 50                   | 10/12             | 1001                         | 0.63                               | 0.28  | 3.14              | 0.81   | 0.12   | 0.48   |
| F   | Unexposed control    | 6/8               | 899                          | 0.62                               | 0.27  | 3.20              | 0.63   | 0.12   |        |
| F   | Air exposed control  | 7/8               | 867                          | 0.66                               | 0.25  | 3.28              | 0.67   | 0.11   |        |
| F   | 200                  | 7/8               | 897                          | 0.74 <sup>b</sup>                  | 0.27  | 3.60 <sup>a</sup> | 0.64   | 0.13   |        |
| F   | 100                  | 7/8               | 949                          | 0.58                               | 0.26  | 3.50              | 0.64   | 0.12   |        |
| F   | Unexposed control    | 9/12              | 728                          | 0.78                               | 0.34  | 3.41              | 0.69   | 0.15   |        |
| F   | Air exposed control  | 8/12              | 884                          | 0.68                               | 0.28  | 3.84              | 0.66   | 0.14   |        |
| F   | 50                   | 11/12             | 908                          | 0.69                               | 0.28  | 3.44              | 0.64   | 0.14   |        |

(a)  $P = 0.05$ (b)  $P = 0.24$ (c)  $P = 0.23$ 

TABLE VI  
Summary of Terminal Average Body and Organ Weights of Rabbits Receiving Repeated Daily 7-Hour Exposures to Vinyl Chloride 5 Days per Week for 6 Months

| Sex | Concentration in ppm | Ratio of Survival | Final Average Body Weight, g | Organ Weights, g/100 g Body Weight |       |       |        |        |        |
|-----|----------------------|-------------------|------------------------------|------------------------------------|-------|-------|--------|--------|--------|
|     |                      |                   |                              | Lung                               | Heart | Liver | Kidney | Spleen | Testes |
| M   | Unexposed control    | 3/3               | 3.61                         | 0.39                               | 0.31  | 3.27  | 0.43   | 0.08   | 0.16   |
| M   | Air exposed control  | 3/3               | 3.80                         | 0.31                               | 0.18  | 2.41  | 0.46   | 0.02   | 0.16   |
| M   | 200                  | 3/3               | 3.48                         | 0.32                               | 0.19  | 2.34  | 0.54   | 0.02   | 0.16   |
| M   | 100                  | 3/3               | 3.58                         | 0.33                               | 0.18  | 2.84  | 0.49   | 0.02   | 0.15   |
| M   | Unexposed control    | 3/3               | 3.80                         | 0.32                               | 0.17  | 2.33  | 0.45   | 0.02   | 0.15   |
| M   | Air exposed control  | 1/3               | 3.87                         | 0.37                               | 0.18  | 3.18  | 0.53   | 0.03   | 0.14   |
| M   | 50                   | 3/3               | 3.70                         | 0.36                               | 0.20  | 2.68  | 0.47   | 0.03   | 0.17   |
| F   | Unexposed control    | 3/3               | 4.13                         | 0.31                               | 0.17  | 2.22  | 0.40   | 0.03   |        |
| F   | Air exposed control  | 3/3               | 3.91                         | 0.30                               | 0.18  | 2.18  | 0.41   | 0.04   |        |
| F   | 200                  | 2/3               | 4.10                         | 0.33                               | 0.18  | 2.36  | 0.42   | 0.06   |        |
| F   | 100                  | 3/3               | 4.12                         | 0.29                               | 0.18  | 1.87  | 0.38   | 0.06   |        |
| F   | Unexposed control    | 3/3               | 4.31                         | 0.30                               | 0.17  | 1.94  | 0.46   | 0.04   |        |
| F   | Air exposed control  | 2/3               | 3.96                         | 0.30                               | 0.17  | 1.88  | 0.39   | 0.04   |        |
| F   | 50                   | 3/3               | 4.31                         | 0.32                               | 0.17  | 2.49  | 0.38   | 0.04   |        |

TABLE VII  
Summary of Final Body and Organ Weights of Dogs Receiving Repeated Daily 7-Hour Exposures to Vinyl Chloride 5 Days per Week for 6 Months

| Sex | Dog No. | Concentration in ppm | Ratio of Survival | Final Body Weight, kg | Organ Weights, g/100 g Body Weight |       |       |        |        |        |
|-----|---------|----------------------|-------------------|-----------------------|------------------------------------|-------|-------|--------|--------|--------|
|     |         |                      |                   |                       | Lung                               | Heart | Liver | Kidney | Spleen | Testes |
| M   | 101     | Unexposed control    | 1/1               | 13.0                  | 0.66                               | 0.62  | 2.48  | 0.38   | 0.32   | 0.15   |
| M   | 113     | Air exposed control  | 1/1               | 8.5                   | 0.68                               | 0.77  | 2.63  | 0.47   | 0.19   | 0.14   |
| M   | 111     | 200                  | 1/1               | 10.2                  | 1.03                               | 0.96  | 2.50  | 0.52   | 0.25   | 0.13   |
| M   | 98      | 100                  | 1/1               | 12.0                  | 0.86                               | 0.80  | 2.50  | 0.42   | 0.26   | 0.15   |
| M   | 152     | Unexposed control    | 1/1               | 13                    | 0.80                               | 0.75  | 2.69  | 0.53   | 0.23   | 0.11   |
| M   | 156     | Air exposed control  | 1/1               | 10.6                  | 0.77                               | 0.87  | 2.05  | 0.45   | 0.36   | 0.14   |
| M   | 163     | 50                   | 1/1               | 9.6                   | 0.89                               | 0.78  | 2.40  | 0.45   | 0.23   | 0.12   |
| F   | 106     | Unexposed control    | 1/1               | 9.6                   | 0.71                               | 0.68  | 2.67  | 0.43   | 0.21   |        |
| F   | 107     | Air exposed control  | 1/1               | 8.7                   | 0.77                               | 0.80  | 3.15  | 0.43   | 0.33   |        |
| F   | 103     | 200                  | 1/1               | 10.5                  | 0.78                               | 0.71  | 1.88  | 0.45   | 0.28   |        |
| F   | 110     | 100                  | 1/1               | 11.9                  | 0.99                               | 0.78  | 2.14  | 0.43   | 0.31   |        |
| F   | 161     | Unexposed control    | 1/1               | 8.6                   | 0.99                               | 0.83  | 4.10  | 0.45   | 0.43   |        |
| F   | 156     | Air exposed control  | 1/1               | 11.3                  | 0.70                               | 0.84  | 3.31  | 0.40   | 0.25   |        |
| F   | 161     | 50                   | 1/1               | 7.4                   | 0.87                               | 0.78  | 2.48  | 0.47   | 0.33   |        |

TABLE VIII

Summary of Terminal Average Body and Organ Weights of Male Rats Receiving Repeated Exposures to Vinyl Chloride 5 Days per Week

| Concentration in ppm | Months on Exposure | Duration of Daily Exposure, hours | Ratio of Survival | Final Average Body Weight, g | Organ Weights, g/100 g Body Weight |       |       |        |        |        |
|----------------------|--------------------|-----------------------------------|-------------------|------------------------------|------------------------------------|-------|-------|--------|--------|--------|
|                      |                    |                                   |                   |                              | Lung                               | Heart | Liver | Kidney | Spleen | Testes |
| Unexposed control    | 0                  | 0                                 | 8/8               | 319                          | 0.80                               | 0.33  | 2.67  | 0.75   | 0.16   | 0.98   |
| Air exposed control  | 6                  | 7                                 | 12/12             | 347                          | 0.51                               | 0.22  | 2.41  | 0.70   | 0.16   | 0.81   |
| 50                   | 6                  | 7                                 | 12/12             | 339                          | 0.50                               | 0.31  | 2.49  | 0.68   | 0.17   | 0.87   |
| 50                   | 6                  | 4                                 | 8/10              | 348                          | 0.51                               | 0.33  | 2.56  | 0.69   | 0.16   | 0.81   |
| 50                   | 6                  | 2                                 | 6/10              | 323                          | 0.49                               | 0.22  | 2.57  | 0.70   | 0.16   | 0.80   |
| 50                   | 6                  | 1                                 | 9/10              | 348                          | 0.47                               | 0.32  | 2.51  | 0.73   | 0.17   | 0.84   |
| Unexposed* control   | 0                  | 0                                 | 8/8               | 326                          | 0.53                               | 0.22  | 2.37  | 0.72   | 0.16   | 0.83   |
| Air exposed*         | 6                  | 7                                 | 12/12             | 370                          | 0.53                               | 0.30  | 2.43  | 0.64   | 0.14   | 0.75   |
| 50*                  | 6                  | 7                                 | 12/12             | 360                          | 0.49                               | 0.33  | 2.51  | 0.68   | 0.15   | 0.82   |

\* Fastened for 6 weeks after exposures ceased.

Thirdly, it is doubtful whether it would be possible for humans to be exposed continuously at 500 ppm in production plants since this high a general concentration would indicate severe leaks in the equipment and extremely high concentrations

TABLE LX  
Summary of Average Hematological Values for Dogs Receiving Repeated 7-Hour  
Exposures to Vinyl Chloride

| Dog #         | Sex | Concentration in ppm | Months on Experiment | No. of Animals | Hemo-globin g/100 g | Hema-tocrit | WBX $\times 10^3$ | Neutro-phils | Lym-phocytes | Mono-cytes | Eosino-phils |
|---------------|-----|----------------------|----------------------|----------------|---------------------|-------------|-------------------|--------------|--------------|------------|--------------|
| Dog #152..... | M   | Unexposed control    | 0                    | 1              | 11                  | 43          | 12.9              | 54           | 41           | 1          | 4            |
| Dog #153..... | M   | Unexposed control    | 3                    | 1              | 15                  | 52          | 19.4              | 42           | 50           | 4          | 4            |
| Dog #153..... | M   | Unexposed control    | 6                    | 1              | 15.5                | 54          | 15.4              | 52           | 40           | 5          | 3            |
| Dog #154..... | M   | Air exposed control  | 0                    | 1              | —                   | —           | —                 | —            | —            | —          | —            |
| Dog #154..... | M   | Air exposed control  | 3                    | 1              | 14.5                | 50          | 12.4              | 45           | 50           | 2          | 3            |
| Dog #154..... | M   | Air exposed control  | 6                    | 1              | 14                  | 50          | 11.1              | 55           | 28           | 5          | 12           |
| Dog #154..... | M   | Air exposed control  | 0                    | 1              | 10.5                | 39          | 13.6              | 48           | 48           | 2          | 2            |
| Dog #152..... | M   | 50                   | 3                    | 1              | 14.5                | 54          | 12.7              | 48           | 48           | 3          | 1            |
| Dog #152..... | M   | 50                   | 6                    | 1              | 15.5                | 53          | 11.2              | 43           | 50           | 4          | 3            |
| Dog #151..... | F   | Unexposed control    | 0                    | 1              | 11                  | 48          | 13.3              | 59           | 30           | 3          | 9            |
| Dog #151..... | F   | Unexposed control    | 3                    | 1              | 14.5                | 52          | 23.6              | 67           | 25           | 0          | 8            |
| Dog #151..... | F   | Unexposed control    | 6                    | 1              | 15.5                | 58          | 15.5              | 46           | 42           | 3          | 9            |
| Dog #155..... | F   | Air exposed control  | 0                    | 1              | 13                  | 46          | 14                | 61           | 37           | 0          | 2            |
| Dog #155..... | F   | Air exposed control  | 3                    | 1              | 16                  | 59          | 18.2              | 60           | 33           | 5          | 2            |
| Dog #155..... | F   | Air exposed control  | 6                    | 1              | 15.5                | 56          | 17.0              | 62           | 31           | 5          | 11           |
| Dog #151..... | F   | 50                   | 0                    | 1              | 10.5                | 35          | 15.3              | 55           | 40           | 5          | 0            |
| Dog #151..... | F   | 50                   | 3                    | 1              | 15.5                | 58          | 13.4              | 56           | 42           | 2          | 0            |
| Dog #151..... | F   | 50                   | 6                    | 1              | 15.5                | 56          | 12.3              | 43           | 43           | 3          | 11           |

adjacent to the leaks. The flammability of vinyl chloride precludes such severe leaks if this hazard of vinyl chloride is to be controlled.

#### Industrial Hygiene Standard

The data presented indicate that little likelihood of injury would be expected if repeated daily 7- to 8-hour exposures are limited to 100 ppm or less.

Although the level of 100 ppm may not appear to offer any margin of safety since rats exposed repeatedly to this level were very slightly affected, the vast amount of human experience that is available while operating under an MAC of 500 ppm indicates that injury is not likely. Likewise the effects of even rather severe over-exposure are not serious, hence this level seems reasonable.

A time-weighted average for all exposure should probably not exceed 50 ppm.

#### Summary

Vinyl chloride ( $\text{CH}_2=\text{CHCl}$ ) is a monomer used in very large quantities in the production of plastics. Repeated exposures of laboratory animals to several concentrations of vinyl chloride in air were conducted to determine the chronic toxicity of this material towards animals in order to assess the hazard to humans. Vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathological changes after repeated daily 7-hour exposures at

500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for six months resulted in micropathological changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers, the other species were not affected. All species studied tolerated repeated daily 7-hour exposures to 50 ppm for six months with no detectable injury.

Repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect, longer exposures caused a slight increase in liver weight.

The standard for evaluating regular daily 7- to 8-hour exposures may be defined as the concentration below which practically all analytical results must fall. The value of 100 ppm is suggested as this standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm.

#### References

1. Manufacturing Chemists Assoc. Chemical Safety Data Sheet 2D-56 (1954).
2. von Oettingen, W. F.: *The Halogenated Hydrocarbons, Toxicity and Potential Dangers*. (U. S. Public Health Service, Publication No. 414.) Government Printing Office, Washington, D. C. (1955).
3. MASTROMATTIO, E., A. M. FISHER, H. CHRISTIE, AND D. DANIGER: Acute Inhalation Toxicity of Vinyl Chloride to Laboratory Animals. *Am. Ind. Hyg. Assoc. J.* 11: 204 (1950).
4. SCHAUMANN, O., cited by E. B. LERMAN AND F. FLURY.

- Toxicol. u. Hyg. der technischen Lösungsmittel, J. Springer, Berlin, 1938 p. 130. (From the translation. *Toxicology and Hygiene of Industrial Solvents* by E. King and H. F. Smyth, Jr., 1941).
5. A.C.G.I.H. Threshold Limit Values for 1960. *AMA Arch. of Envir. Health* 1: 63 (1960).
6. SMITH, H. F., JR.: Improved Communication—Hygiene Standards for Daily Inhalation. *Am. Ind. Hyg. Assoc. J.* 17: 139 (1956).
7. Cherry Hill Farms, Camden, New Jersey.
8. Ralston Purina Company, St. Louis, Missouri.
9. Harris Milling Company, Mount Pleasant, Michigan.
10. SPENCER, H. C., V. K. ROWS, E. M. ADAMS, D. D. MCCOLLISTER, AND D. D. IRIAN: Vapor Toxicity of Ethylene Dichloride as Determined by Experiments on Laboratory Animals. *AMA Arch. Ind. Hyg. and Occup. Med.* 4: 423 (1951).
11. TORRELLSON, T. R., M. A. WOLF, F. OTEN, AND V. K. ROWS: Vapor Toxicity of Allyl Chloride as Determined on Laboratory Animals. *Am. Ind. Hyg. Assoc. J.* 20: 217 (1959).
12. Dual Syringe Feeder Pumps, Modern Metalcraft, Midland, Michigan.
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