3. Perry, K.; Bowler, R. G.; Buckell, H. M.; Druett, H. A.; and Shilling, R. S. F. 1948. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. II. Chemical and environmental investigations. *Br J Ind Med* 5: 6-15.
4. Lee, A. M., and Fraumeni, J. F., Jr. 1969. Arsenic and respiratory cancer in man: An occupational study. *J Natl Cancer Inst* 42: 1045-52.
5. Ott, M. G.; Holden, B. B.; and Gordon, H. L. 1974. Respiratory cancer and occupational exposure to arsenicals. *Arch Environ Health* 29: 250-55.
6. Snegireff, L. S., and Lombard, O. M. 1951. Arsenic and cancer. Observations in the metallurgical industry. *Arch Ind Hyg Occup Med* 4: 199-205.
7. Pinto, S. S., and Bennett, B. M. 1963. Effect of arsenic trioxide exposure on mortality. *Arch Environ Health* 7: 583-91.
8. Nelson, W. C.; Lykens, M. H.; Mackey, J.; Newill, V. A.; Finkles, J. F.; and Hammer, D. I. 1973. Mortality among orchard workers exposed to lead arsenate spray: A cohort study. *J Chron Dis* 26: 105-18.
9. Pinto, S. S.; Warner, M. O.; Nelson, K. W.; Labbe, A. L.; and White, L. D. 1976. Arsenic trioxide absorption and excretion in industry. *J Occup Med* 18: 633-35.
10. World Health Organization. 1957. *International Classification of Diseases, 1955 Revision.* Geneva: World Health Organization Publishers.
11. Henderson, V. Estimating the risk of respiratory cancer due to occupational exposure in smokers vs. non-smokers: a method for adjustment. Unpublished observations.
12. Jones, H. B., and Grendon, A. 1975. Environmental factors in the origin of cancer and estimation of the possible hazard to man. *Food Cosmet Toxicol* 18: 251-68.
13. Enterline, P. E. 1974. Respiratory cancer among chromate workers. *J Occup Med* 16: 523-26.
14. World Health Organization. 1974. *Assessment of the Carcinogenicity and Mutagenicity of Chemicals.* Technical Report Series, No. 546. Geneva: World Health Organization Publishers.
15. Druckery, H. 1967. Quantitative aspects of chemical carcinogenesis. In *Potential Carcinogenic Hazards from Drugs (Evaluation of Risks)*, Ed. Truhart, R. UICC Monograph Series, Vol. 7, pp. 60-78. New York: Springer-Verlag.

Health of Workers Exposed to 1, 1, 1,-Trichloroethane: A Matched-Pair Study

C. G. KRAMER, M.D.
M. GERALD OTT, M.S.
J. E. FULKERSON, B.S.
N. HICKS, R.N., M.S.
The Dow Chemical Company
Midland, Michigan

H. R. IMBUS, M.D.
Burlington Industries
Greensboro, North Carolina

An epidemiologic study of 151 matched pairs of employees was conducted in two adjacent textile plants, one of which used inhibited 1,1,1-trichloroethane as a general cleaning solvent. Employees in the study population had exposures to the solvent for 6 yrs or less at varying concentrations which were measured by breathing zone sampling and personal monitoring.

While cardiovascular and hepatic observations were of primary interest, other health parameters were also studied.

Application of sensitive statistical techniques and careful examination of all data did not reveal any clinically pertinent findings that were associated with exposure to 1,1,1-trichloroethane.

The statistically significant associations that were observed between health measures and nonexposure factors emphasize the need to consider age, sex, race, and other variables in designing epidemiologic studies.

TWO LITERATURE REVIEWS of 1, 1, 1-trichloroethane toxicity have recently been published.[1,2] Although extensive toxicological studies in animals were reported, less information was available on potential effects in humans, especially in employee populations chronically exposed to the solvent. The existing data indicate that 1, 1, 1-trichloroethane is a central nervous system depressant with low hepatotoxicity.[3-10] The chemical is capable of causing a temporary increase of heart sensitivity to epinephrine and similar substances that could result in severe or fatal arrhythmias, but only at levels well above those acceptable as an occupational exposure.[11-14] The recommended 1976 Threshold Limit Value (TLV) published by the American Conference of Governmental Industrial Hygienists is 350 ppm (1.9 mg/l) as a daily time-weighted average (TWA).

The main purpose of this study was to investigate possible health effects of 1, 1, 1-trichloroethane exposure in an industrial population. Particular attention was given to the issue of whether or not chronic exposure resulted in any effect on the heart that would be detectable by electrocardiography. It was also desirable to search for hepatotoxic and central nervous system effects.

Study Design

The manufacture of 1, 1, 1-trichloroethane has involved a limited employee population exposed to relatively low concentrations of the solvent. Therefore, to investigate potential health effects associated with chronic exposure at levels approaching the TLV, it became necessary to design an inter-industry study. This investigation was undertaken by the manufacturer (The Dow Chemical Company), as

and control population, with respect to demographic variables.

Health Examination Procedures

The members of the on-site examining team worked closely with nurses and a physician from Burlington Industries in scheduling examinations and in review and follow-up of individual findings. Extensive orientation and training prior to the study included a 1 wk pretest period during which only nonstudy persons were seen.

The subset of individuals in the paired study was examined within a defined 7-wk period. Upon entering the examination area (a mobile unit especially equipped for the project), the employee's height, weight, blood pressure, and pulse were first obtained. To maximize consistency in the responses, a nurse assisted each person in completing the questionnaire, patterned after the Coronary Drug Project and using similar criteria for interpretation.[16] Emphasis was placed on questions related to possible cardiac problems, with a check list for other body systems.

A venipuncture was performed after the questionnaire had been completed. Laboratory determinations on whole blood and serum included hematocrit, hemoglobin, red blood cells (RBC), white blood cells (WBC), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular volume (MCV). These tests were performed by a local commercial laboratory. The clinical chemistries, alkaline phosphatase serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), Gamma glutamyl transpeptidase (GGT), total bilirubin, urea nitrogen (BUN), lactic dehydrogenase (LDH), uric acid, total protein, albumin/globulin (A/G) ratio, albumin, calcium and phosphorus, were sent to Bio-Science Laboratories in Van Nuys, California. Split samples were mailed separately on Fridays and Mondays to check for variability in clinical chemistries due to potential delays in shipment. The coefficients of variability for the seven sets of samples were comparable, although somewhat higher than internal coefficients published by the laboratory.[17]

Following spirometric evaluation, participants proceeded to the industrial hygiene area where instructions were given for procuring an expired air sample. Samples were immediately analyzed quantitatively for 1, 1, 1-trichloroethane content by gas chromatography.[10]

The last procedure performed was the electrocardiogram (ECG). A computer-interpreted program was chosen because of the objectivity and consistency it would provide. The Smith-Mayo Program, in the version current at the beginning of the study was selected as the best available, given the situation, due to its relative immunity from lead placement variation.[18] The ECG equipment was connected by landlines to a reading computer in Birmingham, Alabama, which immediately responded to any abnormal findings by notifying the nurse examiners. The ECGs were overread clinically by a cardiologist and this reading was utilized in reviewing results for individual patients. The computer readings expressed by the program algorithms were used in the statistical analysis.

All persons were informed of the examination results. Those with abnormal test results were either recalled for repeat studies or referred to a physician.

Environmental Considerations

Operations at the study plant began in 1969 and consisted of producing a dyed yarn suitable for knitting or weaving. During processing, fabric dust and trimer dust (a three-molecule polyester polymer) scattered through the area, contaminating machinery and building structures. These materials were treated as nuisance dusts not known to have any adverse effects on health. The solvent, 1, 1, 1-trichloroethane, was used in many operations to remove dust, oil, and other contaminants either from machinery, floors, or building structures. For approximately one yr

Table 2.—Summary of Estimated TWA Concentrations of 1, 1, 1-Trichloroethane by Job Description, April 1973 Through March 1975 (in ppm and number of samples)

Job Description or Work Area	Date and Sampling technique					
	April 1973 Halide Meter*	July-Aug 1973 Charcoal†	Oct 1973 Charcoal ‡	Nov 1973 -Jan 4, 1974 Charcoal ‡	Jan 15, 1974 -Feb 14, 1974 Charcoal ‡	March 1975 8 hr personal sampling
Machine cleaning	245 (1)	838 (5)	157 (3)	168 (5)		217 (5)
Packer		485 (5)	113 (3)	136 (9)	188 (4)	125 (8)
Conorapid operators		648 (3)	131 (3)	205 (10)	287 (4)	183 (3)
Sweiter operators	194 (3)	439 (5)	191 (3)	170 (10)	175 (3)	201 (5)
Other operators		347 (13)	109 (7)	120 (12)	199 (4)	
Service and yarn loading		435 (5)	97 (3)	162 (10	150 (4)	163 (1)
Winding superintendent						34 (1)
Laboratory				49 (10)	84 (4)	57 (4)
Office		50 (1)		4 (4)		11 (1)
Other work areas			0 (1)			12 (1)
At air conditioner		476 (7)	182 (16)	153 (32)	180 (32)	115‡ (31)

*Sampled for up to 45 min, number of samples in parentheses indicates number of locations.
†Samples collected on charcoal tube at 1/min. for 10 min and analyzed on portable gas chromatograph.
‡Samples collected on charcoal tube at 1/min. for 5 min.

Table 4.—Distribution of Exposure Measures for 151 Workmen Exposed to 1, 1, 1 Trichloroethane (determined from Industrial Hygiene Surveys and Personnel Work Histories)

Exposure Measures	Number of Employees
Duration of exposure	
Total	151
< 12 months	2
12-35 months	87
36-59 months	41
60 + months	21
Current TWA level of exposure	
Total	151
<15 ppm	11
15-49 ppm	5
50-99 ppm	19
100-149 ppm	48
150-249 ppm	68
Estimated career dosage (TWA X months of exposure)	
Total	151
<2000 ppm months	18
2000-3999 ppm months	35
4000-5999 ppm months	57
6000 + ppm months	41

assigned to one of five concentration categories so that exposure measures for individuals could be estimated in conjunction with work history data. The categorizaion was based upon the following class intervals:

Exposure Index	1, 1, 1-Trichloroethane Concentration (ppm)
1	1 – 14
2	15 – 49
3	50 – 99
4	100 – 149
5	150 – 249

Each job was assigned an exposure index which changed in a few instances where the job itself was relocated or restructured. The levels assigned are considered to be conservative since previous work practices, higher consumption of the solvent, and limited hygiene data suggest higher exposure levels during the earlier years. Peak concentrations had exceeded 1000 ppm on occasion.

The control plant did not use 1, 1, 1-trichloroethane. This was verified by an industrial hygiene survey and the negative results of expired air analysis for control employees.

Results

Selected demographic characteristics and smoking history of the exposed and matched control populations are shown in Table 3. A majority of the people were black and there were many more women than men in the populations. The populations also included many individuals under age 35. The Table does not reflect the additional matching for shift, socioeconomic status, or job description. Smoking patterns did not differ between exposed and control groups.

Environmental measures for the 151 exposed employees are summarized in Table 4. Only two employees had been exposed less than one yr; maximum exposure was for 6 yr. Current TWA levels of exposure were skewed to the upper end of the intensity categories, reflecting the selection procedure which favored including individuals with higher exposure. Highest TWA exposure levels for one or more months, although not shown in the Table, were skewed even more with many individuals exceeding exposures of 250 ppm TWA prior to the study period. Estimated career dose was calculated by multiplying months of exposure by the mean TWA concentration in ppm for the appropriate class interval, summed over the individual's work experience. The expired air samples in Table 5 are in reasonable agreement with the estimated dose on day of examination (ppm

Table 6.—Comparison of Dichotomous Health Exam Responses between 1, 1, 1-Trichloroethane Exposed and Matched Controls

Health Exam Items	Positive Responses	
	Exposed	Controls
HISTORY		
Cardiac pain, aching, tightness, or pressure in the chest	1	5
Difficulty in breathing	7	8
Obvious stroke	0	0
Weakness or paralysis of any part of the body	3	5
Fainting spells or blacking out	12	13
Dizziness spells	31	29
Sudden pain or coldness of a foot or leg	3	0
Pains or cramps in legs when walking	4	5
Pain relieved when walking is terminated	3	1
Abnormality in the following systems:		
Circulatory	31	24
Gastrointestinal	28	21
Genitourinary	45	45
Nervous	31	32
Musculoskeletal	17	29
Dermal	26	25
Respiratory	22	31
OBSERVATIONS		
Irregular rhythm	16	26
Positive romberg	0	0
URINALYSIS FINDINGS		
Glucose	0	0
Ketones	1	0
Protein	2	1
Blood	9	4

the exposed population that would account for the observed associations. However, they directed out attention to apparently chance trends in the control population in regard to four health parameters and to several individuals for whom further clinical review was needed.

Table 9 compares positive findings between 121 matched pairs for whom computerized ECGs were obtained. The data were incomplete for the remaining 30 pairs due to transmission problems and delays in equipment servicing. No statistically significant differences were observed in regard to numbers of positive findings for any algorithm. A rank sum test was used to determine if the positive findings on ECGs for the exposed persons were correlated with either estimated cumulative dose or level of 1, 1, 1-trichloroethane in expired air. When the ECG findings were rank ordered, approximately five statistically significant differences were expected at the .05 level, whereas eight were found. Two of the associations were negative. The remaining positive correlations were due to ECG findings from one or more of four exposed individuals. One of these four individuals was functioning well in a high-exposure area although he was one of two persons in the study who had recent silent myocardial infarctions. Based on known history of these individuals, the infarcts were considered to be unrelated to work exposure.

A review of deaths among active employees during the 6 yr of plant operations revealed two accidental deaths unrelated to exposure. During the year since the examination, there have been two nonfatal myocardial infarctions: one was a paired control individual and the other was a non-study employee from the control plant.

Comment

Many technical and social difficulties are encountered when organizing and executing studies where surveying a broad spectrum of potentially exposed individuals is

mize the direct effect of age, sex, race, and job description on comparisons of potential health effects associated with 1, 1, 1-trichloroethane. In view of the need for controlling demographic variables, multiple regression analyses were run separately for men and women to explore associations among the health variables and selected nonexposure factors. The many statistically significant associations that were observed point out the importance of carefully designing studies to minimize confounding effects of work exposure with other factors.

Animal studies and reports of human fatalities indicate that 1, 1, 1-trichloroethane in massive acute exposures may cause apneic deaths or fatal cardiac arrhythmias.[11-14, 20] At this site, no deaths attributable to the solvent have occurred during the 6 yr of plant operation. No statistically significant differences in rhythm were found between the exposed and control populations by either computer-read ECG or nurse observation (60 sec pulse rate). The brief monitoring period of the ECG allowed, at best, a very limited assessment of potential short duration arrhythmias and

Table 8.—Summary of Statistically Significant Associations Based on the Regression of Thirty-One Quantitative Health Measures on Five Environmental Measures Plus Height of Individuals (Matched-Pair Differences)*

Quantitative Health Measure	Independent Variable, Direction of Association and Level of Significance†
Cardiovascular measures	
△P - duration	Cumulative dose ↑ ($P < .05$)
Hepatic measures	
△GGT	Current level of exposure ↑ ($P < .025$)
△Alkaline phosphatase	Breath analysis ↑($P < .05$) estimated dose on day of exam ↓($P < .05$)
Blood Measures	
△WBC	Cumulative dose ↑($P < .05$)
△Hematocrit	Duration ↑ ($P < .05$)
Miscellaneous‡	
△BUN	Duration ↓($P < .05$)

NOTE: ↑refers to a positive association and↓to a negative association.

* Environmental measures were: 1) estimated cumulative dose; 2) estimated current TWA exposure category; 3) duration of exposure; 4) body burden at time of exam (breath analysis [ppm]); and 5) day dose (estimated from hours on job and environmental surveys).

† .05 significance level employed in Table, at slightly above the .05 level △SGP-T was associated with cumulative dose ↑ ($P \simeq .05$) and △Hemoglobin was associated with duration ↑ ($P \simeq .05$).

‡ Two health measures were associated with △height alone: 1) △weight ↑ ($P < .001$) and △R-Duration ↑ ($P < .01$).

certain short duration S-T segment changes in the study. The limitations of 12-lead resting ECGs in comparison with ambulatory ECG monitoring have been reported.[21, 22] Use of ambulatory electrocardiography could provide additional information for evaluating abnormalities associated with cardiac sensitizing agents. No evidence of differences in chronic ECG changes were discovered between the exposed and control groups.

The absence of observed central nervous system effects is consistent with reports of minimal impairment of coordination, and lightheadedness occurring with brief exposure of 900 to 950 ppm. but not occurring with exposures of less than 500 ppm.[3, 4] Finally, no association between increased exposure and hepatic dysfunction, as measured by enzyme studies, was detected in the present population.

Medical results were reviewed in detail by the field physician and the Dow physician who directed the study particularly where trends were thought to show increased response with increased career dose. No recognizable clinical pattern nor other evidence of adverse effects from exposures to 1, 1, 1-trichloroethane were found in this study.

Table 9 (Continued)

Program Algorithm	Exposed	Control	Average Rank Breath Level†	Average Rank Career Dose
E. Axis deviation				
Left ventricular hypertrophy with marked ST-T abnormalities of left ventricular strain	3	7	32.2	35.7
Left axis deviation	1	4	no sample	61.5
marked degree	1	3	no sample	61.5
minimal degree	0	1		
Vertical axis of QRS complex	1	5	33	75.5
Horizontal axis of QRS complex	1	0	68	50
Right ventricular hypertrophy (possible)	0	1		
Low anterior forces	0	1		
F. Other findings				
Unusual late depolarization	0	1		
Abnormal depolarization	2	0	47.8	83.3
probably from inferior infarct	1	0	33	75.5
from inferior infarct	1	0	62.5	91
Inferior infarct	3	3	66.7	91.3
no other qualification	2	2	57	76.5
(high likelihood)	1	0	106	121§
possible	0	1		
Pericarditis	1	0	81	120‡
Repolarization abnormality (hypokalemia)	0	1		

* Excludes 25 pairs for whom transmission of an ECG was either not sent or not received over telephone lines and five pairs where an ECG was judged to be of poor technical quality.

† Breath samples were not available for four persons. Expected mean rank for breath level analysis is 59.0 and for cumulative dose analysis is 61.0. Higher rank scores correspond to higher exposures.

‡ $P < .05$.

§ $P < .01$.

* * * * * * * * * * *

Among those who provided technical and field assistance are: Maxine Coin, Roger Lee, Miriam McCormack, R.N., David R. Spencer, and Theodore R. Torkelson.

Submitted for publication September 9, 1976; revised; accepted June 6, 1977.

Requests for reprints of this article should be addressed to: M. Gerald Ott, Dow Chemical USA, Bio Medical Res., 1603 Bldg., Midland, Michigan 48640.

* * * * * * * * * * *

REFERENCES

1. Aviado, D. M.; Zakhari, S.; Simaan, J. A.; and Ulsamer, A. G. 1976. *Methyl Chloroform and Trichloroethylene in the Environment.* Cleveland, Ohio: CRC Press.
2. Department of Health, Education and Welfare. 1976. *Criteria for a Recommended Standard: Occupational Exposure to 1, 1, 1-trichloroethane.* HEW Publication No. (NIOSH) 76-184. Washington, D. C.: United States Department of Health, Education and Welfare.
3. Torkelson, T. R.; Oyen, F.; McCollister, D. D.; and Rowe, V. K. 1958. Toxicity of 1, 1, 1-trichloroethane as determined on laboratory animals and human subjects. *Am Ind Hyg Assoc J* 19: 353–62.
4. Stewart, R. D.; Gay, H. H.; Erley, D. S.; Hake, C. L.; and Schaffer, A. W. 1961. Human exposure to 1, 1, 1-trichloroethane vapor: Relationship of expired air and blood concentrations to exposure and toxicity. *Am Ind Hyg Assoc J* 22: 252–62.
5. Rowe, V. K.; Wujkowski, T.; Wolf, M. A.; Sadek, S. E.; and Stewart, R. D. 1963. Toxicity of a solvent mixture of 1, 1,1-trichloroethane and tetrachloroethylene as determined by experiments on laboratory animals and human subjects. *Am Ind Hyg Assoc J* 24: 541–54.
6. Prendergast, J. A.; Jones, R. A.; Jenkins, L. J. Jr.; and Siegel, J. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1, 1, 1-trichloroethane, dichlorodifluoromethane, and 1, 1-dichloroethylene. *Toxicol Appl Pharmacol* 10: 270–89.
7. Stewart, R. D.; Gay, H. H.; Schaffer, A. W.; Erley, D. S.; and Rowe, V. K. 1969. Experimental human exposure to methylchloroform vapor. *Arch Environ Health* 19: 467–72.
8. Salvini, M.; Binaschi, S.; and Riva, M. 1971. Evaluation of the psychophysiological functions in humans exposed to the "threshold limit value" of 1, 1, 1-trichloroethane. *Br J Ind Med* 28: 286–92.
9. Gamberale, F., and Hultengren, M. 1973. Methyl chloroform