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Physiological Response to Aerosol Propellants

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Acute exposures to isobutane, propane, F-12, and F-11 in concentrations of 250, 500, or 1000 ppm for periods of 1 min to 8 hr did not produce any untoward physiological effects as determined by the methods employed which included serial EKG's and continuous monitoring of modified V_5 by telemetry during exposure. Repetitive exposures to these four propellants were also without measurable untoward physiological effect with the exception of the eight male subjects repetitively exposed to 1000 ppm, F-11, who did show minor decrements in several of the cognitive tests. Of particular importance is the observation that none of the subjects showed any decrement in pulmonary function or alteration in cardiac rhythm as the result of exposure to concentrations of the gases or vapors far greater than encountered in the normal use of aerosol products in the home.

The "sniffing" of high concentrations of aerosol propellants and organic solvent vapors to obtain a "high" has resulted in the sudden death of approximately 300 teenagers, presumably due to epinephrine sensitization of the heart and the development of a fatal cardiac arrhythmia (*1–9*). Since there had been no reports of industrial workers developing arrhythmias related to exposure to these same compounds at concentrations not exceeding the Threshold Limit Values, concern for the safety of the consumer using aerosol products in the home did not become an issue until the reports of Zuskin (*10*) and Speizer (*11*). In 1974 Zuskin and Bouhuys suggested that aerosol propellants might be responsible for the transient increase in airway resistance observed after the use of hair sprays (*10*). Then Speizer, Wegman, and Ramirez reported that brief exposures to fluorocarbon-22 in the 300 ppm range resulted in the development of severe palpitation in pathology residents in Boston (*11*), and suggested that exposure to "normal-use" concentrations of aerosol propellants might pose health problems not previously recognized.

The paucity of the human toxicological information regarding the health effects resulting from the inhalation of four of the most widely used aerosol propellants over the range of concentration encountered in both the home and industrial setting prompted this investigation.

Experimental Procedure

Healthy adult male and female volunteers were exposed in small groups in a controlled-environment chamber to isobutane, propane, fluorocarbon-12 (F-12, difluorodichloromethane), or fluorocarbon-11 (F-11, fluorotrichloromethane) concentrations ranging from those encountered in the home to those permitted in the industrial setting. First, a series of single exposures to 250, 500, and 1000 ppm to each of the propellants for periods of 1 min to 8 hr were conducted. As there were no untoward health effects, the subjects were then repeatedly exposed 5 days per week for 2 to 4 weeks to 500 ppm isobutane, 1000 ppm propane, 1000 ppm F-12, and 1000 ppm F-11. On several occasions, subjects were exposed to mixtures of the gases and solvents. The exposure schedule is presented in Tables 1–3.

These experiments were so designed that the absorption, excretion, and physiological effects of the four propellant gases and solvent could be studied.

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Table 1. Exposure of human subjects to isobutane (Group I).

Planned isobutane exposure, ppm	Subjects		Duration of exposure	Exposure, ppm (mean ± S.D.)
	Male	Female		
500	4	4	1 min	514.4
	4	4	2 min	506.3
	4	4	10 min	504.2 ± 15
250	1	1	1 hr	245.9 ± 7.2
	1	1	2 hr	245.7 ± 19
	2	2	8 hr	244.5 ± 23.6
1000	1	1	1 hr	1008.2 ± 28.6
	1	1	2 hr	1005.7 ± 26.9
	2	2	8 hr	1000.1 ± 23.6
500	1	1	1 hr	499.9 ± 35
	1	1	2 hr	488.8 ± 15
	2	2	8 hr	493.2 ± 19.7
500, fluctuating concentration	1	1	1 hr	388.6 ± 91.9
	1	1	2 hr	649.8 ± 200
	2	2	8 hr	530.9 ± 258.8
500, 10 repetitive exposures	1	1	1 hr	509.4 ± 14.8
	1	1	2 hr	509.5 ± 21.2
	2	2	8 hr	506.6 ± 23.8
	1	1	1 hr	500.1 ± 58.1
	1	1	2 hr	486.2 ± 20.2
	2	2	8 hr	488.8 ± 33.0
	1	1	1 hr	498.9 ± 9.4
	1	1	2 hr	505.2 ± 22.9
	2	2	8 hr	503.4 ± 25.9
	1	1	1 hr	508.6 ± 29.1
	1	1	2 hr	513.0 ± 16.6
	2	2	8 hr	501.7 ± 31.6
	1	1	1 hr	504.5 ± 24.7
	1	1	2 hr	497.7 ± 16.3
	2	2	8 hr	502.6 ± 19.5
500, 10 repetitive exposures	1	1	1 hr	488.4 ± 30.6
	1	1	2 hr	497.1 ± 22.4
	2	2	8 hr	503.8 ± 28.2
	1	1	1 hr	492.6 ± 29.6
	1	1	2 hr	504.1 ± 23.6
	2	2	8 hr	504.2 ± 29.6
	4	4	8 hr	498.5 ± 26.7
	4	4	8 hr	506.9 ± 22.6
	4	4	8 hr	495.9 ± 29.9
	Mean concentration, 10 repetitive exposures:		1 hr	500.4
			2 hr	501.8
			8 hr	501.2

Table 2. Exposure of human subjects to propane (Group II).

Planned propane exposure, ppm	Subjects		Duration of exposure	Exposure, ppm (mean ± S.D.)
	Male	Female		
1000	4	4	1 min	995.9
	4	4	2 min	1002.5
	4	4	10 min	981.8
250	1	1	1 hr	284.1 ± 37
	1	1	2 hr	262.1 ± 20.5
	2	2	8 hr	255.5 ± 27.3
500	1	1	1 hr	506.5 ± 13.4
	1	1	2 hr	502.1 ± 31.4
	2	2	8 hr	504.1 ± 24.9
500, fluctuating concentration	2	2	8 hr	496.8 ± 140.7
1000, 9 repetitive exposures	2	2	8 hr	1005.9 ± 140.1
	2	2	8 hr	992.9 ± 215.7
	2	2	8 hr	1001.7 ± 44.5
	2	2	8 hr	994.3 ± 69.5
	2	2	8 hr	1006.4 ± 44
	2	2	8 hr	999.3 ± 61.6
	2	2	8 hr	961.8 ± 54.6[b]
	2	2	8 hr	1029.9 ± 38.7[b]
	2	2	8 hr	1014.5 ± 37.5

[b] Combined with isobutane (see Group II experiments, Table 3).

Table 3. Exposure of human subjects to isobutane–propane mixtures (Group III).

Planned exposure	Subjects		Duration of exposure, hr	Exposure, ppm (mean ± S.D.)
Isobutane / Propane	Male	Female		
82.5%/17.5%	1	1	1	Isobutane: 461.5 ± 74.5
				Propane: 106.8 ± 15.0
82.5%/17.5%	1	1	1	Isobutane: 536.5 ± 38.1
				Propane: 77.4 ± 7.4
	1	1	2	Isobutane: 482.6 ± 74.2
				Propane: 102.0 ± 10.8
	2	2	8	Isobutane: 501.8 ± 82.0
				Propane: 100.2 ± 18.4
89%/11%	2	2	8	Propane: 961.8 ± 54.6
				Isobutane: 110.7 ± 6.2
87.5%/12.5%	2	2	8	Propane: 1029.9 ± 38.7
				Isobutane: 142.7 ± 5.7

Special emphasis was placed on monitoring cardiac and pulmonary performance.

Subjects

A group of 43 male and 32 female subjects was selected from the Caucasian, middle-class Milwaukee population. Of these, 24 were college students, nine were housewives, five were nurses, and two were physicians. The investigation was performed with strict adherence to the ethical and technical requirements for human inhalation experimentation previously detailed (*12, 13*). This included obtaining the informed consent of each subject after the nature of the procedure had been fully explained.

The ages of the male subjects ranged from 18 to 46 years, height from 177.8 to 187.2 cm, and weight from 70.0 to 81.5 kg. The ages of the females ranged from 18 to 35 years, their height from 155 to 174 cm, and their weight from 57.2 to 72.9 kg.

All subjects were cautioned to abstain from the use of drugs and to limit their use of alcohol to very moderate amounts. Subjects who were smokers were not allowed to smoke during their stay in the controlled-environment chamber. Subjects who

Table 4. Exposure of human subjects to fluorotrichloromethane vapor.

Planned group exposure, ppm	Subjects	Duration of exposure, hr	Exposure, ppm Mean	S.D.	(%) C.V.[a]
Group I: 9 males in Chamber No. 1					
0	2 males	8	0		
500	3 males	8	495.8	15.3	3.09
	3 males	2	497.9	10.0	2.03
	2 males	1	489.8	27.1	5.53
0	3 males	8	0		
	3 males	2			
	3 males	1			
1000	3 males	8	997.0	31.8	3.19
	3 males	2	1001.5	28.1	2.80
	3 males	1	1016.7	24.1	2.37
0	3 males	8	0		
	3 males	2			
	3 males	1			
250	3 males	8	250.2	7.8	3.11
	3 males	2	246.1	9.0	3.68
	2 males	1	257.2	5.5	2.14
250	3 males	8	246.9	10.4	4.21
(F-11)	3 males	2	241.1	12.8	5.30
	2 males	1	239.6	3.1	1.27
Combined with	3 males	8	512.8	15.5	3.02
(F-12), 500	3 males	2	507.5	10.9	2.15
	2 males	1	527.6	0.3	.06
0	3 males	8	0		
	2 males	2			
	2 males	1			
Group II: 8 males in Chamber No. 2					
0	8 males	8	0		
0	8 males	8	0		
0	8 males	8	0		
250	8 males	8	250.1	15.3	6.13
500	8 males	8	499.9	13.7	2.75
1000	8 males	8	1000.3	42.6	4.26
1000	7 males	8	999.5	31.6	3.16
1000	8 males	8	1001.1	27.7	2.77
1000	8 males	8	999.1	41.5	4.15
1000	8 males	8	999.7	20.7	2.07
1000	8 males	8	991.1	61.1	6.16
1000	8 males	8	1001.0	22.1	2.30
1000	8 males	8	1000.8	27.8	2.78
1000	8 males	8	994.4	20.6	2.08
1000	8 males	8	996.0	23.8	2.39
1000	8 males	8	996.8	23.3	2.34
1000	8 males	8	1001.3	18.6	1.85
1000	8 males	8	1000.7	24.1	2.50
1000	8 males	8	1000.0	23.3	2.33
1000	8 males	8	998.7	17.4	1.74
1000	8 males	8	999.9	12.6	1.26
Fluctuating	8 males	8	273.7	146.1	53.69
1000	8 males	8	1000.6	16.8	1.68
1000	8 males	8	1000.2	20.2	2.02
	1 male	1	1014.3	30.7	3.03
	1 male	1	1000.8	15.6	1.55
	1 male	1	1003.5	24.6	2.45
1000	8 males	2	1016.4	16.7	1.65
	1 male	1	1015.1	19.1	1.88
0	8 males	8	0		
0	8 males	8	0		
Group III: 10 females in Chamber No. 1					
500	2 females	1	502.9	4.48	0.89
	4 females	2	500.7	5.59	1.12
	4 females	8	501.5	7.84	1.56
1000	2 females	1	1016.8	19.59	1.93
	4 females	2	1009.9	18.44	1.82
	4 females	8	1012.59	16.00	1.58
250	2 females	1	253.81	3.67	1.45
	4 females	2	253.11	4.21	1.66
	4 females	8	254.36	18.04	7.09
Group IV: 4 males and 4 females in Chamber No. 2					
1000	1 male 1 female	1	978.8	58.9	6.02
1000	1 male 1 female	2	1011.5	27.9	2.76
1000	2 males 2 females	8	1004.8	38.8	3.86
Group V: 7 males and 4 females in Chamber No. 2					
1000	8 males	10	987.1	15.7	1.59
1000	5 males 2 females	1	983.0	11.3	1.15
	5 males	1	1008.1	2.9	0.29
	6 males 2 females	2	1001.0	0.0	—
1000	5 males	10	1001.8	5.1	0.51
1000	4 males 2 females	10	1021.8	11.9	1.17
1000	5 males	2	1015.2	1.6	.16

[a] C.V. = coefficient of variation.

underwent behavioral testing were asked to refrain from consuming any caffeine prior to the end of each day's study (1 hr post-exposure).

Exposure Schedule

Tables 1–5 list the exposure sequences, the number of subjects, the gas or vapor concentration investigated, and the duration of each exposure.

Exposure Chamber

The experiments were conducted in a controlled-environment chamber having a 20 ft × 20 ft × 8 ft testing room with an attached shielded room and an attached toilet facility. The air flow through the suite of rooms to the exhaust was approximately 1500 ft^3/min, which created a slight negative pressure within the chamber. The ambient temperature within the chamber was maintained at

Table 5. Exposure of human subjects to dichlorodifluoromethane vapor.

Planned Group exposure, ppm	Subjects	Duration of exposure, hr	Exposure, ppm Mean	S.D.	C.V.
Group I: 11 males in Chamber No. 2					
0	11 males	8	0	0	0
0	4 males	6	0	0	0
	4 males	2	0	0	0
250	4 males	8	246.7	9.5	3.85
	4 males	2	250.9	4.2	1.67
	3 males	1	246.3	8.9	3.61
1000	4 males	8	1012.6	44.1	4.35
	4 males	2	1013.6	46.9	4.63
	3 males	1	1021.3	29.8	2.92
1000	4 males	8	1016.4	39.7	3.91
	4 males	2	1010.0	28.8	2.85
	3 males	1	1036.5	27.8	2.68
500	4 males	8	498.2	10.5	2.10
	3 males	2	511.5	12.7	2.48
	2 males	1	538.5	48.0	8.91
0	4 males	8	0	0	0
	3 males	2	0	0	0
	3 males	1	0	0	0
Group II: 8 males in Chamber No. 2					
0	8 males	8	0		
0	8 males	8	0		
0	8 males	8	0		
1000	8 males	8	1000.8	30.6	3.06
1000	8 males	8	1005.37	19.5	1.94
1000	8 males	8	1001.1	24.1	2.4
1000	8 males	8	999.1	21.5	2.15
1000	8 males	8	1000.0	16.6	1.66
1000	8 males	8	1000.6	62.2	6.22
1000	8 males	8	1004.7	17.6	1.76
1000	8 males	8	999.6	44.5	4.45
1000	7 males	8	1000.7	17.6	1.76
1000	8 males	8	1000.4	18.9	1.89
1000	8 males	8	1000.2	20.9	2.08
1000	8 males	8	1006.7	18.9	1.88
1000	8 males	8	999.6	23.0	2.30
1000	8 males	8	1000.9	19.5	1.95
1000	8 males	8	999.7	16.6	1.66
1000	8 males	8	999.1	16.5	1.65
1000	4 males	2	1000.2	21.5	2.15
1000	4 males	1	1002.5	18.5	1.85
1000	8 males	8	999.4	21.7	2.17
Fluctuating	8 males	8	284.7	139.9	49.14
0	8 males	8	0		
0	8 males	8	0		
Group III: 10 females in Chamber No. 1					
0	3 females	1	0	0	0
	4 females	2	0	0	0
	4 females	8	0	0	0
0	3 females	1	0	0	0
	4 females	2	0	0	0
	4 females	8	0	0	0
500	3 females	1	502.3	8.76	1.74
	4 females	2	503.7	7.56	1.50
	4 females	8	501.5	8.53	1.70
1000	2 females	1	1013.2	17.96	1.77
	4 females	2	1012.5	19.74	1.95
	4 females	8	1008.4	20.12	1.99

Table 5 continued

Planned Group exposure, ppm	Subjects	Duration of exposure, hr	Exposure, ppm Mean	S.D.	C.V.
0	2 females	1	0	0	0
	4 females	2	0	0	0
	4 females	8	0	0	0
250	3 females	1	250.4	2.49	0.99
	4 females	2	251.1	3.00	1.19
	3 females	8	250.6	2.80	1.12
0	2 females	1	0	0	0
	4 females	2	0	0	0
	4 females	8	0	0	0
Group IV: 4 males and 4 females in Chamber No. 2					
500	1 male 1 female	1	508.6	16.2	3.18
500	1 male 1 female	2	500.3	21.2	4.23
500	2 males 2 females	8	501.5	18.2	3.63
Group V: 9 males in Chamber No. 2					
1000	3 males	1	952.0	8.0	0.8
	3 males	2	963.3	15.6	1.62
	3 males	10	986.6	24.0	2.43

72–74°F, while the relative humidity ranged between 45 and 55%.

The propellant gases or vapor were mixed with the air supplying the chamber, entering through four diffusers in the ceiling of the testing room. To obtain the desired concentration, the gases were metered from a cylinder into the return air duct of the air conditioner while the liquid F-11 was pumped at a constant rate into a flask through which a stream of air swept the vapor into the return air duct.

Chemicals

The isobutane used in these experiments had a boiling point of 10.89°F, a vapor pressure of 3733 mm Hg at (100°F), a vapor density of 2.068 at (60°F and 24.7 psig), and a specific gravity of 0.563 at (60/60°F).

The propane had a boiling point of −44.48°F, a vapor pressure of 6612 mm Hg, a vapor density of 1.549, and a specific gravity of 0.509 (60/60°F).

The F-12 and F-11 used in these experiments was shown by infrared analysis to be 99.9% pure.

Analysis of Exposure Chamber Atmosphere

Two independent systems were used to monitor the chamber atmosphere. In both cases, air was withdrawn from the chamber through a ¼ in I.D. polyethylene tube at approximately 7 *l*/min, through or past the analytical device, to a small diaphragm pump which discharged back into the chamber.

The concentration of the gases or vapor in the chamber atmosphere was recorded continuously by a Wilks Miran-I infrared spectrometer equipped with a gas cell of 20 m path length. The following infrared absorbances were measured: 3.4 μ for isobutane and propane, 9.1 μ for F-12, and 11.9 μ for F-11. The voltage output was connected in a strip-chart recorder, and a voltage proportional to the pen position of that recorder was conducted to the analog-to-digital input of a PDP-12 (DEC) computer. The computer sampled pen position voltage each second, averaged those voltages every 30 sec, recorded the average on magnetic tape, and used the average to write on a CRT the concentration over that 30-sec interval and the cumulative or time-weighted average concentration since the beginning of the exposure session.

Gas chromatography (GC) was the second method of chamber air analysis. The Varian Aerograph Series 2700 GC was used. An automatic device injected a sample of air into the GC every 170 sec. Output of the GC was connected to a strip-chart recorder. After each exposure ended, a calibration curve for the GC values was established with the computer using regression analysis on the standards that had been analyzed during the day. With that equation, peak-height values read manually were transformed into concentrations which were then used to calculate time-weighted averages and standard deviations for exposure increments to compare with the values obtained using the infrared spectrometer. Concentrations found by the two

methods were in agreement throughout the study.

Standards were prepared by filling saran bags with room air pumped in sequence through a charcoal column, a wet test meter, a Drierite column, and a type N all-service gas mask canister. After filling a bag with a known amount of clean, dry air, a known volume of F-11, F-12, isobutane, or propane was injected into the bag. Calibration of analytical devices was accomplished by attaching the saran bag standard to the sampling probe within the chamber. At least three standards were analyzed prior to allowing subjects to enter the chamber each day and then standards were analyzed at approximately 1 hr intervals throughout the day.

Clinical Testing

Prior to exposure, each subject was given a comprehensive medical examination which included a complete history and physical examination and the laboratory studies listed below. None of the subjects was taking medication. Periodic urine screen for drugs confirmed none of the subjects was taking illicit drugs.

All exposures of 1 hr or more duration were conducted by using a double-blind format.

Prior to commencing the actual exposures, the subjects underwent a training program in the controlled environmental chamber during which time they became accustomed to the chamber setting and the testing procedures.

Each subject was given a repeat physical examination prior to each exposure. At this time each completed a "symptom check list." This form had designated spaces for noting the presence of headache, nausea, dizziness, abdominal pain, eye, nose, throat irritation, or other subjective symptoms. Each subject reviewed this list of symptoms immediately upon entering the chamber and each hour during and for 5 hr following each exposure. The adjectives, "mild, moderate, and strong," appeared on the sheet as cue words, and the phrase, "only abnormalities recorded," was prominently typed at the bottom. The home telephone numbers of each of the Department physicians appeared on the form and the subjects were told to phone should they become ill while away from the laboratory.

Prior to and following the exposures, the following laboratory determinations were made: complete blood count, urinalysis, alkaline phosphatase, SGOT, LDH, bilirubin, blood sugar, calcium, phosphorus, BUN, blood and alveolar breath samples for propellant analysis. A 24 hr urinary fluoride excretion determination was made on each subject exposed to F-12 or F-11. The following studies completed the pre-exposure evaluation: computerized spirometry, 12-lead EKG, and a modified V_5 EKG rhythm strip by telemetry.

During each exposure in the environmental chamber the subjects were under continual visual surveillance by medical personnel and all important chamber activities were videotaped by closed-circuit TV. Modified V_5 was monitored continuously by telemetry. A hard copy of this EKG was obtained after 30 min of exposure and hourly thereafter. When a change in cardiac rhythm was observed, a hard copy rhythm strip was obtained.

Immediately after entering the environmental chamber, each subject performed a modified Romberg test followed by a heel-to-toe test. These tests were first performed with eyes open and then repeated with closed eyes. Then, each subject completed his subjective symptom check list as previously discussed. Each subject repeated the modified Romberg test and the heel-to-toe test 5 min before leaving the exposure chamber.

Subjects exposed for 2 hr or more performed the following during the final 40 min of exposure: computerized spirometry measurement, which included the maximum mid-expiratory flow rate, Flanagan coordination test, Marquette time estimation test (*14*) and random number inspection test. During the repetitive studies the above tests were performed twice a week during the final 2 hr of exposure.

During the repetitive exposures to F-12 and F-11 systolic time interval measurements were made before exposure and immediately following 8 hr of exposure (*15*). During the repetitive exposures to isobutane and propane the second systolic time interval measurement was made during the final hour of exposure.

The spontaneous EEG and VER of selected subjects were recorded four times each Monday, Wednesday, and Friday during the repetitive exposures (*16–18*). Recordings were made once during the first hour and three times between the fifth and seventh hours of exposure. All recordings were obtained while the subjects were seated in a comfortable upholstered chair in the shielded room in which the hydrocarbon concentrations were identical to those in the controlled environmental chamber.

Alveolar breath samples were obtained daily from each subject prior to entry into the environmental chamber, and serially following each exposure. These samples were each collected in 5-liter saran bags by using the technique previously described in detail (*19*).

Blood samples for propellant analysis were obtained from an antecubital vein of each subject pre-exposure, 15 min pre-exit, and 15 min post-

exposure in Vacutainer tubes with edetic acid anticoagulant. The pre-exit sample was obtained by having the exposed subject stick his arm through an armport in the chamber wall into the uncontaminated adjacent laboratory.

Analysis of Ambient Air, Expired Breath and Blood

Air and breath samples for propellant analysis were injected directly onto a Porapak Q column of a Varian Aerograph Series 2700 gas chromatograph equipped with a hydrogen flame ionization detector. A headspace sampling technique was utilized for measuring the concentration of the propellants in the blood. The details of the analytical procedures used have been presented elsewhere (*16–19*).

Medical Surveillance After Exposure

A resting 12-lead electrocardiogram was obtained 15–30 min post-exposure. All of the pre-exposure clinical studies were repeated on a weekly basis during the period of exposure. On the day following the last exposure of any sequence, each subject was given a repeat comprehensive medical examination. This included a complete history and physical examination with the following laboratory studies: complete blood count, urinalysis, complete panel of clinical chemistries (23 values plus 2 calculated), computerized spirometry, and a 12-lead electrocardiogram (EKG).

Those subjects who had been exposed repetitively underwent the standard 2-day ACTH stimulation test to assess the adrenal gland's ability to respond to stress. Then the health of each subject was monitored for one year by the investigators.

Results

Analysis of Exposure Chamber Atmosphere

The daily time-weighted average concentrations of the propellants in the controlled-environment chamber for each of the exposure situations are found in Tables 1–5. The actual concentrations were within a few percent of those desired.

Medical Surveillance

No untoward subjective symptoms or objective signs of illness were noted during exposure or in the surveillance period which followed each exposure. Pre- and post-exposure comprehensive medical examinations revealed that all subjects remained in good health during the study. All of the clinical hematologies and chemistries remained within the limits of normal. The comprehensive history and physical forms used in the study and a listing of the clinical laboratory values obtained are available for review in the three project reports (*16–18*).

Effects of Exposure on the Heart

None of the subjects experienced any untoward signs or symptoms referrable to his heart during exposure or in the post-exposure period of surveillance. No change from the pre-exposure control EKG tracing was observed in the post-exposure standard 12-lead EKGs or in modified lead V_5 monitored continuously during exposure by telemetry. With one exception, none of the subjects had an arrhythmia during exposure.

One subject in the acute series of exposures to F-12 was observed to be experiencing premature ventricular contractions at a rate of 1–2/min prior to commencing a 1 hr exposure to 1000 ppm F-12. This subject was exposed for 1 hr during which time his telemetered EKG was continuously recorded. The rate at which the premature ventricular contractions occurred was unaltered by the exposure and continued unchanged for 3 hr post-exposure. The following day no premature ventricular contractions were observed during two, 30 min monitoring periods. The subject was monitored for 4 hr one week later, and no premature ventricular contractions were observed.

The systolic time interval measurements were unaltered by the exposures to the four propellants. The normal diurnal variation was observed. The pre-ejection period (PEP), ejection time (LVET), the PEP/LVET ratio, and total electromechanical systole (the Q-A2 interval) remained normal and unchanged. Table 6 presents the data for those subjects repetitively exposed to F-11 (*16*).

Pulmonary Function Studies

The functional integrity of the pulmonary airways as monitored by the pulmonary function tests did not appear to be affected by either the acute or the repetitive series of exposures. A summary of the spirometric data are listed in Tables 7–10. No trends or consistent changes were noted.

Neurological Studies

No neurological abnormalities occurred during the observation period. The modified Romberg test and the heel-to-toe remained normal. The routine neurological test was unaltered by the exposures (*16–18*).

Table 6. Systolic time intervals of eight subjects who were repetitively exposed to F-11, 1000 PPM, 8 hr/day.

Exposure	F-11 concentration, ppm	Mean times and standard deviations, msec: Electromechanical time period QS_2	Left ventricular ejection time (LVET)	Pre-ejection period (PEP)	PEP/LVET
AM	0 (control)	542.64 ± 14.99	436.55 ± 14.24	103.67 ± 21.69	0.23 ± 0.06
AM	0	543.90 ± 20.71	438.09 ± 14.94	109.56 ± 20.12	0.25 ± 0.05
PM	(control)	534.82 ± 19.12	419.46 ± 12.67	115.35 ± 21.73	0.28 ± 0.06
AM Day 19	1000	543.01 ± 13.53	438.71 ± 15.24	104.24 ± 16.45	0.23 ± 0.05
PM		537.70 ± 14.34	423.33 ± 14.56	114.37 ± 16.90	0.26 ± 0.05
AM Day 20	1000	545.20 ± 14.48	441.29 ± 14.68	103.94 ± 25.15	0.23 ± 0.07
PM		539.68 ± 13.03	428.16 ± 15.28	111.52 ± 21.15	0.26 ± 0.06
AM Day 22	Fluctuating (mean 275)	548.76 ± 14.38	438.56 ± 13.18	110.20 ± 22.44	0.25 ± 0.06
PM		536.97 ± 10.82	427.02 ± 19.24	109.95 ± 21.98	0.25 ± 0.07
AM Day 23	1000	543.19 ± 16.61	435.84 ± 17.53	107.23 ± 25.67	0.25 ± 0.07
PM		537.73 ± 11.20	424.97 ± 15.12	112.75 ± 17.66	0.26 ± 0.05
AM Day 24	1000	547.40 ± 21.13	441.49 ± 19.28	105.90 ± 25.48	0.23 ± 0.06
PM		531.15 ± 16.52	427.21 ± 13.76	103.94 ± 23.48	0.24 ± 0.06

Table 7. Pulmonary function after 5 hr exposure to isobutane.[a]

Condition	FVC, l. BTPS	$\frac{FEV_1}{FVC}$, %	PEFR, l./sec	MMEF, l./sec
Repetitive exposure, 500 ppm, n = 4				
Control	4.30 ± 0.97	87.58 ± 3.49	9.42 ± 2.56	4.74 ± 1.24
1st day, 1st wk	4.44 ± 1.23	85.58 ± 7.67	8.84 ± 2.46	4.54 ± 0.49
3rd day, 1st wk	4.27 ± 1.29	88.65 ± 7.42	8.65 ± 2.71	4.69 ± 0.29
2nd day, 2nd wk	4.32 ± 1.15	86.8 ± 6.29	8.64 ± 2.48	4.44 ± 0.16
5th day, 2nd wk	4.53 ± 1.16	83.85 ± 4.88	8.44 ± 2.27	4.49 ± 0.37
Single exposure, 1000 ppm, n = 3				
Control	4.14 ± 1.01	85.63 ± 5.53	8.67 ± 1.88	4.20 ± 0.30
Single exposure	4.15 ± 0.98	85.17 ± 4.38	8.58 ± 1.72	4.13 ± 0.65

[a] Pulmonary function: FVC = maximum volume of air exhaled after a maximum inspiration; FEV_1/FVC = percent of FVC exhaled in 1 sec; PEFR = maximum rate of air flow during FVC maneuver; MMEF = maximum rate of air flow at midpoint of FVC.

Table 8. Pulmonary function after 5 hr exposure to propane.[a]

Condition	FVC, l. BTPS	$\frac{FEV_1}{FVC}$ %	PEFR, l./sec	MMEF, l./sec
Repetitive exposures, 1000 ppm, n = 4				
Control	5.18 ± 1.30	82.9 ± 4.26	10.62 ± 2.36	5.51 ± 1.82
1st day, 1st wk	5.18 ± 1.74	82.93 ± 3.36	10.26 ± 3.58	5.72 ± 3.13
5th day, 1st wk	5.31 ± 1.80	83.15 ± 1.70	10.53 ± 3.50	5.66 ± 2.62
4th day, 2nd wk	5.10 ± 1.37	83.86 ± 2.76	10.48 ± 2.62	5.34 ± 1.57
5th day, 2nd wk	5.16 ± 1.32	83.91 ± 3.34	10.58 ± 2.56	5.58 ± 1.83
Single exposure, 1000 ppm, n = 4				
Control	5.26 ± 1.47	85.26 ± 2.95	11.25 ± 2.24	5.46 ± 1.37
Single exposure	5.22 ± 1.37	84.13 ± 4.04	10.72 ± 2.38	5.30 ± 1.76

[a] Pulmonary function: FVC = maximum volume of air exhaled after a maximum inspiration; FEV_1/FVC = percent of FVC exhaled in 1 sec; PEFR = maximum rate of air flow during FVC maneuver; MMEF = maximum rate of air flow at midpoint of FVC.

Table 9. Pulmonary function after 6 hr exposure to fluorocarbon-11.[a]

Condition	FVC, l. BTPS	$\frac{FEV_1}{FVC}$, %	PEFR, l./sec	MMEF, l./sec
Repetitive exposure F-11, 1000 ppm, $n = 8$				
Control	5.94	80.6	11.41	4.92
	0.6	5.6	0.7	0.4
4th day, 1st wk	5.76	82.4	11.47	5.09
	0.5	9.1	0.5	0.7
	6.12	81.1	11.73	5.01
4th day, 2nd wk.	0.7	6.2	0.3	0.6
4th day, 3rd wk	6.26	81.1	12.02	5.20
	0.4	4.1	0.6	0.6
4th day, 4th wk	5.81	81.1	11.41	5.10
	0.7	5.1	0.4	0.5
Single exposure F-11, 1000 ppm, $n = 7$				
Control	4.76	76.1	9.08	4.32
	0.4	9.1	0.5	0.7
Single exposure	4.87	74.5	9.81	4.45
	0.7	11.0	0.3	1.1

[a] Pulmonary function: FVC = maximum volume of air exhaled after a maximum inspiration; FEV_1/FVC = per cent of FVC exhaled in 1 sec; PEFR = maximum rate of air flow during FVC maneuver; MMEF = maximum rate of air flow at midpoint of FVC.

Electroencephalography

No significant alterations occurred in the EEGs of any of the subjects under any of the exposure conditions. Time constraints precluded the obtaining of a complete EEG, thus limiting the value of these data. Actual EEG tracings are reproduced in the three project reports (*16–18*).

Visual Evoked Response

The visual evoked responses recorded during the single exposures were remarkedly reproducible and did not indicate any changes attributable to acute exposure to the four propellants at the concentrations studied.

During the repetitive exposures the only significant VER changes observed occurred during the second week of exposure to 500 ppm isobutane During this period a definite reduction in wave amplitude was observed. Representative VER tracings are presented in the three project reports (*16–18*).

Cognitive Tests

With the exception of F-11, exposure to the propellants or to mixtures of propellants did not result in cognitive test performance decrements. The eight male subjects repetitively exposed to F-11 did show statistically significant decrements in cognitive test performance (*16*).

The mean test performances under control and exposure conditions were plotted for each control and exposure day. Then a linear regression line with 75% confidence limits was drawn through the 0 ppm data. After adjusting for the trend through the 0 ppm data, *t*-tests were performed to determine if the exposure data were significantly different from the regression line. The results of these *t*-tests are presented in both graphic and tabular form in the three project reports (*16–18*).

Sporadic individual improvement or decrement in test performance was observed from time to time. However, in the absence of a consistent decrement in test performance or a dose-related response, the test results are interpreted as showing no effect of exposure at the concentrations studied.

ACTH Stimulation Test

Following the repetitive exposures the subjects had normal 24 hr urinary 17-ketosteroid and 17-hydroxyketosteroid excretion. The subjects given an 8 hr ACTH stimulation test (40 units) on two successive days showed a normal response (*16–18*).

Table 10. Pulmonary function after 6 hr exposure to fluorocarbon-12.[a]

Condition	FVC, l. BTPS	$\frac{FEV_1}{FVC}$, %	PEFR, l./sec	MMEF, l./sec
Repetitive exposure F-12, 1,000 ppm, $n = 8$				
Control	5.84 ± 0.6	80.6 ± 5.6	11.41 ± 0.7	4.92 ± 0.4
4th day, 1st wk	5.89 ± 0.5	82.6 ± 6.1	11.51 ± 0.5	4.97 ± 0.7
4th day, 2nd wk	5.85 ± 0.7	83.2 ± 6.2	11.27 ± 0.3	5.13 ± 0.6
4th day, 3rd wk	5.85 ± 0.4	82.5 ± 5.1	11.46 ± 0.6	4.92 ± 0.6
4th day, 4th wk	5.62 ± 0.5	84.9 ± 4.1	11.42 ± 0.4	5.05 ± 0.5
Single exposure F-12, 1000 ppm $n = 7$ males				
Control	4.76 ± 0.4	76.1 ± 9.1	9.08 ± 0.5	4.32 ± 0.7
Single exposure	4.77 ± 0.7	78.5 ± 10.6	9.72 ± 0.6	4.55 ± 0.8
Single exposure F-12, 1000 ppm, $n = 4$ females				
Control	4.10 ± 0.7	78.2 ± 6.1	8.93 ± 0.5	5.10 ± 0.7
Single exposure	4.00 ± 0.5	76.7 ± 9.2	9.10 ± 0.6	4.85 ± 0.6

[a] Pulmonary function: FVC = maximum volume of air exhaled after a maximum inspiration; FEV_1/FVC = percent of FVC exhaled in 1 sec; PEFR = maximum rate of air flow during FVC maneuver, MMEF = maximum rate of air flow at midpoint of FVC.

Breath Analysis

Isobutane, propane, F-12, and F-11 were readily detected in the expired breath of each of the subjects following exposure to the concentrations investigated. These post-exposure breath data are detailed in the project reports (*16–18*). Examination of these breath data reveals that a predictable excretion pattern exists for each of the exposure conditions studied, and that the following factors influence the concentration of the propellant in the breath: concentration of inspired gas or vapor, duration of exposure, and length of time post-exposure that the breath sample is obtained. From the data presented a "family" of post-exposure breath excretion curves useful in estimating the magnitude of exposure can be constructed (*16–18*).

Blood Analysis

Isobutane, propane, F-12, and F-11 were present in detectable concentrations in the blood of the subjects exposed under the conditions of this experiment. However, the sensitivity of the analytic method severely limits the usefulness of this technique for monitoring the body burden except in the early post-exposure interval (*16–18*).

Comments

Acute exposures to isobutane, propane, F-12, and F-11 in concentrations of 250, 500, or 1000 ppm for periods of 1 min to 8 hr did not produce any untoward physiological effects as monitored by the methods employed. Repetitive exposures to these four propellants were also without measurable untoward physiological effect with the exception of the eight male subjects repetitively exposed to 1000 ppm F-11, who did show minor decrements in several of the cognitive tests. Should these observations prove representative of the general population, a significant percentage of persons identically exposed to the upper industrial limits of F-11 would be expected to show similar decrements in cognitive function. Fortunately, the magnitude of the decrements observed was minute and transient. In the opinion of the investigators, these small decrements occurring during repetitive exposures were spurious in that similar decrements were not observed in the subjects acutely exposed to the same concentration for equal periods of time. Further research on the effect of F-11 on cognitive function is merited.

Of particular importance is the observation that none of the subjects showed any decrement in pulmonary function or alteration in cardiac rhythm as the result of exposure to concentrations of the gases or vapors far higher and of much greater duration than would occur in the normal use of commercial aerosols in the home. Thus, it would seem that exposure to the current Threshold Limit Value (TLV) for American industry does not have the potential to adversely affect a normal heart or lungs.

These extended observations fail to corroborate the speculation of Speizer et al., who performed less comprehensive studies and suggested that brief exposures to fluorocarbons could result in the development of cardiac arrhythmias (*11*).

The analysis of expired breath for isobutane, propane, F-12, or F-11 in the early post-exposure period provides a feasible diagnostic test of exposure. The use of gas chromatography permits the detection of the gases or vapors for at least 5 hr after exposure to the TLV. Serial breath analyses following exposure provides a means to estimate the magnitude of exposure since the amount of a gas present following exposure is determined by the inspired concentration, the duration of exposure, and the elapsed time following exposure.

Summary

Acute exposures to isobutane, propane, F-12, and F-11 in concentrations of 250, 500, or 1000 ppm for periods of 1 min to 8 hr did not produce any untoward physiological effects as determined by the methods employed which included serial EKGs and continuous monitoring of modified V_5 by telemetry during exposure. Repetitive exposures to these four propellants were also without measurable untoward physiological effect with the exception of the eight male subjects repetitively exposed to 1000 ppm F-11, who did show minor decrements in several of the cognitive tests. Of particular importance is the observation that none of the subjects showed any decrement in pulmonary function or alteration in cardiac rhythm as the result of exposure to concentrations of the gases or vapors far greater than encountered in the normal use of aerosol products in the home.

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