Isobutane was not mutagenic in the Ames assay with or without activation. No studies were found in the literature evaluating the carcinogenicity of isobutane.

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文献 17

SKIN IRRITATION INHALATION TOXICITY STUDIES OF Aerosols USING METHYLENE CHLORIDE

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Research has established the performance characteristics of methylene chloride as a solvent and vapor depressant in hydrocarbon propellant systems; fast drying rate, low odor, reduced flammability, and lower cost compared with fluorocarbons. Recently, two toxicology studies were completed by Helene Curtis Industries and Dow Chemical. One was conducted to determine the effect on skin of a deodorant and an antiperspirant using methylene chloride with a hydrocarbon propellant system. Results of this study show that the formulations tested pose no skin irritation hazard under normal use conditions.

The second study involved inhalation toxicity characteristics of the same deodorant formulation on monkeys. The only effect seen was a lens nuclear outline in the eyes of monkeys exposed at the highest level. Since the low exposure level did not produce an observable lens nuclear outline, even though it is also an exaggerated exposure, and since no other effects were observed, it is unlikely that an opthalmologic effect would occur in users of the test deodorant.

Purpose of this study was to determine the effect on skin of a deodorant and an antiperspirant employing a hydrocarbon propellant system with methylene chloride as the vapor pressure depressant and solvent. The study, conducted by an independent research laboratory[1] utilized formulations typical of those being considered for propellant systems utilizing hydrocarbon gas and methylene chloride. Aerosol

TABLE I

TEST FORMULATIONS

DEODORANT #433181-10

	Wt.%
Concentrate (Powder Type)*	14.0
Methylene Chloride (AEROTHENE MM)	21.5
Hydrocarbon A-46 (Propane-isobutane)	64.5
	100.0

*CONCENTRATE
- **Sodium bicarbonate
- Starch
- Isopropyl myristate
- SD Alcohol 40-C
- PEG-8 Laurate
- Hydrated silica
- Stearalkonium hectorite
- Triclosan
- Fragrance
- Propylene carbonate

**Comprises 2% total product weight

ANTIPERSPIRANT #D4247-41A

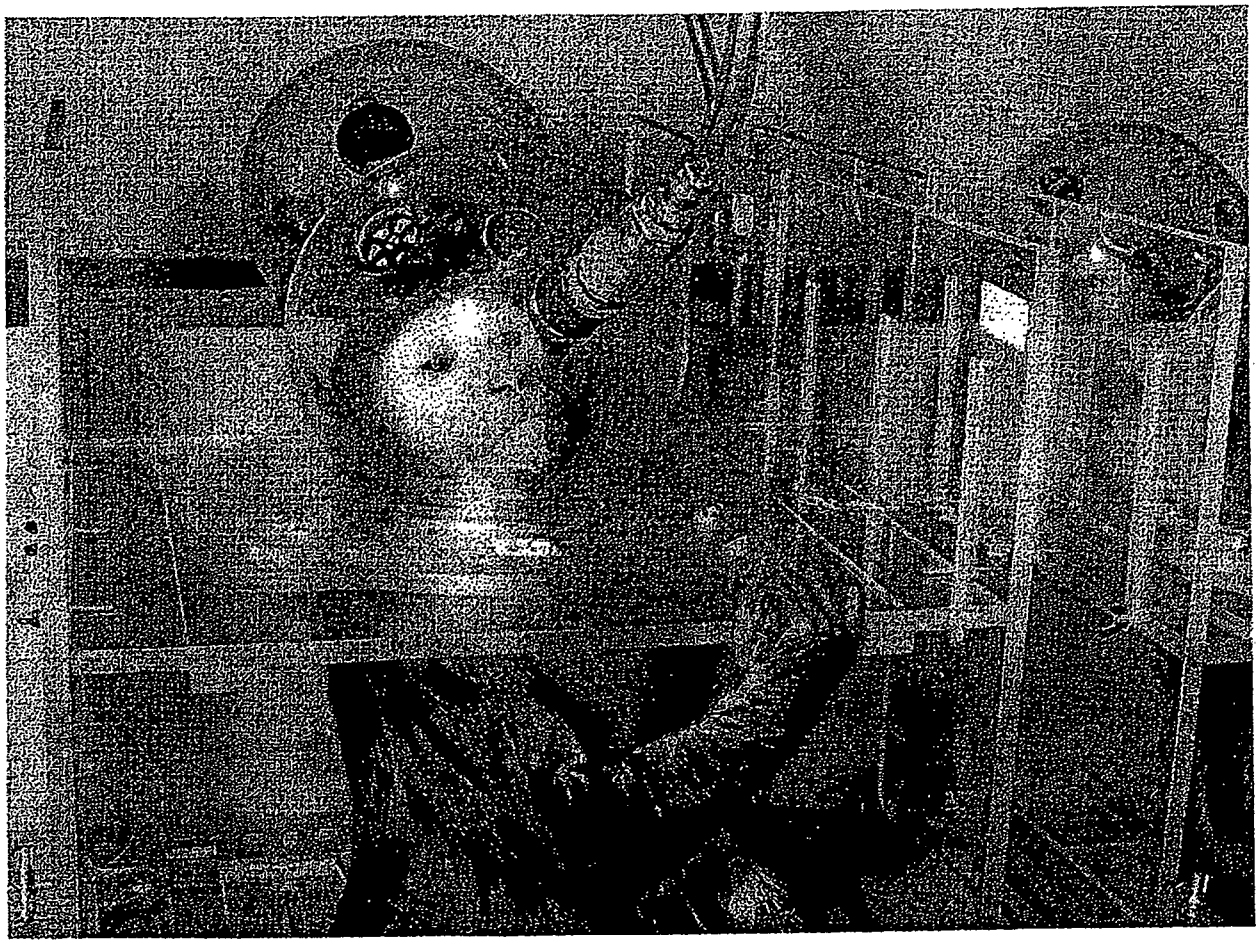
	Wt.%
Concentrate (Aluminum chlorohydrate type)*	10.0
Methylene Chloride (AEROTHENE MM)	20.0
Hydrocarbon A-46 (Propane-isobutane)	70.0
	100.0

*CONCENTRATE
- **Aluminum chlorohydrate
- Isopropyl myristate
- Fumed silica
- Fragrance

**Comprises 4.7% total product weight

[1]Work conducted by the Clinical Evaluation Department of Industrial Bio-Test Inc., Northbrook, Ill.

38~40, 42, 45, 150, 152



products submitted for clinical evaluation were identified as deodorant formulation #443181-10 and antiperspirant formulation #D4247-41A (compositions shown in Table I).

A population of 125 human adult subjects, ranging from 18 to 60 years, was utilized, with the study conducted under the supervision of a consulting dermatologist. Both products were evaluated for 12 weeks. An initial pre-usage examination of the subjects was conducted by the dermatologist, at which time a baseline demography was recorded and all subjects filled out a product questionnaire. Examinations then were conducted by the dermatologist after 1, 2, 4, 8 and 12 weeks of product usage. Scoring criteria used by the dermatologist for grading irritation are:

0 No reaction
1 Very slight erythema (reddening)
2 Slight erythema
3 Distinct, moderate erythema
4 Erythema plus edema (swelling)
5 Vesicles (small localized eruption)
6 Bulla (blister)

Following initial examination by the dermatologist, the subjects were randomly divided into two groups. Group 1 consisted of 75 subjects who received the deodorant: Group 2 of 50 subjects using the antiperspirant. The distribution broke down like this:

Group	Test Material	Number of Males	Number of Females	Total
1	Deodorant	47	28	75
2	Antiperspirant	25	25	50

Each subject was issued deodorant or antiperspirant at the time of the initial exam and again as needed for duration of the 12-week study. Subjects were instructed not to change their normal hygiene habits or use of cosmetics, the exception being that no other underarm products be used. Directions for use were as follows:

"You must shake the can well before use and spray the entire axillary vault of both arms for two seconds at a distance of six

TABLE II

TEST MATERIAL: Aerosol Spray Deodorant #443181-10
In-Use Safety Study
Summary of Axillary Condition (Twice-A-Day Use)

		Initial		Week 1		Week 2		Week 4		Week 8		Week 12		
		R	L	R	L	R	L	R	L	R	L	R	L	Total*
Incidence of scores of:	0	54	56	65	64	62	58	60	61	63	63	67	63	626
	1	20	19	6	6	11	15	12	11	12	12	8	11	104
	2	1	0	1	2	0	0	2	2	0	0	0	1	9
	3	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total	75	75	72	72	73	73	74	74	75	75	75	75	

*Total excluding initial examination

TABLE III

TEST MATERIAL: Aerosol Spray Antiperspirant #D4247-41A
In-Use Safety Study, Summary of Axillary Condition
Twice-A-Day Use

		Initial		Week 1		Week 2		Week 4		Week 8		Week 12		
		R	L	R	L	R	L	R	L	R	L	R	L	Total*
Incidence of scores of:	0	46	46	45	45	43	43	44	48	44	45	49	49	455
	1	4	4	5	4	6	6	5	1	6	5	1	1	40
	2	0	0	0	1	1	1	0	0	0	0	0	0	3
	3	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total	50	50	50	50	50	50	49	49	50	50	50	50	

*Total excluding initial examination

inches. You must rinse your underarms prior to each application of test material and you are to use the product twice a day for 12 weeks."

All subjects were requested to report immediately any adverse reaction so it could be observed and diagnosed by the dermatologist.

Tables II and III summarize the results for both test products. The results showed only very slight transient erythema at random examination periods. In view of the very low order of severity and random occurrence, reactions were reported to be normal, negligible, and not necessarily product-induced.

Results for the antiperspirant showed only very slight transient erythema at random examination periods. In view of the very low order of severity and random occurrence, reactions were reported to be normal, negligible, and not necessarily product-induced.

In the opinion of the consulting dermatologist both the tested deodorant and antiperspirant would be considered safe for marketing under normal conditions of use based on results of this study. This study shows methylene chloride in levels of usage up to 21.5 per cent by weight causes axillary area irritation.

INHALATION TOXICITY STUDY IN STUMP-TAIL MONKEYS

This study, also conducted by an independent research laboratory[2] was designed to determine the toxicity in monkeys of an aerosol spray deodorant containing methylene chloride with a hydrocarbon propellant. The study was conducted for Helene Curtis Industries, Inc.

The aerosol spray test material was identified as follows:

"Deodorant; 443181-10; Shake Well Before Using; 11/25/75"

This formulation is described in Table I and is the same formulation used in the skin irritation study.

[2]Food and Drug Research Laboratories Inc., Waverly, N.Y.

Nine male and nine female stumptail monkeys (Macaca arctoides) were obtained from a licensed commercial primate importer and held in quarantine 30 days before shipment to the laboratories. The animals had twice been tuberculin tested at the laboratories and found negative (and tested at three month intervals thereafter). They were observed for evidence of illness and absence of ophthalmologic abnormalities during a six-week period, and found to be healthy.

The animals were housed in individual primate cages in an air conditioned and humidity controlled room. Twice, prior to start of the study, physical, clinical and physiological parameters were measured.

Eighteen normal monkeys were distributed by sex into three equal groups consisting of three males and three females each. These groups were exposed as follows:

Group A—Control or sham-treated (air, chair control).

Group B—Exposed to air drawn from a mixing chamber which received a one-second spray of the test material at 42-minute intervals for 6 hours. (0.5 mg/liter).

Group C—Exposed to air drawn from a mixing chamber which received a five-second spray at 21 minute intervals for six hours. (5.0 mg/liter).

The animals were trained to sit in restraining chairs and to accept individual inhalation helmets. The mixing chamber air containing the test material was drawn through the individual chambers at a rate of four liters per minute by an exhaust pump to produce a total flow of 24 1/min. The spray cans delivered 0.5 g of formulation per second of spray. Thus the average nominal concentrations for the exposure group were Group B, 0.5 mg/liter and Group C, 5.0 mg/liter.

At varying intervals during the study, particle size and number were determined suing a light scattering device for a complete interval i.e., 42 minutes for the low concentration, 21 minutes for the high concentration. Samples for particle size measurements were taken directly from the exposure helmets. Concentration of methylene chloride as a function of time was estimated for the mixing chamber and helmets using a kinetic model. It was assumed that all methylene chloride entered the vapor state instantaneously in the mixing chamber.

All animals were observed daily for 30 days prior to start of the study and during the study's 90 days for general appearance, behavior, morbidity, mortality, appetite and stool consistency. Body weights were recorded weekly.

Opthalmoscopic Examinations: Prior to initiation and immediately before sacrifice of the animals, a thorough opthalmoscopic examination was performed on each animal by a veterinary ophthalmologist. For these examinations the animals were sedated with sernylan and their pupils dilated with 1% mydriacyl. Anterior and posterior segments were examined with the indirect microscope.

Electrocardiograms: Twice prior to initiation and at 30 and 90 days of the study electrocardiograms were made on anesthetized animals.

Tidal volume of each animal was measured twice prior to initiation and at 30 and 90 days. Expired air used to measure tidal volume was collected using hoses, exhalation and inhalation check valves from a veterinary anesthesia machine. The animals were placed in a chair, the mask secured over the face. An empty gas bag was secured over the exit of the exhalation check valve. The inspired air entered through the inhalation check valve, expired gases exiting through the exhalation check valve and collected in the gas bag. Respiratory rate was counted during the collection period and length of time required to collect the volume of gases was recorded. Volume of expired gases in the bag was measured by water displacement.

Twice during the pretest period and 30 and 90 days into the study the animals were not fed, but allowed water **ad libitum** for a period of 18-24 hours, after which blood samples were taken. The blood samples were used to determine values for fasting blood sugar, blood urea nitrogen, serum transaminases (SGOT/SGPT), alkaline phosphatase, pH, pCO_2, pO_2 total protein and bilirubin. At the same intervals as the clinical chemistry, hematology values were determined for white blood cell count, differential white blood cell count, red blood cell count, platelets, reticulocytes, erythrocyte sedimentation rate, hematocrit and hemoglobin. Urine also was collected at these intervals and determinations made for glucose, protein, ketones, pH, and microscopic examination of sediment.

Necropsies were performed on all animals at termination of the study and any gross abnormalities recorded. The following tissues were fixed in 10 per cent neutral buffered formalin, sectioned, stained with hematoxylin-eosin and ex-

amined for histopathologic lesions: brain, nasopharynx, pituitary, eye, thyroid, esophagus, trachea, lung, liver, heart, spleen, pancreas, mesenteric lymph node, stomach, small and large intestines, kidney, adrenals, spinal cord, sciatic nerve, skeletal muscle, gallbladder, salivary gland, thymus, aorta, nose, turbinates, and urinary bladder. Special attention was given to tissues and organs of the respiratory tract.

After removal of eyes, brain, and pituitary, the skull was bisected sagittally into right and left halves, to expedite fixation of nasal and respiratory mucosa by formalin. Lungs and trachea were removed **in toto** and formalin was instilled through the trachea into the lungs to a final volume approximating their normal **in situ** size. The trachea was occluded by ligation and the entire organ saved in formalin.

For microscopic examination, tissues were trimmed, processed for, and embedded in paraffin, sections microtomed at 3 to 5 microns thickness, and stained with hematoxylin and eosin. One or more cross sections of trachea and esophagus and 1 to 3 cross sections of main bronchi were prepared from each animal. Three to six large sections of lung were prepared. From one side of the head, three large sections were taken to include margins of the nostril with vestibule and septum, turbinates, and posterior nasopharynx. These sections were submitted for extended decalcification in EDTA (ethylenediaminetetraacetic acid).

Concentrations of formulation and methylene chloride reached in the mixing chamber and helmets as a function of time in each spraying cycle are listed in Table IV. The kinetic model shows that the concentration of formulation and methylene chloride should have reached zero at both exposure levels before start of the next spraying cycle.

Particle size measured in the helmets showed the mean particle size to be below one micron. For example, in a typical high exposure spray cycle, ten minutes after spraying, the median diameter of the particles was 0.57μ with a geometric standard deviation of 1.79μ. The particle count exceeded the capacity of the instrument in the first five to six minutes of the spray cycle for the high exposure group. In a typical low exposure helmet, the median diameter was 0.61μ with a geometric standard deviation of 1.86μ. Virtually all particles were less than 10μ in both exposure groups. Particle size measurements showed that particle counts reached background levels between 10-15 minutes in the high exposure level, 5-7 minutes in the low exposure group. Some solid material from the spray collected in the mixing chanber and did not carry through the exposure helmets.

All animals survived the experiment, and none of the monkeys exposed to the deodorant formulation showed significant behavioral changes after exposure of six hours per day, five days per week for 90 days. All animals appeared similar to the controls which were sham-treated. No significant differences in body weight changes were observed from those of the controls. With regard to hematological findings, biochemical data and urinalysis, all clinical parameters were within normal limits, with no significant differences between control and treated animals.

Final ophthalmoscopic examinations showed no ocular abnormalities in the control or low exposure group. However, all animals in the high test group had an observable lens nuclear outline. Electrocardiograms did not reveal any significant change between pretest and test period readings. Tidal volumes and respiratory rates of the individual animals and/or groups of animals were not significantly changed from pretest values after 90 days of inhalation exposure to the deodorant formulation.

(Continued on page 150)

TABLE IV

Calculated Concentrations of Deodorant Formulation and Methylene Chloride in Mixing Chamber and Exposure Helmets During Each Spray Cycle

High Exposure Group — 21 Minute Spray Cycle

	Mixing Chamber		Helmets	
Time (Min)	Formulation (Mg/l)	Methylene Chloride (ppm)	Formulation (Mg/l)	Methylene Chloride (ppm)
0	129	7964	—	—
0.5	70	4322	54.3	3365
1.0	38	2347	51.7	3199
1.5	20.6	1274	37.1	2295
2.0	11.2	691	23.8	1474
3.0	3.3	204	8.4	523
5.0	0.29	17.7	0.84	52
7.0	0.025	1.5	0.076	5
Low Exposure Group — 42 Minute Spray Cycle				
0	26	1587	—	—
0.5	14	861	10.8	670
1.0	7.6	468	10.3	637
1.5	4	253	7.4	457
2.0	2.2	138	4.7	294
3.0	0.66	41	1.7	104
5.0	0.06	4	0.17	10
7.0	0.005	0.3	0.02	1

tranquilizer and a smaller increase for Enduron and Enduronyl, drugs to treat hypertension.

Sterling Drug's sales increased a modest 6.1 per cent, in spite of currency devaluation problems and regulatory problems with the parenteral plant at Rensselaer, N.Y. Construction of a new 263,-000 square foot plant in McPherson, Kan. for production of injectible medicines, is completed and this is expected to fill some production gaps in evidence last year.

A.H. Robbins says it now ranks fifth among U.S. pharmaceutical manufacturers, based on new prescriptions written last year in the U.S. Consolidated net sales grew 18 per cent last year to $284.9 million, net earnings by 23 per cent (though in the latter category, a fund set aside to defend against suits in that Dalkon intrauterine device problem will bring earnings down to 13 per cent).

Pfizer's sales climbed close to $2 billion (to $1.887 billion), with pharmaceutical and hospital products accounting for $930.2 million (up 11 per cent). Research and development expenses reached 88.1 million, but capital additions fell from $177.4 million to 82 million. The giant company now boasts 134 production facilities in 40 countries, with 40,081 employees worldwide. Some important new products are slated for introduction soon: bacampicillin, an improved broad spectrum semisysnthetic penicillin; piroxicam, a new non-steroidal agent for treating rheumatoid arthritis; and oxantel/pyrantel, a new broad spectrum anthelmintic. □

METHYLENE CHLORIDE

(From page 45)

Careful gross and microscopic examination of 18 monkeys after 90 days of inhalation study showed expected evidence of parasitism but no changes related to test material or testing methodology.

It is not evident to what degree observation of a lens nuclear outline at this high exposure level should affect hazard evaluation. Certainly, concentration of formulation was very high for this exposure group. To compare this exposure to a situation, the following calculation can be made. In the worst likely use situations, the spray might

be used in a confined space (an unventilated bathroom, 6′ × 8′ × 8′ in dimensions or about 10,000 liters in volume). If each axilla is sprayed for two seconds, then two sprays or four seconds × 500 mg/sec (the spray rate of the can) or 2000 mg of aerosol formulation would be dispensed per use cycle. If this amount is diluted in one-third the volume of the room, the concentration which the user is exposed would be 2000 mg ÷ 3300 l of air or 0.6 mg/l. (This represents 37 ppm of methylene chloride in the air). The user is not likely to remain in the atmosphere more than a few minutes, and is not likely to use the formulation more than two or three times per day. Levels to which the monkeys were exposed were much higher. Assuming the formulation was distributed instantaneously in the mixing chamber, the highest concentration of formulation reached would be 500 mg/19.6 l or 25.5 mg/l for the low exposure group and 2,500 mg/19.6 l or 127 mg/l for the high exposure group. Although these concentrations begin to drop immediately after spraying stops, theoretically the monkeys could get a brief exposure to levels of nearly 25.5 or 127 mg/l. These represent concentrations of 5.48 and 27.3 mg/l of methylene chloride (1580 and 7860 ppm respectively). In order for humans to get concentrations as high as 27.3 mg/l a two-second spray of 1000 mg would have to be diluted in only 37 l of air. That means it would have to be sprayed directly into the face. It should also be noted that this occurred 17 times each day for the monkeys.

CONCLUSION

No adverse physiological or behavioral responses were observed following inhalation exposure to the deodorant formulation at nominal dosage levels of 0.5 and 5 mg per liter for six hours daily, five days per week for 13 consecutive weeks. Gross and microscopic pathological examination of the monkeys and their tissues revealed no changes in animals exposed to the formulation which differed from the control animals. However opthalmoscopic examination at the end of the exposure period revealed an observable lens nuclear outline in all animals in the high exposure group.

Since the low exposure level did not produce an observable lens nuclear outline, even though it is also an exaggerated exposure, and since no other effects were observed, it is not likely that an opthalmologic effect would occur in users of the test deodorant spray. □

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TOXICITY OF AEROSOL PROPELLANTS IN THE RESPIRATORY AND CIRCULATORY SYSTEMS

VIII. RESPIRATION AND CIRCULATION IN PRIMATES*

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SUMMARY

The low-pressure propellants influence predominantly the circulation, whereas the high pressure propellants affect the respiration in anesthetized monkeys. There are four groups according to the level of toxicity: *Class 1*, low-pressure propellants of high toxicity that cause tachycardia and hypotension; *Class 2*, low-pressure propellants of intermediate toxicity that influence either circulation or respiration or both; *Class 3*, high-pressure propellants of intermediate toxicity that cause bronchoconstriction; and *Class 4*, high-pressure propellants of low toxicity that do not influence respiration or circulation even when inhaled at levels of up to 20% concentration.

INTRODUCTION

So far in this series of investigations the effects of 8 propellants have been identified in two animal species: 7 in the rat [7] and 3 in the mouse [4]. 3 of the propellants cause bronchoconstriction and respiratory depression, and 5 influence only bronchomotor tone or respiration but not both. Since there are 15 propellants that are being compared, the respiratory profile is still unknown for 7. For the sake of completeness, all 15 are presently compared in the monkey with measurements of respiratory minute volume, pulmonary resistance and pulmonary compliance. The aortic blood pressure and heart rate are also recorded to arrive at a general statement as to the comparative sensitivity of the respiratory and circulatory systems.

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This is the third comparison of all 15 propellants which has not been hitherto attempted. The first one was for the detection of proarrhythmic activity in mice [1] and the second concerned depression of cardiac contractility in the monkey [3]. The results were used to classify the propellants on the basis of their potency and the nature of the cardiotoxicity involved. The differentiation of the propellants on the basis of their vapor pressure was completely ignored. However, since recent events have prompted the necessity to discard some widely used propellants, the choice of substitutes would be facilitated if the classification would separate the high-pressure propellants from the low-pressure ones. The differentiation between the two is based on the vapor pressure and boiling point: propellants with vapor pressure less than 31 psig and boiling point above −11° are *low-pressure* ones and those with a higher vapor pressure and lower boiling point are characterized as *high-pressure*. The classification which is proposed below takes into consideration the pressure as well as the level of toxicity affecting the respiratory and circulatory systems.

EXPERIMENTAL MATERIALS AND METHODS

Propellants administered by inhalation

The fifteen compounds are grouped according to their vapor pressure and boiling point into high- and low-pressure propellants. All but five are fluorinated and are identified by fluorocarbon (FC) numbers which denote the position of the fluorine and chlorine substitution. The chemical structures of the compounds arranged in the decreasing order of the boiling point at one atmosphere are as follows:

	Boiling point °C	Vapor pressure psig at 20°C
Low-pressure propellants		
Trichloroethane	74.1	−12.5
FC 113; Trichlorotrifluoroethane	47.6	− 9.2
Methylene chloride	40.1	− 7.3
FC 11; Trichlorofluoromethane	23.8	− 1.3
FC 21; Dichloromonofluoromethane	8.9	8.4
FC 114; Dichlorotetrafluoroethane	3.8	12.9
FC C-318; Octafluorocyclobutane	− 5.8	25.4
FC 142b; Monochlorodifluoroethane	−10.0	29.1
Isobutane	−10.2	30.0
High-pressure propellants		
Vinyl chloride	−13.9	31.5
FC 152a; Difluoroethane	−24.7	63.0
FC 12; Dichlorodifluoromethane	−29.8	70.2
FC 115; Chloropentafluoroethane	−38.7	103.0
FC 22; Monochlorodifluoromethane	−40.8	121.4
Propane	−42.2	130.3

With the exception of FC 11, all of the compounds examined exist in the vapor or gaseous phase at normal ambient temperature and pressure and were therefore stored in pressure cylinders. The desired concentrations were attained by delivering a metered volume of the gas from the cylinder and diluting it with a known volume of air. The vapor of fluorocarbon 11(boiling point 23.8°) was generated by heating the compound in a water bath. The following concentrations were used: 2.5, 5, 10 and 20% of the vapor or gas in air. The mixture was administered for 5 min alternately with room air for 15 min.

Measurement of bronchopulmonary function

Rhesus monkeys (*Macaca mulatta*), weighing from 1.8 to 2.7 kg, were anesthetized by intravenous injection of 30 mg/kg sodium pentobarbital and the trachea was cannulated. Lead II electrocardiogram and femoral arterial blood pressure were recorded. Pulmonary resistance and compliance were estimated from measurements of tracheal air flow and transpulmonary pressure. The tracheal cannula was connected to a mesh screen Fleisch pneumotachograph with a heating unit to maintain inspired air at a constant temperature, and the pressure difference across the screen was measured by a differential pressure transducer. The signal from the transducer corresponding to air flow was in turn integrated and recorded as tidal volume. Respiratory minute volume was obtained by means of an integrating preamplifier which converted the flow measurements into volume.

The pressure difference between the trachea and the intrapleural space was measured with a second differential transducer. To determine pulmonary resistance, the flow and pressure signals were displayed simultaneously on both axes of the oscilloscope screen to show a Pressure-Flow loop. Subsequently an amount of pressure proportional to volume was subtracted, so that the loop was closed at zero flow. The slope of the line thus obtained corresponded to pulmonary resistance. The values for compliance were obtained similarly by displaying the Pressure-Volume signals and subtracting pressure due to resistance, or by calculation from the subtracted pressure when closing the resistance loop [8].

RESULTS

The classification that is being used is based on consideration of the vapor pressure of the propellant as well as of the minimal concentration that influences the various parameters relating to the circulatory and respiratory systems. The 9 *low-pressure* propellants are divided into two classes: *Class 1*, those that influence cardiovascular function in concentrations of 2.5 to 5%; and *Class 2*, those that influence cardiovascular and bronchopulmonary function in concentrations of 10 to 20%. The 6 *high-pressure* propellants also are divided into two classes; *Class 3*, those that influence bronchopulmonary function in concentrations of 10 to 20%; and *Class 4*, those that do not influence cardiovascular and bronchopulmonary function in inspired concen-

tration levels of up to 20%. For brevity, the concentrations are identified as follows: 2.5 to 5% to represent a *high* level of toxicity, 10 to 20% as *intermediate*, and the *low* level for those that had no detectable toxicity when inhaled in concentrations of up to 20%.

Class 1: Low-pressure propellants of high toxicity

The 5 members are listed in Table I with their respective effects on the various measurements. The characteristic features common to all 5 propellants are tachycardia and hypotension at concentrations of 2.5 to 5%. The effects on respiration are varied; two of them cause depression of respiratory minute volume, three an increase in compliance, and four a decrease in pulmonary resistance. The special features for each propellant are as follows: FC 11 causes the most intense tachycardia and hypotension. FC 21 is the most potent depressant for respiratory minute volume. FC 113 is second to FC 11 in the degree of cardiovascular effect, but FC 113 is more potent than FC 11 in decreasing pulmonary resistance and increasing compliance. Trichloroethane is the propellant that causes a significant fall in resistance and respiratory minute volume but an increase in compliance. Methylene chloride has no effect on respiratory minute volume but has the most potent action on pulmonary resistance and compliance.

Class 2: Low-pressure propellants of intermediate toxicity

The 4 members are listed in Table II. The effective inhaled concentrations are 10 to 20%, which influence either respiration or circulation or both. FC 114 affects both and causes specifically tachycardia, hypotension, respiratory depression and an increase in pulmonary resistance. FC 142b causes hypotension but also respiratory stimulation, an effect that is unique, since no other propellants belonging to this class or other classes exert such an action. Isobutane does not influence circulation but increases resistance and depresses respiratory minute volume. FC C-318 causes an increase in resistance but has no effect on minute volume, heart rate or blood pressure.

Class 3: High-pressure propellants of intermediate toxicity

The characteristic feature of the 4 members is an increase in pulmonary resistance or bronchoconstriction (Table III). The additional effects vary among the propellants, as follows: FC 12 decreases compliance, reduces blood pressure and accelerates the heart rate. FC 22 does not decrease compliance but influences the other four parameters. Propane has the most limited influence — only bronchoconstriction and respiratory depression. Vinyl chloride affects all three respiratory parameters but not circulation.

Class 4: High-pressure propellants of low toxicity

The 2 members listed in Table IV do not influence respiration or circulation, even when inhaled in levels up to 20% concentration.

DISCUSSION

The most important conclusion drawn from the above experiments is the

TABLE I

LOW-PRESSURE PROPELLANTS OF HIGH TOXICITY (MEAN ± SEM)

Propellant	% Conc. v/v	Monkey No.	Pulm. resistance			Pulm. compliance			Resp. min. vol.		
			Control	Response	%Δ	Control	Response	%Δ	Control	Response	%Δ
			cm H_2O/l/sec			ml/cm H_2O			ml/min		
FC 11 (Trichloro-fluoromethane)	2.5	3	28.6 ± 1.0	27.9 ± 0.7	− 2.00 ± 2.00	7.6 ±0.7	7.3 ±0.6	+ 3.00 ± 3.00	699 ± 197	744 ± 238	± 4.00 ± 4.00
	5.0	4	35.3 ± 2.3	33.0 ± 3.1	− 7.00 ± 4.00	7.0 ±0.1	7.4 ±0.4	+ 7.00 ± 4.00	612 ± 142	541 ± 104	− 9.00 ± 4.00
FC 21 (Dichloro-fluoromethane)	2.5	3	27.9 ± 2.2	27.2 ± 1.4	− 2.00 ± 2.00	7.7 ±0.6	7.8 ± 0.6	+ 1.00 ± 1.00	442 ± 59	274 ± 68	−39.00 ±10.00
	5.0	4	32.7 ± 1.00	29.4 ± 1.0	−10.00[a] ± 1.00	7.4 ±0.6	8.0 ±0.7	+ 8.00 ± 1.00	455 ± 91	203 ± 24	−50.00[a] ± 9.00
FC 113 (Trichlorotri-fluoroethane)	2.5	3	21.78 ± 3.49	19.69 ± 2.71	− 8.87 ± 4.75	6.87 ±0.43	7.27 ±0.41	+ 5.97 ± 2.30	1230 ± 47.3	1250 ± 28.9	+ 1.80 ± 1.80
	5.0	3	21.58 ± 3.00	18.84 ± 2.47	−12.07 ± 6.64	6.67 ±0.58	7.50 ±0.25	+13.95 ± 8.80	1292 ± 99	1302 ± 72	+ 1.10 ± 3.20
Trichloro-ethane	2.5	3	20.38 ± 2.56	18.52 ± 2.11	− 8.87 ± 1.07	7.20 ±0.72	7.80 ±0.72	+ 8.49 ± 1.55	1352 ± 30.3	1243 ± 32.4	− 8.1[a] ± 0.5
	5.0	3	21.22 ± 2.99	18.08 ± 3.04	−15.43 ± 2.30	7.06 ±0.56	8.16 ±0.71	+15.52 ± 3.55	1352 ± 30.3	1183 ± 11.9	−12.4[a] ± 2.1
Methylene chloride	2.5	3	20.38 ± 2.56	18.53 ± 3.43	−10.48 ± 7.80	6.90 ±0.38	7.63 ±0.47	+10.90 ± 6.18	1280 ± 111	1247 ± 79	− 2.22 ± 2.20
	5.0	3	22.83 ± 3.72	13.72 ± 3.83	−32.08 ±12.93	6.90 ±0.56	8.26 ±0.39	+20.58[a] ± 5.99	1300 ± 100	1227 ± 37	− 5.00 ± 4.20

[a] $p < 0.05$.

TABLE I (continued)

Propellant	% Conc. v/v	Monkey No.	Heart rate			Aortic blood pressure		
			Control beats/min	Response	%Δ	Control mm Hg	Response	%Δ
FC 11 (Trichloro-fluoromethane)	2.5	3	183 ± 7	213 ± 19	+16.00 ± 7.00	91.7 ± 8.3	71.7 ± 6.0	−22.00[a] ± 2.00
	5.0	4	175 ± 7	239 ± 23	+36.00[a] ±10.00	85.0 ± 5.8	45.0 ± 2.9	−46.00[a] ± 5.00
FC 21 (Dichloro-fluoromethane)	2.5	3	145 ± 22	168 ± 32	+15.00 ±10.00	87.7 ± 1.4	76.2 ± 5.9	−13.00 ± 7.00
	5.0	4	150 ± 12	177 ± 17	+17.00 ± 5.00	81.2 ± 6.6	60.0 ± 2.0	−25.00[a] ± 5.00
FC 113 (Trichlorotri-fluoroethane)	2.5	3	169 ± 13.65	199 ± 19.09	+18.07 ± 8.14	101.67 ± 1.67	93.00 ± 3.05	− 8.54[a] ± 2.36
	5.0	3	173.33 ± 12.02	221.67 ± 21.67	+27.85[a] ± 8.58	110.67 ± 5.78	82.33 ± 2.33	−25.15[a] ± 4.75
Trichloro-ethane	2.5	3	175.66 ± 18.96	182.66 ± 13.53	+ 4.23 ± 4.26	105.66 ± 0.66	95.66 ± 0.66	− 9.44[a] ± 1.04
	5.0	3	175.66 ± 10.90	202.66 ± 8.97	+18.13[a] ± 7.75	108.33 ± 1.66	85.00 ± 2.88	−21.43[a] ± 3.81
Methylene chloride	2.5	3	174.33 ± 15.56	187.33 ± 18.70	+ 7.00 ± 4.29	− 3.00 ± 4.58	90.00 ± 2.89	−12.46[a] ± 2.63
	5.0	3	174.66 ± 12.66	205.66 ± 6.69	+18.68[a] ± 6.88	106.66 ± 4.41	86.33 ± 3.48	−19.05[a] ± 0.95

TABLE II

LOW-PRESSURE PROPELLANTS OF INTERMEDIATE TOXICITY (MEAN ± SEM)

Propellant	% Conc. v/v	Monkey No.	Pulm. resistance			Pulm. compliance			Resp. min. vol.		
			Control	Response	%Δ	Control	Response	%Δ	Control	Response	%Δ
			cm H_2O/l/sec			ml/cm H_2O			ml/min		
FC 114 (Dichlorotetra-fluoroethane)	5.0	3	21.70 ± 1.74	22.03 ± 1.71	+ 1.59 ± 1.59	6.83 ±0.60	6.77 ±0.43	—0.56 ±2.42	1413 ± 52	1394 ± 146	— 1.84 ± 6.80
	10.0	3	19.75 ± 0.80	20.89 ± 1.31	+ 5.58 ± 3.32	6.90 ±0.56	6.80 ±0.37	—1.48 ±2.77	1507 ± 52	1379 ± 123	— 8.17 ± 9.20
	20.0	3	22.42 ± 2.89	25.07 ± 3.76	+11.38 ± 6.04	6.63 ±1.17	5.97 ±0.61	—7.78 ±6.80	1480 ± 30.1	1217 ± 77.9	—17.60[a] ± 6.10
FC 142b (Monochloro-difluoroethane)	5.0	3	28.7 ± 2.5	28.7 ± 2.5	0.0 ± 0.0	8.30 ±0.1	8.30 ±0.1	0.0 ±0.0	543 ± 9	599 ± 26	+10.0[a] ± 5.0
	10.0	4	26.7 ± 0.7	26.7 ± 0.7	0.0 ± 0.0	7.1 ±0.6	7.1 ±0.6	0.0 ±0.0	487 ± 82	532 ± 101	+ 9.0 ± 6.0
Isobutane	5.0	3	21.36 ± 1.84	22.77 ± 1.75	+ 6.75 ± 2.38	6.50 ±0.49	6.33 ±0.60	—2.76 ±2.76	1440.26 ± 120.03	1364.67 ± 159.86	— 5.76 ± 3.12
	10.0	3	21.11 ± 1.59	25.05 ± 3.68	+19.39 ±10.79	6.83 ±0.44	6.37 ±0.63	—6.70 ±7.38	1370 ± 104	1231.07 ± 194	—13.36 ± 5.01
FC C-318 (Octafluoro-cyclobutane)	5.0	3	29.4 ± 1.4	29.4 ± 1.4	0.0 ± 0.0	8.8 ±1.0	8.5 ±0.8	—3.00 ±3.00	403 ± 44	407 ± 43	+ 1.00 ± 1.00
	10.0	4	28.2 ± 0.4	32.3 ± 0.8	+15.0 ± 2.0	8.4 ±1.3	7.9 ±0.8	—4.00 ±4.00	443 ± 45	424 ± 38	— 5.00 ± 2.00

[a] $p < 0.05$.

TABLE II (continued)

Propellant	% Conc. v/v	Monkey No.	Heart rate			Aortic blood pressure		
			Control beats/min	Response	%Δ	Control mm Hg	Response	%Δ
FC 114 (Dichlorotetra-fluoroethane)	5.0	3	168.00 ± 13.58	180.67 ± 6.36	+ 8.64 ± 7.76	118.33 ± 3.33	114.33 ± 1.20	—3.27 ±2.10
	10.0	3	170.00 ± 14.42	188.58 ± 7.26	+11.90 ± 7.65	116.33 ± 5.36	105.00 ± 5.77	—9.78 ±2.14
	20.0	3	173.33 ± 12.35	212.00 ± 2.00	+23.32[a] ± 7.13	111.33 ± 3.67	87.63 ± 3.71	—21.22[a] ± 2.56
FC 142b (Monochloro-difluoroethane)	5.0	3	186 ± 9	188 ± 9	+ 1.0 ± 1.0	91.7 ± 9.3	89.3 ± 8.1	— 2.00 ± 1.00
	10.0	4	180 ± 9	183 ± 9	+ 2.0 ± 1.0	93.8 ± 6.9	90.0 ± 7.4	— 6.00 ± 3.00
Isobutane	5.0	3	172 ± 5.29	177.33 ± 6.43	+ 3.06 ± 0.62	115.66 ± 4.70	113 ± 2.08	— 2.13 ± 2.13
	10.0	3	182.66 ± 9.96	194.00 ± 8.72	+ 6.35 ± 1.89	117.33 ± 5.04	94 ± 3.79	—21.66 4.08
FC C-318 (Octafluoro-cyclobutane)	5.0	3	148 ± 20	154 ± 25	+ 3.00 ± 3.00	80.0 ± 2.9	79.0 ± 3.2	— 1.00 ± 3.00
	10.0	4	146 ± 12	150 ± 14	+ 3.00 ± 2.00	89.2 ± 7.6	88.0 ± 7.3	— 1.00 ± 4.00

TABLE III

HIGH-PRESSURE PROPELLANTS OF INTERMEDIATE TOXICITY (MEAN ± SEM)

Propellant	% Conc.	Monkey	Pulm. resistance			Pulm. compliance			Resp. min. vol.		
			Control cm H_2O/LPS	Response	%Δ	Control. ml/cm H_2O	Response	%Δ	Control ml/min	Response	%Δ
FC 12 (Dichlorodi-fluoromethane)	5.0	3	26.9 ± 1.2	28.6 ± 2.6	+ 5.0 ± 5.0	9.7 ±0.9	9.0 ±0.6	— 6.0 ± 6.0	500 ± 63	500 ± 63	0.00 ± 0.00
	10.0	4	29.1 ± 0.9	33.5 ± 1.2	+15.0[a] ± 2.0	9.0 ±0.4	8.0 ±0.4	—11.0 ± 6.0	511 ± 65	507 ± 69	— 1.00 ± 2.00
FC 22 (Monochloro-difluoromethane)	10.0	3	20.46 ± 0.96	21.57 ± 1.28	+ 5.55 ± 5.55	6.83 ±0.83	6.66 ±0.66	— 1.96 ± 1.96	1609 ± 312	1598 ± 328	— 1.00 ± 1.90
	20.0	3	19.73 ± 0.64	23.82 ± 0.59	+15.89[a] ± 4.83	7.13 ±0.90	6.65 ±0.73	— 6.40 ± 2.86	1563 ± 276	1377 ± 239	—11.76 ± 1.50
Propane	10.0	3	21.71 ± 1.24	22.08 ± 1.02	+ 1.85 ± 1.85	6.23 ±0.67	6.13 ±0.73	— 1.84 ± 1.11	1386 ± 99	1327 ± 116	— 8.02 ± 2.32
	20.0	3	20.54 ± 1.61	22.57 ± 1.29	+10.33 ± 2.82	6.50 ±0.50	6.06 ±0.76	— 7.22 ± 5.64	1394 ± 132	1127 ± 168	—20.10 ± 4.80
Vinyl chloride	2.5	3	21.44 ± 0.44	21.81 ± 0.41	+ 1.76 ± 1.76	6.30 ±0.85	6.27 ±0.88	— 0.66 ± 0.66	1417 ± 44	1407 ± 72	— 0.80 ± 2.10
	5.0	3	20.70 ± 0.35	21.98 ± 0.23	+ 6.20 ± 0.73	6.33 ±0.88	4.53 ±0.84	— 2.91 ± 3.56	1355 ± 108	1274 ± 89	— 5.80 ± 1.00
	10.0	3	20.00	23.07 ± 0.97	+15.35[a] ± 4.83	6.33 ±0.88	5.90 ±1.23	— 8.61 ± 6.49	1380 ± 12	1211 ± 16	—12.30[a] ± 1.20

[a] $p < 0.05$.

TABLE III (continued)

Propellant	% Conc. v/v	Monkey No.	Heart rate			Aortic blood pressure		
			Control beats/min	Response	%Δ	Control mm Hg	Response	%Δ
FC 12 (Dichlorodi-fluoromethane)	5.0	3	133 ± 13	149 ± 8	+13.00 ± 7.00	81.7 ± 0.9	74.3 ± 0.7	− 9.00[a] ± 2.00
	10.0	4	147 ± 9	170 ± 7	+10.00[a] ± 4.00	84.9 ± 5.2	72.2 ± 6.1	−15.00 ± 3.00
FC 22 (Monochloro-difluoromethane)	10.0	3	167.66 ± 10.40	174 ± 10.69	+ 3.78 ± 0.51	110 ± 5	110 ± 5	0.00
	20.0	3	167.33 ± 15.07	186.00 ± 18.50	+11.09 ± 4.75	112.33 1.45	91.66 ± 11.66	−18.61 ± 9.31
Propane	10.0	3	170.33 ± 3.18	171.33 ± 3.18	+ 0.60 ± 1.22	117.66 ± 3.93	116 ± 4	− 1.41 ± 0.73
	20.0	3	173.33 ± 3.33	180 ± 0	+ 3.92 ± 1.96	117.66 ± 3.38	110.66 ± 2.33	− 5.82 ± 2.87
Vinyl chloride	2.5	3	171.33 ± 5.93	171.33 ± 5.93	0.00	113.33 ± 3.28	114.33 ± 2.33	+ 0.93 ± 0.93
	5.0	3	171.33 ± 5.93	173.00 ± 7.23	+ 0.92 ± 0.92	110.66 ± 5.21	111.66 ± 3.28	+ 0.43 ± 1.34
	10.0	3	174 ± 7.02	178 ± 6.11	+ 2.44 ± 2.93	116.33 ± 5.21	106.66 ± 2.73	− 7.73 ± 6.55