TABLE 3. IMPURITIES.[a]

	Isobutane	*Max. conc. (percent)*	*Isopentane*	*Max. conc. (percent)*	*n-Butane*	*Max. conc. (percent)*	*Propane*	*Max. conc. (percent)*
Vapor Press (56.7°C)	2.14–2.32 kg/cm²				1.05–1.34 kg/cm²		7.31–8.01 kg/cm²	
Conc. of Main Constituent	95.0% (Min.)		95.0% (Min.)		95.0% (Min.)		95.0% (Min.)	
	1. n-Butane	5.0	1. n-Pentane	5.0	1. Isobutane	4.0	1. Isobutane	5.0
	2. Propane	3.0	2. n-Butane	1.0	2. Isopentane	N/A[b]	2. Ethane	1.0
	3. Pentanes	1.5	3. Sulfur Compounds	1 ppm	3. Propane	0.1	3. n-Butane	1.0
	4. Unsaturated Hydrocarbons	0.10	4. Moisture	5 ppm	4. n-Pentane	2.0	4. Methane	0.1
	5. Sulfur Compounds	5 ppm			5. Cyclopentane		5. Isopentane	
	6. Moisture	25 ppm			6. Unsaturated Hydrocarbons	0.1	6. n-Pentane	0.1
					7. Sulfur Compounds	5 ppm	7. Unsaturated Hydrocarbons	0.1
					8. Moisture	25 ppm	8. Sulfur Compounds	5 ppm
							9. Moisture	25 ppm

[a]From Ref. 15.
[b]N/A = Data not available.

3. n-Butane is used in organic syntheses and in the manufacture of ethylene, rubber, and high octane liquid fuels. It is also used as a household and industrial fuel, a solvent, a refrigerant, a standby and enricher gas, a propellant in aerosols, a GRAS food additive, and an instrument calibration fluid.[2,16,17]

4. Propane is used in organic syntheses and in the manufacture of ethylene. It is also a household and industrial fuel, a solvent, refrigerant, gas enricher, aerosol propellant, extractant,[2] and GRAS food additive.[16,18]

Cosmetic Uses

Isobutane, n-Butane and Propane, usually in combination, are used as aerosol propellants. Along with Isopentane, they are also used as solvents and carriers in other cosmetic formulations. The specific cosmetic uses of these ingredients, along with their corresponding concentration ranges, are listed in Table 4.[19]

Scope and Extent of Use in Cosmetics

Of these ingredients, Isobutane has the widest range of uses. Table 4 lists 191 product formulations for Isobutane from the voluntary Cosmetic Formulation Data provided by the FDA on August 31, 1976.[19] As of June 20, 1979, however, the FDA lists 228 cosmetic formulations[20] in concentrations of 0.1% to 25-50%.

The FDA's 1976 data list Isopentane in two product formulations at concentrations of 25-50%, and n-Butane in 28 formulations in concentrations of less than 0.1-25%. According to the 1979 data, n-Butane is used in 51 cosmetic products.

According to 1976 formulation data, 40 product formulations contain Propane in concentrations ranging from less than 0.1-5.0%; however, the 1979 data list Propane in 130 formulations.

Common Surfaces of Application

These alkanes are generally used as aerosol propellants; therefore, they may come in contact with most body areas through spraying. Since the ingredients are highly volatile, their concentration at points of contact with the body may be small and the duration of bodily contact may be short.

Isobutane comes in contact with the general body surface (bath preparations, moisturizers, skin care preparations); the face (makeup, shaving preparations, cold creams); hair and scalp (hair sprays, hair conditions); axillae (underarm deodorants); body orifices (feminine hygiene and other cleanliness products); and eye and respiratory mucosa (aerosols).

Isopentane is used over the general body surface in various personal cleanliness products.

n-Butane can be applied to the hair and scalp (hair conditioner); the face (makeup, foundation, shaving and cleansing cream); and the general body surface (personal cleanliness products). It may also come in contact with the eyes and respiratory mucosa (aerosols).

Propane can come in contact with the face, eye, and respiratory epithelia (aerosol shaving creams and skin fresheners), and with the body in general (face, body, and hand preparations).

Potential Interactions with other Ingredients

Isobutane, Isopentane, n-Butane, and Propane are relatively stable,[2] and no interactions with other cosmetic components are reported.

Frequency or Duration of Application

These alkanes are included in cosmetics that may be applied several times a day (moisturizers, skin fresheners), on a daily basis (hair and bath products, deodorants, shaving preparations), or occa-

TABLE 4. PRODUCT FORMULATION DATA.[a]

Ingredient/Cosmetic product type	*Concentration (percent)*	*No. of product formulations*
Isobutane		
Other bath preparations	>1-5	1
Hair conditioners	>1-5	3
Hair sprays (aerosol fixatives)	>10-25	3
	>5-10	32
	>1-5	68
Blushers (all types)	≤0.1	1
Foundations	>0.1-1	1
Makeup bases	>0.1-1	1
Deodorants (underarm)	>25-50	2
	>5-10	3
	>1-5	1
Feminine hygiene deodorants	>10-25	3
Other personal cleanliness products	>10-25	1
	>5-10	8
	>1-5	3
	>0.1-1	1
Shaving cream (aerosol, brushless, and lather)	>1-5	42
	>0.1-1	9
Cleansing (cold creams, cleansing lotions, and pads)	>1-5	1
Face, body and hand (excluding shaving preparations)	>1-5	2
Moisturizing	>1-5	2
Foot powders and sprays	>1-5	1
Skin fresheners	>1-5	1
Other skin preparations	>0.1-1	1
Isopentane		
Other personal cleanliness products	>25-50	2
n-Butane		
Hair conditioners	>1-5	3
Blushers (all types)	>1-5	5
Foundations	>1-5	3
Makeup bases	>1-5	1
Other personal cleanliness products	>10-25	1
Shaving cream (aerosol, brushless, and lather)	>0.1-1	6
	≤0.1	8
Cleansing (cold cream, cleansing lotions, liquids, and pads)	>0.1-1	1
Propane		
Shaving cream (aerosol brushless, and lather)	>1-5	2
	>0.1-1	34
	≤0.1	1
Face, body, and hand (excluding shaving preparations)	>0.1-1	2
Skin fresheners	≤0.1	1

[a]From Ref. 19.

sionally (nail products, hair conditioners). Daily or occasional use may extend over a period of years.

The calculated discharging rate for an antiperspirant aerosol product containing 67.5% Isobutane was 0.44 g of Isobutane per second. A second antiperspirant product containing 65% Isobutane was calculated to discharge the gas at a rate of 0.73 g of Isobutane per second. A hair spray product containing 30% of an isobutane-propane propellant mixture in an 80:20 ratio

delivers 0.192 g per second Isobutane and 0.48 g per second propane. A foot spray, 45% of which contains an Isobutane-Propane mixture in an 80:20 ratio, delivers 0.144 g per second Isobutane and 0.036 g per second Propane. For shave foams, a maximum of 0.12 g propellant would be delivered with the product, 0.06 g of which is assumed to contact skin. It would remain in contact only long enough for the consumer to shave and wash. The amount of hydrocarbon gas coming into contact with the body would be difficult to calculate due to the extreme volatility of these gases.[21]

Single application to the general body surface may last from a few minutes (bath preparations, skin fresheners) to several days (nail products, hair conditioners).

BIOLOGICAL EFFECTS

Ames Test

The mutagenic potential of Isobutane, Isopentane, n-Butane, and Propane was tested on *Salmonella typhimurium* strains. Bacteria were exposed to various concentrations of the compounds in dessicators and incubated at 37°C, with and without metabolic activation. None of the four alkanes was mutagenic.[22]

Anesthetic Activity

The anesthetic property of Isobutane was studied using 48 mice. At a 35% concentration in air for 25 min, the compound was fairly effective as an anesthetic, but a 41–52% concentration was lethal in two to three minutes.[23]

Isobutane's anesthetic activity was tested in dogs in a closed system. This gas does not produce good anesthesia at reasonable concentrations. A 45% concentration of Isobutane in air was required for relaxation, and a 55% concentration was lethal.[23]

When tested on mice, Isopentane in 9–12% concentrations in air, produced anesthesia in 11–2 min, respectively. It was less lethal than n-pentane. At a 12% concentration by volume, Isopentane was not anesthetic in dogs, but it was lethal at 15–17%.[23]

n-Butane, at 13% concentration by volume, produced light anesthesia and excitement in 48 mice in 25 min. A 22% concentration induced anesthesia in 1 min. Butane was not a good anesthetic in dogs. Twenty to 25% concentration of the gas was required for relaxation, and this concentration was lethal.[23]

Animal Toxicology

Acute

Eye irritation

A hair spray containing 22% concentration of Isobutane was tested for eye irritation in five rabbits. A 0.1 ml of the undiluted product was sprayed into one eye, and after 4 sec the eye was irrigated. There was no sign of corneal irritation after 1 h. There was transient iritis and mild conjunctivitis after one hour, but these soon disappeared.[24]

Inhalation toxicity

The potentiation of epinephrine-induced cardiac arrhythmia by Isobutane was studied in 20 male Swiss Strain anesthetized mice.[25] Ten mice inhaled only the hydrocarbon, and another 10 inhaled hydrocarbon and then received a single intravenous injection of 6 μg/kg epinephrine hydrochloride 2 min after the inhalation started. When inhaled for 6 min, 20% Isobutane alone did not induce arrhythmia, but it did sensitize the heart to epinephrine-induced arrhythmia.

The 2 h LC50 value of inhaled Isobutane in mice was 52%.[26]

The acute inhalation toxicity of Isobutane, in a concentration of 22% in a hair setting spray, was tested on eight New Zealand albino rabbits. The animals were placed in an enclosed area, approximately 0.34 M^3, into which the substance was sprayed in 10 aerosol bursts at 13.2 g/30 second burst (2.904 g Isobutane/burst). No deaths, abnormal behavior, or changes in body weight occurred in test or control animals during either the exposure or the 14 days of observation. Gross

and microscopic examinations revealed no changes attributable to inhalation of the test material, and the respiratory tissues of the test animals were similar to those of the untreated controls.[24]

The effects of Isobutane on cardiac arrhythmia and its ability to depress myocardial contractility were studied on six rhesus monkeys. The animals were anesthetized, their tracheae cannulated, and the propellants delivered at concentrations of 2.5%, 5%, 10%, and 20% for 5 min. At inhalation concentrations of 5–10%, Isobutane produced arrhythmia and myocardial depression. It also caused tachycardia, a drop in aortic blood pressure, and a rise in left atrial pressure.[27]

The effect of Isobutane inhalation was studied on six young rhesus monkeys (*Macaca mulatta*) weighing from 1.8 to 2.2 kg. In this experiment Isobutane, a low pressure propellant, had no influence on circulation, but at concentrations of 5–10%, it increased pulmonary resistance and depressed respiratory minute volume.[28-30]

In similar studies with dogs, Isobutane in concentrations as high as 20% percent did not cause tachycardia, but did induce early respiratory depression more intense bronchospasm, and decreased pulmonary compliance.[29] Moreover, the compound induced apnea and electrocardiographic silence, slowed respiration rate, and reduced tidal volume in rats.[31]

Electrocardiograms recorded from three unanesthetized dogs that had received intravenous injections of epinephrine (0.01 mg/kg) showed that the myocardium was sensitized when the dogs inhaled Isobutane at concentrations of 15–90%.[32]

Stoughton and Lamson[23] found the 2 h LC50 of Isopentane in mice to be 14 volume percent.

A series of hydrocarbons, including Isopentane, was tested by inhalation on cardiac automaticity. Isopentane sensitized the myocardium of all of three dogs to epinephrine at concentrations of 10–25%.[32]

The concentration of n-Butane in the tissues, including the brains, of ten mice exposed to the gas for 2 h and 10 rats exposed for 4 h was determined by gas–liquid chromatography. The 2 h LC50 for mice was 680 mg/l and the 4 h LC50 for rats was 658 mg/l. The quantity of hydrocarbon found in the brain correlated with the degree of central nervous system depression and narcosis. Mixtures of n-Butane and isobutylene had a potentiating effect in 10 of 12 experiments and an additive effect in two experiments.[33]

In concentrations of 15–90%, n-Butane inhaled for 10 min sensitized the myocardium to epinephrine in both of two dogs.[32]

The combined effect of n-Butane and epinephrine on the ventricle was studied in dogs. Of fifteen trials made with the gas in concentrations of 1–20% v/v, with varying doses of epinephrine, three terminated in ventricular fibrillation. Inhalation times varied between 2 min and 2 h and were inversely proportional to the concentrations of the gas.[34]

Propane sensitization to epinephrine-induced cardiac arrhythmia was studied on 20 Swiss Strain anesthetized mice. Group I, consisting of 10 mice, inhaled only hydrocarbon; Group II, also of 10 mice, inhaled hydrocarbon and received a single intravenous injection of 6 μg/kg body weight epinephrine hydrochloride. Propane in 10% concentration did not induce arrhythmia in mice, but it did sensitize the heart to epinephrine-induced arrhythmia in both mice and dogs.[25,32]

Propane in 10–20% concentrations caused bronchoconstriction and respiratory depression in mice,[28,30] but no arrhythmias or myocardial depressions in the animals.[27]

Skin irritation

Several formulations containing Isobutane or a Propane-Isobutane mixture were tested for acute primary dermal irritation in rabbits according to 16 CFR 1500.41. They produced no to moderate erythema and edema and were considered mild to moderate irritants. Test methods, concentrations, and results are listed in Table 5.[35]

Subchronic

Inhalation toxicity

A hair spray containing 22% concentration of Isobutane by weight was tested for subchronic inhalation toxicity in 16 New Zealand albino rabbits. The rabbits were exposed twice daily, five days a week, for 90 days by means of 11.5 g per 30-second aerosol sprayings over their heads in an inhalation chamber. The animals remained in the chamber for 15 min after each spray discharge.

TABLE 5. PRIMARY DERMAL IRRITATION.[a]

Ingredient	Conc. (Percent)	No. of rabbits	Route	Erythema Score[b]			Edema score[b]			Total[b] erythema and edema	PII Score[b]
				24 h	72 h	Subtotal	24 h	72 h	Subtotal		
Isobutane	83.20	6	Intact, shaved, back skin	1.95	1.85	3.80	0.25	0	0.25	4.05	2.025
Isobutane Propane	65.94 12.56	6	Intact, shaved, back skin	0.87	0.40	1.27	0.08	0.10	0.18	1.45	0.725
Isobutane Propane	62.916 11.984	6	Intact, shaved, back skin	0.75	0	0.75	0	0	0	0.75	0.38
Isobutane Propane	65.44 12.46	6	Intact, shaved, back skin	0.79	0.04	0.83	0	0	0	0.83	0.42
Isobutane	74.25	6	Intact, shaved, back skin	2.08	1.54	3.62	0	0.17	0.17	3.79	1.895
Isobutane	75.75	6	Intact, shaved, back skin	1.71	0.38	2.09	0.08	0	0.08	2.17	1.085
Isobutane Propane	68.54 13.06	6	Intact, shaved, back skin	1.17	0.54	1.71	0	0	0	1.71	0.855
Isobutane	77.75	6	Intact, shaved, back skin	2.17	1.25	3.42	0	0	0	3.42	1.71
Isobutane	80.75	6	Intact, shaved, back skin	0.50	0.13	0.63	0	0	0	0.63	0.315
Isobutane Propane	65.562 12.488	6	Intact, shaved, back skin	0.92	0.21	1.13	0	0	0	1.13	0.565

Isobutane	76.75	6	Intact, shaved, back skin	2.08	0.46	2.54	0.25	0.08	0.33	2.87	1.435
Isobutane	84.55	6	Intact, shaved, back skin	1.04	0.5	1.09	0	0	0	1.09	0.545
Isobutane	89.55	6	Intact, shaved, back skin	0.50	0.5	1.0	0.04	0	0.04	1.04	0.52
Isobutane Propane	65.94 12.56	6	Intact, shaved, back skin	0.65	0.15	0.80	0.05	0	0.05	0.85	0.425
Isobutane	75.75	6	Intact, shaved, back skin	1.42	0.88	2.30	0.08	0	0.08	2.38	1.19
Isobutane	80.40	6	Intact, shaved, back skin	0.75	0.15	0.90	0	0	0	0.90	0.45
Isobutane	78.55	6	Intact, shaved, back skin	0.96	0.08	1.04	0	0	0	1.04	0.520
Isobutane	85.35	6	Intact, shaved, back skin	1.17	0.33	1.50	0	0	0	1.50	0.75
Isobutane	80.75	6	Intact, shaved, back skin	2.04	0.21	2.25	0.13	0	0.13	2.38	1.19
Isobutane	80.75	6	Intact, shaved, back skin	2.25	0.5	2.75	0.13	0	0.13	2.88	1.44
Isobutane	79.30	6	Intact, shaved, back skin	0.54	0	0.54	0.04	0	0.04	0.58	0.29

[a] From Ref. 35.

[b] PII (Primary Irritation Index) Scores: 0.0–2.0 = Mildly irritating. 2.0–5.0 = Moderately irritating. 6.0–8 = Severely irritating.

There were no differences between the tested 10 animals and the six controls, and no changes in body weight, hematology, blood chemistry, and urine analysis. There was no gross or microscopic pathology, and no deaths occurred.[24]

An aerosol spray deodorant containing a mixture of Isobutane and Propane in a concentration of 64.5% by weight was tested for 90 days on nine male and nine female stump-tail monkeys (*Macaca arctoides*) in three groups (A, B, and C) of three males and three females each. Group A was the control. Group B was exposed to air drawn from a mixing chamber which received a 1 sec spray of the test material at 42 min intervals for 6 (0.5 mg/l). Group C received a 5 sec spray at 21-minute intervals for 6 h (5.0 mg/l). All animals survived the experiment and showed no changes in behavior, body weight, hematology, biochemistry, or urinalysis. Electrocardiograms and tidal volume rates showed no significant changes, and gross and microscopic examinations showed no abnormalities.[36]

A 90-day subchronic inhalation study was conducted on an antiperspirant containing the propellant Propane in a greater than 50% concentration. Twenty-one cynomolgus monkeys were exposed to 750 ppm of the gas for the 90 consecutive days. No formulation-induced toxicity occurred from this study.[24]

A hair spray formulation containing Isobutane was tested on 21 cynomolgus monkeys in a 90-day subchronic inhalation study. Isobutane concentrations up to 4000 ppm produced no toxicity.[24]

Clinical Assessment of Safety

Primary Skin Irritation

Two products, a deodorant and an antiperspirant, with a mixture of Isobutane and Propane at 64.5% and 70.0% by weight, respectively, were tested for human skin irritation. Each product was used twice a day for 12 weeks by 125 adult subjects 18–60 years old. The subjects were assigned to two groups and an irritation grading score of zero (no reaction) to six (blisters) was used to evaluate the results. Group 1, with 75 subjects (47 males, 28 females) used the antiperspirant, while Group 2, with 50 subjects, used the deodorant. Very slight and transient erythema occurred randomly among the subjects and the reactions were reported to be negligible.[36]

Inhalation

Acute inhalation toxicity

Eight human subjects were repeatedly exposed to Isobutane at 500 ppm or to mixtures of gases and solvents, for one minute to eight hours per day, five days a week for two to four weeks. The subjects were asked to abstain from drugs, limit their use of alcohol, refrain from consuming caffeine, and not smoke during exposure to Isobutane. The results showed no deviations in EEG, adrenocortical function, pulmonary function, neurological response, subjective response, cardiac function, or cognitive response. There were no abnormalities even though Isobutane was readily detectable in the breath and blood. There was a reduction in wave amplitude in the Visual Evoked Response (VER) during the second week of repetitive 8-hour exposure per day to Isobutane at 500 ppm.[37]

n-Butane inhaled at 10,000 ppm for ten minutes caused drowsiness in human subjects, with no other evidence of systemic effect. Its odor is not detectable below 5,000 ppm (0.5%).[38]

Eight men and women were exposed to Propane concentrations of 250 to 1000 ppm for periods of 1 min to 8 h. During this same study, two men and two women were exposed to an atmosphere containing 1000 ppm Propane for 8 h per day, five consecutive days of one week and four consecutive days of the following week. No abnormal reactions occurred during the exposures. There were no deviations in EEGs, adrenocortical functions, pulmonary function, neurological response, subjective response, cardiac function, cognitive response, or VER. Propane was readily detectable in both blood and expired air.[37]

Another human inhalation study reported that Propane caused no symptoms in man under brief exposures (length of time not specified) to 10,000 ppm (1.0%). The ingredient's odor was not

detectable below 20,000 ppm (2.0%), and a concentration of 100,000 ppm (10%) was not noticeably irritating to the eyes, nose, or respiratory tract, but did produce slight dizziness within a few minutes.[38]

Patty and Yant[39] exposed six men and women to varying amounts of Propane and n-Butane. Subjects exposed to 1.0% Propane in air for 10 min experienced no symptoms. Exposure to up to 10% Propane for two minutes produced distinct vertigo. Exposure to 1.0% n-Butane in air for 10 min produced drowsiness.

Mucosal Irritation

Concentrations up to 10% Propane caused no eye, nose, or respiratory tract irritation.[38]

Recommended Limits of Exposure

The National Institute for Occupational Safety and Health (NIOSH) has recommended that the Time Weighted Average (TWA) for Isopentane in occupational exposure be limited to 350 mg/m^3.[40]

Isobutane is a GRAS food ingredient.[16]

n-Butane is a multipurpose GRAS food substance under 21 CFR 182.1165. The Threshold Limit Value (TLV) for n-Butane has been put at 600 ppm.[41]

Propane is a multipurpose GRAS food substance[18] when used as a propellant and aerating agent and for foamed or sprayed food products.

In 1971, the American Conference of Government Industrial Hygienists (ACGIH) recommended that the TLV for Propane be set at 1000 ppm. The revised 1976 ACGIH report described it as a simple asphyxiant with no prescribed TLV.[41]

SUMMARY

Isobutane, Isopentane, n-Butane, and Propane are low molecular weight alkanes, generally used in the cosmetic industry as aerosol propellants. They are derived from natural gas and petroleum and are inert to most chemical reagents.

Isobutane, Isopentane, n-Butane, and Propane were found not to be mutagenic in Ames Tests, both with and without metabolic activation.

The anesthetic activity of Isobutane, Isopentane, and n-Butane was studied in animals. Isobutane produced anesthesia in mice in 25 min at 35%; death occurred in 2 min at 41–52%. In dogs, Isobutane was not fully anesthetic at 45%, but was lethal at 55%. A 9–12% concentration of Isopentane was anesthetic to mice but not to dogs, but was lethal to dogs at 15–17%. n-Butane was anesthetic to mice in one minute at a concentration of 22 percent. A 20–25% concentration of the gas was lethal to dogs.

In eye irritation studies in rabbits, Isobutane caused very slight iridial and corneal irritation. Both n-Butane and Propane were mildly to moderately irritating to the skin of rabbits.

Isobutane, at 22% in a hair spray, was not toxic to rabbits in an acute inhalation study, but 20% for 6 min did sensitize the hearts of mice to epinephrine-induced arrhythmia. In monkeys, the inhalation of Isobutane at 5–10% for 5 min increased pulmonary resistance, depressed respiratory minute volume, and produced arrhythmia, tachycardia, and myocardial depression. Isobutane at 15–90% in air when inhaled by dogs caused respiratory and pulmonary complications, and sensitized the myocardium to simultaneous injections of epinephrine. When rats inhaled Isobutane, they suffered apnea, electrocardiographic silence, slowed respiration, and a reduction of tidal volume.

Acute inhalation of Isopentane and n-Butane sensitized the myocardium of dogs to epinephrine. After a 4 h inhalation time, n-Butane was found in the nervous tissue of mice and rats at levels correlating with the degree of central nervous system depression.

Acute inhalation of Propane by mice caused epinephrine-induced arrhythmia. Propane was not irritating to the skin.

Subchronic inhalation of Isobutane, Propane, and a mixture of the two by rabbits and monkeys produced no toxicity.

A Propane-Isobutane mixture, present at 64.5% and 70.0% in two different products, caused no skin irritation in 125 human volunteers.

No systemic abnormalities occurred in human subjects during an acute inhalation study of Isobutane, n-Butane and Propane, except that n-Butane at 1% percent for 10 min and 10% Propane for 2 min caused drowsiness and dizziness, respectively. Propane caused no human mucosal irritation.

The TWA for Isopentane is 350 mg/m^3. The TLV for n-Butane is 600 ppm and for Propane is 1000 ppm. Isobutane, Butane, and Propane are GRAS food ingredients.

DISCUSSION

Isobutane, Isopentane, n-Butane, and Propane have extensive noncosmetic applications that include use in or as aerosol propellants, aviation fluid additives, industrial and household fuel, blowing agents, solvents, refrigerants, and GRAS food additives. Of some 261 cosmetic formulations that contain the four ingredients, 176 are used as aerosol propellants in hair sprays and shaving creams. In the other formulations they are used as carriers and solvents. Since they are used predominantly as aerosol propellants, inhalation toxicity testing rather than contact toxicity has been emphasized.

Many studies have been conducted on the anesthetic effects of these ingredients on laboratory animals. Mice, rabbits, dogs, and monkeys that inhaled 25–35% concentrations of the ingredients in air became anesthetized to varying degrees; at somewhat greater concentrations, the animals died. The range of concentrations between those producing anesthesia and death is narrow. In some experiments, acute inhalation of high concentrations of Isobutane produced respiratory and cardiac distress in dogs and monkeys. A consistent effect of inhalation in all animals tested was a sensitization of the myocardium to epinephrine. It is believed, however, that these observations have little relevance to the advisability of the use of these ingredients in cosmetic formulations, because of the brief and low level exposures involved in their use.

The human skin studies on these alkanes are few and incomplete, but such studies are not considered particularly important. As aerosols, Isobutane, Propane, Isopentane, and n-Butane are so greatly diluted in air when discharged that the amount coming into contact with the skin is much less than the stated amounts used in the clinical tests. Since alkanes are highly volatile and have low water solubility, it is estimated that, as propellants, they would remain on the skin no longer than 10 seconds. Even the alkanes in foam products would not remain in contact with the skin longer than 10 sec. Such a short period of contact makes the absence of sensitization, phototoxicity, and photosensitization studies relatively unimportant. We are reminded that the TWA isopentane exposure standard set by NIOSH is 350 mg/m^3.[6,40] However, though the alkane propellant discharge rate in use ranges from 144 mg/sec to 440 mg/sec, most of the substance is volatilized before it can come in contact with the skin.

CONCLUSION

On the basis of the available information presented herein, Isobutane, Isopentane, n-Butane, and Propane are considered safe as cosmetic ingredients under present conditions of concentration and use.

ACKNOWLEDGMENT

Ms. Anne F. Moore, Scientific Analyst and writer, prepared the literature review and technical analysis used by the Expert Panel in developing this report.

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Environmental Health Perspectives
Vol. 26, pp. 275–285, 1978

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 (F-11)	3 males	8	246.9	10.4	4.21
	3 males	2	241.1	12.8	5.30
	2 males	1	239.6	3.1	1.27
Combined with (F-12), 500	3 males	8	512.8	15.5	3.02
	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 ft³/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 (control)	543.90 ± 20.71	438.09 ± 14.94	109.56 ± 20.12	0.25 ± 0.05
PM		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.