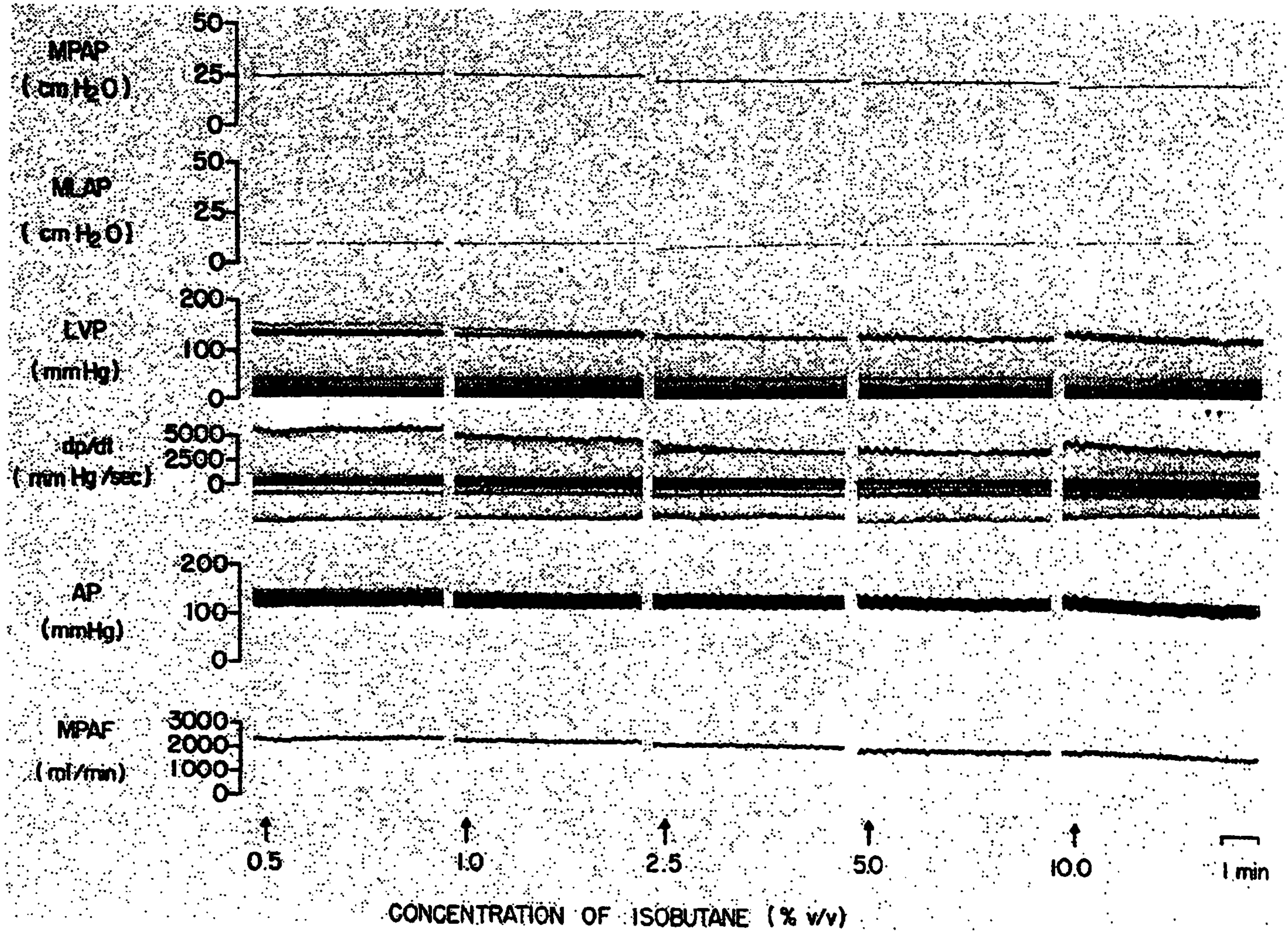

FIGURE 6.1. The effects of inhalation of progressively increasing concentrations of isobutane in the open-chest dog preparation. Abbreviations are explained in the text.

FIGURE 6.1. The effects of inhalation of progressively increasing concentrations of isobutane in the open-chest dog preparation. Abbreviations are explained in the text.

maximum rate of rise of left ventricular pressure and the stroke work. These effects are depicted in Figure 6.2.

No significant change was observed in mean pulmonary arterial pressure, mean left atrial pressure, effective mean pulmonary arterial pressure, left ventricular end-diastolic pressure, heart rate, and systemic vascular resistance.

Effects of inhalation of isobutane and halogenated hydrocarbons or ketones – The threshold effective concentrations of halogenated solvents (methyl chloroform MC, and trichloroethylene TCE),[68] and of ketones (methyl ethyl ketone MEK, and methyl isobutyl ketone MIK)[69] were previously determined in this laboratory in a similar dog preparation. In the present investigation, it was felt necessary to study the effect of these compounds alone and mixed with isobutane especially because most, if not all, of the consumer products examined contain these solvents mixed with isobutane as a propellant.

The minimal effective concentration of isobutane was determined in each of the preparations studied; its value varied between 1.0% and 2.5%, averaging 2.0% ± 0.32. In this concentration, isobutane brought about a decrease in left ventricular pressure, left ventricular dp/dt, mean pulmonary arterial flow, stroke volume, and stroke work, averaging to 5.6%, 10.4%, 5.9%, 7.0%, and 10.6%, respectively. Inhalation of 0.1% methyl chloroform brought about a decrease of 3.4%, 7.2%, 4.5%, 4.2%, 4.3%, and 8.7% in left ventricular pressure, left ventricular dp/dt, mean arterial pressure, mean pulmonary arterial flow, stroke volume, and stroke work, respectively. Trichloroethylene, on the other hand, inhaled in a concentration of 0.05%, elicited a decrease of 7.5% in left ventricular dp/dt, and of 3.8%, 4.9%, and 4.0% in mean pulmonary arterial flow, stroke volume, and stroke work, respectively.

Inhalation of a mixture of 2% isobutane and 0.1% methyl chloroform brought about a decrease of 6.8%, 6.4%, 10.5%, 6.5%, 7.9%, and 13.9% in mean arterial pressure, left ventricular pressure, left ventricular dp/dt, mean pulmonary arterial flow, stroke volume, and stroke work, respectively. A mixture of a threshold concentration of isobutane and a threshold concentration of trichloroethylene brought about a decrease in left ventricular pressure, left ventricular dp/dt, mean

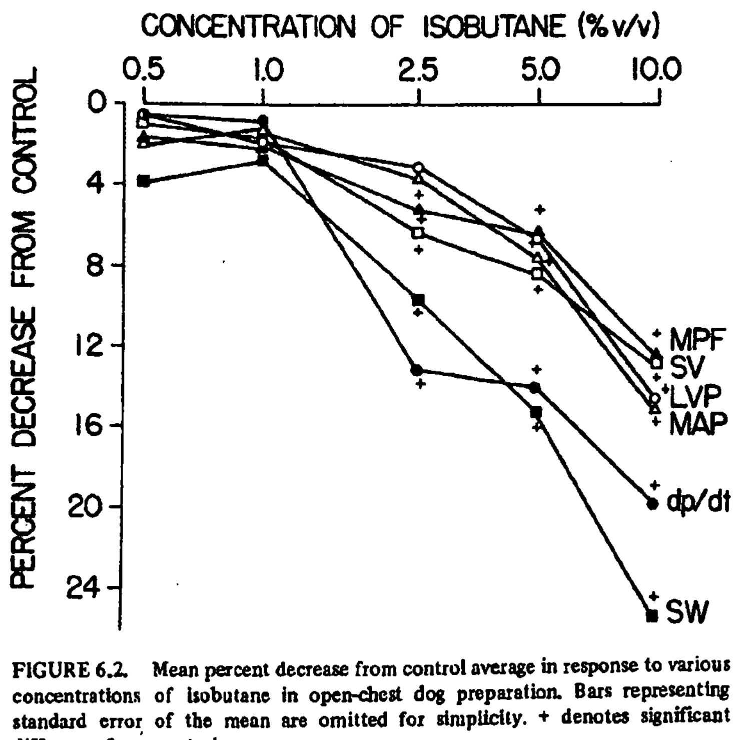

FIGURE 6.2. Mean percent decrease from control average in response to various concentrations of isobutane in open-chest dog preparation. Bars representing standard error of the mean are omitted for simplicity. + denotes significant difference from control.

pulmonary arterial flow, stroke work, and stroke volume, averaging 6.6%, 9.1%, 4.1%, 6.3%, and 8.4%, respectively. The Student t-test revealed no significant difference ($P < 0.05$) between the effects of isobutane alone or mixed with methylchloroform or trichloroethylene. These results are depicted in Figure 6.3 and summarized in Table 6.3.

In a previous study, ketones (MEK and MIK), especially in suprathreshold concentrations, caused a unique effect on the pulmonary circulation, namely, increase in pulmonary pressure and resistance. Isobutane (2%), on the other hand, decreased pulmonary arterial pressure and increased pulmonary vascular resistance mainly because of decreased pulmonary arterial flow (Figure 6.4). No significant difference could be observed between the effect of isobutane alone or mixed with the threshold concentrations of ketones (Table 6.4).

D. Discussion of Hemodynamic Effects

The present investigation was mainly concerned with the hemodynamic effects of various concentrations of isobutane in the intact, anesthetized, open-chest dog preparation. No significant changes were observed with concentrations of 0.5% and 1.0% of isobutane. However, at a concentration of 2.5%, significant decreases in myocardial contractility, mean pulmonary arterial flow, stroke volume, and stroke work were observed. These effects gradually intensified with increase in the concentration to 10%. In a concentration of 5% or 10%, furthermore, isobutane decreased the left ventricular and mean aortic pressures. A significant increase in the pulmonary vascular resistance was observed only with a 10% concentration. The results of this study demonstrate that the most predominant cardiovascular effect of isobutane is its ability to cause depression of myocardial contractility and output as shown from the decrease in the maximum rate of rise of left ventricular pressure (dp/dt) and pulmonary flow. The cardiac negative inotropic effect of isobutane is not associated with a similar negative chronotropic effect, as the heart rate is not significantly

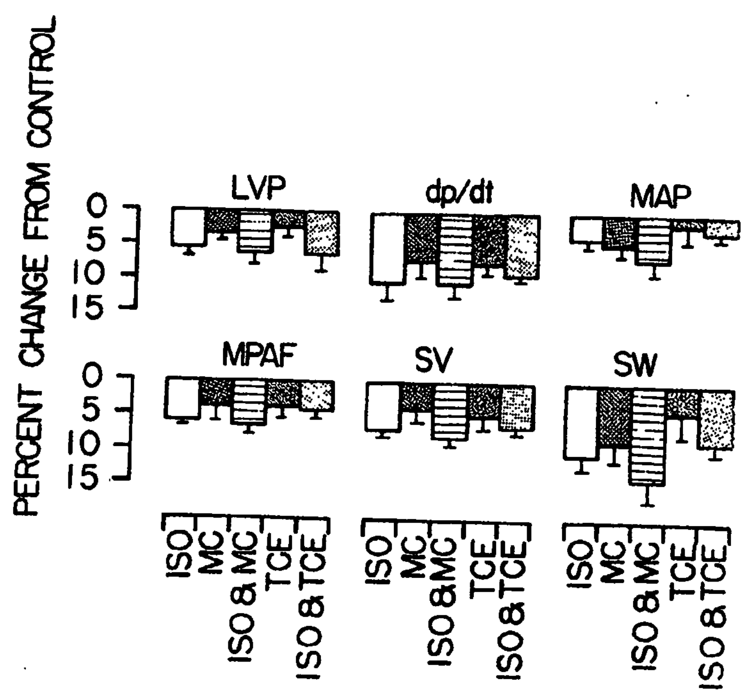

FIGURE 6.3. Effects of the threshold concentration of isobutane (ISO), methyl chloroform (MC), and trichloroethylene (TCE), and a mixture of ISO and MC or TCE, on various hemodynamic parameters. Abbreviations are explained in the text.

TABLE 6.3

The Effect of Minimal Effective Concentrations of Isobutane, Methyl Chloroform, and Trichloroethylene on the Open-chest Dog*

	MPAP cm H_2O	MLAP cm H_2O	EMPAP cm H_2O	LVP mmHg	LVEDP mmHg	dp/dt mmHg/sec	MAP mmHg	MPAF ml/min	HR beats/min	Vascular resistance dynes·sec/cm[5] Pulmonary	Vascular resistance dynes·sec/cm[5] Systemic	Stroke vol ml	Stroke work g·meter
	C E	C E	C E	C E	C E	C E	C E	C E	C E	C E	C E	C E	C E
Isobutane 2.0%	51.3 49.6	6.5 6.3	44.4 43.1	150 142	2.9 4.2	4646 4167	124 119	2358 2217	167 169	1225 1258	4231 4283	14.6 13.5	25.6 22.8
	−1.7 ± 0.9	−0.2 ± 0.3	−1.3 ± 0.9	−8 ± 1.8	+1.3 ± 1.3	−479 ± 113	−5 ± 1.5	−141 ± 20	+2 ± 0.9	+33 ± 15	+52 ± 46	−1.1 ± 0.2	−2.8 ± 0.7
	NS	NS	NS	0.01	NS	0.02	0.05	0.001	NS	NS	NS	0.01	0.02
Methyl chloroform (MC) 0.05%	38.2 37.6	7.6 6.7	30.3 30.3	139 134	3.3 3.2	4042 3782	119 114	1954 1871	159 160	960 1017	4891 4871	12.4 11.9	20.9 19.2
	−0.6 ± 1.0	−0.9 ± 0.4	0 ± 1.0	−5 ± 1.1	−0.1 ± 0.2	−260 ± 69	−5 ± 1.7	−83 ± 36	+1.0 ± 0.5	+57 ± 53	−20 ± 78	−0.5 ± 0.2	−1.7 ± 0.5
	NS	NS	NS	0.01	NS	0.02	0.02	NS	NS	NS	NS	0.05	0.02
Trichloro-ethylene (TCE) 0.05%	43.0 39.7	7.4 7.4	35.3 31.8	139 135	2.3 2.3	4021 3744	115 115	1863 1796	159 162	1195 1147	5048 5247	11.9 11.3	19.5 18.8
	−3.3 ± 2.3	0 ± 0.4	−3.5 ± 2.3	−4 ± 1.9	0 + 0.7	−277 ± 48	0 ± 2.5	−77 ± 25	+3 ± 1.3	−48 ± 82	+198 ± 96	−0.6 ± 0.2	−0.7 ± 0.6
	NS	NS	NS	NS	NS	0.01	NS	0.05	NS	NS	NS	0.05	NS
Isobutane + 0.1% MC	45.8 44.6	6.5 6.5	39.3 37.9	140 131	2.5 1.9	4125 3729	118 109	1988 1863	159 161	1219 1275	4729 4622	12.8 11.8	21.4 18.5
	−1.2 ± 0.7	0 ± 0.2	−1.4 ± 0.6	−9 ± 2.1	−0.6 ± 0.6	−396 ± 38	−9 ± 2.8	−125 ± 26	+2 ± 0.7	+56 ± 46	−107 ± 186	−1 ± 0.2	−2.9 ± 0.7
	NS	NS	NS	0.01	NS	0.001	0.05	0.01	0.05	NS	NS	0.01	0.01
Isobutane + 0.05% TCE	43.4 41.9	7.3 6.6	35.3 34.3	137 128	3.0 4.0	3875 3529	117 114	1829 1758	159 162	1206 1236	5168 5212	11.7 11.0	19.4 17.9
	−1.5 ± 0.6	−0.7 ± 0.4	−1 ± 0.7	−9 ± 3.6	+1 ±0.6	−346 ± 48	−3 ±1	−71 ± 12	+3 ± 0.7	+30 ± 27	+44 ± 65	−0.7 ± 0.1	−1.5 ± 0.2
	NS	NS	NS	0.05	NS	0.001	0.05	0.01	0.01	NS	NS	0.001	0.001

*Each set of numbers consists of mean control (C), mean experimental (E), mean difference ±SE of difference and the P value. NS = nonsignificant (i.e., P > 0.05). Abbreviations are explained in the text.

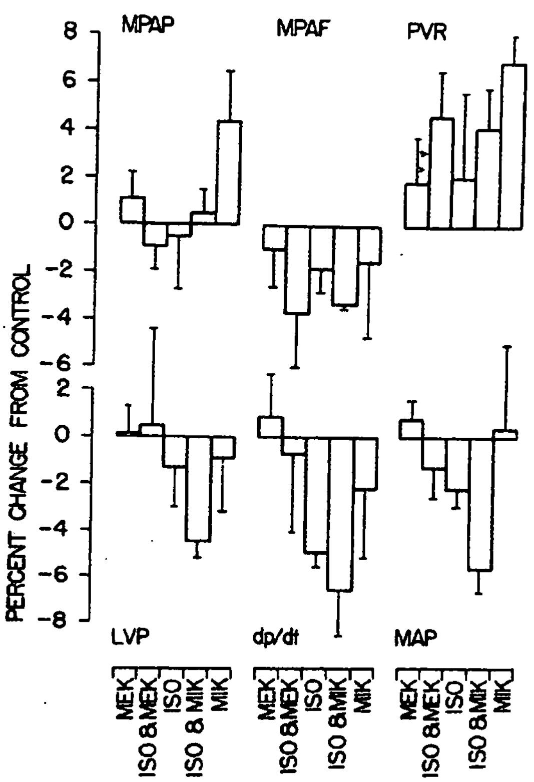

FIGURE 6.4. Effects of the threshold concentration of isobutane (ISO), methyl ethyl ketone (MEK), methyl isobutyl ketone (MIK), and a mixture of ISO and MEK or MIK. Abbreviations are explained in the text.

changed. The parameters that were significantly altered by a concentration of 2.5% of isobutane were the myocardial contractility and the pulmonary artery blood flow. At this concentration, the significant decrease in cardiac output appears to be due mainly to the attenuation of myocardial inotropic activity, since the heart rate was not significantly changed. At higher concentrations, however, pooling of blood in the capacitance vessels with the consequent decrease in venous return might participate in decreasing cardiac output. That this mechanism is involved is suggested in the light of the decrease in systemic vascular resistance elicited with the concentration of 10%.

The nonsignificant increase in pulmonary vascular resistance elicited by 5.0% concentrations of isobutane can be explained as follows: with these concentrations, no significant change in pulmonary arterial pressure, left atrial pressure, or effective mean pulmonary arterial pressure was observed. The pulmonary vascular resistance is the quotient of the effective mean pulmonary arterial pressure divided by cardiac output. Since there was no significant change in the effective mean pulmonary arterial pressure, when the cardiac output decreased, the pulmonary vascular resistance increased. Nonetheless, the significant increase in pulmonary vascular resistance observed with 10% concentration of isobutane, and averaging to 16.6% of the mean control value, seems to be due to the involvement of other components in the pulmonary circulation. The exact mechanism of action has to await further exploration.

Inhalation of threshold concentrations of isobutane, methyl chloroform, and trichloroethylene separately revealed that these three compounds share the property of depressing the myocardial contractility. Nevertheless, administration of the minimal effective concentration of isobutane mixed with the threshold concentration of trichloroethylene or methyl chloroform showed that there is no addition, potentiation, or synergism of the action of these agents. Also, no significant interaction could be detected between isobutane and ketones. This might imply a different basic mechanism of action of these substances on the cardiovascular system.

E. Summary

Isobutane exerts the following pharmacologic profile in the open-chest dog preparation: a) decrease in cardiac output, stroke volume, and stroke work; b) decrease in myocardial contractility; and c) decrease in left ventricular and aortic pressures. The threshold effective concentration of isobutane is 2.0%. No interaction could be observed between the threshold concentration of isobutane and those of methyl chloroform, trichloroethylene, methyl ethyl ketone, and methyl isobutyl ketone.

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TABLE 6.4

The Effects of Minimal Effective Concentrations of Isobutane, Methyl Ethyl Ketone, and Methyl Isobutyl Ketone on the Open-chest Dog*

	MPAP cm H_2O		MLAP cm H_2O		EMPAP cm H_2O		LVP mmHg		LVEDP mmHg		dp/dt mmHg/sec		MAP mmHg		MPAF ml/min		HR beats/min		Vascular resistance dynes·sec/cm^5: Pulmonary		Vascular resistance dynes·sec/cm^5: Systemic		Stroke vol ml		Stroke work g·meter	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
Isobutane 2%	35.0	34.8	7.8	7.6	27.2	27.2	125	123	5.5	6.3	3656	3469	109	107	1438	1413	177	179	1112	1132	6076	5950	8.3	8.0	12.9	12.2
	−0.2 ± 0.8		−0.2 ± 0.2		0 ± 0.9		−2 ± 2.2		+0.8 ± 0.8		−187 ± 36		−3 ± 1.0		−25 ± 14		−2 ± 0.9		+20 ± 42		−126 ± 46		−0.3 ± 0.1		−0.7 ± 0.2	
	NS		NS		NS		NS		NS		0.02		NS		NS		NS		NS		NS		0.05		0.05	
MEK 0.09%	32.3	32.6	5.2	5.5	27.0	27.1	161	161	3.1	3.8	4531	4563	139	140	1420	1410	173	174	1193	1204	8167	8332	8.3	8.2	16.1	16.3
	+0.3 ± 0.3		±0.3 ± 0.3		+0.1 ± 0.5		0 ± 2		+0.7 ± 0.6		+32 ± 79		+1 ± 1		−10 ± 19		+1.9 ± 0.9		+11 ± 21		+165 ± 183		−0.1 ± 0.1		+0.2 ± 0.3	
	NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS	
MIK 0.08%	33.5	35.0	7.2	7.2	26.3	27.8	132	131	8	8	4156	4094	114	114	1413	1388	179	181	1102	1176	6398	6463	8.0	7.8	13.1	12.7
	+1.5 ± 0.8		0 ± 0		+1.5 ± 0.8		−1 ± 2.7		0 ± 0		−62 ± 108		0 ± 3.5		−25 ± 43		+2 ± 1.9		+74 ± 9.9		+65 ± 119		−0.2 ± 0.3		−0.4 ± 0.8	
	NS		NS		NS		NS		NS		NS		NS		NS		NS		0.01		NS		NS		NS	
Isobutane + MEK	31.0	30.8	4.5	3.7	26.5	27.0	161	162	3.8	5.6	4344	4281	141	139	1450	1410	167	168	1109	1167	7819	8013	8.7	8.4	17.6	16.7
	−0.2 ± 0.3		−0.8 ± 0.5		+0.5 ± 0.7		+1 ± 6.9		+1.8 ± 1.9		−63 ± 149		−2 ± 1.8		−40 ± 25		+1 ± 0.4		+58 ± 20		+194 ± 361		−0.3 ± 0.1		−0.9 ± 0.4	
	NS		NS		NS		NS		NS		NS		NS		NS		NS		0.05		NS		NS		NS	
Isobutane + MIK	35.5	35.7	7.4	7.4	28.2	28.3	131	125	1.5	1.5	3813	3563	115	108	1513	1463	180	181	1087	1130	5941	5802	8.5	8.2	13.9	13.0
	+0.2 ± 0.3		0 ± 0		+0.1 ± 0.3		−6 ± 1.2		0 ± 0		−250 ± 88		−6 ± 0.8		−50 ± 10		+1 ± 1.6		+43 ± 12		−139 ± 55		−0.3 ± 0.1		−0.9 ± 0.3	
	NS		NS		NS		0.02		NS		0.05		0.01		0.01		NS		0.05		NS		0.05		0.05	

*Each set of numbers is calculated from four preparations and consists of mean control (C), mean experimental (E), mean difference ± SE of difference, and the P value. NS = non-significant (i.e., $P > 0.05$). Abbreviations are explained in the text.

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Part III
Aerosol Formulations

Chapter 7
HYDROCARBON MIXTURE: PROPANE, BUTANE, AND ISOBUTANE

Until recently, fluorocarbons were the major propellants used in the aerosol industry. However, the potential health hazards associated with the use of fluorocarbons and other considerations have made it necessary to develop aerosols using hydrocarbons as propellants. The propellant mixtures consisting of propane, butane, and isobutane described from 1966 to 1970 are becoming important because they represent a means of continuing to use aerosols without fluorocarbons.[1-4]

A new hydrocarbon mixture has been developed specifically for the purpose of substituting for fluorocarbons. The mixture called A-46 has a vapor pressure of 46 psig (at 21.1°C) resulting from the appropriate blending of the following hydrocarbons, having the respective vapor pressures at 21.1°C and the concentrations indicated:

Isobutane (31 psig)	80.4%
Butane (17 psig)	2.5%
Propane (108 psig)	17.1%
Mixture A-46 (46 psig) =	100%

The purpose of this chapter is to describe an investigation to determine whether the mixture of the three hydrocarbons is more toxic than each of the individual components.

A. Inhalational Toxicity in Mice

The LC_{50} of A-46 was determined using male mice (CF-1 strain, Charles River Laboratories, Wilmington, Massachusetts) according to the method described previously (Chapter 2). All gaseous mixtures were balanced by adding oxygen (25% of the volume of A-46), and mortality rate was calculated after a 120-min exposure period.

Results are summarized in Table 7.1. The LC_{50} of A-46 is 57.42% v/v with fiducial limits of 53.96 and 60.88%. There is no significant difference between the LC_{50} of A-46 and that of isobutane alone (52.04% ± 3.26%, as reported in Chapter 6). However, the tendency of A-46 to exhibit less toxicity than isobutane alone might be attributed to the presence of propane which is less toxic than butane or isobutane.

B. Hemodynamic Effects in Dogs

The myocardial and hemodynamic effects of butane, isobutane, and propane in an open-chest dog preparation have been previously reported (Chapters 4, 5, and 6). This is the continuation of an investigation started in this laboratory concerning various gaseous propellants. The hemodynamic effect of a blend of 17.1% propane, 80.4% isobutane, and 2.5% butane (v/v), a hydrocarbon propellant mixture known as A-46, was studied in the same animal preparation along similar lines as methylene chloride (Chapter 2). All data were analyzed by the t-test for paired replicates. The chi-squared test was used to test the association of observed and expected responses. In both cases, the criterion for significance was P less than or equal to 0.05.

The various myocardial and hemodynamic responses to inhalation of various concentrations of A-46 in a typical experiment are illustrated in Figure 7.1. Results are summarized in Table 7.2. The most prominent effect is exhibited on the myocardium. The various effects are as follows.

Decrease in myocardial contractility – Myocardial contractility, as gauged by the maximal rate of rise of left ventricular dp/dt, is attenuated after inhalation of various concentrations of A-46. Thus, inhalation of 0.5%, 1.0%, 2.5%, 5.0%, and 10.0% was accompanied by a decrease in myocardial contractility of 0.6%, 4.6%, 6.3%, 8.5%, and 12.6%, respectively. The negative inotropic effect of A-46 on the heart was not accompanied by a similar negative chronotropic effect; no significant changes were observed in the heart rate.

Decrease in cardiac output – Inhalation of the

TABLE 7.1

Acute Inhalation Toxicity of a Mixture of Propane, *n*-Butane, and Isobutane in Mice after 120 min of Exposure*

Group	Concentration % v/v	% Mortality	LC_{50}	Regression coefficient
1	45	0		
2	50	20	57.42	0.9811
3	55	50	±	
4	60	60	3.46%	
5	70	80		
6	75	100		

*Each group consisted of ten mice.

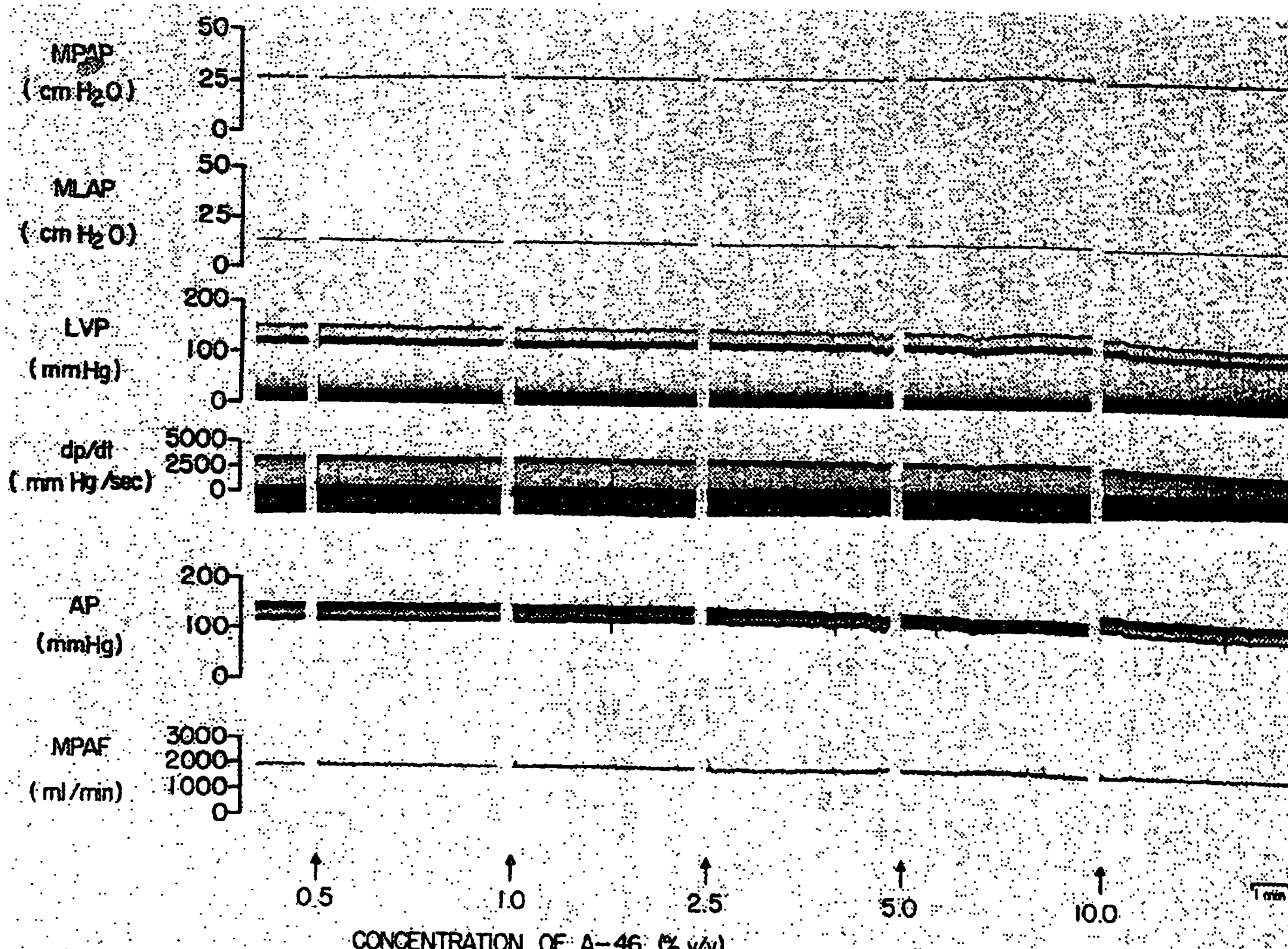

FIGURE 7.1. The effect of progressively increasing concentrations of A-46 on myocardial and hemodynamic parameters in the open-chest dog. MPAP = mean pulmonary arterial pressure; MLAP = mean left atrial pressure; LVP = left ventricular pressure; dp/dt = maximal rate of rise of left ventricular pressure; AP = aortic pressure; MPAF = mean pulmonary arterial flow.

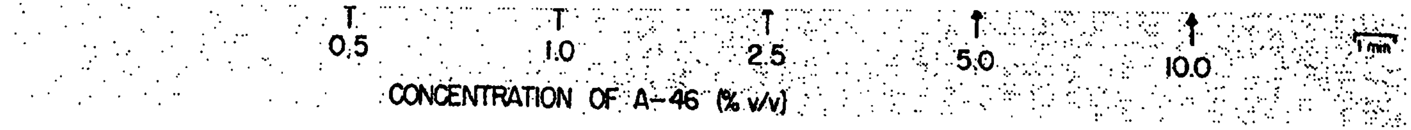

FIGURE 7.1. The effect of progressively increasing concentrations of A-46 on myocardial and hemodynamic parameters in the open-chest dog. MPAP = mean pulmonary arterial pressure; MLAP = mean left atrial pressure; LVP = left ventricular pressure; dp/dt = maximal rate of rise of left ventricular pressure; AP = aortic pressure; MPAF = mean pulmonary arterial flow.

TABLE 7.2

The Myocardial and Hemodynamic Effects of Progressively Increasing Concentrations of A-46 in Dogs*

	MPAP cm H_2O	MLAP cm H_2O	EMPAP cm H_2O	LVP mmHg	LVEDP mmHg	dp/dt mmHg/sec	MAP mmHg	MPAF ml/min	HR beats/min	Vascular resistance dynes·sec/cm^5 Pulmonary	Systemic	Stroke vol ml	Stroke work g·meter
Control	25.2 ± 0.9	8.0 ± 1.6	17.2 ± 2.2	139 ± 10	1.5 ± 1.0	2945 ± 423	113 ± 7	1880 ± 171	174 ± 10	552 ± 90	4892 ± 523	11.0 ± 1.3	17.7 ± 1.9
A-46 0.5%	25.5 ± 1.3 +0.3 ± 0.2 NS	7.8 ± 1.9 −0.2 ± 0.2 NS	17.7 ± 2.6 +0.5 ± 0.3 NS	138 ± 11 −1 ± 0.6 NS	3.1 ± 2.4 +1.6 ± 2.4 NS	2907 ± 357 −38 ± 54 NS	111 ± 6 −2 ± 1.0 0.05	1842 ± 202 −38 ± 24 NS	174 ± 10 0 ± 0.5 NS	581 ± 103 +29 ± 20 NS	4846 ± 727 −46 ± 72 NS	10.9 ± 1.7 −0.1 ± 0.1 NS	16.9 ± 2.1 −0.8 ± 0.4 NS
A-46 1.0%	25.0 ± 1.1 −0.2 ± 1.3 NS	7.8 ± 1.7 −0.2 ± 0.2 NS	17.2 ± 1.7 0 ± 1.2 NS	136 ± 9 −3 ± 1.2 NS	1.5 ± 1.0 0 ± 0.8 NS	2800 ± 386 −145 ± 48 0.05	109 ± 8 −4 ± 1.3 0.05	1750 ± 196 −130 ± 34 0.02	172 ± 12 −2 ± 2.0 NS	579 ± 90 +27 ± 35 NS	5094 ± 619 +202 ± 127 NS	10.5 ± 1.5 −0.5 ± 0.3 NS	16.0 ± 2.0 −1.7 ± 0.4 0.01
A-46 2.5%	24.3 ± 2.0 −0.9 ± 2.4 NS	7.8± 1.9 −0.2 ± 0.3 NS	16.5 ± 2.1 −0.7 ± 2.3 NS	134 ± 10 −5 ± 1.3 0.02	2.0 ± 0.5 +0.5 ± 0.5 NS	2770 ± 411 −175 ± 63 0.05	107 ± 7 −6 ± 1.4 0.02	1760 ± 199 −120 ± 49 0.05	173 ± 12 −1 ± 1.9 NS	571 ± 90 +19 ± 77 NS	5050 ± 620 +158 ± 164 NS	10.3 ± 1.4 −0.7 ± 0.2 0.02	15.6 ± 1.8 −2.1 ± 0.3 0.01
A-46 5.0%	25.3 ± 1.2 +0.1 ± 1.4 NS	7.9 ± 2.0 −0.1 ± 0.5 NS	17.4 ± 1.5 +0.2 ± 1.0 NS	130 ± 9 −9 ± 3.6 0.02	2.6 ± 1.0 +1.1 ± 1.0 NS	2775 ± 430 −170 ± 60 0.05	102 ± 6 −11 ± 3.3 0.02	1730 ± 192 −150 ± 42 0.02	176 ± 13 +2 ± 3.3 NS	623 ± 95 +71 ± 28 NS	4842 ± 543 −50 ± 105 NS	10.0 ± 1.3 −1.0 ± 0.1 0.001	14.3 ± 1.7 −3.4 ± 0.6 0.01
A-46 10.0%	24.1 ± 2.3 −2.1 ± 2.3 NS	7.9 ± 1.6 −0.1 ± 0.7 NS	16.2 ± 1.5 −1.0 ± 1.8 NS	121 ± 7 −18 ± 5 0.02	2.6 ± 0.7 +1.1 ± 0.9 NS	2580 ± 390 −365 ± 114 0.05	96 ± 5 −17 ± 3.3 0.01	1680 ± 192 −200 ± 42 0.01	170 ± 14 −4 ± 5.4 NS	570 ± 95 +18 ± 50 NS	4717 ± 556 −175 ± 142 NS	10.0 ± 1.3 −1.0 ± 0.2 0.02	13.7 ± 1.7 −4.0 ± 0.5 0.01

*Each group of numbers represents the mean value of six experiments, and consists of mean response ± SEM, mean difference ± SE of difference, and the significance level.

previously mentioned concentrations of A-46 was associated with a decrease of 38, 130, 120, 150, and 200 ml/min in mean pulmonary arterial flow. The decrease in cardiac output was almost parallel to the decrease in myocardial contractility (Figure 7.2). Since there was no change in heart rate, the decrease in cardiac output was therefore accompanied by a decrease in stroke volume.

Decrease in left ventricular pressure and mean aortic pressure – The decrease in left ventricular pressure following the inhalation of 0.5%, 1.0%, 2.5%, 5.0%, and 10.0% of A-46 averaged to 0.7%, 2.2%, 3.4%, 6.4%, and 12.8% respectively. The mean corresponding decreases in aortic pressure were 2.3%, 3.9%, 5.3%, 10.0% and 14.7%, respectively. The combined effect of A-46 on the heart and blood vessels was shown by the decrease in stroke work of 4.2%, 9.8%, 11.9%, 18.8%, and 22.6%, after inhalation of 0.5%, 1.0%, 2.5%, 5.0%, and 10%, respectively. No remarkable changes were observed in pulmonary arterial pressure or left atrial pressure.

Comparison of propane, butane, isobutane, and the hydrocarbon mixture – The effects of propane, butane, and isobutane have been previously studied in this laboratory in a similar open-chest dog preparation. The most prominent effect, in fact, an effect that is observed with the lowest concentration of all the studied hydrocarbons, is myocardial depression. Figures 7.3 and 7.4 show the comparative myocardial and hemodynamic effects of all these gases. The differences among the effects of these compounds seem to be quantitative and are summarized in Tables 7.3 and 7.4. These three hydrocarbons can be arranged, according to our findings, in the following order of descending toxicity:

butane > isobutane = A-46 > propane

C. Discussion of Hemodynamic Effects

Results of the present investigation show that A-46, like other saturated gaseous aliphatic hydrocarbons, possesses a myocardial depressant effect. This effect is shown by the decrease in myocardial contractile force as gauged by the changes in the left ventricular dp/dt. Since the decrease in cardiac output is almost parallel to the decrease in myocardial contractile force, it is most probable that the decrease in the former parameter is due mainly to the decrease in the latter. However, the possibility of a decrease in venous return, with the consequent decrease in ventricular filling pressure as a contributing mechanism for the decrease in cardiac output, cannot be excluded.

The decrease in systemic arterial pressure is an expected consequence of attenuation of myocardial contraction and cardiac output. The depressant effect of these gases on the central nervous system with the consequent depression of vasomotor tone might contribute to the observed decrease in the systemic blood pressure.

Comparison of the effects of various gaseous

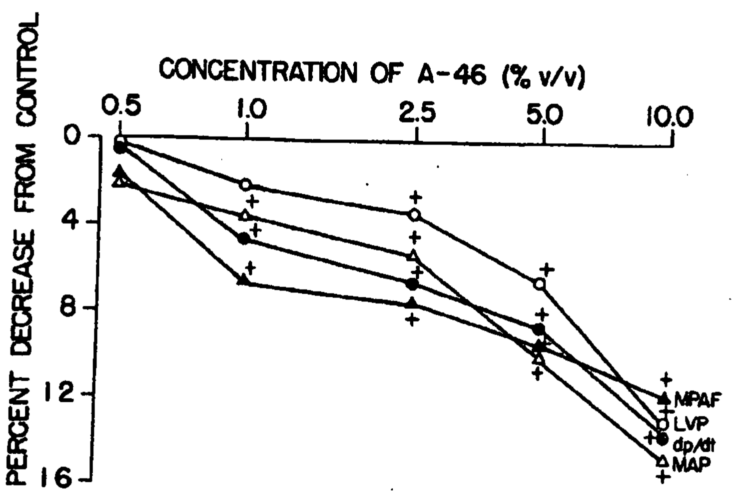

FIGURE 7.2. Mean percentage changes from control averages in response to progressively increasing concentrations of A-46. Abbreviations are the same as for Figure 7.1. Asterisk denotes significant changes. Bars representing standard errors of means are omitted for simplicity.

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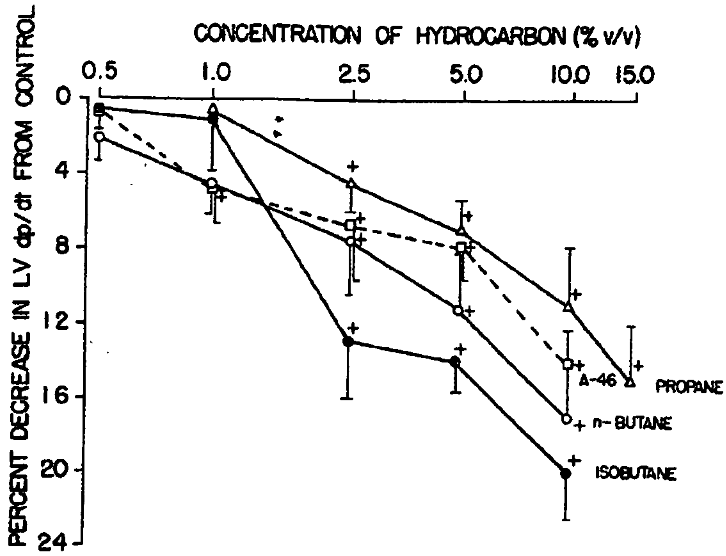

FIGURE 7.3. Concentration-response curves of the myocardial depressant effects of various aliphatic hydrocarbons in the open-chest dog preparation. Note that propane is the least toxic of all the studied compounds.

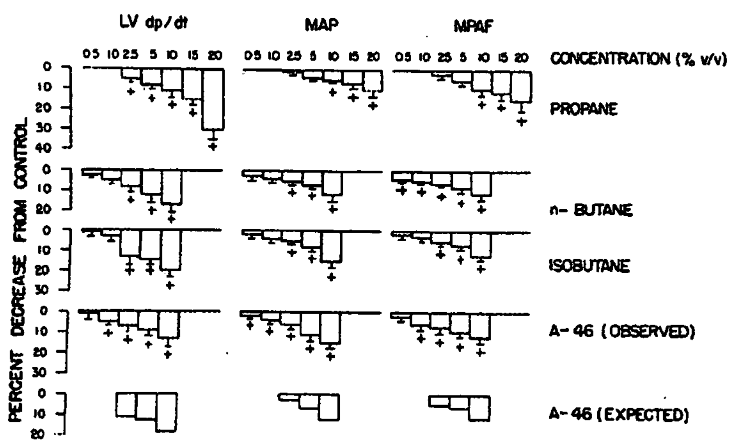

FIGURE 7.4. Mean percent decrease in myocardial contractility (dp/dt), mean aortic pressure (MAP), and mean pulmonary arterial flow (MPAF), brought about by various hydrocarbons studied. The expected effects of A-46 were calculated according to the molar percent of each component.

TABLE 7.3

Comparison of Propane, *n*-Butane, Isobutane, and A-46

	Propane	*n*-Butane	Isobutane	A-46
Formula	$CH_3-CH_2-CH_3$	$CH_3-CH_2-CH_2-CH_3$	$CH_3-CH(CH_3)-CH_3$	19.7 mol % propane 77.8 mol % isobutane 2.5 mol % *n*-butane
Molecular weight	44.09	58.12	58.12	
Boiling point	-42.1°C	-0.5°C	-0.5°C	
Solubility	All are soluble in alcohol, ether, chloroform			
Threshold effective concentration*	3.3%	0.5%	2.0%	1.9%

*Values as obtained in this laboratory.

hydrocarbons studied in this laboratory shows that propane is the least toxic, having a threshold effective concentration (TEC) of 3.3%; butane is the most toxic (TEC 0.5%), and isobutane and A-46 are intermediate and almost identical (TEC 2.0% and 1.9%, respectively). At higher concentrations, e. g., 5.0% and 10.0%, butane and isobutane exert comparative hemodynamic effects. The combination of 19.7 mol % of propane, 77.8 mol % of isobutane, and 2.5 mol % of *n*-butane to give A-46 seems to show an inclination to a decrease in myocardial toxicity, though not significantly different from that of isobutane alone. The expected effects of A-46, calculated according to the molar concentration of various components versus the observed values, are depicted in Figure 7.4. There is no significant difference between the expected and observed values which indicates that there is no potentiation of myocardial depression brought about by the combination of gases at the concentration levels studied. Propane, on the other hand, seems to possess the lowest toxicity of all studied compounds. The basis of selection of a suitable propellant from these gases depends, among other factors, on various physicochemical properties, stability, volatility, vapor pressure, etc., which are beyond the scope of this report.

D. Summary

The inhalation of the hydrocarbon propellant mixture A-46 in the anesthetized open-chest dog preparation brought about the following hemodynamic changes: a) decrease in myocardial contractility, b) decrease in cardiac output, and c) decrease in left ventricular pressure and systemic blood pressure. The minimum effective concentration was 1.9 ± 0.4% v/v. The propellant A-46 possesses the same pharmacologic effect as other studied hydrocarbons, though it has a tendency to be less toxic than isobutane alone. With the hydrocarbon propellant mixtures, there is no potentiation of the individual effects of isobutane, butane, and propane.

A-46

19.7 mol % propane
77.8 mol % isobutane
2.5 mol % n-butanc

1.9%

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TABLE 7.4

Summary of Percent Changes in Various Parameters by Various Concentrations of Hydrocarbons in Dogs

Concentration		Myocardial contractility				Mean aortic pressure				Mean pulmonary arterial flow				Pulmonary vascular resistance				Systemic vascular resistance				Stroke work			
% v/v	m*M*/l	P	*n*-B	i-B	A-46	P	*n*-B	i-B	A-46	P	*n*-B	i-B	A-46	P	*n*-B	i-B	A-46	P	*n*-B	i-B	A-46	P	*n*-B	i-B	A-46
0.5	0.20	–	-2.3	-0.5	-0.6	–	-2.8	-2.8	-2.3*	–	-4.1*	-1.9	-2.0	–	+7.9	+2.2	+4.9	–	-0.2	-1.3	-1.6	–	-5.9*	-4.8	-4.2
1.0	0.41	–	-4.5	-0.6	-4.6*	–	-3.0	-0.4	-3.9*	–	-4.8*	-2.1	-6.9*	–	+10.7	+1.1	+10.0	...	+1.1	-2.0	+3.3	–	-7.8*	-2.1	-9.8*
2.5	1.02	-4.5*	-7.6*	-13.1*	-6.3*	-0.1	-3.8*	-3.7*	-5.3*	-1.3	-6.0*	-5.3*	-7.0*	+2.6	+10.4	-0.4	+7.1	+1.6	+0.8	-0.3	+2.5	-2.6	-9.2*	-9.8*	-11.9*
5.0	2.04	-7.2*	-11.2*	-13.8*	-8.5*	-3.1*	-5.7*	-7.8*	-10.0*	-4.7	-7.4*	-6.2*	-8.5*	+7.2*	+12.4	+4.9	+13.9	+1.9	-0.3	+4.1	-1.2	-10.3*	-13.6*	-15.4*	-18.8*
10.0	4.09	-11.0*	-17.1*	-19.8*	-12.6*	-4.3*	-12.4*	-15.0*	-14.7*	-8.4*	-10.1*	-12.3*	-11.2*	+10.3*	+11.1	+16.5*	+5.7	+5.0	-5.5	-3.2	-4.0	-15.0*	-21.7*	-25.6*	-22.6*
15.0	6.13	-14.9*	–	–	–	-6.9*	–	–	–	-10.8*	–	–	–	+11.1*	–	–	–	+3.3	–	–	–	-18.0*	–	–	–
20.0	8.18	-29.4*	–	–	–	-9.3*	–	..	–	-14.7*	–	–	–	+17.2*	–	–	–	+2.2	–	–	–	-24.2*	–	–	–

Note: The various concentrations studied are expressed in m*M*/l and % v/v. P = propane, *n*-B = *n*-butane, *i*-B = isobutane. A-46 consists of the following molar percentages: 19.7 propane, 77.8 isobutane, 2.5 *n*-butane. See Section C, Discussion of Hemodynamic Effects.
*Significant change ($P < 0.05$).

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文献 14

Final Report of the Safety Assessment of Isobutane, Isopentane, n-Butane, and Propane

Isobutane, Isopentane, n-Butane, and Propane are low molecular weight alkanes, generally nsed in cosmetic products as aerosol propellants. Isobutane, Isopentane, n-Butane, and Propane were found not to be mutagenic in Ames Tests, both with and without metabolic activation. 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. Subchronic inhalation of Isobutane and Propane produced no toxicity in two animal species. Acute inhalation of Isopentane, n-Butane, and Isobutane was shown to sensitize the myocardium of test animals to epinephrine. No significant systemic abnormalities occurred in human subjects during an acute inhalation study of Isobutane, n-Butane and Propane. Propane caused no human mucosal irritation. A Propane-Isobutane mixture, present at 64.5% and 70.0% in two different cosmetic formulations, caused no skin irritation in 125 human volunteers. 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.

INTRODUCTION

ISOBUTANE, Isopentane, n-Butane, and Propane are used in the cosmetic industry as aerosol propellants to replace the chlorofluoro-carbon propellants. Isopentane is listed in the 1976 Food and Drug Administration (FDA) Voluntary Submission of Cosmetic Product Formulation data; however, it is not registered in the 1979 data. The FDA does not mandate submission of the manufacturers' product formulation data; therefore it is possible that certain uses and concentrations of these ingredients were not reported, or that they are no longer used.

CHEMICAL AND PHYSICAL PROPERTIES

Isobutane, Isopentane, n-Butane, and Propane are alkanes characterized by singly bonded carbon atoms. They conform to the generic formula C_nH_{2n+2}, where "n" represents the number of carbon atoms. Alkanes with four or fewer carbon atoms are gases at room temperature, whereas those with from five to 17 carbons are liquids. Alkanes with more than 17 carbon atoms are waxy solids at ambient temperatures.[1]

n-Butane and Isobutane are structural isomers. Without exception, the branching (isomerization) of an alkane chain lowers the boiling point from that of the straight chain isomer.[1,2]

The alkanes have a low specific density, are nonpolar and cannot form hydrogen bonds. They are practically insoluble in water, but are generally soluble in such low polarity liquids as benzene, carbon tetrachloride, chloroform, and other alkanes.[1,2]

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Structure of the Pure Hydrocarbons

1. Isobutane, synonymous with 2-methyl propane and trimethyl methane, is a saturated hydrocarbon with the formula:

$$\begin{array}{l} CH_3-CH-CH_3 \\ \qquad\;\; | \\ \qquad CH_3 \end{array}$$

2. Isopentane, also called 2-methyl butane or ethyl dimethyl methane, is a saturated, liquid hydrocarbon having the structure:

$$\begin{array}{l} CH_3-CH-CH_2-CH_3 \\ \qquad\;\; | \\ \qquad CH_3 \end{array}$$

3. n-Butane, is a colorless gas having the structural formula:

$$CH_3-CH_2-CH_2-CH_3$$

4. Propane, or dimethyl methane, is a gaseous alkane with the following structural formula:[2,42]

$$CH_3-CH_2-CH_3$$

Properties

Table 1 gives a listing of chemical and physical properties of these alkanes.[2-6]

Reactivity

Isobutane, Isopentane, n-Butane, and Propane are characteristically inert to many chemical reagents, hence the name paraffin (having little affinity). Although carbon-carbon and carbon-hydrogen bonds are strong, they can be broken when heated to high temperatures. Also, carbon and hydrogen have similar electronegativity values, making these molecules only very slightly polarized; consequently, they do not react with bases. Alkanes possess no unshared electrons and, therefore, are not attacked by most acids. However, very strong acids react with alkanes by protolysis (cleavage by a proton). The combination produces the highly reactive carbonium ion or carbocation, but this reaction would exist only under laboratory conditions. Alkanes are neither reactive with moisture nor corrosive to metals.[1,2,7]

Alkanes do undergo thermal reactions, including "cracking," isomerization, dehydrogenation, and cyclization. At elevated temperatures, these compounds undergo halogenation and nitration reactions, and react vigorously with oxygen; thus they can present risks of fire or explosion in air. However, they can be oxidized by atmospheric oxygen at temperatures below their ignition points. The rate of oxidation in the vapor phase increases with chain length and diminishes with chain branching.[7]

Production

Alkanes are primarily derived from petroleum and natural gas, and from the hydrogenation of alkenes. The synthetic methods of producing the pure alkanes are: The Corey-House alkane synthesis which combines lithium diakyl cuprate compounds with alkyl halides to produce hydrocarbons; the Wurtz reaction, combining an alkyl halide with sodium metal; and the reduction of alkyl halides. These methods are commercially unfeasible.[1]

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES

Properties	*Isobutane*	*Isopentane*	*n-Butane*	*Propane*	*Ref.*
Boiling pt. (°C)	−11.73	27.854	−0.5	−42.07	2–5
Freezing pt. (°C)	−159.42	−159.89	−138.35	−189.69	2–4
Flash pt. (°C)	−82.7	−56.6	−60	−104.4	2,3
Density ($d^{20}4$)	0.549	0.6201	0.5788	0.5005	2–4
Molecular wt.	58.12	72.15	58.12	44.11	3,4
Refractive index ($n^{20}D$)		1.3537	1.3326	1.2898	2,4
Autoignition pt. (°C)	462.2	420	405	468	2
Critical temperature (°C)			153.2		2
Tolerance in air (TLV) (ppm)			600	1000	5,6
Explosive limit in air (percent)	1.8–8.4	1.4–8.3	1.9–8.5	2.2–9.5	5
Odor	Slight, natural gas	Pleasant	Natural gas	Odorless when pure	2
Color	Colorless	Colorless	Colorless	Colorless	2
State	Gas	Liquid	Gas	Gas	2
Solubility:					
Water	Soluble	Insoluble	Soluble	Soluble	2–4
Alcohol	Very soluble	Miscible	Very soluble	Soluble	
Ether	Very soluble	Miscible	Very soluble	Very soluble	
Acetone				Slightly soluble	
Benzene				Very soluble	
Chloroform	Very soluble		Very soluble	Very soluble	

Methods of production, and grades and handling procedures for this group of alkanes are listed in Table 2.[2]

Analytical Methods

Gas chromatography and mass spectroscopy are useful for the analysis of alkanes. In addition, infrared spectroscopy and thermal conduction detection are used to identify this group. Flame ionization and electron capture can detect trace amounts of them in biological samples.[8-14]

Impurities

This group of alkanes may be contaminated with other organic compounds, nonorganic chemicals or moisture. Table 3 lists these impurities and their respective concentrations.[15]

USE

Noncosmetic Uses

1. Isobutane is used in organic syntheses, as a refrigerant, as an aerosol propellant, and as high octane aviation fuel, in the manufacture of rubber, as an instrument calibration fluid, and is a Generally Recognized as Safe (GRAS) food ingredient.[2,16]

2. Isopentane is used as a solvent, as a blowing agent for polystyrene, and in the manufacture of chlorinated derivatives.[2]

TABLE 2. DERIVATIONS, PURITY GRADES, AND HANDLING PROCEDURES.[a]

Compound	Derivation/ Purification	Technical	Grades research	Other	Handling
Isobutane	1. Component of natural gas, refinery gas, wet natural gas 2. Isomerization of butane	99 mole (pure grade)	99.96 mole		1. Pressurized cylinders 2. Tank cars 3. Tank trucks
Isopentane	1. Fractional distillation from petroleum 2. Purified by rectification	95 mole	99.99 mole	1. Pure-99 2. Commercial	1. Pure-55 gal. drums 2. Tech. and comm. drums, tank cars
n-Butane	1. By-product of petroleum refining or gasoline manufacturing	95 mole	99.99 mole	1. Pure-99 mole 2. Mixtures	1. Steel cylinders 2. Tank cars, tank trucks 3. Ocean tankers
Propane	1. Fractional distillation of petroleum and natural gas	99.9	99.9		1. Cylinders 2. Tank cars

[a]From Ref. 2.