Table 2 The concentrations of inhaled chemicals causing effects on the central nervous system of rats after 10 min, death in rats after 15 min and cardiac sensitization in dogs after 5 min. Activity ratios expressed as the ratios of the concentrations causing death or cardiac sensitization to the concentrations causing effects on the central nervous system. (S = CNS stimulant; D = CNS depressant)

Chemical	*Toxic effects (vols % in air and 95% confidence intervals)*			*Activity ratios*		
	CNS	*Mortality*	*Cardiac*			
	EC_{50} *(CNS)*	LC_{50}	EC_{50} *(C.S.)*	LC_{50}: EC_{50} *(CNS)*	EC_{50} *(C.S.):* EC_{50} *(CNS)*	*CNS action*
FC 112	0.24 (0.2–0.3)	2.0 (1.6–2.5)	0.12 (0.10– 0.14)	8.3	0.5	S
FC 114 B2	1.0 (0.8–1.4)	12 (9–16)	0.25 (0.20– 0.31)	12	0.3	S
Carbon tetrachloride	0.8 (0.6–1.0)	3.0 (2.2–4.1)	0.4 (0.3 – 0.6)	3.8	0.5	D
Trichloroethylene	0.4 (0.3–0.6)	>6.8	0.7 (0.5 – 1.1)	>17	1.8	D
Trichloroethane	0.5 (0.4–0.6)	3.8 (2.9–5.0)	0.7 (0.4 – 1.1)	7.6	1.4	D
FC 113	2.8 (2.2–3.5)	13 (10–17)	0.7 (0.5 – 0.8)	4.6	0.3	S
FC 11	3.5 (2.8–4.5)	13 (10–16)	1.25 (0.5 – 1.6)	3.7	0.4	S
Chloroform	1.6 (1.2–2.0)	7.6 (6.7–9.6)	1.6 (1.2 – 2.0)	4.8	1.0	D
BCF	5.0 (4.1–6.3)	20 (15–27)	1.9 (1.2 – 2.6)	4.0	0.4	S
Methylene chloride	0.9 (0.7–1.2)	5.7 (4.5–7.5)	2.5 (1.9 – 3.4)	6.3	2.8	D
Isobutane	20 (16–23)	57 (48–65)	7.0 (4.7–10.6)	2.9	0.4	S
Vinyl chloride	3.8 (2.9–5.0)	18 (14–23)	7.1 (6.1 – 8.3)	4.7	1.9	D
FC 12	25 (19–33)	>80	7.7 (7.0 – 8.5)	> 3.2	0.3	S
FC 22	14 (11–18)	35 (28–45)	14 (10–21)	2.5	1.0	D
Propane	28 (22–35)	>80	18 (12–26)	> 2.8	0.6	D
FC 13 B1	42 (30–53)	>80	20 (15–27)	> 1.9	0.5	S
FC 13	>80	>80	approx. 80	—	<1.0	—

Death following exposure to a CNS stimulant was as follows: slight tremors of the limbs, marked tremors of the limbs and head, convulsions, narcosis, shallow respiration and death from respiratory depression. Death always occurred during exposure, never afterwards. Recovery from a non-lethal exposure was rapid and the rats appeared normal within 10 min with no delayed after effects. Examination of the LC_{50}:EC_{50} ratios (Table 2) shows that the concentrations causing death were several times the concentrations causing visible effects on the CNS.

All the chemicals tested caused cardiac sensitization in dogs at concentrations ranging from 0.12–80% in the inspired air (Table 2). Cardiac sensitization that resulted in ventricular tachycardia was characterized by an increased heart rate followed by one or two ventricular ectopic beats, then a 5 or 6 second run of multifocal ventricular ectopic beats before the ECG returned to normal. The events leading to ventricular fibrillation were similar, but after 1 or 2 seconds of ventricular tachycardia, fibrillation occurred. No other arrythmias were ever seen.

The similarity of the ratio EC_{50} (cardiac sensitization):EC_{50} (CNS effects) (Table 2) indicated that with these chemicals the two effects appeared to go together and that the more potent a chemical was on the CNS, the more potent it was in causing cardiac sensitization.

Neither the effects on the CNS nor the effects on the heart could be correlated with chemical structure, molecular weight, the presence or absence of various halogen atoms or the degree of saturation, but there was an approximate relationship between toxicity and boiling point (Table 3). A relationship between boiling point or vapour pressure and narcotic potency has been known for volatile anaesthetic agents for many years. On the basis of this relationship Ferguson (1939) developed his theory that substances present in a given medium at equal thermodynamic activities have the same degree of biological action. Using the ratio of the partial pressure of the chemical causing the toxic effect to the saturated vapour pressure as a measure of the thermodynamic activity, it can be seen (Table 4) that despite a several hundred-fold variation in potency when expressed as volumes per cent, all the chemicals tested produced their effects at similar thermodynamic activities—the potencies being reduced to a ten-fold variation only.

Discussion

All the chemicals tested caused either stimulation or depression of the CNS of rats, leading to death from profound respiratory depression if exposure concentrations were increased. In dogs, all the chemicals caused cardiac sensitization. The non-lethal toxic effects were rapidly reversed on cessation of exposure, indicating the rapid elimination of the chemicals from the body (Clark & Tinston, 1971; Morgan *et al.*, 1972; Beck *et al.*, 1973).

Although the effects of each chemical were qualitatively similar, quantitatively their potencies differed markedly from each other. Despite this wide difference, the ratios of the concentrations causing cardiac sensitization in dogs to those

Table 3 The concentrations of inhaled chemicals causing central nervous system effects in rats or cardiac sensitization in dogs related to their formulae, molecular weight, number of halogen atoms and boiling point

Chemical		EC_{50}s (vols %)		Molecular Wt.	No. of halogen atoms			Boiling pt (°C)
		CNS	Cardiac		Cl	F	Br	
FC 112	$CFCl_2CFCl_2$	0.24	0.12	206	4	2	0	93
FC 114 B2	CF_2BrCF_2Br	1.0	0.25	260	0	4	2	48
Carbon tetrachloride	CCl_4	0.8	0.4	156	4	0	0	77
Trichloroethylene	$CHCl:CCl_2$	0.4	0.7	132	3	0	0	87
Trichloroethane	CH_3CCl_3	0.5	0.7	135	3	0	0	74
FC 113	$CFCl_2CF_2Cl$	2.8	0.7	189	3	3	0	48
FC 11	$CFCl_3$	3.5	1.25	139	3	1	0	24
Chloroform	$CHCl_3$	1.6	1.6	121	3	0	0	61
BCF	CF_2ClBr	5.0	1.9	166	1	2	1	−4
Methylene chloride	CH_2Cl_2	0.9	2.5	86	2	0	0	40
Isobutane	$CH_3CH(CH_3)CH_3$	20	7.0	58	0	0	0	−12
Vinyl chloride	$CH_2:CHCl$	3.8	7.1	63	1	0	0	−14
FC 12	CF_2Cl_2	25	7.7	122	2	2	0	−30
FC 22	CHF_2Cl	14	14	86	1	2	0	−41
Propane	$CH_3CH_2CH_3$	28	18	44	0	0	0	−42
FC 13 B1	CF_3Br	42	20	149	0	3	1	−58
FC 13	CF_3Cl	>80	approx. 80	105	1	3	0	−81

Table 4 The physico-chemical properties of the chemicals and their thermo-dynamic activities expressed as relative saturations

Chemical	*Vapour pressure at 37°C (mm Hg) (Ps)*	*Partial pressure at EC_{50} (mmHg)*		*Relative saturation for:*	
		CNS (Pcns)	*Cardiac (Pcs)*	*CNS effects (Pcns/Ps)*	*Cardiac sensitization (Pcs/Ps)*
FC 112	99	1.8	0.9	0.02	0.01
FC 114 B2	517	7.6	1.9	0.02	0.004
Carbon tetrachloride	190	6.1	3.0	0.03	0.02
Trichloroethylene	122	3.0	5.3	0.03	0.04
Trichloroethane	210	3.8	5.3	0.02	0.03
FC 113	524	21	5.3	0.04	0.01
FC 11	1186	27	9.5	0.02	0.01
Chloroform	320	12	12	0.04	0.04
BCF	2888	38	14	0.01	0.01
Methylene chloride	661	6.8	19	0.01	0.03
Isobutane	3520	152	53	0.04	0.02
Vinyl chloride	4218	29	54	0.01	0.01
FC 12	6764	190	58	0.03	0.01
FC 22	10700	106	106	0.01	0.01
Propane	9538	213	137	0.02	0.01
FC 13 B1	15276	319	152	0.02	0.01
FC 13	40696*	>608	608	—	0.02

*Extrapolated

causing CNS effects in rats were similar for each chemical. There was, therefore, a correlation between the CNS effect concentrations and the cardiac sensitization concentrations.

When the toxicities of the chemicals were expressed on a thermodynamic scale rather than a simple volumes % scale, however, the chemicals displayed similar potencies. That such a wide range of relatively inert, stable, lipid soluble chemicals producing a rapidly reversible effect were equipotent when expressed in this way indicates that the effect on the CNS and the heart are probably structurally non-specific actions, occurring as soon as the chemical occupies a constant fraction of the critical biophase. Both actions may therefore be regarded as examples of 'physical toxicity' (Ferguson, 1939). That is, the chemicals exert their toxic effects not by combining with some specific target or receptor, but by simply being present in some part of the cell and disorganizing its function temporarily. Such a relationship does not explain their toxic mode of action, but does indicate that cardiac sensitization and CNS depression or stimulation are unlikely to be specific effects related to one class or type of chemical. They may be general phenomena related to physico-chemical properties only, and the ability to sensitize the heart or affect the CNS may be possessed by many inert, lipid soluble chemicals. This ability should be revealed on administration at a relative saturation of 0.004–0.04 or, alternatively, may be predictable from the saturated vapour pressure or the boiling point, or indeed, any physico-chemical property that is a measure of

intermolecular attraction. Structure activity predictions will therefore be relevant only insofar as they predict these changes in physico-chemical properties (Clark & Tinston, 1973). That cardiac sensitization by several of these chemicals with boiling points between −30–+24°C has been associated with blood concentrations of 20–35 μg/ml in dogs (Clark & Tinston, 1971; Beck *et al.*, 1973) tends to support these observations.

In extrapolating the experimental toxicity data to man the relevance of the animal models has to be assessed. Qualitatively there can be no doubt that the animal data are relevant since the effects on the CNS are what the abusers are seeking, and the effects on the heart are now well documented. There can also be little doubt that chemicals that are deliberately inhaled but have not been assessed in these animal models will also have similar toxic properties. Thus, it may be predicted that toluene will be a potent chemical. Recent work by Bruckner and Peterson (1981) tends to confirm this prediction. Quantitatively the extrapolation is less certain, but on the basis of the limited evidence available (Reinhardt & Reinke, 1972; Clark, 1972), it may be predicted that man may show signs of dizziness after two or three minutes' inhalation of concentrations near the animal EC_{50} (CNS) and may have the potential for cardiac sensitization after inhaling concentrations near the animal EC_{50} (CS).

Cardiac sensitization is unlikely to occur in man in the absence of any effects on the CNS, and the dizziness should act as an early warning that a dangerous concentration was being reached. However, since the purpose of deliberately inhaling volatile chemicals is to produce an effect on the CNS, there will inevitably be a risk of cardiac sensitization and sudden death.

Acute toxic effects on the CNS and the heart due to physical toxicity should be transient and should disappear when the chemical has been eliminated from the body. Thus, there should be no permanent structural damage to the heart and brain cells resulting from this toxicity. It would be dangerous, however, to assume that there were no long-term effects of 'sniffing' since some of these chemicals may have other effects that are not due to physical toxicity but which could be a serious consequence of long-term abuse. The effects of carbon tetrachloride on the liver and benzene on the blood are well known examples.

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Non-fluorinated Propellants and Solvents for Aerosols

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Chapter 4
PROPANE

Propane is one of three hydrocarbon propellants used in aerosol products. In a classification proposed in 1974, propane was grouped together with vinyl chloride and dichlorodifluoromethane (FC 12), which are characterized as high-pressure propellants of intermediate toxicity.[1] This chapter reviews the literature and describes some experiments that will permit a comparison of the inhalational toxicity of propane with that of other hydrocarbons (Chapters 5 and 6) and with that of chlorinated solvents and alcohols (Chapters 1 to 3) used in aerosol products.

A. Review of the Literature

Propane is a paraffinic hydrocarbon that is present in natural gas to the extent of 12% by volume. Its structural formula is $CH_3CH_2CH_3$; the molecular weight is 44.09, the freezing point is -187°C, and the boiling point is -42.1°C. At a temperature of about 650°C, propane breaks down to ethylene and methane. Partial dehydrogenation of propane gives rise to propylene. Its vapor pressure is 130.3 psig at 70°C. Various chemical and physical properties are mentioned elsewhere.[2-5]

The occurrence of propane in the atmosphere is due to natural gas emissions, auto exhaust, and furnaces. The propane concentration in auto exhaust equals only about 1% that of ethylene.[6] Bida[7] found that propane is present in the atmosphere of gas refineries to the extent of 65.4 mg/m^3 at 250 m distance and 45 mg/m^3 at 1000 to 3000 m distance. The same author also found that in the autumn and winter period the concentration of propane in air is higher than in the spring and summer. Kopczynski et al.[8] found a value of 47.6 ppb of propane in the St. Louis area in December 1972. Propane is also detected in the air exhaled by healthy people,[9] and in the condensable phase of cigarette smoke to the extent of 0.7 mol %.[10] Propane can be detected in the atmosphere and in various tissues by gas chromatography.[11] The properties and safety precautions to be taken in dealing with propane and butane were discussed by Wenzel.[12]

1. Consumer Products

Bergwein[13,14] reported on the use of propane mixed with fluorocarbons, isobutane, methylene chloride, and other propellants in the manufacture of shaving creams, perfumes, dyes, automobile wax emulsion polishes, and insecticides. Propane is also contained in a disinfectant spray to the extent of 2.5 to 4.5%.[15] The efficacy of the halogenated hydrocarbons as propellants has been increased by adding propane and butane.[16] The use of propane in the aerosol industry was discussed by Larde[17] and various propellant blends containing propane have been reported on elsewhere.[18,19] However, the amount of propane that can be added to fluorocarbons is limited in quantity to render the mixture nonflammable.[20] The properties and flammability of mixtures of propane and various fluorocarbons were also discussed.

2. Industrial and Laboratory Uses

Besides its use as a fuel, propane is also used as a solvent for preparing low-pressure ethylene copolymers[21] and as a fuel in the canning industry.[22] Alone or mixed with liquid nitrogen, propane is also used for tissue preservation. The study of Epstein and O'Connor[23] on neurons quenched in liquid gases showed no significant difference in oxygen uptake of cells prepared in either liquid propane or liquid nitrogen. They concluded that propane is a more reasonable choice as it has no significant toxic effect on cells. On the other hand, Fishbein and Stowell[24] found an 80% loss in the activity of succinate-cytochrome C reductase complex isolated from mouse liver, after quenching in liquid propane. Winckler[25] found that artifacts develop within 24 hr after quenching of tissue in liquid nitrogen, due to recrystallization of the frozen tissues.

3. Human Toxicity

Ambrosio et al.[26] reported on some laboratory investigations of workers bottling commercial liquid gases (butane and propane). Most of the workers complained of respiratory symptoms, e.g., dry cough and dry throat, and gastrointestinal symptoms. Of particular interest are the electrocardiographic findings in some workers, which indicate sinus tachycardia, extrasystole, and incomplete right bundle branch block.

An attempted murder by "calor gas," which contains 5 to 18% propane, was reported in 1970 by Baldok.[27] A case of death from incomplete

combustion of fuel propane gas was reported by Watanabe et al. in 1970; mortality was attributed to the formation of carbon monoxide.[28] Lactic acid production in propane poisoning was reported as slight.[29]

4. Toxicologic Investigation in Animals

There is limited information on the toxicity of propane in animals. Exposure to a 50% mixture of propane-butane for about ½ hr daily for 30 days resulted in slight hypochromic anemia in guinea pigs.[30]

Cardiac and pulmonary effects – Inhalation of 10% propane did not induce arrhythmia in the mouse; however, propane sensitized the heart to epinephrine-induced arrhythmia.[31] In the monkey, inhalation of 10% propane induced an insignificant decrease in myocardial force of contraction and aortic blood pressure (1.1% and 1.5%, respectively).[32] Inhalation of 20% propane aggravated these changes and caused 13.9% and 8.9% decreases in the same parameters.[32] Krantz et al. found that propane and isobutane sensitize the myocardium of the dog to epinephrine.[33] In a 10% concentration, propane caused respiratory depression in monkeys without any effect on pulmonary compliance.[34,35]

Anesthetic activity – In 1926, Brown and Henderson[36] examined the anesthetic property of propane in cats. They concluded that propane is not a useful anesthetic because the percent concentration required for relaxation of the skeletal muscles and true anesthesia is high, e.g., 89% propane failed to induce anesthesia in the cat within 4 min of inhalation; blood pressure showed a steady fall from 125 to 30 mmHg at the end of 4 min.

Miscellaneous effects – Propane, among other aliphatic gaseous hydrocarbons, exhibits an effect on the surface tension and electrical conductivity of model membranes of lipids, proteins, and mixtures of both.[37] Furthermore, propane induces swelling in mitochondria prepared with good respiratory control.[38] Propane has no effect on the color of a 2% suspension of rabbit erythrocytes in saline; however, after contact for 18 hr in closed Turner bulbs, propane changed the pH from 6.8 to 5.5.[39] It also inhibits the lysis of whole cells and cell wall fragments of *Micrococcus lysodeikticus* by lysozyme.[40] Patty and Yant[41] found the odor and physiological response augmented with increasing C atoms from propane to butane.

B. Hemodynamic Effects in Dogs

The study of the myocardial and hemodynamic effects of propane followed practically the same procedure used with chlorinated solvents (Chapter 2). The hemodynamic effects of propane in the open-chest dog preparation are summarized in Table 4.1. A record from a typical experiment is shown in Figure 4.1. In a concentration of 1%, propane elicited no significant effect on any of the parameters studied. The minimal effective concentration of propane varied from one experimental animal to another. Thus while a 2.5% concentration of propane induced various hemodynamic changes in one preparation, a 5% concentration was needed to elicit the same changes in another preparation. The threshold effective concentration averaged 3.3 ± 0.53%. However, a progressive increase in concentration of inhaled propane brought about a decrease in the various parameters depicted in Figure 4.2. These changes are as follows.

Decrease in myocardial contractility – The first significant change induced by propane is a decrease in myocardial contractility, as reflected by the decrease in maximal rate of rise of left ventricular pressure (dp/dt). This effect is brought about by as low a concentration as 2.5%. Increase of the concentration of propane in the inhaled mixture brought about a progressive and concentration-dependent decrease in myocardial contractility; thus inhalation of 2.5%, 5.0%, 10.0%, 15.0%, and 20.0% was associated with 4.5%, 7.2%, 11.0%, 14.9%, and 29.4% decreases in inotropic activity of the myocardium, respectively. The 20% concentration of propane was balanced by the appropriate volume of oxygen to prevent any hemodynamic changes due to hypoxia.

Decrease in mean aortic pressure and stroke work – At a concentration of 5%, propane induced a significant decrease in aortic pressure averaging 3.1% of the control value. This decrease in aortic pressure is gradually intensified by increasing the concentration of propane in the inhaled mixture. Thus, 10%, 15%, and 20% propane brought about decreases of 4.3%, 6.9%, and 9.3%, respectively. Concentrations of propane, amounting to 5%, 10%, 15%, and 20% brought about a decrease in stroke volume of 7.5%, 11.8%, 12.8%, and 17.4% and in stroke work of 10.3%, 15.0%, and 18.0%, and 24.2%, respectively.

Decrease in cardiac output – Propane induced not only a decrease in myocardial contractility but also a decrease in cardiac output. This latter effect

TABLE 4.1

The Myocardial and Hemodynamic Effects of Progressively Increasing Concentrations of Propane in Dogs*

	MPAP cm H_2O	MLAP cm H_2O	EMPAP cm H_2O	LVP mmHg	LVEDP mmHg	dp/dt mmHg/sec	MAP mmHg	MPAP ml/min	HR beats/min	Vascular resistance dynes-sec/cm^5		Stroke vol ml	Stroke work g-meter
										Pulmonary	Systemic		
Control	29.1 ± 4.1	6.7 ± 1.5	22.6 ± 3.2	150 ± 9.4	3.8 ± 1.3	3417 ± 341	126 ± 4.4	1610 ± 81	180 ± 10	818 ± 95	6012 ± 340	8.8 ± 0.7	15.6 ± 1.2
Propane 2.5%	29.4 ± 3.7	6.6 ± 1.5	22.8 ± 3.1	149 ± 9.8	3.8 ± 1.3	3333 ± 348	126 ± 4.3	1590 ± 89	182 ± 9	835 ± 89	6100 ± 332	8.5 ± 0.5	15.1 ± 1.2
	+0.3 ± 0.7	−0.1 ± 0.3	+0.2 ± 0.7	−1 ± 1.4	0 ± 0	−84 ± 26	0 ± 0.8	−20 ± 26	+2 ± 2.6	+17 ± 18	+88 ± 98	−0.3 ± 0.3	−0.5 ± 0.6
	NS	NS	NS	NS	NS	0.02	NS	NS	NS	NS	NS	NS	NS
Propane 5.0%	29.3 ± 3.6	6.3 ± 1.4	22.9 ± 3.1	145 ± 9.6	4.3 ± 1.5	3188 ± 359	122 ± 4.1	1540 ± 107	184 ± 9	867 ± 78	6122 ± 367	8.1 ± 0.6	14.0 ± 1.3
	+0.2 ± 0.6	−0.4 ± 0.3	+0.3 ± 0.6	−4 ± 2.0	+0.5 ± 0.5	−229 ± 50	−4 ± 1.0	−70 ± 30	+4 ± 2.8	+49 ± 19	+110 ± 113	−0.7 ± 0.3	−1.6 ± 0.4
	NS	NS	NS	NS	NS	0.01	0.02	NS	NS	0.05	NS	NS	0.02
												*	
Propane 10.0%	28.9 ± 3.6	6.1 ± 1.2	22.8 ± 3.2	144 ± 9.7	5.0 ± 1.8	3063 ± 356	121 ± 4.5	1480 ± 107	186 ± 9	899 ± 97	6318 ± 420	7.7 ± 0.5	13.2 ± 1.2
	−0.2 ± 0.8	−0.6 ± 0.3	+0.2 ± 0.3	−6 ± 2.6	+1.2 ± 0.8	−354 ± 81	−5 ± 1.3	−130 ± 37	+6 ± 3.0	+81 ± 12	+306 ± 157	−1.1 ± 0.4	−2.4 ± 0.6
	NS	NS	NS	0.05	NS	0.01	0.01	0.05	NS	0.01	NS	0.05	0.02
Propane 15.0%	27.9 ± 3.8	5.5 ± 1.1	22.4 ± 3.4	138 ± 10.1	6.3 ± 2.0	2938 ± 366	117 ± 5.5	1440 ± 112	184 ± 9	913 ± 117	6213 ± 404	7.6 ± 0.5	12.7 ± 1.3
	−1.2 ± 0.7	−1.2 ± 0.6	−0.2 ± 0.6	−12 ± 3.2	+2.5 ± 0.9	−479 ± 75	−9 ± 2.2	−170 ± 66	+4 ± 1.4	+95 ± 32	+201 ± 137	−1.2 ± 0.5	−2.9 ± 1.0
	NS	NS	NS	0.02	0.05	0.001	0.01	0.05	0.05	0.02	NS	0.05	0.05
Propane 20.0%	27.8 ± 3.7	5.0 ± 1.1	22.7 ± 3.9	130 ± 10.8	8.8 ± 3.0	2458 ± 384	115 ± 6.9	1380 ± 125	185 ± 10	963 ± 123	6192 ± 565	7.2 ± 0.5	11.8 ± 1.4
	−1.3 ± 1.1	−1.7 ± 0.9	+0.1 ± 1.2	−20 ± 3.4	+5.0 ± 1.9	−959 ± 160	−11 ± 3.2	−230 ± 78	+5 ± 2.0	+145 ± 33	+180 ± 238	−1.6 ± 0.6	−3.8 ± 1.2
	NS	NS	NS	0.001	0.05	0.001	0.01	0.05	0.05	0.01	NS	0.05	0.02

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

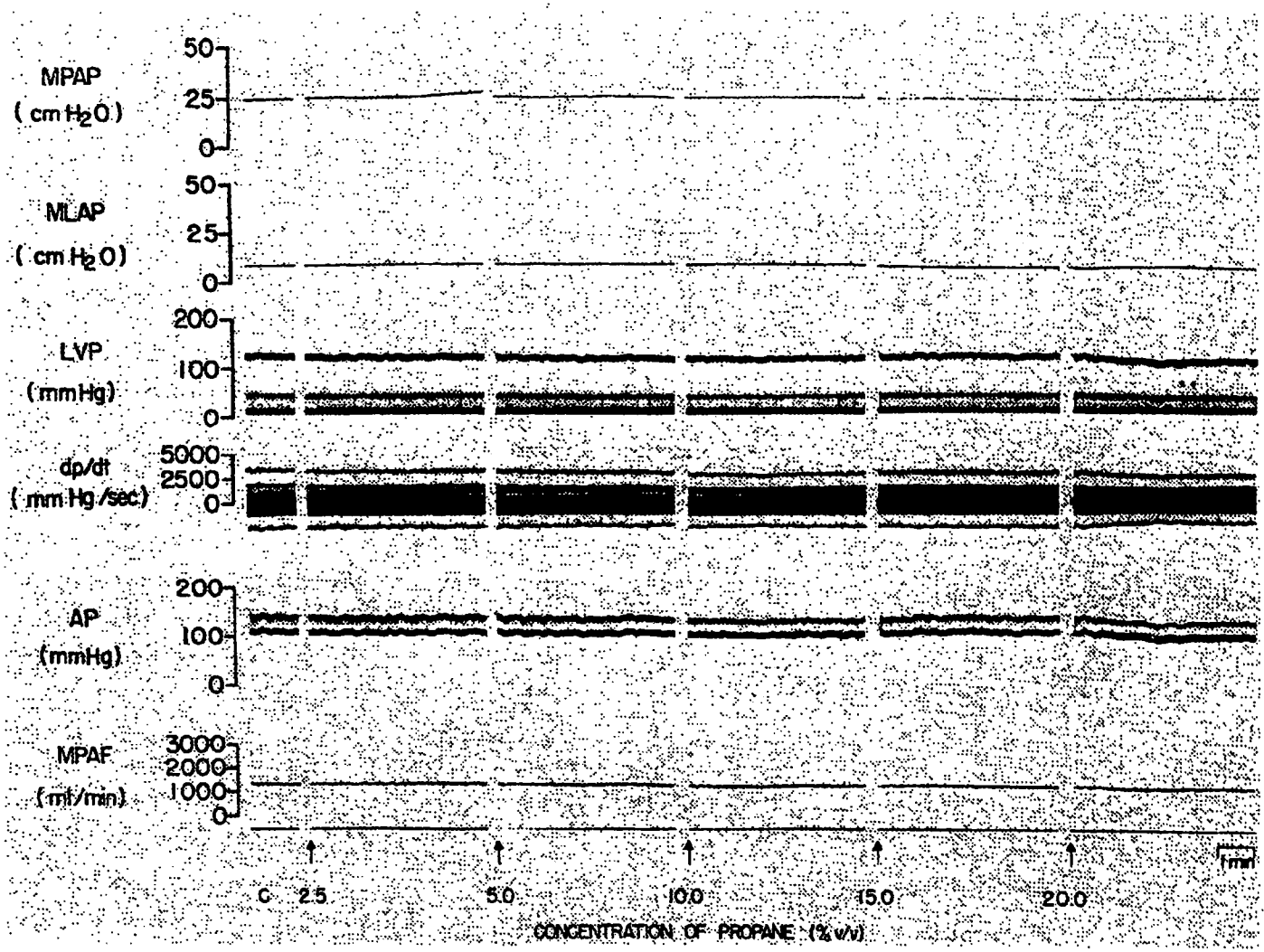

FIGURE 4.1. The effect of inhalation of progressively increasing concentrations of propane in the open-chest dog. Abbreviations are explained in the text.

FIGURE 4.1. The effect of inhalation of progressively increasing concentrations of propane in the open-chest dog. Abbreviations are explained in the text.

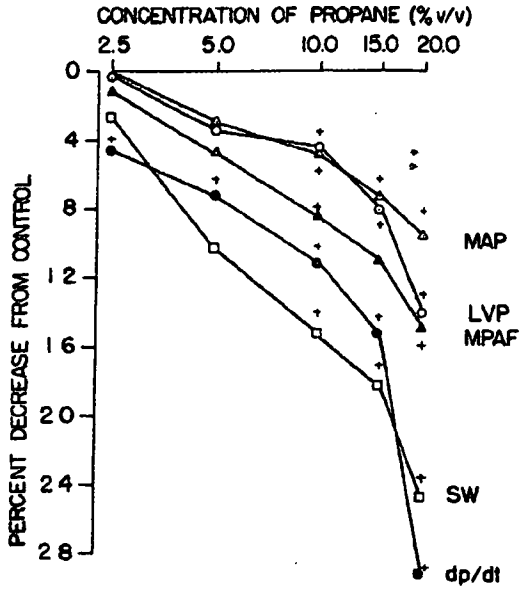

FIGURE 4.2. Mean percent decrease from control average, in response to various concentrations of propane in the open-chest dog preparation. Bars representing standard error of the mean are omitted for simplicity. + denotes significant change from control.

is due most probably to the former. A decrease in cardiac output of 4.7%, 8.4%, 10.8%, and 14.7% was induced by 5%, 10%, 15%, and 20% concentrations of propane, respectively. A decrease in left ventricular pressure of 3.4%, 4.2%, 7.9%, and 13.8% was induced by the same concentrations of propane, respectively.

Increase in pulmonary vascular resistance – A gradual increase in pulmonary vascular resistance, averaging 2.6%, 7.2%, 10.3%, 11.1%, and 17.2%, was elicited under the influence of 2.5%, 5.0%, 10%, 15%, and 20% of propane, respectively.

C. Discussion of Hemodynamic Effects

The major effects of propane are elicited on the myocardium. Thus, the first significant change in any of the parameters studied, in fact an effect that appeared at as low a concentration as 2.5%, was a decrease in myocardial contractility of 4.5%. This negative inotropic effect is concentration-dependent and is not accompanied by a negative chronotropic effect. An increase in heart rate was observed in this study. This effect is due to the stimulation of baroreceptors as a consequence of hypotension. The decrease in cardiac output, in the absence of any significant decrease in heart rate, is mainly secondary to the decrease in myocardial contractility.

The gradual and significant increase in pulmonary vascular resistance deserves a comment. A nonsignificant and slight increase in mean pulmonary arterial pressure was observed with the lower concentrations of propane. Meanwhile, a decrease in mean pulmonary arterial flow was elicited by the same concentrations of propane. Since pulmonary vascular resistance is the quotient of the effective mean pulmonary arterial pressure and pulmonary arterial flow, it appears that the increase in pulmonary vascular resistance does not necessarily reflect the actual state of the pulmonary blood vessels. The increase in pulmonary vascular resistance is a consequence of the relative changes in pulmonary blood pressure and pulmonary blood flow. Other factors affecting pulmonary circulation either directly or indirectly cannot be excluded.

D. Summary of Hemodynamic Effects

Propane, administered by inhalation to the open-chest dog preparation, induced the following myocardial and hemocynamic changes: (a) decrease in inotropism of the heart, (b) decrease in mean aortic pressure and stroke work, (c) decrease in cardiac output, and (d) increase in pulmonary vascular resistance. The minimal effective concentrations eliciting significant hemodynamic changes in a group of seven dogs averaged 3.3% v/v.

Chapter 5
BUTANE

Butane (*n*-butane) and propane are used as aerosol propellants both in the United States and Europe. In 1968, Kaempfer[42] stated that "... propane and butane are excellent solvents. They may be mixed to a very large extent with alcohol, with mineral and vegetable oils and also with chlorinated and fluorinated hydrocarbons. They are completely inert ... and ... their natural odour is hardly perceptible." The purity of the butane-propane mixture used in the aerosol industry is different from that used as fuel gas, and the butane content of the former is usually a mixture of butane and isobutane in an approximate ratio of 3:1. Butane is also used as a fuel and as a starting material for polymerization plants to convert it to iso-octane which in turn is used to increase the antiknock rating of aviation and motor fuel.[43]

A. Review of the Literature

Butane is a flammable gas that boils at -0.5°C. It is slightly soluble in water (0.15 v/v) but highly soluble in alcohol (18 v/v), ether (25 v/v) and chloroform (30 v/v). The molecular weight is 58.12.

Butane (C_4H_{10}) is a saturated aliphatic hydrocarbon occurring in natural gas. Its presence in the atmosphere is attributed to natural gas leakage, petroleum gas leakage, or diffusion through soil from petroleum deposits. Butane, resulting from radical polyethylene decomposition, has been detected in milk stored in polyethylene containers.[44]

Gordon et al.[45] have determined the average concentration of butane and isobutane in the Los Angeles atmosphere in the fall of 1967 and found values for butane ranging from 132 to 304 ppb (parts per billion parts air) and for isobutane, 44 to 74 ppb. These values varied according to the hour of sampling. Altshuller et al.[46] conducted a similar experiment and concluded that butane appears to arise from sources other than the pentanes or fuel hydrocarbons.

Inhalation toxicity in animals – In 1969, Shugaev[47] determined the concentration that kills 50% (LC_{50}) of mice and rats. Furthermore, he also determined the hydrocarbon content in various tissues by gas-liquid chromatography. The LC_{50} is 680 mg/l for mice (exposed for 2 hr) and 658 mg/l for rats (exposed for 4 hr). The effective concentration of butane, at LC_{50} level, in the mouse brain is 77.9 mg/100 g. The following concentration of butane was also found in various tissues of rat: 75.1, 49.2, 44.1, 52.2, and 208.6 mg/100 g in brain, liver, kidneys, spleen, and perinephric fat, respectively. The author also found parallelism between toxicity and effective butane concentration in the brain. This finding seems to be in contradiction to what was reported by the same author a year earlier.[48] Potentiation of the narcotic effect of butane and isobutylene was observed in 83% and an additive effect in the other 17% of experiments conducted on rats and mice.[47,49]

Neurotoxicity – The effect of butanes and pentanes on the central nervous system was studied by Stoughton and Lamson.[50] They found that butane in a concentration of 13% v/v produced light anesthesia within 25 min in mice. Only 1 min was required to induce the same effect with 22%; this concentration produced loss of posture within 15 min. Isobutane, on the other hand, in concentrations of 15%, 20%, and 23% produced light anesthesia in mice within 60, 17, and 26 min, respectively. In a concentration of 35%, however, isobutane induced loss of posture in mice in 25 min. They concluded that branched isomers of alkane series are less active and less toxic than the straight chain compounds.

Cardiotoxicity – In the course of investigating the ability of butane to sensitize the heart to the action of epinephrine in dogs, Chenoweth[51] found that only 3 out of 15 trials terminated in ventricular fibrillation.

Other biologic effects – Irradiated butane has been reported to cause eye irritation. The average threshold time for eye irritation of individuals exposed to 2 ppm of irradiated butane was 240 sec.[52] However, 3 ppm irradiated with nitrogen oxide failed to cause any sign of eye irritation; 6 ppm caused low but significant eye irritation.[53] Frommer and associates[54,55] found that butane is hydroxylated by rat liver microsomes to the isomeric alcohol.

The negative logarithm of the odor threshold concentration is 3.31 for propane and 4.28 for butane.[56] The concentration of butane that would have a noticeable odor is 5.24×10^{-5} mol/l or

3.05 mg/l. Chambers,[43] however, reported that butane itself is odorless and a small amount of stench is added to it to detect any leakage.

Butane, amongst other *n*-alkanes, has a pronounced inhibitory effect on the growth of bacteria, actinomycetes, fungi, algae, plant seeds, chick embryos, and the various states of metamorphosis of the fruit fly.[57] This effect is increased with elongation of the chain length in a series of hydrocarbons.

Butane inhibits the cell lysis of *Micrococcus lysodeikticus* by egg-white lysozyme.[58] Furthermore the release of mucopeptide from the spore coats of *Bacillus megaterun* by egg-white lysozyme was also inhibited by bubbling butane into the enzyme solution.[40] It was concluded that butane inhibits the binding of the enzyme to the bacterial cell or spore.

Ethylene, which is supposed to serve as a natural plant hormone, brings about swelling of the mitochondria prepared from heads of cauliflower (*Brassica oleracea* var. *botrytis L.*) and seedlings of Alaskan pea.

B. Hemodynamic Effects in Dogs

The hemodynamic effects of butane were examined in the anesthetized open-chest dog preparation, similar to that used for the study of methylene chloride (Chapter 2). The preparation was allowed to stabilize for a period of up to 30 min after which 0.5%, 1.0%, 2.5%, 5%, and 10% concentrations of butane in air were administered via the inlet of the respirator, for 5 min. Various concentrations were administered in an ascending order and successively. All data were analyzed by paired t-test, the criterion for significance being P less than 0.05. The results are summarized in Table 5.1, Figure 5.1 and Figure 5.2.

Decrease in mean pulmonary arterial flow and stroke volume – The inhalation of 0.5% butane brought about a significant decrease (4.1%) in cardiac output, as reflected in the measurement of pulmonary arterial blood flow. Increase in butane concentration was accompanied by a further decrease in cardiac output; thus concentrations of 1, 2.5, 5, and 10% butane were associated with reductions of 4.8, 6.0, 7.4, and 10.1%, respectively. In the absence of any significant changes in the heart rate, decrease in the cardiac output was also reflected by a decrease in stroke volume. This parameter is reduced by 2.8, 4.8, 6.3, 8.0, and 10.2% after the inhalation of 0.5, 1.0, 2.5, 5.0, and 10% concentrations of butane in air, respectively.

Decrease in myocardial contractility and stroke work – Myocardial contractility, as gauged by the rate of rise in left ventricular pressure, dp/dt, was gradually decreased by inhalation of butane. Thus 0.5% butane induced a decrease in dp/dt of 2.3% of the average control value. Increase in the butane concentration to 1.0, 2.5, 5, and 10% was associated with a progressive decrease in myocardial contractility of 4.5, 7.6, 11.2, and 17.1%, respectively. The decrease in myocardial contractility was accompanied by a greater decrease in stroke work.

Decrease in left ventricular and aortic pressure – A gradual decrease in the left ventricular pressure was observed under the influence of gradually increasing concentrations of butane. Thus a decrease of 2.3, 3.7, 5.2, 7.5, and 11.7% was induced by 0.5, 1.0, 2.5, 5.0, and 10% concentrations of butane, respectively. A decrease of 2.8, 3.0, 3.8, 5,7, and 12.4% in the aortic pressure was also induced by the above-mentioned concentrations, respectively.

No effect on vascular resistance and other parameters – Various concentrations of butane did not bring about significant changes in left atrial and pulmonary arterial pressures, and in pulmonary and systemic vascular resistances. However, at high concentrations (10%) a trend towards a decrease in the systemic vascular resistance was observed.

C. Discussion of Hemodynamic Effects

The effect of butane on the central nervous system was studied by Stroughton and Lamson[50] but its effect on the cardiovascular system has not been reported hitherto. The most significant feature of the present investigation is the decrease in cardiac output (4.1%), accompanied by a decrease in myocardial contractility (2.3%), which suggests that the former effect might be due, at least partly, to the latter action. The possibility of a decrease in venous return due to pooling of blood in capacitance vessels cannot be excluded. The effect of butane on vasculature could be a direct one, or partly induced via central depression of the vasomotor center. This effect on venous return, with the consequent decrease in filling pressure, is also shown from the decrease in stroke volume induced by butane. However, it is important to point out that there is no significant effect

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TABLE 5.1

Hemodynamic Effects of Inhalation of Progressively Increasing Concentrations of Butane 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		Stroke vol ml	Stroke work g·meter
										Pulmonary	Systemic		
Control	23.6 ± 1.97	8.8 ± 2.16	14.9 ± 2.07	147 ± 10.1	7.6 ± 1.12	3630 ± 477.9	123 ± 9.3	1710 ± 153.6	191 ± 16.7	536 ± 102.8	3472 ± 545.2	9.1 ± 0.97	15.8 ± 1.74
0.50%	24.0 ± 2.03	8.5 ± 2.15	15.5 ± 2.22	144 ± 9.9	8.2 ± 0.92	3545 ± 468.2	120 ± 10.6	1640 ± 146.1	191 ± 17.1	578 ± 109.2	3490 ± 615.9	8.8 ± 0.94	14.9 ± 1.70
	+0.4 ± 0.54	−0.3 ± 0.15	+0.6 ± 0.52	−3 ± 1.03	+0.6 ± 0.60	−85 ± 47.2	−3 ± 1.8	−70 ± 12.2	−0.6 ± 1.43	+42 ± 19.8	+18 ± 104.1	−0.3 ± 0.11	−0.9 ± 0.15
	NS	NS	NS	0.05	NS	NS	NS	0.01	NS	NS	NS	0.05	0.01
1.0%	24.3 ± 2.16	8.5 ± 2.05	15.6 ± 2.14	142 ± 10.9	8.2 ± 0.92	3460 ± 449.3	120 ± 10.4	1630 ± 151.3	192 ± 16.8	591 ±107.5	3563 ± 636.8	8.7 ± 0.97	14.6 ± 1.87
	+0.7 ± 0.70	−0.3 ± 0.32	+0.7 ± 0.66	−5 ± 1.58	+0.6 ± 0.60	−170 ± 85.7	−3 ± 2.1	−80 ± 12.2	+1.0 ± 0.51	+55 ± 20.5	+91 ± 118.7	−0.4 ± 0.09	−1.2 ± 0.26
	NS	NS	NS	0.05	NS	NS	NS	0.01	NS	NS	NS	0.01	0.01
2.5%	24.2 ± 2.06	8.7 ± 1.97	15.4 ± 2.35	140 ± 10.4	9.2 ± 0.49	3350 ± 451.4	119 ± 10.1	1610 ± 153.6	193 ± 18.4	595 ± 116.0	3542 ± 610.9	8.5 ± 1.00	14.2 ± 1.72
	+0.6 ± 0.98	−0.1 ± 0.35	+0.5 ± 1.13	−7 ± 2.29	+1.6 ± 1.02	−280 ± 119.7	−4 ± 1.6	−100 ± 0.2	+2.0 ± 2.11	+59 ± 42.5	+70 ± 111.7	−0.6 ± 0.09	−1.6 ± 0.10
	NS	NS	NS	0.05	NS	0.05	0.05	0.001	NS	NS	NS	0.01	0.001
5.0%	24.2 ± 2.16	8.7 ± 2.01	15.4 ± 2.45	136 ± 10.4	9.8 ± 0.92	3200 ± 413.8	116 ± 9.9	1590 ± 169.1	194 ± 18.9	601 ± 116.4	5521 ± 708.7	8.5 ± 1.14	13.7 ± 1.80
	+0.6 ± 1.14	−0.1 ± 0.35	+0.5 ± 1.43	−11 ± 3.12	+2.2 ± 0.97	−430 ± 168.3	−7 ± 1.0	−120 ± 25.5	+3.0 ± 2.67	+65 ± 56.9	+49 ± 166.2	−0.6 ± 0.17	−2.1 ± 0.15
	NS	NS	NS	0.05	NS	0.05	0.01	0.01	NS	NS	NS	0.02	0.001
10.0%	23.4 ± 1.84	8.9 ± 1.93	14.5 ± 1.98	130 ± 9.9	9.8 ± 1.53	2995 ± 393.7	108 ± 10.0	1550 ± 189.7	194 ± 20.0	586 ± 104.8	5256 ± 752.8	8.3 ± 1.24	12.6 ± 2.02
	−0.2 ± 1.23	+0.1 ± 0.45	−0.4 ± 1.33	−17 ± 2.54	+2.2 ± 0.58	−635 ± 167.1	−15 ± 1.6	−160 ± 50.9	+3.0 ± 3.77	+50 ± 58.3	−216 ± 230.6	−0.8 ± 0.30	−3.2 ± 0.42
	NS	NS	NS	0.01	0.02	0.02	0.001	0.02	NS	NS	NS	0.05	0.001

*Each set of numbers is the mean value of 6 experiments and consists of mean response ± SEM, mean difference ± SE of difference, and the significance level.

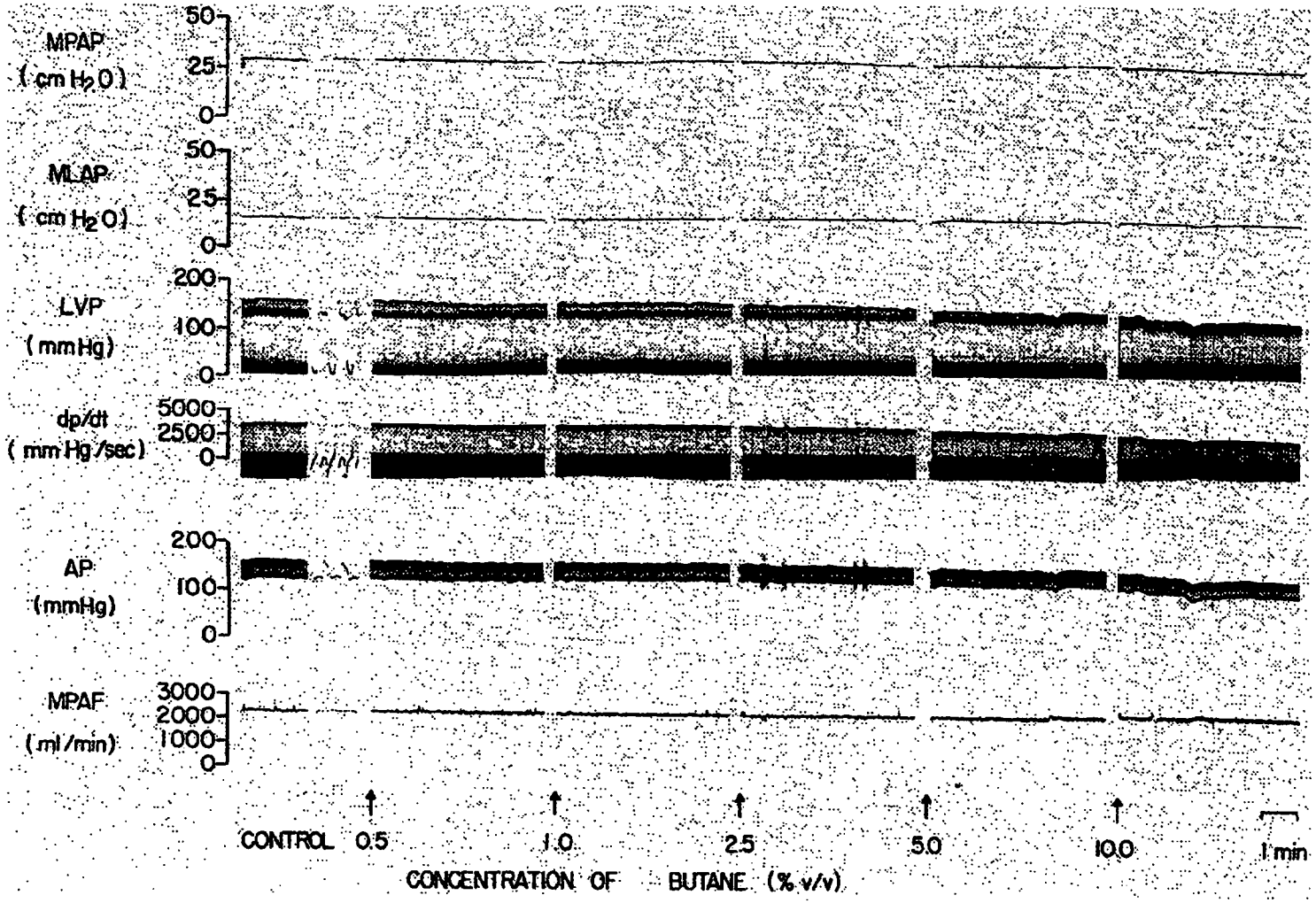
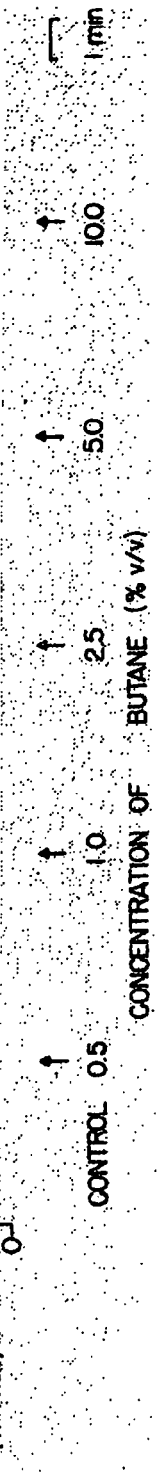


FIGURE 5.1. The effects of progressively increasing concentrations of butane on the hemodynamics of the open-chest dog preparation. MPAP = mean pulmonary arterial pressure, MLAP = mean left atrial pressure, LVP = left ventricular pressure, dp/dt = maximal rate of rise of left ventricular pressure, AP = aortic pressure, MPAF = mean pulmonary arterial flow.



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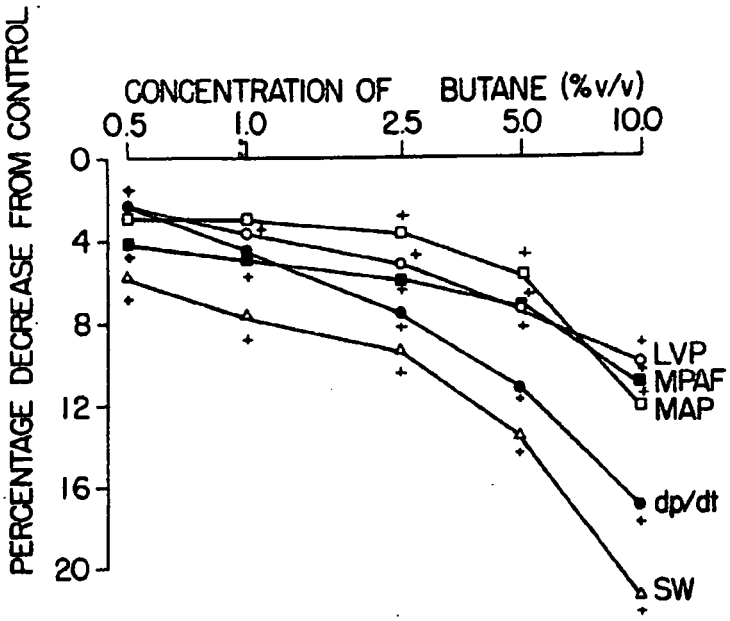

FIGURE 5.2. Concentration-response curves of butane administered by inhalational route in anesthetized open-chest dogs. LVP = left ventricular pressure, MPAF = mean pulmonary arterial flow, MAP = mean aortic pressure, dp/dt = maximal rate of rise of left ventricular pressure, SW = stroke work. + denotes significant change ($P < 0.05$).

of butane on the systemic and pulmonary blood vessels so that it appears that butane is a selective depressant of the heart.

D. Summary

The inhalation of butane in the anesthetized open-chest dog preparation brought about the following hemodynamic effects: a) decrease in cardiac output, left ventricular pressure, stroke volume, and stroke work in as low a concentration as 0.5%. b) decrease in myocardial contractility, and c) decrease in mean aortic pressure. No significant changes were observed in pulmonary arterial pressure or in vascular resistance.

Chapter 6
ISOBUTANE

Isobutane (2-methyl propane) is the third hydrocarbon used as a propellant for aerosol products. In the classification proposed in 1974, isobutane, together with dichlorotetrafluoroethane (FC 114), belonged to the group of low-pressure propellants of intermediate toxicity.[1]

A. Review of the Literature

Isobutane is a flammable gas that melts at -138.3°C and boils at -0.5°C. Its molecular weight is 58.12. It is soluble in alcohol, ether, or chloroform.

Isobutane occurs usually mixed with propane and *n*-butane in natural gas. Baldok,[27] in 1970, reported on an attempted murder by "calor gas," which contains 5 to 18% propane, and not less than 82% of a mixture of *n*-butane and isobutane in varying amounts. The case history, as he reported, was as follows:

> A woman hid a cylinder of calor gas in her husband's bedroom. Following an argument, one morning, whilst her husband was still in bed, she left the room and then returned after allowing sufficient time for her husband to fall asleep. She closed the window and turned on the cylinder, closing the door behind her as she left. After about three hours, she found her husband still apparently asleep, and felt his pulse, waking him.

Isobutane can be detected with gas chromatographs equipped with a flame ionization detector.[6,27] The presence of isobutane in the atmosphere is attributed to natural gas leakage, petroleum gas leakage, or diesel exhaust. Battigelli[60] has determined the concentration of various gases in air samples obtained in a railroad roundhouse, 6 to 8 ft away from the exhaust of diesel engines. He found 1.4 ppm of isobutane, which does not exceed the maximal allowable concentration in air. A value of 11 ppm was found in samples taken directly over the exhausts of running engines. The average concentration of isobutane in the Los Angeles atmosphere was determined in 1967 by Altshuller et al.[46] who found that the concentration of isobutane in air is almost 25% of that of *n*-butane. Gordon et al.[45] found that isobutane occurs in from 44 to 74 ppb in air in Los Angeles. Isobutane and *n*-butane are also detected in cigarette smoke in a concentration of 0.001 and 0.006% v/v, respectively.[61]

Isobutane is used not only as a lighter fuel, but also as a propellant in several household products, such as hair spray (five products), arts and paint spray (four products), deodorant spray, color spray decorator, antirust spray, and insecticide aerosol (two products of each), room deodorant, coating spray, foam bathroom cleaner, shoe spray, shaving foam, rug shampoo and spot remover (one product of each).[62] Bergwein[14] reported on a water-containing spray product containing 76% isobutane and 24% propane.

Narcotic activity – In concentrations of 15%, 20%, and 23% in air, isobutane induced light anesthesia in mice within 60, 17, and 26 min, respectively. However, it induced loss of posture in mice inhaling 35% in 25 min.[50] Using houseflies, Bradbury and O'Carroll[63] found that the partial saturation of *n*-butane and isobutane that produces the same average knock-down time as chloroform at a partial saturation of 0.005, are 0.088 and 0.052, respectively.

Cardio- and pulmonary toxicity – Isobutane sensitizes the heart to epinephrine-induced arrhythmia in the mouse.[31] Twenty-seven percent isobutane produced apnea after 8.7 min and respiratory arrest after 15 min in anesthetized rats.[64]

Other biological effects – Isobutane inhibits the cell lysis of *Micrococcus lysodeikticus* by egg-white lysozyme.[65] *Mycobacterium phlei* is capable of growth on isobutane as its sole carbon and energy source.[66] Isobutane is hydroxylated by rat liver microsomes to the isomeric alcohol.[55]

B. Inhalational Toxicity in Mice

To determine the inhalational LC_{50}, male mice (CF-1 strain, Charles River Laboratories, Wilmington, Massachusetts) weighing 20 to 25 g were divided into six groups, each group with ten mice. The mice were then introduced into a 10-liter glass chamber and were allowed to breathe isobutane in air for 120 min; the gaseous mixture was flushed into the chamber at a rate of 3 l/min. Since high concentrations of isobutane in air were used, oxygen (25% of the volume of isobutane) was added to the gaseous mixture to prevent any death due to hypoxia. Results were then calculated according to the probit method.[67]

Table 6.1 summarizes the results of 120-min

TABLE 6.1

Acute Inhalational Toxicity of Isobutane in Mice after 120 min of Exposure*

Group	Concentration % v/v	% Mortality	LC_{50} 120 min	Regression coefficient
1	36	0		
2	40	10		
3	50	30	52.04	
4	55	50	±	0.9662
5	60	90	3.26%	
6	65	100		

*Each group consisted of ten mice.

exposures of mice to various concentrations of isobutane in air. The highest concentration that elicited no mortality was 36% v/v, while the lowest concentration that was associated with 100% mortality was 65%. The LC_{50} (95% fiducial limits) was 52.04 ± 3.26% v/v (i.e., 520,400 ppm). Mice showed signs of central nervous system depression, rapid and shallow respiration, loss of posture, and apnea.

C. Hemodynamic Effects in Dogs

The experiments reported in this section were designed to identify the cardiovascular effects of isobutane in the anesthetized dogs, as well as to find any evidence for interaction with any of the previously investigated solvents. The methods are described in Chapter 2.

Each of seven preparations was allowed to stabilize for a period of up to 30 min, after which 0.5%, 1.0%, 2.5%, 5%, and 10% concentrations of isobutane in air were administered via the inlet of the respirator, for 5 min. A period of approximately 10 min elapsed before the administration of the subsequent concentration, to allow for recovery of the preparation.

In each preparation, the concentration of isobutane that produced minimal cardiovascular effects was determined. The minimal effective concentrations of each of methyl chloroform,[68] trichloroethylene,[68] methyl ethyl ketone,[69] and methyl isobutyl ketone[69] previously determined in a similar preparation, viz., 0.1%, 0.05%, 0.09%, and 0.08%, respectively, were administered to the animals for 5 min, either separately or mixed with the threshold concentration of isobutane. The sequence of administration of the threshold concentration of isobutane, methyl chloroform, trichloroethylene, methyl ethyl ketone, and methyl isobutyl ketone, and a mixture of the threshold concentration of isobutane and various compounds, was alternated from one preparation to the other. All data were analyzed by paired comparison and Student t-test, the criterion for significance being P less than 0.05.

Effects of inhalation of various concentrations of isobutane – The effect of various concentrations of isobutane on the cardiovascular system is summarized in Table 6.2. A record from a typical experiment is shown in Figure 6.1. In concentrations of 0.5% and 1.0%, isobutane produced no significant change in any of the studied parameters. However, in a concentration of 2.5% isobutane brought about a decrease in the myocardial contractility, as shown by the decrease in maximal rate of rise of the left ventricular pressure (dp/dt), a decrease in cardiac output, stroke volume, and stroke work, averaging to 13.1%, 5.3%, 6.1%, and 9.8%, as compared with the average control, respectively. Increasing the concentration of the inhaled mixture of isobutane in air to 5% not only aggravates the above-mentioned decreases in various parameters but also decreases the left ventricular and the aortic pressures by 6.7% and 7.8%, respectively. In a 10% concentration, isobutane brought about a significant decrease in left ventricular pressure, left ventricular dp/dt, mean arterial pressure, mean pulmonary arterial flow, stroke volume, and stroke work averaging to 14.4%, 19.8%, 15.0%, 12.3%, 12.6%, and 25.6%, respectively. Furthermore, a significant increase in pulmonary vascular resistance of 16.6% was noticed with the highest concentration used, namely 10%. It is evident from these figures that the most pronounced effect of isobutane is on the myocardial contractility as reflected by the decrease both in the

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TABLE 6.2

The Hemodynamic Effects of Progressively Increasing Concentrations of Isobutane 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				Stroke vol ml		Stroke work g·meter	
																			Pulmonary		Systemic					
	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 0.5%	50.3	49.5	6.8	7.1	43.3	42.8	140	139	3.0	3.4	4521	4500	126	123	2358	2325	168	166	1259	1284	4387	4341	14.6	14.5	25.7	24.7
	−0.8 ± 0.5		−0.3 ± 1		−0.5 ± 0.3		−1 ± 2.9		+0.4 ± 0.4		−21 ± 93		−3 ± 2.3		−33 ± 40		−2 ± 1.8		+25 ± 36		−46 ± 61		−0.1 ± 0.3		−1 ± 0.9	
	NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS	
Isobutane 1.0%	48.6	48.5	6.5	6.0	41.7	41.9	141	139	1.3	3.3	4313	4294	123	122	2283	2203	165	168	1243	1240	4476	4365	14.2	13.9	24.8	24.0
	−0.1 ± 1.1		−0.5 ± 0.2		+0.2 ± 1.0		−2 ± 2.7		+2 ± 0.8		−19 ± 137		−0.7 ± 1.9		−80 ± 40		+3 ± 2.1		−3 ± 25		−111 ± 125		−0.4 ± 0.4		−0.8 ± 0.5	
	NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS	
Isobutane 2.5%	49.0	47.4	6.3	6.8	42.4	40.3	146	141	2.5	4.2	4458	3875	121	116	2233	2108	166	167	1246	1245	4401	4414	13.9	13.0	24.1	21.5
	−1.6 ± 0.5		+0.5 ± 0.6		−2.1 ± 0.8		−5 ± 4		+1.7 ± 1.2		−583 ± 173		−5 ±1.5		−125 ± 31		+1 ± 0.7		−1 ± 23		+13 ± 36		−0.9 ± 0.3		−2.6 ± 0.8	
	NS		NS		NS		NS		NS		NS		NS		0.01		NS		NS		NS		0.02		0.02	
Isobutane 5.0%	47.2	46.4	7.0	7.1	39.7	38.9	146	136	1.7	1.7	4354	3771	123	114	2175	2042	165	169	1142	1185	4566	4741	13.4	12.3	23.2	19.8
	−0.8 ± 0.5		+0.1 ± 0.1		−0.8 ± 0.5		−10 ± 1.7		0 ± 0		−583 ± 53		−9 ± 2.3		−133 ± 40		+4 ± 1.5		+43 ± 46		+175 ± 218		−1.1 ± 0.3		−3.4 ± 0.6	
	NS		NS		NS		0.01		NS		0.001		0.01		0.02		NS		NS		NS		0.02		0.01	
Isobutane 10.0%	43.5	42.3	7.7	7.2	35.8	35.2	142	121	2.9	2.7	4177	3365	119	101	2138	1875	164	164	1019	1185	4418	4303	13.3	11.7	22.6	16.8
	−1.2 ± 0.5		−0.5 ± 0.4		−0.6 ± 0.9		−21 ± 3.9		−0.2 ± 0.5		−812 ± 95		−18 ± 2.6		−263 ± 41		0 ± 0.9		+166 ± 21		−115 ± 99		−1.6 ± 0.3		−5.8 ± 0.8	
	NS		NS		NS		0.01		NS		0.001		0.001		0.01		NS		0.01		NS		0.01		0.01	

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

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