50000 to 100000 ml/m^3 for 5 minutes. In addition, tachycardia, decreased arterial blood pressure and an increase in pressure in the left atrium were detected (Belej *et al.* 1974). The exposure of 3 rhesus monkeys to isobutane in concentrations of 50000 to 100000 ml/m^3 caused an increase in pulmonary resistance and a decrease in the respiratory minute volume. The cardio-vascular parameters of the animals were not affected (Aviado and Smith 1975).

5.2 Subacute, subchronic and chronic toxicity

Daily exposure (6 hours/day, 5 days/week, 3 weeks) of 10 male and 10 female Sprague-Dawley rats to 11800 mg/m^3 of a mixture of 25 % of each of *n*-butane, *n*-pentane, isobutane and isopentane (corresponding to 1224 ml/m^3 of each of *n*-butane and isobutane, i.e. a butane isomer concentration of 2500 ml/m^3) did not produce clinical symptoms or histopathological changes in the brain, heart, liver, kidneys, spleen, adrenal gland or reproductive organs (Halder *et al.* 1986). From the same group of authors there is a 90-day inhalation study, in which groups of 10 male and 5 female F344 rats were exposed to a mixture of *n*-butane and *n*-pentane or of isobutane and isopentane (both mixtures 50:50) in concentrations of 1000 or 4500 ml/m^3 (i.e. *n*-butane or isobutane concentrations of 500 or 2250 ml/m^3) (6 hours/day, 5 days/week). Satellite groups of 10 male and 5 female animals were killed after 28 days. In the animals of the treated groups but not in those of the control group, transient humped backs, intermittent tremor and lethargy were observed. These symptoms were not concentration-dependent. Details of the clinical symptoms were not given. Body weights, liver and kidney weights, haematopoietic and clinico-chemical parameters did not deviate from the corresponding control values. Autopsy did not yield pathological findings. Only the kidneys of the animals were examined histologically. The extent and severity of the nephropathy, which also occurs spontaneously in these animals, were significantly increased only in the male animals of the satellite group exposed to the lowest iso-isomer concentrations. At the end of the study no differences between the groups were recognizable. This finding was therefore considered by the authors not to be an important nephrotoxic effect (Aranyi *et al.* 1986). From this study, a NOAEC (no observed adverse effect concentration) for organ damage of 2250 ml/m^3 can therefore be deduced for *n*-butane or isobutane.

5.3 Local effects on skin and mucous membranes

n-Butane is not irritative in the respiratory tract or eye of the rabbit. In guinea pigs, exposure to concentrations of 21000 to 56000 ml/m^3 led to sniffing, chewing movements and an increased respiration rate (Low *et al.* 1987).

Preparations containing isobutane in concentrations of 74 % to 90 % (vehicle not stated) applied to the intact, shaved rabbit skin, caused no or moderate erythema and oedema. The irritation index was in the range of 0.29 to 2.025 on a scale with a maximum value of 8 (Moore 1982).

A hair spray containing 22 % isobutane was tested for irritative effects on the eye in 5 rabbits. 100 µl of the hair spray was sprayed into an eye and then rinsed out after 4 seconds. No corneal irritation was visible one hour after the treatment. Transient iritis and weak conjunctivitis were observed (ECB 1995b).

5.4 Genotoxicity

In the *Salmonella* mutagenicity test carried out according to OECD guideline 479, modified for testing gases, *n*-butane and isobutane were not found to be mutagenic at concentrations of 50000 to 500000 ml/m^3. Testing was carried out with the strains TA98, TA100, TA1535, TA1537 and TA1538, both with and without the addition of a metabolic activation system. The highest tested concentration of isobutane had weak cytotoxic effects (Kirwin and Thomas 1980). In a second study, *n*-butane was tested with the same *S. typhimurium* strains and also *E. coli* Wp2uvrA, both with and without metabolic activation. *n*-Butane was not found to be mutagenic at concentrations of 250 to 10000 ml/m^3. Cytotoxic effects were not observed (BUA 1994).

There are no data available for allergenic effects of the butane isomers, toxic effects on reproduction or carcinogenicity.

6 Manifesto (MAK value/classification)

The critical effect of *n*-butane and isobutane is central nervous depression. There are no data for the effect threshold in man.

Single exposures of volunteers to isobutane concentrations of 1000 ml/m^3 for 8 hours did not have any effects, likewise repeated exposure to the only concentration tested of 500 ml/m^3. There are no data for effects of *n*-butane in man which are relevant for the evaluation. From the octanol/water distribution coefficients, the same high level of lipophilia and thus also the same high level of central nervous effects is to be assumed for both butane isomers. There are no studies of the toxicity of the two isomers in man after repeated exposure at the level of the current MAK value of 1000 ml/m^3.

A 90-day study with exposure of rats to a mixture of butane and pentane yielded a NOAEC of 2250 ml/m^3 for organ damage caused by *n*-butane and by isobutane. Transient signs of central nervous depression, which were not concentration-dependent, were, however, detected. Exposure of rats to a mixture of butane and pentane isomers for 3 weeks did not have any effects up to *n*-butane and isobutane concentrations of 1224 ml/m^3 (i.e. a butane isomer concentration of 2500 ml/m^3); in particular no central nervous depression was detected. Thus the available data confirm the MAK value for *n*-butane and isobutane of 1000 ml/m^3 (2400 mg/m^3).

Because exposure of rats (6 h/day, 5 days/week, 3 weeks) to a mixture of butane and pentane in concentrations up to 11800 mg/m^3 (about 4000 ml/m^3) produced no clinical symptoms and because exposure of persons to butane in a concentration of 10000 ml/m^3 caused dizziness but no signs of systemic toxicity, the butane isomers are classified in Peak limitation category II with an excursion factor of 4.

There are no carcinogenicity studies available with the butane isomers. On the basis of the chemical structure of the isomers and the lack of positive results in genotoxicity studies, genotoxicity is not suspected. This also applies for germ cell mutagenicity. As there are no data available for the toxic effects of the isomers on reproduction, *n*-butane and isobutane are listed in Section IIc of the *List of MAK and BAT Values*. Because the data are inadequate, the isomers are not designated with an "H" (for substances for which there is danger from cutaneous absorption) or "Sa" or "Sh" (for substances which cause sensitization).

7 References

Aranyi C, O'Shea WJ, Halder CA, Holdsworth CE, Cockrell BY (1986) Absence of hydrocarbon-induced nephropathy in rats exposed subchronically to volatile hydrocarbon mixtures pertinent to gasoline. *Toxicol Ind Health 2*: 85–98

Aviado DM, Smith DG (1975) Toxicity of aerosol propellants in the respiratory and circulatory systems. VIII. Respiration and circulation in primates. *Toxicology 3*: 241–252

Belej MA, Smith DG, Aviado DM (1974) Toxicity of aerosol propellants in the respiratory and circulatory systems. IV. Cardiotoxicity in the monkey. *Toxicology 2*: 381–395

BUA (Beratergremium für Altstoffe der Gesellschaft Deutscher Chemiker) (1994) *Flüssiggas (Propan, Butan, Isobutan und Gemische)* also available in English: *Liquefied petroleum gases*, BUA Report 144, S. Hirzel, Stuttgart

Dahl AR, Damon EG, Mauderly JL, Rothenberg SJ, Seiler FA, McClellan RO (1988) Uptake of 19 hydrocarbon vapors inhaled by F344 rats. *Fundam Appl Toxicol 10*: 262–269

DECOS (Dutch Expert Commitee on Occupational Standards) (1994) *1-, 2- and t-butanol, health-based recommended occupational exposure limit.* Publication No. 1994/10, Health Council of the Netherlands, Den Haag

Drummond I (1993) Light hydrocarbon gases: a narcotic, asphyxiant, or flammable hazard? *Appl Occup Environ Hyg 8*: 120–125

ECB (European Chemicals Bureau) (1995a) *IUCLID data sheet, butane, pure*, 23.10.1995, Ispra, Italy

ECB (European Chemicals Bureau) (1995b) *IUCLID data sheet, isobutane*, 23.10.1995, Ispra, Italy

Evans AC, Raistrick D (1987) Phenomenology of intoxication with toluene-based adhesives and butane gas. *Br J Psychiatry 150*: 769–773

Fernàndez F, Hernàndez R, Sànchez C, Quero J, Pèrez-Higueras A, Verdú A, Gonzàlez A (1986) Hydranencephaly after maternal butane-gas intoxication during pregnancy. *Dev Med Child Neurol 28*: 361–363

Gray MY, Lazarus JH (1993) Butane inhalation and hemiparesis. *Clin Toxicol 31*: 483–485

Halder CA, van Gorp GS, Hatoum NS, Warne TM (1986) Gasoline vapor exposures. Part II. Evaluation of the nephrotoxicity of the major C_4/C_5 hydrocarbon components. *Am Ind Hyg Assoc J 47*: 173–175

Kirwin CJ, Thomas WC (1980) *In vitro* microbiological mutagenicity studies of hydrocarbon propellants. *J Soc Cosmet Chem 31*: 367–370

Low LK, Meeks JR, Mackerer CR (1987) *n*-Butane. in: Snyder R (Ed.) *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, Vol 1: Hydrocarbons, Elsevier, Amsterdam, 267–272

Moore AF (1982) Final report of the safety assessment of isobutane, isopentane, *n*-butane, and propane. *J Am Coll Toxicol 1*: 127–142

Roberts MJD, McIvor RA, Adgey AAJ (1990) Asystole following butane gas inhalation. *Br J Hosp Med 44*: 294

Rohrig TP (1997) Sudden death due to butane inhalation. *Am J Forensic Med Pathol 18*: 299–302

Sandmeyer EE (1981) Aliphatic hydrocarbons. in: Clayton GD, Clayton FE (Eds) *Patty's Industrial Hygiene and Toxicology*, Vol 2B, John Wiley & Sons, New York, 3182–3184

Shugaev BB (1969) Concentrations of hydrocarbons in tissues as a measure of toxicity. *Arch Environ Health 18*: 878–882

Siegel E, Wason S (1997) Sudden sniffing death following inhalation of butane and propane: changing trends. *Subst Use Misuse 32*: 1877–1882

Stewart RD, Herrmann AA, Baretta ED, Forster HV, Sikora JJ, Newton PE, Soto RJ (1977) Acute and repetitive human exposure to isobutane. *Scand J Work Environ Health 3*: 234–243

Tsukamoto S, Chiba S, Muto T, Ishikawa T, Shimamura M (1985) Study on the metabolism of volatile hydrocarbons in mice. *J Toxicol Sci 10*: 323–332

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Substance [CAS number]	Formula	MAK ml/m³ (ppm)	MAK mg/m³	Peak limitation	H;S	Carcinogen category	Pregnancy risk group	Germ cell mutagen categ.	Vapour pressure in hPa at 20°C
Bromine [7726-95-6]	Br_2	see Section IIb							
2-Bromo-2-(bromomethyl)glutaronitrile	see 1,2-Dibromo-2,4-dicyanobutane								
2-Bromo-2-(bromomethyl)pentanedinitrile	see 1,2-Dibromo-2,4-dicyanobutane								
Bromochloromethane [74-97-5]	CH_2BrCl	–	–	–	H	3B	–		147
2-Bromo-2-chloro-1,1,1-trifluoroethane	see Halothane								
★ **Bromodichloromethane** [75-27-4]	$CHBrCl_2$	–	–	–	H	2	–	3B	
Bromoethane [74-96-4]	H_3C-CH_2Br	–	–	–	H	2	–		507
Bromoform	see Tribromomethane								
Bromomethane	see Methyl bromide								
2-Bromo-2-nitro-1,3-propanediol [18] [52-51-7]	$HOCH_2-CBr(NO_2)-CH_2OH$	see Section IIb			H Sh				
Bromotrifluoromethane [75-63-8]	$BrCF_3$	1000	6200	II(8)			C		
Brown coal tars (soft coal tars)	see Pyrolysis products of organic materials								
Brucite (fibrous dust)	see Nemalite								
Brya ebenus	see Woods								
1,3-Butadiene [106-99-0]	$H_2C=CH-CH=CH_2$	see Section XIII		–		1	–	2	2477
1,3-Butadiene diepoxide	see Diepoxybutane								
Butane (both isomers): *n*-Butane [106-97-8], Isobutane [75-28-5]	$H_3C-(CH_2)_2-CH_3$ $(H_3C)_3CH$	1000	2400	II(4)			D		

[18] Use in metal-working fluids is not permitted: see TRGS 611.

文献 1

Concentrations of Hydrocarbons in Tissues as a Measure of Toxicity

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Mice and rats were exposed of vapors of butane, butadiene, isoprene, isobutylene, hexenes, and styrene. The concentrations of hydrocarbons in tissues after exposure were determined by gas liquid chromatography. Lethal concentration (LC_{∞}) values for two- and four-hour exposures, and the corresponding LC_{50} in brain tissues were determined for several hydrocarbons. The hydrocarbon concentration found in the brain correlated with the degree of central nervous system depression and narcosis. Mixtures of butane and isobutylene had a potentiating effect in 10 of 12 experiments, and an additive effect in two experiments.

TOXIC effects are determined primarily by the concentration of a substance in biological systems which are most susceptible to the action of a chemical.[1] As for substances having a "chemical" toxicity, one may find the most toxic metabolite and determine its toxic action selectively.

The idea of establishing the effective concentrations for surgical narcotics originated as far back as the last century, and the topic is dealt with by many workers. In this connection, however, little light has so far been shed on organic commercial chemicals. The principal obstacle in establishing effective concentrations of organic compounds in tissues was the lack of sensitive analytical methods. For serial studies on small laboratory animals, the techniques previously used have proven impracticable.[2]

The above considerations provided the stimulus for using gas-liquid chromatography to determine the effective concentrations and the distribution of volatile commercial chemicals in animals.[3,4] As "nonreacting" substrates, the aliphatic hydrocarbons, butane, butadiene, isoprene, isobutylene, and hexenes, were used. Styrene was chosen as a hydrocarbon capable of being metabolized.[5] Styrene in the central nervous system is responsible for the narcotic effect under conditions of an acute test.

Experimental Procedure

The hydrocarbon content in tissues was determined by gas-liquid chromatography. A 0.1 to 0.15-mm diatomaceous brick was used as a solid support in the chromatographic column, whereas triethylene glycol, *n*-butyric acid ester served as a stationary phase, and nitrogen as a carrier gas. Ether, benzene, and more often, iso-octane extracts of brain and other organs were injected into a preconditioned chromatographic column. It was found that the results of the analysis were virtually independent of the extracting agents. The choice of a particular extracting agent was determined by the elution rate and the resolution obtained with the gas under investigation. A 300- to 500-mg sample of the organ was placed in a test tube containing 10 cc of extracting agent and kept overnight in a refrigerator. Homogenization was carried out using a glass pestle, and the homogenate was placed in the same ground-glass stopper test tube in the refrigerator for an additional 24 hours. The efficiency of the extraction under these conditions was checked by special tests. The extraction process may be accomplished by other techniques as well.

In analyses for aliphatic hydrocarbons, columns preconditioned to 50 C and 60 C were used. When determining styrene, the stationary phase was polyethylene glycol (molecular weight, 1,500) and the column was preconditioned to 90 C. Nitrogen served as the carrier gas. The analyses were carried out using the chromatographic device with a flame ionization detector and an ink-pen recorder. The concentrations were calculated by peak area which is

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Table 1.—*Hydrocarbon Lethal Concentrations for Rats and Mice

Product	Species	LC_{50}	LC_{50} Confidence Limits at P = 0.05	LC_{16}	LC_{84}
Isoprene	Mice	157	130 + 181	117	212
	Rats	180	129 + 252	92	381
Butadiene	Mice	270	251 + 290	203	375
	Rats	285	219 + 370	175	460
Isobutylene	Mice	415	314 + 546	250	680
	Rats	620	550 + 700	514	720
Butane	Mice	680	596 + 775	530	860
	Rats	658	598 + 716	537	790
Hexene (2-methyl pentene-1)	Mice	127	114 + 141	108	153
	Rats	115	93 + 142	80	165
Hexene (2-methyl pentene-2)	Mice	130	104 + 163	94	185
	Rats	114	87 + 151	100	208
Styrene	Mice	21.0	17.8 + 24.8	17.7	25.1
	Rats	11.8	10.3 + 13.5	9.7	14.0

* Milligrams per liter. The experimental data obtained were treated by the probit-analysis according to Litchfield and Wilcoxon. Dynamic flow exposure of rats was performed for four hours, that of mice for two hours. The concentration of hydrocarbons as well as the content of carbon dioxide and oxygen in the flow exposure chamber was controlled by gas chromatography.

Table 2.—*Hydrocarbon Content in Rat Organs

Product	Brain	Liver	Kidney	Spleen	Perinephric Fat	Hypodermic Fat
Isoprene	39.5†	43.3†	39.6‡	28.0‡	275.7‡	178.4‡
	32.1+46.2	34.7+51.9	26.7+52.5	19.1+36.9	178.4+337.1	149.0+207.8
Butadiene	50.8†	51.4†	36.3‡	45.0‡	152.1‡	—
	43.3+58.3	45.3+57.5	29.2+43.4	39.7+50.3	120.6+183.7	
Isobutylene	126.0†	77.4†	63.7†	59.1†	219.0†	—
	89.9+169.1	61.6+93.1	52.1+75.2	50.2+68.1	188.9+249.1	
Butane	75.1†	49.2†	44.1†	52.2†	208.6†	—
	47.9+102.4	41.8+56.6	37.0+51.2	46.5+57.9	182.4+234.0	
Hexene (2-methyl pentene-2)	122.6‡	131.1‡	51.7‡	132.4‡	—	157.3‡
	107.9+137.3	109.8+152.4	45.1+58.3	105.5+159.3		114.4+200.2
Hexene (2-methyl pentene-1)	138.3‡	125.6‡	56.0‡	—	206.8‡	157.3‡
	127.5+149.1	108.7+142.5	49.4+62.6		129.8+283.8	131.3+183.3
Styrene	25.0‡	20.0‡	14.7‡	19.1‡	132.8‡	—
	17.7+32.4	12.7+27.3	2.8+26.7	11.1+27.1	109.9+155.7	

* Milligrams percent.
† Mean concentration and its confidence limits was calculated on the ten-test basis.
‡ Same on the seven-test basis. The confidence limits were computed at P = 0.05.

Table 3.—*Hydrocarbon Content in Mouse Brain*

Product	Effective Concentration at LC_{50} Level (mg/100 cc)	No. of Tests
Butadiene	54.4 (39.9 + 69.0)	10
Butane	77.9 (64.7 + 91.2)	10
Isobutylene	264.1 (197.7 + 330.5)	10
Hexene (2-methyl pentene-2)	129.4 (103.2 + 155.6)	7
Styrene	18.02 (14.35 + 21.69)	7

a product of peak height and mid-high width, using the direct instrument calibration method.

The death of the animals was considered as a product-action criterion, this coming for mice in the second hour, and for rats in the third or fourth hour of dynamic flow exposure. The animals dying after exposure, which was often observed in tests involving styrene, were not used for establishing the concentrations in tissues.

When studying the combined product action, the volume ratios of butane to isobutylene in a gaseous mixture were 1:1, 1:2, and 2:1. The concentration of gaseous mixtures in the chamber air was set so that mice died in the second hour, and rats in the third or fourth hour of dynamic exposure. The effective concentrations were defined only on the animals who died during the second half of the test. The choice of a four-hour exposure for rats, and a two-hour exposure for mice was determined by the lung ventilation to body weight ratio of the animals.[6] These exposures resulted in approximately equal saturation of mice and rats with gaseous products.

Table 4.—*Distribution of Butadiene and Isobutylene in Various Sections of the Central Nervous System of the Cat*

Tissue	Butadiene Concentration (mg/100 cc)		Isobutylene Concentration (mg/100 cc)
	Cat No. 1	Cat No. 2	
Cortex cerebri in region Gyrus centralis anterior	32	24	36
Substantia alba in region Capsula interna	42	33	73
Cortex cerebelli	34	22	38
Medulla oblongata	46	44	71
Mesencephalon in region corpora quadrigemina	36	42	94
Pons Varolii	67	50	63
Spinal cord jugular section	70	59	77
Liver	31	28	33

Table 5.—*Statistical Evaluation of Combined Action of Hydrocarbon Mixtures*

Species	Summation Probability P = 0.05	Potentiation Probability P = 0.05
Mice	2 of 12 (4.2% + 45.4%)	10 of 12 (54.5% + 95.8%)
Rats	9 of 12 (45.4% + 91.1%)	3 of 12 (8.9% + 54.5%)

Table 6.—*Concentrations of Butadiene, Hexene, and Styrene Found in Brain and Liver of Rats**

Product	Time After Removal From Chamber (min)	Brain (mg/100 cc)		Liver (mg/100 cc)	
		Average*	Range	Average*	Range
Butadiene	0-1	34.6	24.1-42.3	33.8	27.6-39.2
Hexene	0-5	38.2	31.7-47.8	61.8	46.2-82.8
Styrene	0-1	21.8	14.8-30.1	20.2	11.3-29.7
Butadiene	15	6.7	7.1-12.3	10.9	6.2-15.7
Hexene	15	15.3	10.0-20.3	26.2	18.4-30.9
Styrene	15	22.2	13.5-31.6	23.5	12.9-32.0
Butadiene	30	4.3	3.1- 5.3	5.9	3.4- 7.6
Hexene	30	4.6	3.5- 6.1	11.0	9.0-14.5
Styrene	30	17.7	10.7-22.4	19.1	14.2-29.0
Butadiene	60	2.9	1.8- 4.2	3.3	2.7- 4.2
Hexene	60	3.9	1.4- 8.8	5.1	3.9- 7.1
Styrene	60	8.6	3.3-14.7	12.8	5.7-20.2
Butadiene	90	0-traces	0-traces	0-traces	0-traces
Hexene	90	Traces	Traces	Traces	Traces
Styrene	90	Traces to 4.4	—	6.8	5.2-11.0

* Average of four experiments and range.

Results and Comment

Under the above conditions of dynamic flow exposure the LC_{50} values obtained for mice and rats are shown in Table 1.

The concentrations of hydrocarbon found in the brain and other organs are presented in Table 2. The hydrocarbon concentrations in the brains of mice ranged in approximately the same order as in the case of rats, as shown in Table 3.

Comparison of the toxicity and effective concentrations in the brain of rats and mice reveals a distinct parallelism between toxicity and tissue concentrations in the series of hydrocarbon monomers, styrene, isoprene, butadiene, and isobutene.

Tests were performed on cats to determine the hydrocarbon concentrations in various parts of the brain and spinal cord. The concentrations of hydrocarbons in the chamber air were set so that the animals died during dynamic inhalation exposure of about one hour.

As evidenced by butadiene and isobutene, the concentrations were higher in those sections of the central nervous system containing substantia alba. As more facts are gained, one might accept as a toxicity criterion minimal lethal concentrations in the

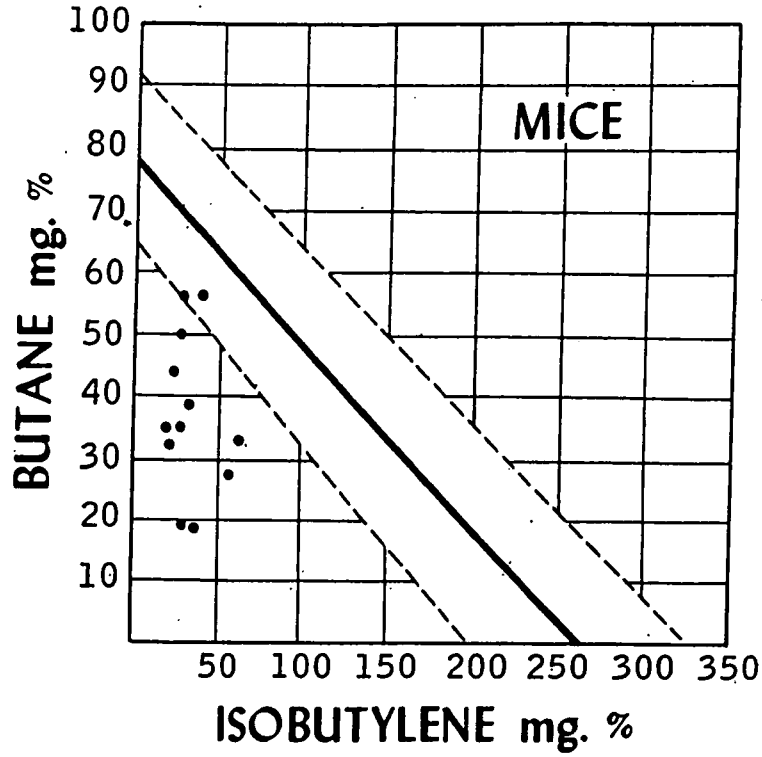

Fig 1.—Isodynamic diagram of butane and isobutylene combined action in mice. Criterion is lethal concentrations in brain. Isobol (solid line), upper and lower confidence limits of isobol at P = 0.05 (broken lines).

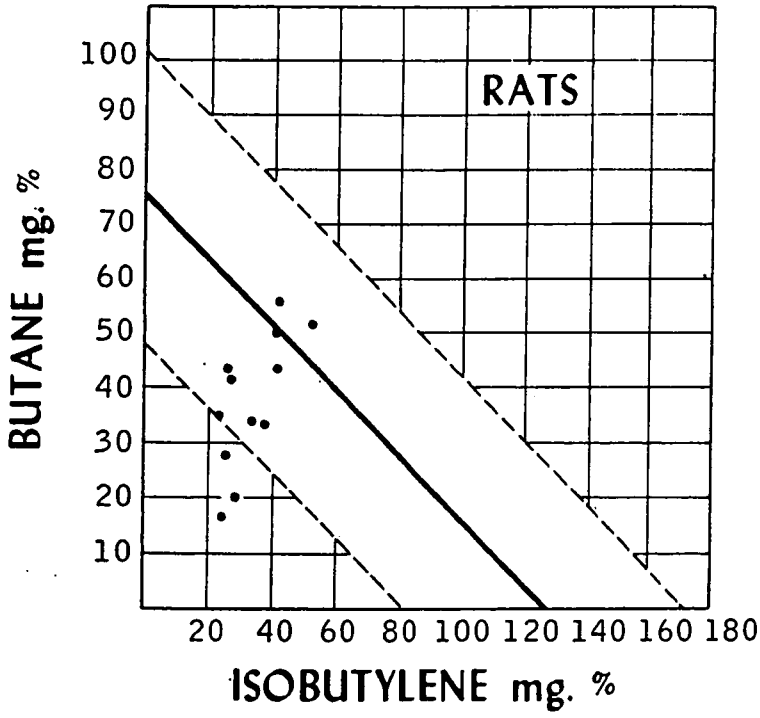

Fig 2.—Isodynamic diagram of butane and isobutylene combined action in rats. Criterion is lethal concentrations in brain. Isobol (solid line), upper and lower confidence limits of isobol at P = 0.05 (broken lines).

medulla oblongata, since it is these concentrations in this tissue which result in respiratory arrest and death during acute intoxication. The distribution of butadiene and isobutene in various sections of the central nervous system of the cat is shown in Table 4.

The combined action of aliphatic hydrocarbons was studied by their concentrations in the brain of rats and mice.[7] The effects of inhaling various butadiene-isobutylene gaseous mixtures under the above experimental conditions was investigated. Each product in the brain of the animals dying from exposure was individually identified by gas-liquid chromatography.

Isodynamic plots of the effective concentrations for individual gases and gaseous

mixtures were drawn according to Loewe.[8] Isobols in these plots were supplemented by calculating confidence limits at $P = 0.05$. Figure 1 shows that all 12 mice died after exposure to the gaseous mixture having effective concentrations below the isobol. Of all 12 determinations, only two were within the isobol confidence range. In ten of all 12 cases, we observed a statistically significant aggravation of butane and isobutylene action, ie, a potentiating effect, whereas in two experiments addition was obtained.

Figure 2 shows that the effective concentrations for rats exposed to a gaseous mixture is somewhat lower than the isobol: nine of 12 determinations were within the isobol confidence range, while in three other cases the effective concentration values exceeded the lower confidence limit. Thus, of all 12 tests involving rats, three cases yielded a statistically significant potentiation, and nine cases resulted in summation. The results of combined gaseous mixture actions were treated statistically using the binomial distribution tables in terms of confidence limit percentage (Table 5).

In no tests involving mice and rats was antagonism observed by combining the above hydrocarbons at the effective concentrations.

Study of tissue concentrations makes it possible to trace the elimination of products from the organism and to establish the concentrations in tissues which corresponds to signs of intoxication. Rats inhaling hydrocarbons for one hour at the LC_{50} were in a state of deep narcosis. After removal from the flow chamber, the animals were killed at different times as soon as they recovered from the narcotic state. Three test series were performed involving butadiene, hexene (2-methyl pentene-2) and styrene. The concentrations found in brain and liver are shown in Table 6.

A definite correlation was found between the concentrations in brain and the degree of narcosis ranging from deep anesthesia to a slight disturbance of coordination of movement. Thus, some movement appeared four to five minutes after deep butadiene and hexene narcosis. In 30 minutes, a slight disturbance of coordination of movement was observed, and after 60 minutes, muscular coordination was normal. On the other hand, the effects of styrene intoxication persisted for a much longer time. This is due to a slower removal of styrene from the organism as compared with the aliphatic hydrocarbons.

The above approach also makes possible a quantitative evaluation of skin absorption. With this purpose in mind, the skin absorption of styrene—the least volatile and most toxic among the compounds under test—was studied. The tests involved ten rats whose tails were immersed in styrene for one hour. Under the test conditions, the possibility of styrene inhalation poisoning was completely avoided. The styrene concentration in the brain and liver of the rats killed immediately after the exposure ended was determined by gas-liquid chromatography. In these tests, the styrene concentration as a result of the skin absorption was 14.2 (11.1 to 17.3) mg/100 cc in the brain, and 14.7 (10.7 to 18.7) mg/100 cc in the liver. The values are 50% to 70% of the lethal styrene concentrations found in brain and liver during inhalation exposure of rats (Table 2). Thus, a high styrene skin absorption has been quantitatively shown.

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References

1. Dubois, K., and Geiling, E.: *Textbook of Toxicology,* New York: Oxford University Press, Inc., 1959, pp 22-23.

2. Brusilovskay, A.I., and Staritsyna, T.V.: Determining of Certain Volatile Narcotics in Tissues: Distribution of Saturated Hydrocarbons in Organism, *Fiziol Zhur* 18:935-943, 1935.

3. Burchfield, H.P., and Storrs, E.E.: *Biochemical Application of Gas Chromatography,* New York: Academic Press, Inc., 1962.

4. Littlewood, A.B.: Gas Chromatography, Principles, Techniques and Applications, New York: Academic Press, Inc., 1962.

5. Gerarde, H.W.: Toxicology and Biochemistry of Aromatic Hydrocarbons, New York: Elsevier Publishing Co., 1960.

6. Guyton, A.C.: Measurement of Respiratory Volumes of Laboratory Animals, *Amer J Physiol* 150:70-77 (July) 1947.

7. Shugaev, B.B.: Kombinirovannoe deistvie alifaticheskikh uglevodorodnov na primere butana i ozobutilena po ikh effektivnym kosentratiiam v mozgovoi tkani, *Farmakol Toksik* 30:102-105 (Jan-Feb) 1967.

8. Loewe, S.: Die quantitativen probleme der pharmakologie, *Ergebn Physiol* 27:47-187, 1928.

THE RELATIVE ANAESTHETIC ACTIVITY OF THE BUTANES AND PENTANES

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Of the straight-chain, saturated hydrocarbons methane (1), propane (2), pentane (3, 4), hexane (3, 4), heptane (3, 4), and octane (3, 4) have been examined for their anaesthetic properties. Butane (5), although investigated as an industrial hazard, has not been studied as an anaesthetic.

With the exception of 2-methyl hexane (4), we have been unable to find reference to anaesthetic studies on branched saturated hydrocarbons.

The work here reported deals with all the isomers of butane and pentane—butane and isobutane, and pentane, isopentane and neopentane. Ether and cyclopropane were used for the sake of comparison. The experiments here reported were carried out on mice. A few dogs were also anaesthetized with some of these substances. The time taken to produce "light anaesthesia" was determined by placing two mice in a 2-liter bottle filled with a gas mixture of known concentration, and revolving the bottle mechanically at fourteen revolutions per minute. The endpoint used was the time taken to produce that degree of anaesthesia in which the mouse was unable to maintain an upright position. "Complete anaesthesia" was obtained by placing five mice at one time in a 20-liter bottle containing the gas mixture, in which was suspended a bag of soda lime, and determining the time taken to cause inability to regain an upright position after shaking the bottle. Lethality was determined by noting the percentage of mice that died after two hours exposure in this bottle to a given gas concentration. Our results obtained on pentane by these

TABLE 1

Anaesthetic action of various substances

COMPOUND	CONCENTRATION		AVERAGE ONSET OF		LETHALITY		AVERAGE TIME OF RECOVERY	NUMBER OF MICE
	Millimoles per liter	Volume	Light anaesthesia	Loss of posture	Per cent dead in 2 hours	Average time of death		
		per cent	*minutes*	*minutes*		*minutes*	*minutes*	
n-Butane	5.8	13	25					6
	9.8	22	1	15	0		1	10
	12.0	27		4	40	84	5	10
	13.8	31		3	60	65	3	10
Isobutane	6.7	15	60					6
	8.9	20	17					6
	11.3	23	26					6
	15.6	35		25	0		3	10
	17.9	41		3	60	72	4	10
	23.1	52		2	100	28		10
n-Pentane	3.0	7	10					6
	3.5	8	3					6
	4.2	9	1.3	8.2	0		4	10
	4.5	10		4.5	45	73	8	11
	4.9	11		2.0	90	62	7	10
Isopentane	4.2	9	11.6					6
	4.9	11	3.9	10.0	0		4	6
	5.4	12	2.2					6
	5.8	13		5.0	20	94	8	10
	6.3	14		3.4	50	84		10
Neopentane	8.9	29	30	∞	0		0.1	5
	12.0	27		3.0	0		2	5
	15.2	34		2.0	40	35	4	5
Ether	1.5	3.5		15.0	0		5	12
	2.0	5	3	6.5	90	64		12
	2.5	6		3.0	100	59		12
Cyclopropane	5.8	13		3.0	0		1.5	10
	6.7	15		1.5	40	81	3.5	10
	8.0	18		1.25	90	39		10

methods check very well with the previous work of Führer and Lazarew.

In the case of neopentane, which was kindly given to us by Dr. Frank C. Whitmore of Pennsylvania State College, the amount available (9 grams) did not allow as many experiments, but by using a 5-liter bottle we were able to make three determinations on five mice each. The results of these studies are given in table 1.

All of these substances produce considerable excitement in mice during anaesthesia—cyclopropane and isopentane the least, ether and normal butane more, isobutane and normal pentane still more. Neopentane differed from the others in causing still more excitement and a general cramp-like effect just before anaesthesia was induced.

On removal from the jar after two hours anaesthesia the mice recovered very quickly, usually in one or two minutes, running about normally except after ether where recovery was definitely delayed. Those recovering from neopentane showed marked hyperexcitability when stimulated by noise or touch. All mice that did not die during the period of anaesthesia remained normal for the twenty-four to forty-eight hours observed after anaesthesia.

Pentane was definitely more active as well as more toxic than butane, which fits in with the findings of Führer and Lazarew who found an increasing activity and lethality as the number of carbon atoms was increased.

The effect of branching in these compounds was quite striking. Isobutane was less active and less lethal than normal butane. Isopentane was also less active and less lethal than normal pentane, while neopentane was much less active and caused fewer deaths in the same concentration than either pentane or isopentane. There was, however, no correlation between the degree of branching and the degree of excitability.

A few experiments on dogs were carried out with butane, isobutane, and isopentane. Although enough experiments were not done to give accurate, quantitative results, we found that it was extremely difficult to produce good anaesthesia and relaxa-

tion with any of them, while control experiments with cyclopropane were carried out with great ease.

Anaesthesia was induced by using a gas-oxygen machine, mask, soda-lime tube, and gas bag. A Magill catheter with Guedel inflatable cuff was then introduced and the dog connected with a spirometer containing the gas mixture. In order to avoid the high initial concentration necessary for insertion of the cannula, some dogs were anaesthetized by forcing their heads through a rubber membrane into a specially devised gas chamber in which the anaesthetic concentration could be controlled at will.

None of these gases gave good anaesthesia and relaxation except in concentrations which were practically lethal. Butane required a concentration of about 20 to 25 per cent for relaxation, but this caused death after a short time. Isobutane required about 45 per cent for anaesthesia, and death occurred with 55 per cent. Isopentane caused fair anaesthesia with about 12 per cent and death with 15 to 17 per cent. A much more extensive pharmacological study together with blood analyses would be necessary to determine definitely the practical value of these gases as inhalation anaesthetics, but our experience would lead us to believe that there is only a small margin of safety between the anaesthetic concentration and that causing death.

CONCLUSIONS

1. The anaesthetic activity and lethality of butane fall below that of pentane.

2. Branched isomers of the saturated hydrocarbons, butane and pentane, showed less activity as well as lethality than the straight-chain compounds, isobutane being less active and less lethal than butane, and the series, pentane, isopentane, and neopentane, showing this effect very strikingly.

REFERENCES

(1) Brown: J. Pharmacol. & Exper. Therap., 23, 485, 1924.
(2) Brown and Henderson: Anesth. & Analg., 4, 340, 1925.
(3) Führer: Biochem. Ztschr., 115, 235, 1921.
(4) Lazarew: Arch. f. exper. Path. u. Pharmakol., 143, 223, 1929.
(5) Patty and Yant: U. S. Bureau of Mines, Report of Investigations, No. 2979, December, 1929.

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(Propane, Butane, Isobutane
and Mixtures)

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Foreword

The German Chemicals Act (Chemikaliengesetz - ChemG) of 1980 stipulates that certain existing chemicals must be reported to the competent authority, if they exhibit properties which indicate that they may be hazardous, either alone or in combination with other substances.
In the summer of 1982, an Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) was set up by the German Chemical Society (Gesellschaft Deutscher Chemiker - GDCh). It brings together representatives from the scientific community, the chemical industry and the governmental authorities. This Advisory Committee is responsible for elaborating appropriate solutions for substances of relevance for health and the environment on the basis of voluntary measures. It selects and examines existing chemicals from the aforementioned angles. The testing and evaluation are based on scientific criteria alone.
It was, therefore, necessary to develop priority setting procedures. In a first phase reports were only prepared for priority chemicals. Within the framework of a first priority setting procedure, chemicals were compiled from several priority lists and 135 chemicals were selected for detailed substance reports.
In a second priority setting procedure the survey of the German Chemical Industry Association (VCI) on all substances with a production volume of more than 10 tons per year was used as a starting list. Since this survey covered 4,600 chemicals, BUA decided to process the corresponding list in several stages. The first stage included approx. 1,050 substances with a production volume of more than 1,000 tons per year.
Detailed reports are drawn up on chemicals suspected of having a hazard potential and abridged reports on those presenting only a minor hazard potential, according to the current state of knowledge.
The detailed BUA reports take in both the published literature and data from industry. If data for the evaluation of the chemicals are not available, additional studies are recommended and the results are published as updates to the reports. The reports serve as a basis for the instigation of administrative measures, when there are indications of risks to health or the environment.

Tübingen, May 1993

Ernst Bayer
Chairman of the Advisory Committee
on Existing Chemicals
of Environmental Relevance

Contents

Summary and conclusions ..... **XI**

Recommendations ..... **XVII**

1	**Chemistry of LPG**	**1**
1.1	Product description	1
1 .2	Composition of the technical product	2
1 .3	Chemical properties	5
2	**Physical properties**	**7**
3	**Analytical methods**	**11**
3.1	Analysis of LPG	11
3.2	Determination in air	16
3.3	Determination in water	19
3.4	Determination in soil	20
3.5	Determination in biological material	21
4	**Discharge into the environment via manutacture processing use and waste disposal**	**23**
4.1	Manufacture of liquefied petroleum gas	23
4.2	Production and consumption of LPG in the Federal Republic of Germany	26
4.2.1	Production	26
4.2.2	Consumption	29
4.3	Discharge into the environment	31
4.3.1	Discharge into the atmosphere	32
4.3.1.1	Emissions from production of crude oil and natural gas	33
4.3.1.2	Emissions from mineral-oil processing	35
4.3.1.3	Emissions during transfer and storage of gasoline	36
4.3.1.4	Emissions from refuelling of and evaporation from motor vehicles	38
4.3.1 .5	Traffic exhaust gases	39
4.3.1.6	Industry	40
4.3.1.7	Households and small consumers	41
4.4	Discharge into the hydrosphere	41
4.5	Discharge into the geosphere	41
4.6	Discharge via waste and waste disposal	41
4.7	Summary of discharge into the environment	42