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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 used 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

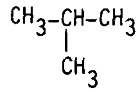
Isobutane, Isopentane, n-Butane, and Propane are alkanes characterized by singly bonded carbon atoms. They conform to the generic formula C_nH_{2n+2}, where "n" represents the number of carbon atoms. Alkanes with four or fewer carbon atoms are gases at room temperature, whereas those with from five to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

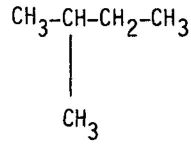
The alkanes have a low specific density, are nonpolar and cannot form hydrogen bonds. They are practically insoluble in water, but are generally soluble in such low polarity liquids as benzene, carbon tetrachloride, chloroform, and other alkanes.[1,2]

Structure of the Pure Hydrocarbons

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



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



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.

TABLE 3. IMPURITIES.[a]

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

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

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

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

Cosmetic Uses

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

Scope and Extent of Use in Cosmetics

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

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

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

Common Surfaces of Application

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

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

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

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

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

Potential Interactions with other Ingredients

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

Frequency or Duration of Application

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

TABLE 4. PRODUCT FORMULATION DATA.[a]

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

[a]From Ref. 19.

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

The calculated discharging rate for an antiperspirant aerosol product containing 67.5% Isobutane was 0.44 g of Isobutane per second. A second antiperspirant product containing 65% Isobutane was calculated to discharge the gas at a rate of 0.73 g of Isobutane per second. A hair spray product containing 30% of an isobutane-propane propellant mixture in an 80:20 ratio delivers 0.192 g per second Isobutane and 0.48 g per second propane. A foot spray, 45% of which contains an Isobutane-Propane mixture in an 80:20 ratio, delivers 0.144 g per second Isobutane and 0.036 g per second Propane. For shave foams, a maximum of 0.12 g propellant would be delivered with the product, 0.06 g of which is assumed to contact skin. It would remain in contact only long enough for the consumer to shave and wash. The amount of hydrocarbon gas coming into contact with the body would be difficult to calculate due to the extreme volatility of these gases.[21]

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

BIOLOGICAL EFFECTS

Ames Test

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

Anesthetic Activity

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

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

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

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

Animal Toxicology

Acute

Eye irritation

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

Inhalation toxicity

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

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

The acute inhalation toxicity of Isobutane, in a concentration of 22% in a hair setting spray, was tested on eight New Zealand albino rabbits. The animals were placed in an enclosed area, approximately 0.34 M^3, into which the substance was sprayed in 10 aerosol bursts at 13.2 g/30 second burst (2.904 g Isobutane/burst). No deaths, abnormal behavior, or changes in body weight occurred in test or control animals during either the exposure or the 14 days of observation. Gross and microscopic examinations revealed no changes attributable to inhalation of the test material, and the respiratory tissues of the test animals were similar to those of the untreated controls.[24]

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

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

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

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

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

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

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

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

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

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

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

Skin irritation

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

Subchronic

Inhalation toxicity

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

TABLE 5. PRIMARY DERMAL IRRITATION.[a]

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

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

[a]From Ref. 35.
[b]PII (Primary Irritation Index) Scores: 0.0–2.0 = Mildly irritating. 2.0–5.0 = Moderately irritating. 6.0–8 = Severely irritating.

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

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

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

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

Clinical Assessment of Safety

Primary Skin Irritation

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

Inhalation

Acute inhalation toxicity

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

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

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

Another human inhalation study reported that Propane caused no symptoms in man under brief exposures (length of time not specified) to 10,000 ppm (1.0%). The ingredient's odor was not detectable below 20,000 ppm (2.0%), and a concentration of 100,000 ppm (10%) was not noticeably irritating to the eyes, nose, or respiratory tract, but did produce slight dizziness within a few minutes.[38]

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

Mucosal Irritation

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

Recommended Limits of Exposure

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

Isobutane is a GRAS food ingredient.[16]

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

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

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

CONCLUSION

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

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