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Final Report on the Safety Assessment of n-Butyl Alcohol

n-BuOH is a primary aliphatic alcohol that is used in cosmetic nail products as a solvent at concentrations up to 10%. In vitro tissue permeability studies indicate that human epidermis and dermis were permeable to n-BuOH. The single oral dose LD_{50} of n-BuOH for rats ranged from 0.8 to 4 g/kg. The dermal LD_{50} has been reported as 4.2 g/kg. n-BuOH does not cause skin irritation in rabbits but is a severe rabbit eye irritant. Inhalation of n-BuOH vapors caused intoxication of laboratory animals; high concentrations were sometimes fatal. n-BuOH was not mutagenic in the *Salmonella*/mammalian-microsome mutagenicity test. The ingredient did not induce sister chromatid exchange or chromosome breakage in chick embryo cells or in Chinese hamster ovary cells and did not induce micronuclei formation in V79 Chinese hamster cells. Two nail formulations containing 3.0% n-BuOH were tested on 558 and 421 subjects, respectively; neither was considered an irritant or sensitizer. Clinically, n-BuOH produced edema in 4 of 105 dermatological patients. Additional clinical studies indicated that nail enamel products containing n-BuOH were neither irritants, sensitizers, nor photoallergens. Inhalation of n-BuOH can cause human nose, throat, and eye irritation. On the basis of the information in the report and only as it regards the use of n-BuOH in nail products, the ingredient is considered to be safe in the present practices of use and concentration.

INTRODUCTION

The Expert Panel is aware that the published literature contains voluminous information on n-Butyl alcohol dependency and withdrawal. This information is not relevant to the use of n-Butyl Alcohol in cosmetic products, and it is not reviewed in this report.

CHEMICAL AND PHYSICAL PROPERTIES

Structure

n-Butyl Alcohol (CAS No. 71-36-3) (n-BuOH) is a primary aliphatic alcohol with the chemical formula as follows[1,2]:

$$CH_3—CH_2—CH_2—CH_2—OH$$

Other names for n-BuOH include Normal Butyl Alcohol, Butyl Alcohol, Normal Butanol, n-Butanol, 1-Butanol, Butanol, and Propyl Carbinol.[1-3]

Properties

n-BuOH is a colorless liquid with a vinous odor. This odor is similar to that of fusel oil but weaker. n-BuOH is soluble in water, alcohol, ether, acetone, benzene, and other organic solvents.[3-6] Chemical and physical properties of n-BuOH are presented in Table 1.

Reactivity

A mixture of 63% n-BuOH and 37% water forms a constantly boiling mixture with a temperature of 92°C.[3]

n-BuOH is a fire hazard when exposed to heat, flame, or oxidizers. It is a moderate explosion hazard when exposed to flame. When heated to

TABLE 1. Chemical and Physical Properties of n-butyl Alcohol

Property	*n-BuOH*	*Reference*
Molecular weight	74.12	
Specific gravity at		
20/4°C	0.810	3
20/4°C	0.8098	6
20/4°C	0.8096	2
Boiling point (°C) at		
760 mm Hg	117–118	3
760 mm Hg	117.2	6
760 mm Hg	117.70	2
Melting point (°C)		
	−90	3
	−89.5	6
	−89.5	2
Vapor pressure (mm Hg) at		
20°C	4.3	2
25°C	6.5	2
Refractive index for D line of the sodium spectrum at		
20°C	1.3993	3
20°C	1.3993	6
20°C	1.39711	2
Autoignition temperature (°C)	367	2

decomposition, it emits toxic fumes. n-BuOH can react with oxidizing materials.[7]

Methods of Manufacture and Impurities

n-BuOH can be produced by a synthetic process based on aldol condensation, by the oxo process, by selective bacterial fermentation of carbohydrate-containing materials, by the Ziegler process, by Reppe synthesis, as a byproduct in the high-pressure oxidation of propane and butane, by the reduction of butyraldehyde with sodium borohydride, from ethylene oxide and triethylammonium, and by oxidation of tributylaluminum. It is purified by distillation.[2-5]

The n-BuOH used in cosmetic products typically contains no more than 0.003% acidity (as acetic acid), no more than 0.1% moisture, or 0.005 g/100 ml nonvolatiles.[4]

Analytical Methods

Qualitative and quantitative determinations of n-BuOH are made by gas chromatography,[8,9] gas chromatography–mass spectrometry, paper chromatography, thin-layer chromatography, x-ray diffraction,[10] infrared spectrophotometry,[10-12] high-pressure liquid chromatography,[9] colorimetry, titrimetry,[13] a fluorophotometric method using alcohol dehydrogenase,[14] activated carbon absorption,[15] an odor reference method,[16] use of an enzyme thermistor probe,[17] an electronic identification method,[18] and an electroadsorptive technique.[19] A gas–liquid chromatographic procedure has been described for the determination of n-BuOH in nail lacquer preparations.[20]

USE

Purpose in Cosmetics

n-BuOH is used as a solvent in nail lacquers and has been used as a clarifying agent in the manufacture of clear shampoos.[20,21] It is used generally as a solvent in cosmetics.[4]

Scope and Extent of Use in Cosmetics

Product types and the number of product formulations containing n-BuOH and reported voluntarily to the Food and Drug Administration (FDA) in 1981 are presented in Table 2. Voluntary filing of this information by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations.[22] Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the true concentration of the finished product; the actual concentration in such a case

TABLE 2. Product Formulation Data[23]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulation within each concentration range (%)			
			> 5–10	> 1–5	> 0.1–1	≤ 0.1
n-Butyl Alcohol						
Nail basecoats and undercoats	44	3	—	2	1	—
Nail polish and enamel	767	107	2	20	64	21
Nail polish and enamel remover	41	2	—	—	—	2
1981 TOTALS		112	2	22	65	23

would be a fraction of that reported to FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration. In 1981, n-BuOH was reported as an ingredient in 112 cosmetic formulations at concentrations ranging from ≤ 0.1% to between 5 and 10%.[23]

Surfaces to which Commonly Applied

Cosmetic products containing n-BuOH are applied typically to the nails. During application of these products, n-BuOH may come in contact with skin or with nasal mucosa and eyes as a result of evaporation from the formulation (Table 2).[23]

Frequency and Duration of Application

Product formulations containing n-BuOH may be applied as many as several times a week and may remain in contact with the nail for variable periods following application. These formulations may be used for many years (Table 2).[23]

Potential Interactions with Other Cosmetic Ingredients

n-BuOH should not be used in suspension-type nail lacquers containing various modified montmorillonite clays. Laboratory studies have shown that such lacquers are incompatible with n-BuOH; adverse reactions can occur because hydroxyl radicals are present. n-BuOH is stable under typical cosmetic use conditions.[4]

Noncosmetic Use

Toxicology and metabolism data for n-BuOH have been reviewed by the Expert Panel of FEMA and the chemical has been judged to be generally recognized as safe (GRAS) under conditions of intended use as a flavoring

TABLE 3. FEMA and NAS Flavor Usage Survey for n-BuOH[10]

Food category	No. firms reporting usage	Weighted means of level of use (ppm)		Variation with age in the average possible daily intake (mg)			
		Usual	Maximum	0–5 mo	6–11 mo	12–23 mo	2–65+ yr
All categories	15			0.117	0.898	1.66	3.78
Baked goods	10	17.1	30.8	0.0581	0.434	0.931	2.34
Frozen dairy	5	8.89	13.9	0.00889	0.0845	0.128	0.228
Soft candy	9	16.2	24.9	0.00324	0.0357	0.0567	0.094
Gelatin puddings	4	16.9	22.2	0.0338	0.216	0.233	0.345
Beverages type I	11	5.5	6.97	0.0132	0.125	0.298	0.572
Beverages type II	[a]	5.55	11.1	0.000000	[b]	[b]	0.18
Hard candy	[a]	27.1	28.1	0.000000	0.00271	[c]	0.0162

[a] 3 or fewer firms.
[b] Not reported.
[c] Not legible.

substance in food.[10] n-BuOH is permitted as a food additive for direct addition to food for human consumption; it may be safely used in food as a synthetic flavoring substance or adjuvant when used in the minimum quantity required to produce the intended effect and otherwise in accordance with all the principles of good manufacturing practice.[22] FEMA and the National Academy of Sciences (NAS) performed a survey in 1970 on the use of n-BuOH as a flavoring substance in the United States (Table 3).[10]

n-BuOH may be safely used as a diluent in color additive mixtures for food use exempt from certification; no residue of n-BuOH may be left in the food. These color additive mixtures may be used for marking food; the inks are used to mark food supplements in tablet form, gum, and confectionary.[22]

n-BuOH is also permitted as an indirect food additive. It may be employed as a constituent of adhesives that may be safely used as components of articles intended for use in packaging, transporting, or holding food.[22] n-BuOH may be used as an adjuvant in the manufacture of resinous and polymeric coatings for polyolefin films that may be safely used as a food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.[22] n-BuOH may be used in formulating defoaming agents used in the preparation and application of coatings for paper and paperboard; these coatings may be safely used as components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.[22] n-BuOH may be used in the formulation of cellophane that may be safely used for packaging food; the n-BuOH residue must be limited to 0.1% by weight of finished packaging cellophane.[22] n-BuOH may be used as a solvent in the formulation of polysulfide polymer-polyepoxy resins that may be safely used as the food-contact surface of articles intended for packaging, transporting, holding, or otherwise contacting dry food.[22]

n-BuOH appears on the May 4, 1982, FDA list of inactive ingredients for approved prescription drug products.[24] n-BuOH is a solvent and bactericide for veterinary use. It has been used in the treatment of frothy bloat in cattle.[25]

n-BuOH is a solvent for fats, waxes, resins and coatings, shellac, varnish, and gums. It is used in the manufacture of lacquers, rayon, detergents, and a variety of other butyl compounds. n-BuOH is used in plasticizers and in hydraulic fluids, as a dyeing assistant, as a dehydrating agent, and in chemical analyses.[3,5] n-BuOH is used as a biological extractant.[26–28] It has also been used as a standard odor comparison substance to quantitate odorant concentrations.[16,29,30]

BIOLOGY

Effects on Enyzmes and Membranes

n-BuOH affects the activity of a variety of enzymes and may stabilize or destabilize a variety of biological membranes. These effects vary with concentration of the alcohol and with temperature and may be due to perturbation of protein conformation, structural changes in membrane lipids, or disturbance of lipid–protein interactions.[31–44]

n-BuOH inhibits rat liver mitochondrial respiration and phosphorylation. At concentrations ranging from 35 to 700 m*M*, n-BuOH inhibited by 50% the activity of a variety of electron transport chain enzymes in submitochondrial particles from bovine heart and rat liver.[45,46]

Action as Hydroxyl Radical Scavenger

n-BuOH is a hydroxyl radical scavenger. It has been claimed that this property of n-BuOH may be responsible for the prevention of neurodegenerative actions of chemicals subsequently injected into mice.[47]

Use as a Biological Tracer

n-BuOH has been used as a biological tracer. It is freely permeable across the blood–brain barrier in rats and has been used to quantitate cerebral blood flow.[48,49] It has also been used to quantitate regional myocardial perfusion in dogs.[50]

Environmental Occurrence

n-BuOH is ubiquitous in the environment, and human exposure is likely. Fusel oil, the congener or byproduct of the fermentation or distillation process in the production of alcoholic beverages, is 95% amyl, butyl, and propyl alcohols and has been reported to be present in liquor in a concentration as high as 0.25%.[51] In addition to its detection in beer, wine, cognac, rum, and whiskey, n-BuOH has been detected in a variety of fruits and cheeses, in beef fat and roast beef, in celery, in cooked chicken and chicken broth, in cream, in green peas and roasted peanuts, in potatoes and tomatoes, and in black and green tea.[10] The mainstream smoke of a nonfilter cigarette contains about 5 μg n-BuOH.[52] n-BuOH has been reported to be a constituent of expired air in a nonsmoking heterogeneous population.[53]

n-BuOH has been detected in the expired air of 3 of 3 male subjects who smoked and in 2 of 5 male subjects who did not smoke.[54] It has also been detected in the headspace over building materials.[55] t-BuOH has been detected in drinking water.[56]

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

It was reported in an early review of the aliphatic alcohols that n-BuOH could be absorbed through the lungs, the gastrointestinal tract, and the skin.[57] Studies since that time have provided considerable detail on the absorption of n-BuOH.

In vitro skin permeability has been studied by using diffusion cells; cells are assembled with skin between donor and receiver half-cells. Scheuplein and Blank[58] studied the in vitro permeability of human abdominal epidermal sheets and full-thickness dermis obtained at autopsy with diffusion cells at 25°C for 24 h. Distilled water was placed in the receiver half-cell and 0.1 *M* aqueous n-BuOH or pure n-BuOH, radioactive (position of label unspecified) in some trials, was placed in the donor half-cell in contact with the stratum corneum or external side of the tissue. Eight trials were performed with aqueous n-BuOH and epidermis, 3 were performed with dermis and aqueous n-BuOH, 7 were performed with epidermis and pure n-BuOH, and 8 were performed with dermis and pure n-BuOH. The permeability constant for epidermis in contact with aqueous n-BuOH was 2.5×10^3 cm/h and for dermis in contact with aqueous n-BuOH was 30×10^3 cm/h. The permeability constant for epidermis in contact with pure n-BuOH was 0.060×10^3 cm/h and for dermis in contact with pure n-BuOH was 1.0×10^3 cm/h. Pure n-BuOH did not cause any permanent alteration of the epidermis. In comparison to the stratum corneum, the dermis was an inferior permeability barrier to n-BuOH.

The in vivo corneal penetration of 92.23×10^{-5} *M* ^{14}C-n-BuOH in Sorenson's buffer at a pH of 7.4 was studied in male albino rabbits (number unspecified).[59] Doses of 25 μL were placed on the corneas of both eyes, the rabbits were killed at various times afterward (schedule unspecified), and the aqueous humor of the eyes was sampled. At 10 min, the aqueous humor concentration of n-BuOH was 56.43×10^{-9} *M*, and at 20 min, the concentration was 35.47×10^{-9} *M*.

DiVincenzo and Hamilton[60] administered by gavage 4.5 mg/kg 1-^{14}C-n-BuOH in corn oil to 2 male Charles River CD rats, 45 mg/kg to 2 rats, and 450 mg/kg to 4 rats. The percentages of total radioactivity recovered as unchanged n-BuOH in expired air for the rats dosed with 450 mg/kg was 0.34 at 24 h, and as CO_2 were 44.4, 69.3, and 83.3 at 4, 8, and 24 h, respectively. At 24 h, the urine of these rats contained 4.4% of the total radioactivity recovered, and the feces contained 0.6%. The percentage of the total radioactivity remaining in the carcasses of the rats administered 450 mg/kg radioactive n-BuOH was 42.2% at 4 h, 27.2% at 8 h, and 12.3% at 24 h. At 24 h, the liver contained 2.65% of the administered radioactivity, the kidney contained 0.11%, the lung contained 0.07%, the heart contained 0.02%, the brain contained

0.04%, the adrenal glands contained 0.009%, the blood contained 0.38%, and the fat contained 0.06% of the administered dose per gram of fat. The overall recovery was 86.7% at 4 h, 99.6% at 8 h, and 101.0% at 24 h. Rats dosed with 4.5 or 45 mg/kg n-BuOH had an excretion pattern similar to that of the rats dosed with 450 mg/kg n-BuOH. The 24-h urine of the rats dosed with 450 mg/kg n-BuOH was pooled; approximately 75% of the radioactivity was detected as n-BuOH, presumably 44.4% as an O-sulfate and 30.7% as an O-glucuronide. Urea accounted for the remainder of the radioactivity. The highest concentration of n-BuOH in the plasma of the rats dosed with 450 mg/kg n-BuOH was 70.9 μg/ml at 1 h. n-BuOH disappeared rapidly from the plasma; at 4 h, n-BuOH was below the limit of detection.

In a similar experiment, ^{14}C-n-BuOH (position of label unspecified) was administered orally to rats.[61] One hour after administration, radioactivity was found in the liver, kidneys, small intestine, and lungs. Three hours later, the amounts of radioactivity in these organs had decreased. Over the first 3 days following administration of the n-BuOH, 95% of the radioactivity was eliminated from the body; 2.8% of the radioactivity was excreted in the urine and feces.

Absorption cells were attached to the thoraxes of 2 male beagle dogs.[60] A 55.6 cm^2 area of the skin was exposed for 1 h to 1-^{14}C-n-BuOH (vehicle unspecified), and expired air and urine were collected for 8 h. The radioactivity excreted was compared to that excreted over 8 h by 3 dogs given an intravenous dose of 1 mg radioactive n-BuOH in physiological saline. The dogs given intravenous n-BuOH eliminated about 15% of the administered dose in the breath as CO_2 and eliminated about 2.7% of the administered dose in the urine; no unchanged n-BuOH was detected in the breath. It was assumed that the metabolic fate and disposition of n-BuOH were the same after intravenous or dermal administration. It was calculated that, after 60 min, about 29 mg of n-BuOH were absorbed through the skin of dogs exposed dermally to n-BuOH and that the absorption rate was about 8.8 μg/min/cm^2.

Four male beagle dogs were exposed to 50 ppm n-BuOH vapor for 6 h.[60] Expired air and venous blood were collected periodically during and after exposure. About 55% of the inhaled vapor was absorbed through the lungs of the dogs exposed to n-BuOH vapor. The concentration of n-BuOH in expired air was about 22 ppm throughout the exposure period, and it rapidly decreased when the exposure was terminated; 1 h after exposure, n-BuOH was below the limit of detection.

Two groups of 6 healthy 21- to 34-year-old male human subjects were exposed to n-BuOH through a breathing valve and mouthpiece.[62] The first group was exposed to 600 mg/m^3 n-BuOH for 30 min during rest, was not exposed for 20 min, and then was exposed for three consecutive 30-min periods to 600 mg/m^3 n-BuOH during light physical exercise. The second group was exposed to 300 mg/m^3 n-BuOH for 30 min during rest, was not exposed for 20 min, and then was exposed to 300 mg/m^3 n-BuOH during three 30-min periods of exercise increasing in intensity. The amount of n-BuOH calculated as absorbed was the difference in the amounts of n-BuOH in the inspiratory and expiratory air. Total uptake for the first group over the 2 h was 535 mg n-BuOH, and total uptake for the second group was 450 mg.

About 46% of the amount of n-BuOH supplied was absorbed by the first group during the initial 3-min exposure; 39, 38, and 36% was absorbed during the three consecutive 30-min periods of light physical exercise, respectively. About 48% of the amount of n-BuOH supplied was absorbed by the second group during the initial 30-min exposure; 37, 40, and 41% was absorbed during the three 30-min periods of increasing intensity of physical exercise, respectively. The percentage uptake of n-BuOH was less during work than during rest. Differing intensity of physical exercise made no difference in the amount of n-BuOH absorbed. In the first group during the initial period at rest, the concentration of n-BuOH in alveolar air was about 25% of the concentration in inspiratory air, and it was about 30% during the three consecutive periods of light exercise.

The arterial blood concentration was about 0.5 mg/kg during the period at rest, and it increased to 1.1 mg/kg and remained constant during the exercise periods. In the second group, the concentration of n-BuOH in alveolar air was 22% during the initial period at rest, and it was about 30% during the three periods of exercise. Arterial blood concentration was 0.3 mg/kg during the period at rest and 0.6, 0.9, and 1.3 mg/kg during the three periods of increasing exercise intensity, respectively. Because n-BuOH has a high blood–air partition coefficient, it was expected that the n-BuOH concentration in the arterial blood would be greater than it was and that the amount of n-BuOH absorbed would be greater also. The researchers stated that the ratio between alveolar air concentration and inspiratory air concentration was small in relation to the percentage uptake. These results may have been due to the ready solubility of n-BuOH in water; n-BuOH may have been soluble in the water of the mucous membranes and may have been retained there, since diffusion of n-BuOH from water to blood is probably very slow. In the expiratory phase, n-BuOH may have been released from the mucous membranes back into the air.

n-BuOH is rapidly oxidized in vivo; it disappears from animal blood rapidly and oxidation products are not detected.[63,64] n-BuOH is a substrate for alcohol dehydrogenase but not for catalase.[65,66] Alcohol dehydrogenase, found primarily in mammalian liver, requires NAD^+ as a cosubstrate and catalyzes the oxidation of primary alcohols to aldehydes. Alcohol oxidation produces a proton, and therefore, the equilibrium position of the reaction depends on the pH of the medium. Physiological pH would favor in vivo aldehyde reduction; this is not observed because aldehydes are rapidly shunted away from the reaction, principally by further oxidation to acids.[67] n-BuOH is oxidized to n-butyraldehyde, to n-butyric acid, and then to CO_2 and water.[57] Videla et al.[68] quantified rat liver alcohol dehydrogenase activity; its activity was 0.32 μmol/g liver/min. n-BuOH is oxidized more rapidly than ethanol. This is presumably due to the high substrate affinity of n-BuOH for alcohol dehydrogenase.[60]

n-BuOH may competively inhibit the metabolism of ethanol by alcohol dehydrogenase.[69,70] The intragastric administration of n-BuOH to rats increased the rate of elimination of subsequently administered ethanol in comparison with the rate of elimination of ethanol by rats not given n-BuOH.[71]

n-BuOH can also be oxidized by the microsomal fraction of rat liver homogenate, and this may account for that fraction of hepatic alcohol metabolism that is independent of the pathway that involves alcohol dehydrogenase.[66]

n-BuOH is a hydroxyl radical scavenger; one pathway of microsomal oxidation is NADPH-dependent and involves the interaction of n-BuOH with hydroxyl radicals generated from the microsomal electron transfer pathway. A second microsomal alcohol-oxidizing pathway appears to be independent of these hydroxyl radicals. Organic hydroperoxides can support the oxidation of n-BuOH by microsomes. It is possible that these two pathways involve different cytochrome P-450 isozymes.[65,72-75]

n-BuOH can be oxidized nonenzymically to n-butyraldehyde by ascorbic acid.[76] Tissue extracts contain some ascorbic acid. The aldehyde was formed when n-BuOH and ascorbic acid were added to perchloric acid-precipitated bovine liver, kidneys, heart, and blood extracts. The researchers stated that the oxidation of aliphatic alcohols in vivo by ascorbic acid is unlikely to occur so rapidly that the products would cause harmful effects.

Kamil et al.[77] administered 16 mmol of n-BuOH by stomach tube to 3 chinchilla rabbits. Although n-BuOH is readily oxidized, a very small amount of the n-BuOH was conjugated with glucuronic acid and excreted in the urine as a glucuronide. As a percentage of dose, the average extra glucuronic acid excreted over 24 h was 1.8%. The researchers suggested that some volatile alcohols also might be eliminated to some extent in an unchanged state by the lungs.

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

Undiluted n-BuOH was administered by gastric intubation to groups of 5 female and 5 male Osborne-Mendel rats and the animals were observed for up to 2 weeks.[78] Time to death was 4–18 h, the LD_{50} was 2.51 g/kg and depression and coma were observed. A similar experiment was performed with groups of 5 male Carworth-Wistar rats. n-BuOH was administered by intubation, and the LD_{50} after 14 days of observation was calculated as 4.36 g/kg.[79,80]

Groups of 4 rats (unspecified strain) were given single doses, ranging from 0.15 to 4.9 g/kg, of n-BuOH by stomach tube.[81] The LD_{50} for males was 2.02 g/kg and for females it was 0.79 g/kg. The 95% confidence intervals overlapped, indicating that the difference in the LD_{50}s was not significant. Rats that died after receiving high doses of n-BuOH survived only 2–6 h. Those that died after low doses survived 5–7 days. Congestion of all the organs and marked hepatic hyperemia were observed with the earlier deaths. Degeneration of liver and kidneys was observed in the rats that died after 5 days; only one section from the liver of one of these rats had any fatty change.

Low-dose rats had renal hyperemia, cloudy swelling with cast formation in the cortex, and necrotic changes in the medulla. More extensive necrotic changes were observed within 24 h at the higher doses.

Ten to 35 rabbits, 1.5–2.5 kg, were given n-BuOH by stomach tube.[82,83] The 24-h LD_{50} was 47 mmol/kg (3.5 g/kg). The ND_{50}, the quantity that caused narcosis in half the rabbits, was 11 mmol/kg (0.8 g/kg). The minimum fatal dose of n-BuOH for dogs was 2.2 ml/kg.[57,84]

n-BuOH was administered orally to rabbits.[57,85] Doses of 1–1.5 g/kg caused a partial paralysis in 20–30 min. Corneal, pupillary, and ciliary reflexes, pulse rate, and respiration were not affected. Doses of 1.6–2.0 g/kg caused excitement and, 5–15 min later, complete paralysis, analgesia, impairment of corneal, pupillary, and ciliary reflexes, and reduction of respiration and body temperature. Recovery occurred 10 h later. Doses of 2.1–2.44 g/kg caused complete paralysis, reduction in corneal, pupillary, and ciliary reflexes, constriction of pupils, nystagmus, salivation, reduction of respiration and body temperature, and deep narcosis that lasted 36 h.

A group of 12 female Wistar rats was given 4 ml/kg n-BuOH in a single oral dose.[86,87] Seventeen hours later, in comparison with a control group of rats, there was no change in the relative weight of the liver, in the liver nitrogen concentration, or in the fatty acid, triglyceride, cholesterol, or phospholipid concentrations in the blood.

Four male Wistar rats were given a single oral dose of 0.56 g/kg n-BuOH.[68] Control rats received saline. Six hours after administration, the hepatic reduced glutathione concentration was decreased, although not significantly, and diene conjugate formation was increased, although not significantly, in comparison with the control rats.

Pretreatment with single oral doses of 0.6 and 1.2 g/kg n-BuOH in distilled water had an antiinflammatory effect on paw edema induced by injections of carrageenan in 8 male Wistar rats.[88] The 0.6 g/kg dose induced anesthesia in half the rats; 1.2 g/kg induced anesthesia in all the rats. Doses higher than 1.2 g/kg were "not tolerated." Pretreatment by gavage with 0.3, 0.6, and 1.2 g/kg n-BuOH had an antiinflammatory effect on pleurisy induced by injections of carrageenan into the pleural cavity of rats. Two of 14 rats given 1.2 g/kg died.

Groups of 4 adult male albino rats (unspecified strain) were given n-BuOH orally through a catheter as a 10% aqueous solution in doses of 1 and 2 ml/kg daily for 7 days.[89,90] Control rats were given water. On day 7, 2 h after the last dose, the rats were decapitated, and the liver vitamin content was determined. Thiamine, riboflavin, pyridoxine, niacin, and pantothenic acid concentrations were significantly reduced in comparison to the concentrations measured in the livers of the control rats.

An unspecified number of male albino Sprague-Dawley rats were given n-BuOH dissolved in corn oil by oral intubation each day (for an unspecified number of days, but 6 days is likely).[91] The n-BuOH dose was equimolar to a standard dose of 2,000 mg/kg dibutyl phthalate (532.6 mg/kg n-BuOH). Control rats received 5 ml/kg corn oil by oral intubation. The n-BuOH did not affect the testicular tissues of the rats.

Subchronic Toxicity

A group of 30 male Wistar rats were given drinking water containing 6.9% n-BuOH and 25% sucrose for 13 weeks.[92] Control rats were given tapwater. Some of the rats (unspecified number) were decapitated at 5 and 9 weeks, and the remainder were decapitated at the termination of the experiment. At 1 month, the hepatic mitochondria were often elongated, constricted, or cup-shaped. The number of cristal membranes per mitochondrial profile was significantly decreased. In some hepatocytes, enlarged mitochondria were observed; these were pale and almost devoid of cristae. Similar observations were made at 2 months. In addition, some megamitochondria with diameters greater than 10 μm were observed. At 3 months, most of the hepatocyte mitochondria were enlarged, but coupling efficiencies were well preserved. The activities of mitochondrial monoamine oxidase and cytochrome oxidase in the treated rats were "moderately" decreased when compared to the control rats.

Dermal Studies

The dermal LD_{50} for rabbits of n-BuOH has been reported to be 4.2 g/kg.[7,93] It has been reported that n-BuOH does not cause skin irritation in rabbits.[2,94]

Ocular Irritation

Carpenter and Smyth[95] scored the injury to albino rabbit eyes caused by n-BuOH on a scale of 0–20 and then graded the injuries caused by n-BuOH on a scale of 1–10. The researchers usually used 5 rabbits at each chemical concentration. They applied 0.005 ml of the chemical to the center of one cornea of each rabbit and retracted the eyelids for 1 min. The eyes were scored 18–24 h later, and the reactions to the chemicals were graded. n-BuOH received a grade of 7, 0.005 ml of a 40% solution had a score of over 5.0, and 0.005 ml of a 15% solution had a score of not over 5.0. A 5.0 score was representative of severe injury; severe injury was necrosis, visible only after staining and covering about 75% of the surface of the cornea or a more severe necrosis covering a smaller area.

n-BuOH has also been evaluated in alternatives to the Draize rabbit eye irritation test.[96–101]

Inhalation Studies

Exposure to n-BuOH vapors can result in the intoxication of laboratory animals; restlessness, irritation of the mucous membranes, ataxia, prostration, and narcosis have been observed. High concentrations of n-BuOH vapors can be fatal.[2,57] Laboratory animals have been reported to adapt to low concentrations of n-BuOH vapors during chronic exposure.[102] Chronic and subchronic exposures can cause changes in various organs of animals and in enzyme activity.[103,104]

Sensory irritation of the upper respiratory tract of mice by n-BuOH vapors was accompanied by a reflex pause in the expiratory phase of respiration.[105] The decrease in the respiratory rate can be measured readily. Groups of 6 male Swiss OFI mice were exposed for 5 min to at least 4 concentrations of n-BuOH vapors. A 1,268 ppm concentration of n-BuOH resulted in a 50% decrease in the respiratory rate of the mice.

Rats exposed to 8,000 ppm n-BuOH for 4 h did not die.[106] Six male albino rats were exposed to a saturated or concentrated n-BuOH vapor. Eight hours was the longest exposure period that allowed all 6 rats to survive for 14 days.[79,80]

Smyth and Smyth[107] exposed 3 guinea pigs to 100 ppm n-BuOH vapor every day for 2 weeks (exposure periods unspecified) and then to 100 ppm n-BuOH vapor for 4-h periods 6 days a week for about $2\frac{1}{2}$ months. All 3 guinea pigs survived the 64 exposures. However, red blood cell counts decreased, and a relative and absolute lymphocytosis was observed. Two of the 3 animals had hemorrhagic areas in the lungs and a transient albuminuria. A second group of 3 guinea pigs was exposed to the same concentration of n-BuOH. After 30 exposures, all 3 developed a severe skin infection and, as a result, 2 of the 3 guinea pigs died at the 38th exposure. A decrease in red blood cell number and hemoglobin and an increase in leukocytes were observed. However, due to the skin infection, the polymorphonuclears dominated toward the end of the exposure period. The surviving guinea pig gained weight and had an improved blood picture by the end of the experiment. The liver of the guinea pigs had early toxic degeneration, and there was "considerable evidence" of renal degeneration; these were probably both attenuated by the infection. Another group of guinea pigs was exposed to the same concentration of n-BuOH vapor for 28 exposure periods; early hepatic cell degeneration and more marked renal degeneration were observed. There was an increased in red blood cells and an absolute and relative lymphocytosis. The skin infection resulted in the deaths of 1 of 3 control guinea pigs placed in the gassing chamber daily with no exposure to n-BuOH and of 1 of 3 untreated controls that remained in cages throughout the experiments. The control guinea pigs appeared clinically normal.

MUTAGENICITY

n-BuOH was nonmutagenic in the *Salmonella*/mammalian-microsome mutagenicity test.[108,109] It has been tested in *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 with metabolic activation.

A 15% aqueous n-BuOH solution did not induce sister chromatid exchanges or chromosome breakage in the "chick embryo cytogenetic test."[110] Doses of 1–10 μl were applied to 3–4-day-old chick embryos in ovo.

Chinese hamster ovary cells were treated for 7 days with 0.1% n-BuOH (v/v).[111] n-BuOH did not increase the number of sister chromatid exchanges observed per mitosis.

n-BuOH did not induce micronuclei formation in V79 Chinese hamster cells.[112] The lung cells were treated with a 50 μl/ml concentration of n-BuOH.

CLINICAL ASSESSMENT OF SAFETY

Dermal Studies and Observations

One hundred five dermatological patients were tested for n-BuOH-induced nonimmunological contact urticaria.[113] The chamber test method was used; 20 μl undiluted n-BuOH was applied to the upper back and with occlusive patches for 20 min. No redness was observed in any patient. Four patients were positive for edema.

Dermatitis of the fingers and hands has been observed after exposure to n-BuOH; fissured eczema particularly around the fingernails and along the sides of the fingers has been described.[114]

Three modified Draize-Shelanski repeat insult patch test studies were conducted with a nail color containing 3.0% n-BuOH.[115–117] Occlusive induction patches were applied 3 times a week for 3 weeks to the upper backs of volunteers. Patches remained in place until replacement and sites were scored on a 0–4 + scale just before patch replacement. Two consecutive 48-h challenge patches were applied to the upper backs adjacent to the original induction sites after a 2-week nontreatment period. Challenge sites were scored at 48 and 96 h after product application. In the first study, a 2 + reaction, a moderately intense erythema, with or without infiltration and involving at least 25% of the test area, was observed at challenge in 182 female and 10 male subjects. Upon further testing, it was determined that this irritant response was not attributable to n-BuOH. In the second study, no clinically significant responses were observed in 173 female and 37 male subjects. In the third study, a 2 + reaction was observed at the second challenge reading in 115 female and 41 male subjects. Under these test conditions, the nail color product was not considered to be an irritant or a sensitizer.

A nail enamel containing 3.0% n-BuOH was used in two modified Draize-Shelanski repeat insult patch test studies.[118,119] In one study, a 3 + reaction, a strong, infiltrated erythema and accompanying vesicles or superficial erosions involving at least 25% of the test area, was observed at challenge in 182 female and 34 male subjects. Upon further testing, it was determined that this irritant response was due to residual solvent. In the other study, a 1 + reaction, a macular, faint erythema involving at least 25% of the test area, was observed during induction in 144 female and 59 male subjects. Under these test conditions, the nail enamel product was considered to be not an irritant or a sensitizer.

A photopatch test was conducted with the nail enamel containing 3.0% n-BuOH.[120] The nail enamel was applied to the backs of 30 subjects and covered with occlusive patches. After 24 h, the patches were removed, and the sites were evaluated and irradiated with three times each individual's MED, using a Xenon Arc Solar Simulator (150 W) filtered to produce continuous emission spectrum in the UVA and UVB region (290–400 nm). The sites were scored 48 h later on a scale of 0–3 + . This product application and light exposure induction procedure was repeated twice weekly for a total of six exposures. This was followed by a 10-day nontreatment period. Then product and patches were placed on previously untreated sites on the backs of the subjects. After 24 h, the patches were removed and the sites were irradiated

for 3 min using a Schott G345 filter over the light source. These challenge sites were scored at 15 min and 24, 48, and 72 h after irradiation. Two control sites on each subject were subjected to the same test procedure except that one site was not irradiated and product was not applied to the other site. No reactions were observed in any of the subjects. Under these test conditions, the nail enamel product was not a phototoxin or photoallergen.

Occupational Observations

Tabershaw et al.[114] studied workers who used n-BuOH alone or in combination with other solvents at six plants where n-BuOH concentrations in the air ranged from 20 to 115 ppm. The major complaints were occular irritation when the air concentration of n-BuOH was greater than 50 ppm, disagreeable odor, slight headache and vertigo, slight irritation of nose and throat, and dermatitis of the fingers and hands. At several plants, the use of n-BuOH was discontinued, and the complaints ceased.

Corneal lesions have been described in workers exposed to n-BuOH and diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) and denatured alcohol.[121] Before the use of n-BuOH, there were no instances of ocular irritation. The n-BuOH air concentration of a manufacturing plant varied from 15 to 100 ppm, and the maximum concentration was found in the area with the greatest number of affected workers. Some workers complained of ocular irritation; foreign body sensation, epiphora, and burning of the eyes were described. Blurring of vision, itching and swelling of lids, and redness of the eyes were described less often. Slight haziness of the cornea was observed in workers with severe symptoms. All affected workers had numerous clear vacuoles in the anteriormost portion of the cornea; this was presumably the epithelium. In some cases, there was an increased amount of amorphous debris in the precorneal tear film. Corneal sensation was normal, and no abnormalities were observed in the endothelium. When workers were absent from work, the number of corneal vacuoles decreased. Upon return to work, corneal changes again appeared rapidly.

Sterner et al.[122] conducted a 10-year study of men exposed to n-BuOH vapors in an industrial setting. An initial group of 16 workers was increased to 100. The initial 200 ppm n-BuOH vapor concentration in the breathing zone was reduced so that the mean value for most of the 10 years was 100 ppm. No eye injuries or symptoms were observed at 100 ppm n-BuOH. Complaints were rare. There was only one transfer among several hundred workers; this single person disliked the odor of n-BuOH. At 200 ppm n-BuOH, some workers described transient corneal inflammation with associated burning feeling, lacrimation, and photophobia. No systemic effects were observed.

The American Conference of Governmental Industrial Hygienists[123] has set a ceiling limit of 50 ppm for n-BuOH. This concentration should not be exceeded even instantaneously. NIOSH has reported that 8,000 ppm of n-BuOH is the concentration immediately dangerous to life or health.[8] This concentration is the maximum from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects.[2]

SUMMARY

n-BuOH is a primary aliphatic alcohol. It is used generally as a solvent in cosmetics. In 1981, n-BuOH was reported as an ingredient in 112 cosmetic formulations at concentrations ranging from ≤ 0.1% to between 5 and 10%.

In vitro tissue permeability of n-BuOH has been studied using diffusion cells; human epidermis and dermis were permeable to n-BuOH. n-BuOH could also penetrate rabbit corneas. n-BuOH, administered orally to rats and humans, dermally to dogs, and by inhalation to dogs and humans, was eliminated rapidly and primarily in the expired air and in the urine. n-BuOH has been used by a biological tracer in blood flow studies. It is rapidly oxidized in vivo. n-BuOH is a substrate for alcohol dehydrogenase and may completely inhibit the metabolism of ethanol by this enzyme. It is also oxidized by two microsomal pathways in rat liver and can be oxidized nonenzymically.

The single oral dose LD_{50} of n-BuOH for rats was 0.79–4.36 g/kg. The dermal LD_{50} for rabbits of n-BuOH has been reported as 4.2 g/kg. It has been reported that n-BuOH does not cause skin irritation in rabbits. n-BuOH caused severe injury to rabbit eyes. Inhalation of n-BuOH vapors caused intoxication of laboratory animals. High concentrations were sometimes fatal.

n-BuOH was not mutagenic in the *Salmonella*/mammalian-microsome mutagenicity test, did not induce sister chromatid exchange or chromosome breakage in chick embryo cells or Chinese hamster ovary cells, and did not induce micronuclei formation in V79 Chinese hamster cells.

One hundred five dermatological patients were tested for reactions to n-BuOH using the chamber test method; four patients were positive for edema. A nail color containing 3.0% n-BuOH was studied in repeat insult patch tests with 558 subjects. Two reactions were observed at challenge. The nail color product was not considered to be an irritant or a sensitizer. A nail enamel containing 3.0% n-BuOH was studied in repeat insult patch tests with 421 subjects. One reaction was observed during induction and one reaction during challenge. The nail enamel product was not considered to be an irritant or a sensitizer. A photopatch test was conducted with the nail enamel product. No reactions were observed in any of 30 subjects. The nail enamel product was not a phototoxin or photoallergen.

Inhalation of n-BuOH can cause human nose, throat, and eye irritation. The ACGIH has set a ceiling limit of 50 ppm for n-BuOH, and NIOSH has reported that 8,000 ppm is the concentration immediately dangerous to life or health.

DISCUSSION

Data submitted to the FDA in 1981 indicate that n-BuOH is used in nail basecoats and undercoats, nail polish and enamel, and nail polish and enamel remover. The Expert Panel has reviewed the information in this report only as regards the use of n-BuOH in nail products.

CONCLUSION

On the basis of the information presented in this report, the CIR Expert Panel concludes that n-BuOH is safe in nail preparations in the present practices of use and concentration.

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