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Final Report on the Safety Assessment of *t*-Butyl Alcohol

The safety of this ingredient has not been documented and substantiated. The Cosmetic Ingredient Review Expert Panel cannot conclude that *t*-Butyl Alcohol is safe for use in cosmetic products until such time that the appropriate safety data have been obtained and evaluated. The data that were available are documented in the report as well as the types of data that are required before a safety evaluation may be undertaken.

INTRODUCTION

t-Butyl Alcohol and *n*-Butyl Alcohol were evaluated originally in one report by the Expert Panel. The data were sufficient to reach a safety conclusion for *n*-Butyl Alcohol, but were insufficient for *t*-Butyl Alcohol, and therefore the original report was divided into a report for each ingredient. The Expert Panel concluded that *n*-Butyl Alcohol is safe as presently used in cosmetics. The report for *t*-Butyl Alcohol follows.

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

CHEMICAL AND PHYSICAL PROPERTIES

t-Butyl Alcohol (CAS No. 75-65-0) (*t*-BuOH) is a tertiary aliphatic alcohol with the chemical formula[1,2] in Figure 1.

Other names for *t*-BuOH include tertiary butyl alcohol, tert-butyl alcohol, tertiary butanol, tert-butanol, *t*-butanol, 2-methyl-2-propanol, and trimethyl carbinol.[1-3]

t-BuOH is available in the form of colorless, hygroscopic crystals with a camphoraceous odor. The crystals become a clear liquid above 25.5°C. *t*-BuOH is soluble in water, alcohol, ether, and other organic solvents.[3-7] Chemical and physical properties of *t*-BuOH are presented in Table 1.

t-BuOH is a fire hazard when exposed to heat or flame, and it can react with oxidizing materials. *t*-BuOH, in the form of vapor, is a moderate explo-

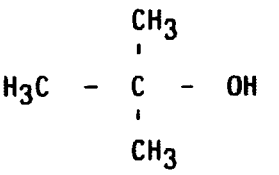

FIG. 1. t-Butyl Alcohol.

sion hazard when exposed to flame. It reacts violently with hydrogen peroxide.[8]

t-BuOH has been prepared from acetyl chloride and dimethylzin, by catalytic hydration of isobutylene, by reduction of tert-butyl hydroperoxide, and by absorption of isobutene, from cracking petroleum or natural gas, and in sulfuric acid with subsequent hydrolysis by steam. It is purified by distillation.[3-5]

t-BuOH used in cosmetics typically contains 99.5% *t*-BuOH, a maximum of 0.002% acidity (as acetic acid), a maximum of 0.1% water, and a maximum of 0.001% nonvolatile matter.[4]

Qualitative and quantitative determinations of *t*-BuOH are made by precipitation colorimetry,[9] gas chromatography,[10,11] gas chromatography–mass spectrometry,[10] photometry,[12] proton magnetic resonance,[13] and a laser

TABLE 1. Chemical and Physical Properties of *t*-BuOH

Property	*t-BuOH*	*Reference*
Molecular weight	74.12	
Specific gravity at		
20/4°C	0.78581	3
20/4°C	0.7887	7
25/4°C	0.78086	3
30/4°C	0.77620	2
Boiling point (°C) at		
760 mm Hg	82.41	3
760 mm Hg	82.30	7
760 mm Hg	82.50	2
31 mm Hg	20	7
Melting point (°C)	25.6	3
	25.5	7
	25.5	2
Vapor pressure (mm Hg) at		
20°C	30.6	2
Refractive index for D line		
of the sodium spectrum at		
20°C	1.38468	3
20°C	1.3878	7
20°C	1.3838	2
25°C	1.38231	3
25°C	1.3811	2
Autoignition temperature (°C)	380	2

absorption spectrometric method.[14] *t*-BuOH does not absorb ultraviolet light at wavelengths of 290 nm or longer.[15,16]

USE

Cosmetic Use

t-BuOH is used in the manufacture of perfumes.[3,5] It is used as a solvent or an alcohol denaturant and as a perfume carrier in cosmetics.[4]

Product types and the number of product formulations containing *t*-BuOH are reported voluntarily to the Food and Drug Administration (FDA). 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.[9] 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 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 2–10-fold error in the assumed ingredient concentration. In 1986, *t*-BuOH was reported to be an ingredient in 10 hair and facial skin care preparations at concentrations ranging from $\leq 0.1\%$ to between 0.1 and 1%.[17]

Cosmetic products containing *t*-BuOH may be applied to, or come in contact with, skin, eyes, hair, nails, mucous membranes, and respiratory epithelium.[17]

Product formulations containing *t*-BuOH may be applied as many as several times a day and may remain in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.[17]

t-BuOH is stable under typical conditions of cosmetic use.[4]

Noncosmetic Use

t-BuOH is permitted as an indirect food additive. *t*-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.[9] *t*-BuOH may be safely used in surface lubricants employed in the manufacture of metallic articles that contact food; it may be used in surface lubricants used in the rolling of metallic foil or sheet stock, provided that the total residual lubricant remaining on the metallic article in the form in which it contacts food does not exceed 0.015 mg/square inch of metallic food–contact surface.[9]

t-BuOH has been used as a denaturant for alcohol in a commercial sunscreen preparations.[18]

t-BuOH has been used as an alcohol denaturant, a flotation agent, a dehydration agent, a solvent, and an octane booster in gasoline. It has been used in paint removers, as a chemical intermediate, and in chemical analyses.[3,5]

BIOLOGY

Effects on Enzymes and Membranes

t-BuOH affects the activity of a variety of enzymes and may stabilize or destabilize a variety of biological membranes. These effects vary with concentration and with temperature and may be due to perturbation of protein conformation, structural changes in membrane lipids, or disturbance of lipid–protein interactions.[19–22]

t-BuOH has no or only a weak effect on rat hepatic mitochondrial respiration and phosphorylation at concentrations of up to 3%.[23]

Action as a Hydroxyl Radical Scavenger

t-BuOH is a hydroxyl radical scavenger. *t*-BuOH has been shown to protect DNA from the effects of radiation, and it is hypothesized that this action may be due to the scavenging of hydroxyl radicals.[24–26]

Environmental Occurrence

t-BuOH is ubiquitous in the environment, and human exposure is likely. Fusel oil, the congeners or byproducts of the fermentation or distillation process in the production of alcoholic beverages, is 95% amyl, butyl, and propyl alcohols and has been detected in liquor in a concentration as high as 0.25%.[27] *t*-BuOH has been detected in drinking water.[28]

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

t-BuOH is not a substrate for alcohol dehydrogenase or for catalase and has been used as an example of a nonmetabolizable alcohol. However, the results of recent investigations have indicated that *t*-BuOH is not as inert metabolically as previously assumed.[29,30] *t*-BuOH is a hydroxyl radical scavenger; in rat liver microsomes, it can be oxidatively demethylated by hydroxyl radicals generated from NADPH-dependent microsomal electron transfer to yield formaldehyde.[29,31] Baker et al.[32] investigated the in vivo metabolism of *t*-BuOH to acetone in Long-Evans rats and inbred Sprague-Dawley rats after intraperitoneal doses of 1 g/kg *t*-BuOH. *t*-BuOH concentration in the blood was measured over a 24 h period; the half-life of *t*-BuOH was 9.1 h. Acetone, produced by the metabolism of *t*-BuOH, was also detected in the blood. Acetone was slowly eliminated from the blood by excretion in the urine and

expired air, but the quantity excreted was highly variable. Baker et al.[32] injected two rats with 1.75 g/kg β-[^{14}C]*t*-BuOH. Over a 24 h period, 68.7% of the total dose was recovered from one rat and 93.2% was recovered from the other rat as CO_2 and acetone. When the animals were injected with 1.5 g/kg of a 1:1 mixture of α-[^{13}C]*t*-BuOH and *t*-BuOH, more acetone than expected was recovered. *t*-BuOH was a source of acetone, but also may have stimulated acetone production from other sources. Treatment of rats with U-[^{14}C]hexadecanoic acid and *t*-BuOH followed by collection of respiratory gases indicated that *t*-BuOH did not affect fatty acid synthesis.

t-BuOH is eliminated slowly from the blood of rats. *t*-BuOH was dissolved in water and a dose of 25 mmol/kg was administered by gastric intubation to female Wistar rats (number unspecified).[33] The *t*-BuOH blood concentration at 2 h was 13.24 mM, at 5 h it was 12.57 mM, and at 20 h it was 11.35 mM.

A 5.7 (w/v) solution of *t*-BuOH in saline was administered by gastric intubation to four to six female Sprague-Dawley rats every 8 h for 1 or 2.5 days; *t*-BuOH was administered in an amount inversely proportional to the degree of intoxication in order to maintain a uniform blood *t*-BuOH concentration of 60–100 mg percent.[34] The rats were then given *t*-BuOH to elevate their blood concentrations to between 125 and 150 mg percent, and blood was taken from the tails and sampled for *t*-BuOH. Eighteen hours were required to eliminate *t*-BuOH completely from the blood when the rats were treated for 2.5 days, and 26 h were required when the rats were treated for 1 day; the rate of elimination of 1.2 g/kg *t*-BuOH was 0.7 mmol/kg rat/h. Acetaldehyde was not detected in the blood or brain of rats treated for 3 days with *t*-BuOH. *t*-BuOH did not affect the oxygen uptake or pyridine nucleotide redox state of perfused rat liver.

t-BuOH is also slowly eliminated from the blood of mice. McComb and Goldstein[35] administered a single intraperitoneal dose of 8.1 mmol/kg *t*-BuOH to nine male Swiss-Webster mice; *t*-BuOH was eliminated from the blood in 8–9 h. The same mice then inhaled *t*-BuOH vapor for 3 days; the concentration of *t*-BuOH vapor administered was that which maintained a mean blood concentration of 8 mM *t*-BuOH. The researchers found it necessary to raise the *t*-BuOH vapor concentration progressively to maintain a given concentration of *t*-BuOH in the blood. *t*-BuOH was not detected in the blood 3 h after the mice were removed from the vapor chamber. A single intraperitoneal dose of 8.1 mmol/kg *t*-BuOH was administered (to an unspecified number of mice) 4 h after the end of a 3 day inhalation period; no *t*-BuOH was detected in the blood 3 h later. The increased elimination rate of *t*-BuOH may have been due to metabolic tolerance; more *t*-BuOH may have been conjugated and eliminated in animals previously exposed to *t*-BuOH.

The intragastric administration of *t*-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 *t*-BuOH.[36]

Kamil et al.[37] administered 12 mmol of *t*-BuOH by stomach tube to three chinchilla rabbits. *t*-BuOH was conjugated to a large extent with glucuronic acid, and glucuronides were readily isolated from the rabbit urine; as a percentage of dose, the average extra glucuronic acid excreted over 24 h was 24.4%. The researchers suggested that volatile alcohols might also be elimi-

nated to some extent in an unchanged state by the lungs. No aldehydes or ketones were detected in the expired air of a rabbit given 6 ml *t*-BuOH (route unspecified).

t-BuOH is excreted by rabbits as glucuronide conjugates, but these compounds are not present in dog urine.[38]

ANIMAL TOXICOLOGY

Oral Studies

The LD_{50} of *t*-BuOH for white rats (unspecified strain) was 3.5 g/kg (details of experiment unspecified).[39]

Ten to 35 rabbits, weighing 1.5–2.5 kg, were given *t*-BuOH by stomach tube.[40,41] The LD_{50} (the quantity that caused death in half of the rabbits within 24 hours) was 48 mmol/kg (3.56 g/kg). The ND_{50} (the quantity that caused narcosis in half the rabbits) was 19 mmol/kg (1.41 g/kg).

A dose of 25 mmol/kg (1.85 g/kg) *t*-BuOH as a 25% by volume solution in water was administered by gastric intubation to female Wistar rats (unspecified number).[33] Control rats received water. *t*-BuOH concentration in blood dropped only a small amount between 2 and 20 h after dosing. Blood free fatty acid concentration was unchanged at 2 h and increased at 5 h, and triacylglycerol concentration was decreased at 20 h. Hepatic triacylglycerols were increased at 2 and at 5 h. There were no significant changes in hepatic and blood phospholipid concentrations or in the 4 h lactate/pyruvate ratio. Hepatic palmitate uptake into triacylglycerols was increased at 2, 5, and 20 h, and palmitate incorporation into serum triacylglycerols was about 50% of control values at 5 and 20 h. The researchers concluded that *t*-BuOH induced a fatty liver, but not by impairing fatty acid oxidation.

A group of 12 female Wistar rats was given 4 ml/kg *t*-BuOH in a single oral dose.[42,43] Seventeen hours later, in comparison with a control group of rats, the relative weight of the liver was significantly increased, but there was no change in the hepatic nitrogen concentration, or in the fatty acid, triglyceride, cholesterol, or phospholipid concentrations in the blood.

A 3 g/kg dose of *t*-BuOH was administered orally to male Sprague-Dawley rats (unspecified number).[44] Later (unspecified time but 2 h later is likely), the rats were decapitated and brain homogenate was incubated with choline for 4 min at 37°C. Choline uptake was increased in the caudate nucleus and decreased in the hippocampus in comparison with control rats.

Four male Wistar rats were given a single oral dose of 2.54 g/kg *t*-BuOH.[30] 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.

An indwelling gastric fistula was surgically implanted 4 days after birth into eight Long-Evans rats from each of six litters to implement an artificial feeding method.[45] Four rats from each litter received milk formula containing a mean daily dose of *t*-BuOH that ranged from 0.60 to 2.69 g/kg on postnatal

days 4 through 7 and then received only milk formula for the next 11 days. The other 4 rats from each litter received only milk formula. At postnatal day 18, all the rats were decapitated, various organs were weighed, and biochemical analyses were performed. Only 26 of 48 animals survived the experiment; the major cause of death was a poor fistulation procedure or gastric bloating. Blood concentrations of *t*-BuOH ranged from 33.0 to 66.0 mg/100 ml of blood during alcohol administration. No differences between groups were observed in emergence of teeth, eye opening, or unfolding of the ears. No significant differences were observed between treated and control rats in body, liver, and heart weights, but the brains weighed significantly less in the treated rats; treated rats had decreased protein in the forebrains and decreased DNA in the hindbrains.

Groups of 10 male and 10 female Fischer-344 rats were given drinking water containing 0, 0.25, 0.5, 1.0, 2.0, and 4.0% *t*-BuOH for 90 days.[46] Average dosages for males were 0. 235.4, 495.8, 803.7, 1598.9, and 3588.5 mg/kg/day, and average dosages for females were 0, 260.6, 510.5, 758.4, 1451.5, and 3500.1 mg/kg/day. All of the male rats and six of the female rats at the highest dosage level died. There was also an absolute body weight loss in the males and a marked weight gain depression in the females. In male rats, there was a dosage-related depression in weight gain at lower dosages. Water consumption decreased in the females that received water containing 1, 2, and 4% *t*-BuOH and in the males that received water containing 4% *t*-BuOH. Water consumption increased in the male rats given water containing 0.25 and 0.5% *t*-BuOH. Ataxia was observed in both sexes, and hypoactivity was observed in male rats. During the study, total bile acid levels in the blood were elevated for all males except those receiving the 4% concentration. At the end of the study, total bile acid levels were elevated only for females receiving the 4% concentration. Urine volume was decreased for all rats at the 1% and greater concentrations. Crystals, presumed to be uric acid based on their size and shape, were observed in the urine in "high incidence" (in up to one-half of the surviving rats) at the 2 and 4% concentrations. At necropsy, gross findings involving the urinary tract, such as calculi, dilatation, and thickening, and those characteristic of inanition, apparently due to low water consumption, were observed. The kidneys, ureters, and urinary bladder were target organs for *t*-BuOH toxicity in the rat. The no-effect concentration was 1% for male rats and 2% for female rats.

Groups of 10 male and 10 female B6C3F$_1$ mice were given drinking water containing 0, 0.25, 0.5, 1.0, 2.0, and 4.0% *t*-BuOH for 90 days.[47] Average dosages for males were 0, 319.3, 726.3, 1565.8, 2838.8, and 6247.2 mg/kg/day, and average dosages for females were 0, 568.3, 941.7, 1731.8, 4362.9, and 7475.8 mg/kg/day. Six of 10 male mice and 4 of 10 female mice died receiving the highest dosage. There was a dosage-related depression in weight gain in the males that received water containing 1, 2, and 4% *t*-BuOH and in the females that received water containing 2 and 4% *t*-BuOH. Hyperplasia of the transitional epithelium of the urinary bladder and inflammation of the urinary bladder were observed. Other pathologic effects were considered secondary to inanition. The no-effect concentration for direct chemical effects was 1% for male mice and 2% for female mice.

Dermal Studies

Renkonen and Tier[48] conducted an experiment to investigate the intradermal irritation of *t*-BuOH to rabbits. There were no vehicle controls. Eight rabbits were injected intradermally with *t*-BuOH (vehicle unspecified). The size of the local skin reaction after injection of 35 mg *t*-BuOH was 14 mm^2, and after 10 mg *t*-BuOH was 43 mm^2. No explanation of the significance of these results was provided.

SPECIAL STUDIES

Animal Reproduction and Teratology

Groups of 15 pregnant Swiss-Webster mice were fed liquid diets containing *t*-BuOH at concentrations of 0.5, 0.75, and 1.0% (w/v) from days 6 to 20 of gestation.[49] Control mice were fed only the liquid diet. The 1.0% *t*-BuOH group was fed ad libitum. The other groups were pair-fed based on the consumption of the 1.0% *t*-BuOH group. The average maternal weight gain over the 20 days was 64% for the controls and 62, 52, and 51% for the 0.50, 0.75, and 1.0% *t*-BuOH-fed groups, respectively. Approximately one-half of the maternal animals in each group were replaced with untreated surrogate mothers within 24 h of delivery of litters to determine the role of maternal nutritional and behavioral factors on the young. Length of gestation, gross structural abnormalities, and number of deaths were recorded. Weight measurements, pinna detachment, eye opening, and behavioral test scores for the young were determined various times during days 2–22 postparturition. The total number of litters from 15 animals was 11 (77%) in the control group, 12 (80%) in the 0.5% *t*-BuOH group, 8 (53%) in the 0.75% group, and 7 (47%) in the 1.0% group. The average number of neonates per litter was 10.4 in the control group, 10.3 in the 0.5% *t*-BuOH group, 7.4 in the 0.75% group, and 5.3 in the 1.0% group. The average "fetal" weight at day 2 was 1.78 g in the control group, 1.66 g in the 0.5% *t*-BuOH group, 1.45 g in the 0.75% group, and 1.10 g in the 1.0% group. There was a dosage–response relationship between *t*-BuOH concentration in the diet and total number of stillborns (number of stillborns per litter size not given); there were 3 stillborns in the control group, 6 in the 0.5% *t*-BuOH group, 14 in the 0.75% group, and 20 in the 1.0% group. Pinna detachment occurred between days 6 and 8 in all the groups. Eyes opened in the 1.0% *t*-BuOH group at around day 16; this was 2–4 days later than in the other groups. Postnatal weight gain was decreased over the first 10 days in the nonfostered 0.75 and 1.0% groups in comparison to the other groups. There was a general dosage–response relationship between higher *t*-BuOH exposure in utero and poorer behavioral performance of pups. Fostered pups performed significantly better than nonfostered pups in three of four behavioral tests. All the treated groups did eventually recover and acquire the same level of performance on the behavioral tests.

Anderson et al.[50] determined the effect of *t*-BuOH on in vitro fertilization of Swiss-Webster mice gametes. Capacitated epididymal mouse spermatozoa were added to mouse oocytes with cumulus masses and, after a 24 h

incubation, the eggs were examined for fertilization. *t*-BuOH, at a concentration of 87 mM, was added to both the capacitation and the culture media. It did not affect the in vitro fertilization capacity of spermatozoa.

Mutagenicity

t-BuOH was nonmutagenic in the *Salmonella*/mammalian microsome mutagenicity test "even at a high concentration."[51,52] It was nonmutagenic to *Salmonella typhimurium* in the same test with metabolic activation when the bacterial suspension was preincubated with the chemical (concentrations unspecified).[53]

t-BuOH, added at a concentration of 1% to media prior to sterilization by autoclaving, did not increase the incidence of penicillin or streptomycin resistance in *Micrococcus aureus*.[54] In addition, bacterial cell survival was not affected.

t-BuOH did not induce adenine independence in adenine-dependent *Neurospora crassa*.[55] Mutations did not result after exposure to the fungi to a 1.75 mol/L concentration of *t*-BuOH in water.

t-BuOH was considered as a solvent for water-insoluble chemicals to be tested for mutagenicity.[56] *t*-BuOH was moderately toxic to the yeast, *Schizosaccharomyces pombe*, at concentrations of 0.5–10.0% (v/v) and to V79 Chinese hamster cells at 2.0 and 5.0% (v/v) and, therefore, it was not further considered.

t-BuOH was mutagenic to cultured human–Chinese hamster ovary hybrid cells at the mean lethal concentration of 80 mM.[57,58]

Carcinogenicity

Hair was clipped from the backs close to the base of the tail of female ddN mice, chemicals were applied to this bared skin, and the mice were observed for 450 days.[59] Moribund animals were killed and tissues were examined. In the first experiment, 0.05 mg 4-nitroquinoline-1-oxide (4NQO) in benzene was applied to the mice 3 times a week for a total of 20 applications. No acute skin damage was observed. In 50 surviving mice, there was 1 small papilloma and no "skin tumors." In a second experiment, 4NQO was applied as in the first experiment and was followed by applications of 16.6% *t*-BuOH (actual dosage unspecified) in benzene 6 times a week for a total of 270 applications. No acute skin damage was observed within about 100 days. After 350 days, two "erosions" were produced at the application site and these remained for the duration of the observation period. About 150 days after the start of the experiment and after about 100 applications of *t*-BuOH, one neoplasm was observed and "it developed into squamous cell carcinoma rapidly." About 300 days after the start of the experiment, a subcutaneous granuloma was detected. Fifty mice survived after the appearance of the first tumor in the experiment.

t-BuOH is currently under test in the NTP carcinogenicity bioassay program.[60] It is being administered in drinking water to rats and mice.

CLINICAL ASSESSMENT OF SAFETY

A woman who had a positive patch test reaction to ethanol was tested with 100% *t*-BuOH.[61] The alcohol was applied for 48 h and the site was scored at 3, 24, and 48 h after removal of the test material. The woman had a negative reaction to *t*-BuOH.

Four female patients were tested on the upper back with 1 and 10% *t*-BuOH in water.[62] The patches were applied for 24 h and reactions were read 24 and 48 h after removal. None of the women had any reaction to *t*-BuOH.

Edwards and Edwards[18] described a case of allergic contact dermatitis to the *t*-BuOH component of SD-40 alcohol in a commercial sunscreen preparation. A man who had a widespread, pruritic, red, vesicular eruption of his face, neck, arms, and chest and who had used a variety of sunscreens was patch-tested with sunscreens and with the individual components of the product to which he reacted. A 70% concentration of *t*-BuOH was applied to the forearms. At 72 h, erythema was observed and at 96 h, vesiculation was observed. No reactions were observed in two controls who also had applied *t*-BuOH to their forearms.

Dermatitis has also been observed when *t*-BuOH is applied to the skin; it caused slight pain, moderate hyperemia and erythema, dryness, and vesiculation.[63-65]

The ACGIH has set a threshold limit value of 100 ppm and a short-term exposure limit of 150 ppm that is satisfactory to prevent narcosis with *t*-BuOH.[63] The threshold limit value is the time-weighted average concentration for a normal 8 h workday or 40 h workweek and no adverse effects are expected from it. The short-term exposure limit is that concentration to which workers can be exposed for 15 min without suffering ill effects. Four 15 min periods are permitted per day with at least 60 min between exposure periods. In addition, the daily threshold limit value must not be exceeded.[2] NIOSH has reported that 8000 ppm *t*-BuOH is the concentration immediately dangerous to life or health.[11]

SUMMARY

t-BuOH is a tertiary aliphatic alcohol that is used as a solvent or an alcohol denaturant and as a perfume carrier in cosmetics. *t*-BuOH absorbs ultraviolet light at 275 nm and does not absorb at any longer wavelength. In 1986, *t*-BuOH was reported as an ingredient in 10 hair and facial skin care preparations at concentrations ranging from $\leq 0.1\%$ to between 0.1 and 1%.

t-BuOH is not a substrate for alcohol dehydrogenase. In rat liver microsomes, *t*-BuOH can be oxidatively demethylated by hydroxyl radicals to yield formaldehyde. Acetone was found in the blood, urine, and expired air of rats following the intraperitoneal administration of *t*-BuOH. *t*-BuOH was slowly eliminated from the blood of rats and mice; elimination is more rapid in animals previously exposed to *t*-BuOH.

The single oral dose LD_{50} of *t*-BuOH for rats was 3.5 g/kg. The addition of *t*-BuOH to the drinking water of rats and mice for 90 days resulted in gross lesions predominantly involving the urinary tract and those characteristic of inanition. The kidneys, ureters, and urinary bladder were target organs for *t*-BuOH toxicity in the rat. The no-effect concentrations for *t*-BuOH in the drinking water of rats were 1% in males and 2% in females. The urinary bladder was the target organ for *t*-BuOH toxicity in the mouse. The no-effect concentrations for direct chemical effects for *t*-BuOH in the drinking water of mice were 1% in males and 2% in females.

The oral administration of *t*-BuOH to mice during pregnancy resulted in poorer initial behavioral performance of pups. The pups did eventually recover. *t*-BuOH did not affect the in vitro fertilization capacity of mouse spermatozoa.

t-BuOH was not mutagenic in the *Salmonella*/mammalian-microsome mutagenicity test, did not increase the incidences of penicillin or streptomycin resistance in *Micrococcus aureus*, and did not induce adenine independence in adenine-dependent *Neurospora crassa*. *t*-BuOH was mutagenic to cultured human–Chinese hamster ovary hybrid cells at a cytotoxic dose.

t-BuOH in benzene was applied to the skin of 50 mice 6 times a week for a total of 270 applications after the application of 4NQO 3 times a week for a total of 20 applications. One squamous cell carcinoma was observed after 100 applications of *t*-BuOH. Based on this experiment, *t*-BuOH was inactive on mouse skin as a complete carcinogen or as a tumor promoter. *t*-BuOH is currently under test in the NTP carcinogenicity bioassay program. It is being administered in drinking water to rats and mice.

Dermatitis can result from dermal exposure of humans to *t*-BuOH.

The ACGIH has set a threshold limit value of 100 ppm and a short-term exposure limit of 150 ppm that is satisfactory to prevent narcosis due to *t*-BuOH. NIOSH has reported that 8000 ppm *t*-BuOH is the concentration immediately dangerous to life or health.

DISCUSSION

The Expert Panel is aware that data on the ocular irritation of *t*-BuOH in animals are lacking. These data are not required by the Panel. *t*-BuOH is expected to be a severe eye irritant.

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the CIR Procedures, the Panel informed the public of its decision that the data on *t*-BuOH are insufficient to determine whether this ingredient, under each relevant condition of use, is either safe or unsafe. The Panel released a Notice of Insufficient Data Announcement on September 23, 1986 outlining the data needed to

assess the safety of *t*-BuOH. The types of data required included:

1. Data from a 90-day oral study.
2. Data on human sensitization.
3. An ultraviolet absorbance spectrum: if absorbance was observed at greater than 290 nm, then photosensitization data would be required.

Data from a 90-day oral study and an ultraviolet spectrum were received. Data on human sensitization were not received within an appropriate time period.

t-BuOH does not absorb ultraviolet light at wavelengths of 290 nm or longer; it is not expected to be a photosensitizer. The animal and human sensitization data available for *n*-BuOH cannot be used to make a determination of the safety of *t*-BuOH. The Expert Panel has determined that *n*-BuOH is safe as presently used in cosmetics.

The Panel will issue the Final Report in accordance with Section 45 of the CIR Procedures. When new data are available, the Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of *t*-BuOH as used in cosmetics.

ACKNOWLEDGMENT

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