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Final Report of the Addendum to the Safety Assessment of *n*-Butyl Alcohol as Used in Cosmetics[1]

_n_-Butyl Alcohol is a primary aliphatic alcohol historically used as a solvent in nail care cosmetic products, but new concentration of use data indicate that it also is being used at low concentrations in eye makeup, personal hygiene, and shaving cosmetic products. _n_-Butyl Alcohol has been generally recognized as safe for use as a flavoring substance in food and appears on the 1982 Food and Drug Administration (FDA) list of inactive ingredients for approved prescription drug products. _n_-Butyl Alcohol can be absorbed through the skin, lungs, and gastrointestinal tract. _n_-Butyl Alcohol may be formed by hydrolysis of butyl acetate in the blood, but is rapidly oxidized. The single oral dose LD_{50} of _n_-Butyl Alcohol for rats was 0.79 to 4.36 g/kg. The dermal LD_{50} for rabbits was 4.2 g/kg. Inhalation toxicity studies in humans demonstrate sensory irritation of the upper respiratory tract, but only at levels above 3000 mg/m^3. Animal studies demonstrate intoxication, restlessness, ataxia, prostration, and narcosis. Exposures of rats to levels up to 4000 ppm failed to produce hearing defects. High concentrations of _n_-Butyl Alcohol vapors can be fatal. Ocular irritation was observed for n-Butyl alcohol at 0.005 ml of a 40% solution. The behavioral no-effect dose for _n_-Butyl Alcohol injected subcutaneously (s.c.) was 120 mg/kg. Fetotoxicity has been demonstrated, but only at maternally toxic levels (1000 mg/kg). No significant behavioral or neurochemical effects were seen in offspring following either maternal or paternal exposure to 3000 or 6000 ppm. _n_-Butyl Alcohol was not mutagenic in Ames tests, did not induce sister-chromatid exchange or chromosome breakage in chick embryos or Chinese hamster ovary cells, did not induce micronuclei formation in V79 Chinese hamster cells, did not have any chromosome-damaging effects in a mouse micronucleus test, and did not impair chromosome distribution in the course of mitosis. Clinical testing of _n_-Butyl Alcohol for nonimmunological contact urticaria was negative in 105 subjects. Repeat-insult patch test (RIPT) studies of nail colors and enamels containing 3% _n-Butyl_ Alcohol in one study produced reactions on challenge, but further study linked significant positive reactions to another solvent. In other RIPT studies, only minimal reactions were reported. A photopatch test demonstrated that a nail enamel containing 3% _n_-Butyl Alcohol resulted in no reactions. Workers complained of ocular irritation, disagreeable odor, slight headache and vertigo, slight irritation of nose and throat, and dermatitis of the fingers and hands when the air concentration of _n_-Butyl Alcohol was greater than 50 ppm, as compared to an odor threshold in air of 0.83 ppm. The available safety test data were considered adequate to support the safety of _n_-Butyl Alcohol in all cosmetic product categories in which it is currently used.

[1]Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. This final amended report was prepared by Valerie C. McLain, CIR Scientific Analyst and Writer. Address correspondence to Ms. Valerie C. McLain, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) evaluated the safety of *n*-Butyl Alcohol (n-BuOH) in 1987, finding it safe in the practices of use and concentration in nail products (Elder 1987). This original safety assessment was specific in that the conclusion was issued only as regards the use of *n*-Butyl Alcohol in nail products.

Recently, CIR undertook a re-review of this ingredient to determine what additional data relevant to the safety of *n*-Butyl Alcohol have appeared in the published literature. That re-review included information that *n*-Butyl Alcohol uses have expanded to include product categories in addition to nail products (FDA 2002).

The CIR Expert Panel considered that the safety test data in the original safety assessment, along with the additional data available since that time, were sufficient to support the safety of these other uses of *n*-Butyl Alcohol. This addendum describes current uses and available new safety test data. Summaries of data from the original safety assessment are summarized and introduced with a phrase such as "according to Elder (1987)." Details of the studies thus summarized are available in that original safety assessment.

CHEMISTRY

Definition and Structure

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), *n*-Butyl Alcohol (CAS No. 71-36-3) is the aliphatic alcohol that conforms to the formula:

$$CH_3(CH_2)_2CH_2OH$$

and functions in cosmetic formulations as a denaturant, fragrance ingredient, and/or solvent.

Synonyms include

- butanol,
- 1-butanol,
- n-butanol,
- butyl alcohol,

TABLE 1
Physical and chemical properties of *n*-Butyl Alcohol.

Property	*n*-BuOH	Reference
Molecular weight	74.12	Elder 1987
Liquid density at 25°C	809.7 kg/m^3	Billig 1999
Specific gravity at 20/4°C	0.8096–0.810	Elder 1987; NIOSH 2005
Boiling point at 760 mm Hg	117–118°C	Elder 1987; Billig 1999
	243°F	NIOSH 2005
Melting point	−90°C to −89.3°C	Elder 1987; Billig 1999
Freezing point	−129°F	NIOSH 2005
Flash point	36–38°C	Environmental Protection Agency 1989
Vapor pressure at		
20°C	4.3 mm Hg	Elder 1987
25°C	6.5 mm Hg	Elder 1987
Refractive index at		
20°C	1.39711–1.3993	Elder 1987
25°C	1.3971	Billig 1999
Autoignition temperature	367°C	Elder 1987
Solubility in water at 30°C by weight	7.85%	Billig 1999
Solubility of water in n-Butyl Alcohol at 30°C by weight	20.06	Billig 1999

- butyl hydroxide, and
- propyl carbinol.

Physical and Chemical Properties

As described in Elder (1987), *n*-Butyl Alcohol is a colorless liquid with a vinaceous odor. This odor is similar to that of fossil oil, only weaker. It is soluble in water, alcohol, ether, acetone, benzene, and other organic solvents. Ema et al. (2004) describes *n*-Butyl Alcohol as a flammable, colorless liquid with a rancid sweet odor. Table 1 lists physical and chemical properties available from the original safety assessment, the *Kirk-Othmer Concise Encyclopedia of Chemical Technology* (Billig 1999), and the National Institute for Occupational Safety and Health (NIOSH) Web site (NIOSH 2005).

Reactivity

As described in Elder (1987), *n*-Butyl Alcohol is a fire hazard when exposed to heat, flame, or oxidizers. When heated to decomposition, it emits toxic fumes, and can react with oxidizing materials. Under typical cosmetic use conditions, however, *n*-Butyl Alcohol is stable. It was noted that *n*-Butyl Alcohol is not recommended for use in suspension-type nail lacquers containing various modified montmorillonite clays. Billig (1999) recommended that *n*-Butyl Alcohol be stored in baked phenolic-lined steel tanks, but acknowledged that plain steel tanks can also be used under the condition that a fine-porosity filler is installed to remove any contaminating rust. Storage under dry nitrogen was also advised because it limits flammability hazards, as well as minimizes water pickup.

According to NIOSH (2005), *n*-Butyl Alcohol reacts with aluminum forming flammable gas (hydrogen). It is miscible with many organic solvents and reacts with strong oxidants, such as chromium trioxide, causing a fire hazard. In addition, it attacks some plastics and rubbers.

When the temperature of *n*-Butyl Alcohol is above 29°C, explosive vapor/air mixtures may be formed. Therefore, strong oxidizers, strong mineral acids, alkali metals, and halogens are incompatible with *n*-Butyl Alcohol (NIOSH 2005).

Method of Manufacture

According to Elder (1987), *n*-Butyl Alcohol can be produced by a synthetic process based on aldol condensation, the oxo process, selective bacterial fermentation of carbohydrate-containing materials, the Ziegler process, Reppe synthesis, as a by-product in the high-pressure oxidation of propane and butane, the reduction of butyraldehyde with sodium borohydride, from ethylene oxide and triethylammonium, and by oxidation of tributylaluminum. Billig (1999) reported that the general commercial source of *n*-Butyl Alcohol is *n*-butyraldehyde, obtained from the oxo reaction of propylene.

Analytical Methods

Elder (1987) listed the following qualitative and quantitative analytical approaches to *n*-Butyl Alcohol determinations: gas chromatography, gas chromatography–mass spectrometry, paper chromatography, thin-layer chromatography, x-ray diffraction, infrared spectrophotometry, high-performance liquid chromatography, and colorimetry.

Other approaches included titrimetry, a fluorophotometric method using alcohol dehydrogenase, activated carbon absorption, an odor reference method, use of an enzyme thermistor probe, an electronic identification method, and an electroadsorptive technique. A gas-liquid chromatographic procedure was described specifically for the determination of *n*-Butyl Alcohol in nail lacquer preparations (Elder 1987).

The *NIOSH Manual of Analytical Methods* (NIOSH 1994) gives a detailed procedure for the quantitative measurement of n-Butyl Alcohol among other analytes by varying gas chromatography conditions.

The odor threshold for n-Butyl Alcohol is reported to be 7.1 ppm in water and 0.83 ppm in air (Environmental Protection Agency 1989).

Impurities

In cosmetic products, *n*-Butyl Alcohol typically contains no more than 0.003% acidity (as acetic acid), no more than 0.1% moisture, or 0.005 g/100 ml nonvolatiles (Elder 1987).

USE

Cosmetic

Elder (1987) reported 112 uses of *n*-Butyl Alcohol in nail care products at concentrations ranging from ≤0.1% to 10%. While Balsam and Sagarin (1974) had reported that *n*-Butyl Alcohol has been used as a clarifying agent in the manufacture of clear shampoos, no such uses were reported to the Food and Drug Administration (FDA) in 1981 (FDA 1981). Generally, *n*-Butyl Alcohol is used as a solvent in cosmetics, but the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004) includes two other functions: denaturant and fragrance ingredient.

In the most recent frequency of use data available, industry has reported only 29 uses to FDA (FDA 2002). A recent industry survey conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) identified use concentrations for *n*-Butyl Alcohol in a wide variety of product categories (CTFA 2005). These categories include bath products, eye makeup, personal hygiene products, and shaving products, in addition to nail care products. Current use concentrations range from a low of 0.000007% in bath soaps and detergents to a high of 4% in nail polishes and enamels. Table 2 includes all the available original and current frequency of use and use concentration data.

Noncosmetic

Elder (1987) reported that *n*-Butyl Alcohol is generally recognized as safe (GRAS) by FDA under conditions of intended use as a flavoring substance in food. It 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.

n-Butyl Alcohol may be safely used as a diluent in color additive mixtures for food use exempt from certification; but no residue 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. It 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.

n-Butyl Alcohol 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, transporting, or holding food. It also may be used in the formulation of cellophane that may be safely used for packaging food; the *n*-Butyl Alcohol residue must be limited to 0.1% by weight of finished packaging cellophane. It may be used as a solvent in the formulation of polysulfide polymerpolyepoxy resins that may be safely used as the food-contact surface of articles intended for packaging, transporting, holding, or otherwise contacting dry food.

n-Butyl Alcohol is an inactive ingredient approved for prescription drug products.

n-Butyl Alcohol is a solvent and bactericide for veterinary use. It has been used in the treatment of frothy bloat in cattle.

n-Butyl Alcohol 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-Butyl Alcohol is used in plasticizers and in hydraulic fluids, as a dyeing assistant, dehydrating agent, and in chemical analyses. It also is used as a biological extractant, as well as a standard odor comparison substance to quantitate odorant concentrations (Elder 1987).

According to Rowe et al. (1982), *n*-Butyl Alcohol is widely used as a solvent for paints, lacquers, coatings, and a number of other applications. In addition to the noncosmetic uses already listed, a chemical industry Web site (Petrochemicals 2005) included uses as an intermediate in manufacturing herbicide pharmaceutical and veterinary medicine esters; to extract antibiotics, vitamins, and hormones; and in the synthesis of melamine formaldehyde resins.

GENERAL BIOLOGY

Biological Effects

Elder (1987) reported on the effects of *n*-Butyl Alcohol on enzymes and membranes. *n*-Butyl Alcohol was shown to affect the activity of a variety of enzymes and may stabilize or destabilize a variety of biological membranes. These are typical solvent effects and are dependent on the concentration of the alcohol and temperature, and may be due to perturbation of

TABLE 2
Historical and current cosmetic product uses and concentrations for *n*-Butyl Alcohol.

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) (%)	2005 concentrations (CTFA 2005) (%)
Bath products				
Soaps and detergents	—	—	—	0.000007
Eye makeup				
Eyeliners	—	—	—	0.0003
Eye shadow	—	—	—	0.0004
Other eye makeup preparations	—	—	—	0.0001
Makeup				
Foundations	—	—	—	0.002
Lipsticks	—	—	—	0.0005
Nail care products				
Basecoats and undercoats	3	4	>0.1–5	0.5–2
Creams and lotions	—	—	—	1–3
Nail polishes and enamels	107	14	≤ 0.1 – 10	0.5–4
Nail polish and enamel removers	2	3	≤ 0.1	—
Other manicuring preparations	—	7	—	15
Personal hygiene products				
Underarm deodorants	—	—	—	0.00001
Shaving products				
Aftershave lotions	—	1	—	—
Total uses/ranges for *n*-Butyl Alcohol	**112**	**29**	**≤0.1–10**	**0.000007–15**

protein conformation, structural changes in membrane lipids, or disturbance of lipid-protein interactions.

n-Butyl Alcohol restrains rat liver mitochondrial perspiration and phosphorylation. At concentrations ranging from 35 to 700 m*M*, *n*-Butyl Alcohol inhibited by 50% of the activity of a variety of electron transport chain enzymes in submitochondrial particles from bovine heart and rat liver.

n-Butyl Alcohol is a hydroxyl radical scavenger. It has been asserted that this property of *n*-Butyl Alcohol may be responsible for the prevention of neurodegenerative actions of chemicals subsequently injected into mice. *n*-Butyl Alcohol has also 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. It has also been used to quantitate regional myocardial perfusion in dogs (Elder 1987).

Chromosome Segregation

Crebelli et al. (1989) studied the activity of ethyl alcohol and acetaldehyde on mitotic chromosome segregation in *Aspergillus nidulans*. Ethyl alcohol (99.9% pure), methyl alcohol (99.9% pure), n-propanol (99.5% pure), *n*-Butyl Alcohol (99.8% pure), hydroquinone (99% pure), and acetaldehyde (99% pure) were used in this experiment.

Mitotic segregants were discovered as homozygous (yA2/yA2) or hemizygous (yA2/o) yellow sectors or patches in heterozygous (yA2/yA2$^+$) pale-green colonies growing on complete medium. Yellow segregants were isolated, analyzed for their nutritional requirements, and classified as mitotic crossovers, nondysjunctional diploids or haploids. *A. nidulans* conidia underwent treatment with test chemicals during early germination. Monitored by light microscopy, conidia (10^5/ml) were incubated at 37°C with agitation in liquid complete medium supplemented with test chemicals until the emergence of germ tubes.

A wide range of concentrations was applied to determine the lowest and highest effective doses, as well as the lowest concentration halting conidial germination. Treatments were ended by serial dilutions with sterile water. In order to determine the survival and detect mitotic segregants, conidia were plated on agarized complete medium. Plates having more than 15 to 20 colonies were discarded to prevent normal colonies from advancing to abnormal, slow-growing aneuploid colonies.

Cattle brain microtubule preparations (containing tubulin and tubulin-associated proteins) were prepared by three cycles of assembly and disassembly in the absence of glycerol and stored as pellets at −80°C. Assembly of tubulin was followed by measuring the increase in absorbency at 350 nm in an LKB spectrophotometer. The assembly mix, which was kept ice cold, contained 200 μl of microtubule preparation (2 mg of protein with bovine serum albumin as standard), 20 μl of 50 mM GTP, the test agent

and the polymerization buffer (0.1 M PIPES, pH 6.62, containing 0.1 mM Mg^{2+}) in a final volume of 1.0 ml. Polymerization began when the temperature was raised to 37°C by placing the cuvette in the water-heated cell holder of the spectrophotometer.

Ethanol effectively induced malsegregation in a narrow range of concentrations (4.5% to 5.5%, *v*/*v*) and was inactive at doses that arrested conidial germination (above 6%). The same bell-shaped dose-response curve was shown by the spindle poison chloral hydrate, which was active in the range 6 to 10 mM. Acetaldehyde displayed a biphasic dose-response curve. Analysis of induced segregants suggested that the disturbance of chromosome segregation is the primary genetic effect at low doses (0.025% to 0.037%), whereas at higher doses (above 0.1%), when growth was arrested, chromosome damage was primarily induced.

A similar pattern of segregants was produced by hydroquinone, a substance that indirectly affects chromosome segregation in *A. nidulans*. The differences in the genotoxic profiles of ethanol and acetaldehyde suggested that the effect exerted by ethanol on *A. nidulans* mitosis was not dependent on its conversion into acetaldehyde. In the absence of an effect of ethanol on in vitro polymerization of tubulin (actively inhibited by acetaldehyde at doses above 0.075%), a direct effect of ethanol on cell membranes was suggested as an hypothesis by the authors.

According to the authors, comparison of the inhibition of growth and the effectiveness in aneuploidy induction displayed by ethanol, methanol, n-propanol, and *n*-Butyl Alcohol demonstrated a fair correlation with $\log_p$, a descriptor of lipophilicity related to the partitioning of compounds in biological membranes (Crebelli et al. 1989).

Absorption, Distribution, Metabolism, and Excretion

According to Elder (1987), *n*-Butyl Alcohol can be absorbed through the lungs, the gastrointestinal tract, the cornea, and the skin. Dogs given intravenous *n*-Butyl Alcohol 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*-Butyl Alcohol was detected in the breath. *n*-Butyl Alcohol is rapidly oxidized in vivo; it disappears from animal blood rapidly and oxidation products are not detected. *n*-Butyl Alcohol is a substrate for alcohol dehydrogenase, found primarily in mammalian liver, requires NAD^+ as a cosubstrate and catalyzes the oxidation of primary alcohols to aldehydes.

The International Programme on Chemical Safety/World Health Organization (IPCS/WHO) (1987) also reported that the butanols are readily absorbed through the lungs and gastrointestinal tract of animals. *n*-Butyl Alcohol, 2-butanol, and isobutanol are mainly metabolized by alcohol dehydrogenase and are eliminated rapidly from the blood.

Deisinger et al. (2001) described the pharmacokinetics of *n*-butyl acetate and its oxidative metabolites in rats following intravenous administration. *n*-Butyl Alcohol and acetate were produced in vivo by the hydrolysis of *n*-butyl acetate, followed by oxidative metabolism of *n*-Butyl Alcohol to *n*-butyric acid, as expected with butyraldehyde occurring as an intermediate.

ANIMAL TOXICOLOGY

Acute Toxicity

As given by Elder (1987), the single oral dose LD_{50} of *n*-Butyl Alcohol for rats was 0.79 to 4.36 g/kg. The dermal LD_{50} for rabbits was reported as 4.2 g/kg.

Korsak et al. (1992) investigated the effects of acute combined exposure to *n*-Butyl Alcohol and *m*-xylene. The rotarod performance and motor activity were tested in rats and respiratory rate was measured in mice. Male Wistar rats, weighing 250 to 300 g were exposed to the vapors of *m*-xylene, *n*-Butyl Alcohol, and their mixture consisting of 50/50 (by volume) *m*-xylene and *n*-Butyl Alcohol in a 1.3-m^3 volume dynamic inhalation chamber. Vapors were generated by heating liquid solvents in washers. The desired concentrations were obtained by dilution with air. Concentrations of solvents vapor in the exposure chamber were measured every 30 min with a gas chromatograph with a flame ionization detector using a 1.5-m metal column, with 10% OV-17 on chromosorb WHP (80 to 100 mesh) as a stationary phase, at a column temperature of 100°C.

The animals were trained before rotarod performance testing, and only those rats that could perform normally for at least 10 consecutive days were used in the experiment. Rotarod performance was tested prior to exposure and directly following termination of exposure for 1 h. Spontaneous motor activity was measured by using a UMA-2-10 actometer for small laboratory animals immediately after 4 h of exposure. The respiratory rate was determined in Balb/C male mice (25 to 30 g) by using the plethysmographic method. Each animal was attached to a small dynamic inhalation chamber.

A Stattham pressure transducer was linked to each plethysmograph and the respiratory pattern was recorded using a Beckman plethysmograph. The respiratory rate was recorded constantly before the exposure solvents, during 6 min of exposure and 6 min after termination of exposure.

Exposure concentrations of *m*-xylene and *n*-Butyl Alcohol were expressed in ppm (1 ppm *m*-xylene = 4.35 mg/m^3; 1 ppm *n*-Butyl Alcohol = 3.08 mg/m^3). The rats exposed to the tested concentrations of *m*-xylene, *n*-Butyl Alcohol and their mixture for 4 h all survived the exposure.

Mice were exposed to vapors of single solvents and their mixtures at several concentrations. Each exposure group consisted of 8 to 10 mice.

Both solvents and their mixture caused concentration-dependent disturbances in the rotarod performance of rats. Throughout the experiment, all control animals performed normally. In the rotarod perfomance test, the effect of *m*-xylene was more noticeable than that of *n*-Butyl Alcohol. EC_{50} values for *n*-Butyl Alcohol, *m*-xylene, and their mixture are 6530, 1980, and 3080 ppm, respectively. The results of the rotarod performance test indicated the additive toxic effect of combined exposure.

TABLE 3
Spontaneous motor activity in rats exposed to *n*-Butyl Alcohol and *m*-xylene (Korsak et al. 1992).

n-Butyl Alcohol +*m*-xylene (1:1)	Experimental spontaneous motor activity	Expected spontaneous motor activity
968 ppm	+5%	+49%
1976 ppm	+20%	+104%
3041 ppm	+34%	+136%
3761 ppm	+16%	+172%

The spontaneous motor activity in the rats was changed by both solvents and their mixture. Table 3 shows the comparison of experimental values with those expected, assuming the summation of effects of individual solvents.

Significant decreases of spontaneous motor activity were caused by further increases in solvent concentration. Because of a two-phase effect, the concentration dependence of changes in spontaneous motor activity could not be defined. Comparison of combined exposure to *n*-Butyl Alcohol and *m*-xylene in spontaneous motor activity indicated that the solvents' mixture's effect is characteristic for antagonistic effects.

Both *m*-xylene and *n*-Butyl Alcohol caused a concentration-dependent decline in the respiratory rate of mice. The maximum decrease of respiratory rate was always observed in the 1st min of exposure. The effect of *m*-xylene was more distinct than that of *n*-Butyl Alcohol. The effect of the mixture of *m*-xylene and *n*-Butyl Alcohol was similar to that of *n*-Butyl Alcohol. The authors stated that the effect was lower than would be expected assuming the additive effects of individual solvents (Korsak et al. 1992).

Subchronic Toxicity

According to Elder (1987), a group of 30 male Wistar rats received drinking water containing 6.9% *n*-Butyl Alcohol and 25% sucrose for 13 weeks. Control rats received tap water. At 1 month, the hepatic mitochondria were often elongated, constricted, or cupshaped. 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.

The rapid hydrolysis of butyl acetate to *n*-Butyl Alcohol and acetate in the blood suggested to Barton et al. (2000) that any hepatic effects of butyl acetate also might be caused by *n*-Butyl Alcohol. Butyl acetate was administered to rats via intravenous (i.v.) injection or oral dosing. Measured blood levels of *n*-Butyl Alcohol in rats exposed to butyl acetate were about three times higher than blood levels of butyl acetate. A 500 mg/kg/day dose of butyl acetate for 13 weeks was predicted to result in a blood level of 4 to 6 μM *n*-Butyl Alcohol. These authors concluded that the blood level of *n*-Butyl Alcohol was not high enough to result in any hepatoxicity.

Ocular Irritation

According to Elder (1987), *n*-Butyl Alcohol produced injury when 0.005 ml of test material was instilled in albino rabbit eyes as follows: *n*-Butyl Alcohol received a grade of 7 (on a scale of 0 to 20), a 40% solution had a score of over 5.0, and a 15% solution had a score of less than 5.0. A 5.0 score was representative of corneal necrosis, visible only after staining and covering about 75% of the surface of the cornea or a more severe necrosis covering a smaller area.

Inhalation Toxicity

Elder (1987) reported that irritation of the mucous membranes is one effect of exposure of laboratory animals to *n*-Butyl Alcohol; other effects include intoxication, restlessness, ataxia, prostration, and narcosis. High concentrations of *n*-Butyl Alcohol vapors can be fatal. Laboratory animals have been reported to adapt to low concentrations of *n*-Butyl Alcohol vapors during chronic exposure. Chronic and subchronic exposures can cause changes in various organs of animals and in enzyme activity.

Sensory irritation of the upper respiratory tract of mice by *n*-Butyl Alcohol vapors was accompanied by a reflex pause in the expiratory phase of respiration. A 1268-ppm concentration of *n*-Butyl Alcohol resulted in a 50% decrease in the respiratory rate of the mice. Rats exposed to 8000 ppm *n*-Butyl Alcohol for 4 h did not die. Male albino rats exposed to a saturated or concentrated *n*-Butyl Alcohol vapor for 8 h survived for 14 days; survival was reduced for exposure times longer than 8 h.

In another study, three guinea pigs were exposed to 100 ppm *n*-Butyl Alcohol vapor every day for 2 weeks (exposure periods unspecified) and then to 100 ppm *n*-Butyl Alcohol vapor for 4 h periods 6 days a week for about 2½ months. All three guinea pigs survived the 64 exposures. However, red blood cell counts decreased, and a relative and absolute lymphocytosis was observed. Two of the three animals had hemorrhagic areas in the lungs and a transient albuminuria. A second group of three guinea pigs was exposed to the same concentration of *n*-Butyl Alcohol.

After 30 exposures, all three developed a severe skin infection and, as a result, two of the three 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 livers 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*-Butyl Alcohol vapor for 28 exposure periods; early hepatic cell degeneration and more marked renal degeneration were observed. There was an increase in red blood cells and an absolute and relative lymphocytosis. A skin infection resulted in the deaths of one of three control guinea pigs placed in the gassing chamber daily with no exposure to *n*-Butyl Alcohol and of one of three untreated controls that remained in cages throughout the experiments. The control guinea pigs appeared clinically normal (Elder 1987).

Ototoxicity

Crofton et al. (1994) investigated solvent-induced ototoxicity in rats. Male Long Evans hooded rats (60 to 70 days of age) were exposed via inhalation in flow-through chambers. The animals came in contact with the air or vapors of styrene (1600 ppm), 1,1,2-trichloroethylene (3500 ppm), toluene (2500 ppm), or mixed xylene (1800 ppm) for 8 h per day for 5 days (N = 7–8/group). *n*-Butyl Alcohol exposures (4000 ppm) were limited to 6 h per day for 5 days due to cost restraints (N = 10/group). Testing was conducted 5 to 8 weeks after exposure using reflex modification audiometry (RMA). RMA thresholds were determined for frequencies of 0.5 to 40 kHz.

All solvents except *n*-Butyl Alcohol caused hearing defects in the mid-frequency range. *n*-Butyl Alcohol did not affect hearing thresholds in rats (Crofton et al. 1994).

Neurological Effects

Schulze (1988) described a study of 2,4-dichlorophenoxyacetic acid (2,4-D-) esters and related alcohols were administered to rats and tested for their ability to increase landing foot splay, a measure of ataxia. Five adult male albino Wistar rats (approximately 200 days old) were used in this study. 2,4-D-n-butyl ester (99% pure); a 50:50 mixture consisting of 2,4-D-n-butyl ester and 2,4-D-isobutyl ester (99% pure); 2,4-D alone, *n*-Butyl Alcohol; 2-butanol; and a 50:50 mixture of *n*-Butyl Alcohol and 2-butanol were used.

Each test compound or mixture was emulsified into a vehicle of 20% Emulphor® in sterile distilled bacteriostatic (0.9% benzyl alcohol) water and administered via subcutaneous (s.c.) injection in volumes of 1 ml/kg. 2,4-D was diluted into a 3:2:5 mixture of Emulphor®, ethanol, bacteriostatic water and administered via subcutaneous injection in a volume of 1 ml/kg.

The behavioral endpoints measured were landing foot splay or photocell monitored locomotor activity. Motor activity was measured by placing rats in a PAC-001 photobeam activity chamber located in a sound attenuated room for 5 min per day. Landing foot splay was measured by placing colored ink on all four paws and then dropping the animal from a height of 30 cm onto a sheet of absorbent paper. The distance (cm) between each hind-limb was measured.

When administered for 3 to 4 straight days, 2,4-D-n-butyl ester (150 mg/kg/day s.c.) produced significant increases in landing foot splay whereas 2,4-D (120 mg/kg/day s.c.) and 2,4-D mixed butyl esters (150 mg/kg/day s.c.) did not. The ability of acute *n*-Butyl Alcohol, 2- butanol, and a 50:50 mixture of both (2.13 mM/kg s.c.) to increase landing foot splay was then assessed. Only *n*-Butyl Alcohol significantly increased landing foot splay.

When *n*-Butyl Alcohol was administered daily, at doses corresponding to 150 mg/kg/day of the 2,4-D-n-butyl ester, significant increases in landing foot splay were evident. The pattern of splay increases was similar to that of 2,4-D-n-butyl ester.

When locomotor activity was the dependent variable, daily *n*-Butyl Alcohol had no effect. The authors suggested that the in vivo formation of *n*-Butyl Alcohol following administration of 2,4-D-n-butyl ester is responsible for the motor incoordination, but not the depression of locomotor activity observed following 2,4-D-n-butyl ester administration (Schulze 1988).

David et al. (1998) evaluated the subchronic neurotoxicity of *n*-butyl acetate vapor (note: *n*-butyl acetate is metabolized to acetate and *n*-Butyl Alcohol) in male and female Sprague-Dawley rats using a functional observational battery, motor activity, neurohistopathology, and schedule-controlled operant behavior (SCOB) as indicators of neurotoxicity. Animals were exposed to concentrations of 0, 500, 1500, or 3000 ppm of n-butyl acetate for 6 h per day for 65 exposures over a period of 14 weeks. Functional observational battery and motor activity values for ad libitum fed male and female rats were measured during weeks 1, 4, 8, and 13. SCOB testing of food-restricted animals, using a multiple fixed ratio/fixed interval schedule, was conducted daily before each exposure to maintain the operant behavior. The data from weeks 1, 4, 8, and 13 were evaluated for evidence of neurotoxicity.

Short-term signs of sedation and hypoactivity were observed only during exposure to the 1500 and 3000 ppm concentrations. The only signs of systemic toxicity were decreased body weights for the 3000 ppm ad libitum fed groups and occasionally for the female 1500 ppm ad libitum fed group. There was no evidence of neurotoxicity during the functional observational battery examinations.

Motor activity for the 3000 ppm male group was significantly higher than the control group only during week 4 ($p \leq .05$). No significant differences were observed among groups for weeks 8 and 13. No significant differences in motor activity values were observed for female rats. No significant differences were seen in operant behavior at any test vapor concentration.

Microscopic evaluations of sections from the brain, spinal cord (cervical and lumbar regions), dorsal and ventral spinal roots, dorsal root ganglia, sciatic nerve, and tibial nerve of animals in the control and 3000 ppm groups did not show any treatment-related effects. The authors concluded that there was no evidence of cumulative neurotoxicity based on the functional

observational battery, motor activity, neurohistopathology, and schedule-controlled operant behavior end points. The authors suggested that the data are relevant to the neurotoxicity risk assessment of *n*-Butyl Alcohol due to the rapid hydrolysis of *n*-butyl acetate in vivo (David et al. 1998).

According to Deisinger (2001), n-butyl acetate, *n*-Butyl Alcohol, and n-butyraldehyde are known to cause central nervous system depression in experimental animals after oral and inhalation exposures at high concentrations. In a dose-selection study, the maximum tolerated dose was defined as that which resulted in no observable acute toxicity or respiratory depression persisting for greater than 15 s. The no-effect level for i.v. administration of *n*-Butyl Alcohol was 120 mg/kg.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Nelson et al. (1988a) assessed the teratology of *n*-Butyl Alcohol, 2-butanol, and t-butanol administered by inhalation to rats. Groups of about 15 Sprague-Dawley rats were used in this study. Virgin females (200 to 300 g) were individually placed with breeder males. Day 1 was established when spermatozoa were found in vaginal smears after mating. Bred females were individually placed into cages. Weekly food and water intake, as well as maternal weights, were measured on gestation days 0, 7, 14, and 20. Females were also weighed each morning during the first week of exposure.

On gestation days 1 to 19, females were placed into separate compartments within the exposure chambers. The control animals were placed in similar cages within an adjacent exposure chamber for the same hours as the exposed animals. The animals were exposed at 8000, 6000, 3500, or 0 ppm *n*-Butyl Alcohol, 7000, 5000, 3500, or 0 ppm 2-butanol, or 5000, 3500, 2000, or 0 ppm t-butanol on gestation days 1 to 19 (sperm = 0). Exposures occurred 7 h per day, and the animals were left in the chamber for degassing for about ½ h after vapor generation was terminated.

On day 20 of gestation, pregnant females were weighed individually and killed by CO_2 asphyxiation. One half of the fetuses were selected at random, placed into 80% ethanol, eviscerated, macerated in 1.5% KOH, stained in alizarin red S, and examined for skeletal malfunctions and variations. The remaining fetuses were placed in Bouin's solution and examined for visceral malformations and variations using a razor blade cross-sectioning technique.

For each butanol isomer considered, the highest concentration (and the intermediate in some instances) was maternally toxic, as manifest by reduced weight gain and feed intake. Even at a maternally toxic dose, and without being affected by a dose-dependent reduction in fetal weights for each isomer, the only developmental toxicity detected was a slight increase in skeletal malformations (primarily rudimentary cervical ribs), seen with the highest concentration of *n*-Butyl Alcohol. The authors stated that concentrations 50 times the current permissible exposure limits for these three butyl isomers do not produce developmental toxicity in rats (Nelson et al. 1988a).

Nelson et al. (1989b) investigated behavioral teratology of *n*-Butyl Alcohol in rats. A concentration of 6000 ppm was selected as the high concentration due to slight maternal toxicity and 3000 ppm was the low concentration evaluated. These two concentrations were administered via inhalation to separate groups of 15 pregnant Sprague-Dawley rats for 7 h per day throughout gestation; 18 male rats were exposed to the same concentrations of *n*-Butyl Alcohol for 7 h per day for 6 weeks, and mated to unexposed females.

On the day of birth (day 0), litters were culled to 4 females and 4 males (±1) and fostered to untreated controls. Offspring were weighed weekly through 5 weeks of age. On postnatal day 10, one female and one male per litter were randomly assigned to one of the four test groups. The animals were tested on days 10 to 90 using ascent on a wiremesh screen; rotorod; open field, photoelectrically monitored activity; running wheel; avoidance conditioning; and operant conditioning.

Additionally, on day 21, brains from 10 offspring per treatment group (1 male and 1 female/litter) were collected and after microwave fixation, were dissected into four general brain regions (cerebrum, cerebellum, brainstem, and midbrain), and analyzed for steady-state levels of protein and the neurotransmitters acetylcholine, dopamine, norepinephrine, serotonin or 5-hydroxytryptamine, substance P, β-endorphin, and met-enkephalin.

Concentrations measured in the exposure chambers approximated the target concentrations of 3000 and 6000 ppm. Mean *n*-Butyl Alcohol concentrations were 3010 (±50) and 6000 (±80) ppm, and results of periodic confirmatory charcoal tube samples were 3000 (±90) and 5960 (±110) ppm, respectively.

Inhalation of these concentrations of *n*-Butyl Alcohol had no effect on pregnancy rate after maternal or paternal exposure. Results from behavioral testing of the offspring indicated that there were no significant effects on the ascent test, rotorod, open field performance, or operant conditioning. In the photoelectric activity monitor, the counts were significantly lower than controls in the female offspring from paternal animals exposed to 3000 ppm *n*-Butyl Alcohol, $F(2, 39) = 6.01$, $p = .01$.

In avoidance conditioning, there were no effects in the animals tested beginning on day 34; in the animals tested beginning on day 60, both the time receiving shock (the escape period; $F(2, 43) = 39.37$, $p < .01$) and the total number of times the rats crossed one side of the cage to the other (escape and avoidance responses plus random side changes during session; $F(2, 43) = 8.58$, $p < .01$) were elevated from controls in the offspring whose male parent was exposed to 6000 ppm *n*-Butyl Alcohol. At 3000 ppm *n*-Butyl Alcohol, the older male offspring from the paternal exposure group required fewer trials to reach criterion in avoidance conditioning, $F(2, 38) = 6.81$, $p < .01$, than the other groups.

Neurochemical analysis revealed few differences in offspring from exposure and control groups (4 out of 64 [32 measures

times the two exposure groups]), and no treatment-related patterns were discernible. The multivariate analysis of variance for the main effect of group at the higher concentration of *n*-Butyl Alcohol was significant, $F(6, 16) = 4.11$, $p < .045$, but for the lower concentration it was not, $F(6, 16) = 2.63$, $p = .12$.

At the high concentration, the significant analysis of variance, which tested for significant differences between means, were determined for serotonin (the overall mean ± *SEM* from offspring of paternal exposure was 14.48 ± 2.38 versus the control value of 7.802 ± 1.48, $p < .005$, with both brainstem and midbrain means being over twice as high as the control level) and dopamine (the overall mean ± *SEM* from offspring of paternal exposure was 0.715 ± 0.127 versus the control value of 0.515 ± 0.095, $p < 0.046$, with all brain regions being 20% to 40% higher than controls). For norepinephrine and met-enkephalin, the individual comparisons of offspring from maternal or paternal groups were not significant.

Overall, the authors concluded there were few behavioral or neurochemical alterations detected in the offspring following maternal or paternal exposure to either 3000 or 6000 ppm *n*-Butyl Alcohol (Nelson et al. 1989b).

Barilyak et al. (1991) compared embryotoxic effects of methyl alcohol, ethyl alcohol, *n*-Butyl Alcohol, nonanol, and decanol (alcohols with increasing chain length) using rats, as well as the activity of alcohol dehydrogenase in rat hepatocytes. The experiment was performed on random bred white rats weighing 160 to 180 g. Alcohols as 40% water solutions were administered by gavage in a volume of 1 ml from days 1 to 15 of pregnancy; water was used as the control. The day when spermatozoa were found after mating was considered to be day 1 of pregnancy.

The rats were killed by cervical dislocation on day 20 of pregnancy. Following laparotomy, the number of yellow bodies was counted in the ovaries and the numbers of dead and live fetuses were counted in the uterus. The live (normal and abnormal) fetuses were examined; in some embryos (one to two from each female) the liver was excised and the activity of alcohol dehydrogenase (ADH) (EC 1.1.1.1) was determined. Protein was determined by the xanthoprotein reaction. To track changes in the ADH activity in embryonic hepatocytes, these measurements were carried out in fetuses from day 16 until day 21 of antenatal development, as well as on days 1, 3, and 20 of postnatal life. There were 534 live fetuses obtained from these rats, including 194 in the control. Historical control data also were provided.

All tested alcohols produced embryotoxicity as shown in Table 4. Fetal death at both the preimplantation and postimplantation stages were noted. The fertility index was reduced compared to the control. The authors suggested that the embryotoxic effect decreased with increasing alcohol chain length.

The ADH activity was maximal in 20-day-old embryos, but 16.4% lower than that of intact rats and 84.5% lower than in pregnant rats. In the newborn rats, the ADH activity increased by day 20 of postnatal life and was 35.2% greater than in intact rats, but remained 74.8% lower than in pregnant rats. Following administration of monoatomic alcohols to pregnant rats, the ADH activity decreased in the liver of 20 day old embryos. Methyl alcohol decreased the ADH activity by 52.2%, ethyl alcohol by 38%, butyl alcohol by 77.6%, nonanol by 17.2%, and decanol by 69.6% (Barilyak et al. 1991).

Sitarek et al. (1994) assessed the effect of *n*-Butyl Alcohol on the sexual cycle and fertility of female rats and on the development of their offspring. Female rats, approximately 10 weeks old (180 to 200 g), that had never given birth were used. Three treatment groups consisting of 11 to 17 females were given aqueous solutions containing 0.24%, 0.8%, and 4% *n*-Butyl Alcohol (0.3, 1.0, and 5.0 g/kg/day, respectively) for 8 weeks before and during gestation. The 16 control animals were given tap water. The experiment was divided into two stages: (1) assessment of estrus cycle and (2) effect on fertility and fetal development.

Vaginal smears to determine the estrus cycle were taken daily between 8 and 10 AM in all animals for 14 consecutive days prior to exposure, and then during the 4th, 5th, 7th, and 8th weeks of exposure. Eight weeks following treatment, all the females were mated with untreated 17-week-old male rats for a maximum of 3 weeks. The day of detection of spermatozoa in the vaginal smears was considered to be day 0 of gestation. Administration of *n*-Butyl Alcohol was continued throughout the mating and gestation period. The overall behavior of the animals was observed throughout the experiment. Weight increases and the daily food, water, or *n*-Butyl Alcohol solutions intake were monitored every week in the nonpregnant females and on days 3, 7, 10, and 17 of gestation in the pregnant animals. On day 20 of gestation, the female rats were killed.

Table 5 summarizes the findings on the effect of *n*-Butyl Alcohol on pregnant and fetal development in rats. Overall, the appearance and behavior, body weight gain, and food and liquid intake of the animals exposed to *n*-Butyl Alcohol given in drinking water during the 8 weeks were similar to that observed in the control animals. There were no mortalities in either group. There was a similar cycle duration of 4 days on average in the control rats and exposed female rats.

The duration of the individual stages of the estrus cycle was not dependent on exposure to *n*-Butyl Alcohol and was similar to that observed in the control animals. Body weight gain during gestation, food and liquid (water or *n*-Butyl Alcohol solutions) intake, absolute and relative organ weights, hemoglobin concentration, and hematocrit values did not differ between the exposed and control groups.

n-Butyl Alcohol given to the female rats in drinking water during the 8 weeks prior to fertilization and until day 20 of gestation did not adversely affect fetal body weight. The intrauterine mortality in the controls, which were given tap water, was similar to that in the animals exposed to *n*-Butyl Alcohol at 0.3 to 5.0 g/kg daily doses. Fetuses of the animals receiving *n*-Butyl Alcohol at a dose concentration of 5.0 g/kg were significantly smaller than those of the control animals.

TABLE 4
Embryotoxic effects of alcohols administered to rats (Barilyak et al. 1991).

Alcohol	Rats per group	Number of yellow bodies	Number of implantations	Death of fetuses, %[a]			Number of live fetuses	Index of fertility
				Before implantation	After implantation	Total		
Methanol (C_1)	11	111	74	33.5 ± 4.5	25.7 ± 5.1	50.4 ± 4.7	55	5.0
Ethanol (C_2)	16	163	114	29.4 ± 3.5	39.5 ± 4.6	57.1 ± 3.9	70	4.4
n-Butyl Alcohol (C_4)	10	106	83	21.7 ± 4.0	21.7 ± 4.4	38.7 ± 4.7	65	6.5
Nonanol (C_9)	10	101	88	12.9 ± 3.3	25.0 ± 4.6	34.6 ± 4.7	76	7.6
Decanol (C_{10})	10	106	90	15.1 ± 3.5	17.8 ± 4.0	30.2 ± 4.4	74	7.4
Control	20	207	203	2.0 ± 1.0	4.4 ± 1.4	6.3 ± 1.7	194	9.7
Historical Controls	362	3684	3668	5.6 ± 0.4	5.2 ± 0.4	10.5 ± 0.5	3476	9.6

[a]All indices of the embryotoxic activity in the experimental groups are reliably higher than in the control ($p < .001$). C_{1-10}, number of carbon atoms in the alcohol molecules.

TABLE 5
Effect of *n*-Butyl Alcohol on fetal development in rats (Sitarek et al. 1994).

Parameter	Findings			
		n-Butyl Alcohol dose (g/kg/day)		
	Control	0.3	1.0	5.0
Females examined	16	17	17	11
Females inseminated	16	16	15	11
Females pregnant	12	14	12	9
Females not pregnant	4	2	3	2
Live fetuses per litter[a]	10.5 ± 3.1	11.0 ± 1.4	12.2 ± 1.9	11.3 ± 2.2
Litters with resorptions	12	9	7	9
Litters with early resorptions	10	9	7	9
Litters with late resorptions	5	2	3	2
Early resorptions per litter[a]	0.8 ± 0.4	1.1 ± 1.0	1.2 ± 1.5	1.8 ± 1.3
Late resorptions per litter[a]	0.7 ± 1.2	0.1 ± 0.4	0.3 ± 0.5	0.2 ± 0.4
Corpora lutea[a]	14.8 ± 2.6	14.6 ± 1.8	14.5 ± 2.1	15.1 ± 2.6
Total implants[a]	12.0 ± 3.2	12.3 ± 2.1	13.6 ± 2.0	13.3 ± 2.3
Preimplantation losses[a]	2.8 ± 2.1	2.4 ± 0.9	1.5 ± 1.6	2.0 ± 1.9
Postimplantation losses[a]	1.5 ± 1.2	1.3 ± 1.3	1.4 ± 1.8	2.0 ± 1.6
Mean daily food intake (g)[b]	21.2 ± 5.4	19.4 ± 4.6	19.4 ± 3.4	18.8 ± 1.5
Mean daily water intake (ml)[b]	30.3 ± 7.9	30.5 ± 6.9	35.1 ± 9.3	27.7 ± 4.2
Body weight gain of dams (g)[a]	89.6 ± 18.9	90.0 ± 18.5	94.3 ± 16.9	93.9 ± 12.7
Fetal body weight (g)[c]	3.2 ± 0.2	3.2 ± 0.3	3.2 ± 0.2	3.2 ± 0.3
Fetal crown-rump length (cm)[c]	4.0 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.8 ± 0.1[d]
Placental weight (g)[c]	0.55 ± 0.07	0.48 ± 0.07	0.53 ± 0.05	0.60 ± 0.13

[a]Mean ± *SD*.
[b]Total mean ± *SD* calculated through 20 days of gestation.
[c]Mean of litter mean ± *SD*.
[d]Significantly different from control ($p < .05$).

TABLE 6
Skeletal and visceral effects in fetuses of female rats exposed to *n*-Butyl Alcohol (Sitarek et al. 1994).

	Findings			
		n-Butyl Alcohol dose (g/kg/day)		
Parameter	Control	0.3	1.0	5.0
Visceral observations				
No. of fetuses (litters) examined	61 (12)	73 (14)	71 (12)	51 (9)
Percentage of fetuses (litters) with dilation of	2 (8)	25[a](64)[a]	32[a](83)[a]	41[a](100)[a]
Subarachnoid space	0	3 (14)[a]	10[a](25)[a]	20[a] (78)[a]
Lateral ventricle and/ or third ventricle of the brain	2 (8)	23[a] (57)[a]	17[a](67)[a]	25[a] (78)[a]
Unilateral renal pelvis	0	0	7[a] (42)[a]	0
Bilateral renal pelvis	0	0	4 (25)[a]	0
Percentage of fetuses (litters) with congenital defects	0	0	7[a] (33)[a]	4 (22)[a]
External hydrocephalus	0	0	3[a] (17)[a]	0
Internal hydrocephalus	0	0	7[a] (25)[a]	4 (22)[a]
Skeletal observations				
No. of fetuses (litters) examined:	65 (2)	81 (14)	75 (12)	51 (9)
Percentage of fetuses (litters) with delayed ossification:	15 (67)	16 (50)	24 (58)	33[a] (67)
Percentage of fetuses (litters) with congenital defect	0	1 (7)[a]	0	2 (11)[a]
14th rib (L_1)	0	0	0	2 (11)[a]
Wavy ribs	0	1 (7)[a]	0	0

[a]Significantly different from the control ($p < .05$).

Table 6 summarizes the skeletal and visceral effects in fetuses of pregnant rats exposed to *n*-Butyl Alcohol, including a dilation of subarachnoid space, cerebral ventricles, and renal pelvis, and a retarded ossification of the sternum. The authors noted that these changes existed only in the animals exposed to high *n*-Butyl Alcohol doses.

When *n*-Butyl Alcohol was given to female rats before fertilization and during gestation at daily doses of 0.3 to 0.5 g/kg body weight, developmental anomalies in the fetal skeleton and central nervous system defects were observed. Internal hydrocephalus was the anomaly most frequently found in the fetuses of female rats exposed to *n*-Butyl Alcohol.

n-Butyl Alcohol given to female rats before fertilization and during gestation at daily doses of 0.3 to 5.0 g/kg body weight resulted in developmental anomalies in the fetal skeleton, including wavy rib in the 13th rib pair and the presence of an extra rib in the 14th pair and central nervous system defects. Internal hydrocephalus was the most frequent anomaly observed in the fetuses of treated female rats. Other changes include a dilation of subarachnoid space, cerebral ventricles, and renal pelvis, and a retarded ossification of the sternum. According to these authors, *n*-Butyl Alcohol administered to female rats at high doses of 1 and 5.0 mg/kg/day is considered to be a fetotoxic agent (Sitarek et al. 1994).

Ema et al. (2004) reported on a developmental toxicity study using Crj:CD (SD) rats. *n*-Butyl Alcohol used in this study was 99.9% pure and a special grade reagent (lot no. CER 65688; Wako Pure Chemical Industries, Ltd., Osaka, Japan). Healthy male rats at 10 weeks of age and virgin female rats at 9 weeks of age were mated overnight. The day when sperm were detected in the vaginal smear was considered to be day 0 of pregnancy. Pregnant rats weighed 217 to 273 g and were 10 to 11 weeks of age when they were distributed into four groups of 20 rats each and housed individually. On days 0 to 20 of pregnancy, rats were given drinking water containing *n*-Butyl Alcohol at concentrations of 0%, 0.2%, 1.0%, or 5.0% (0, 316, 1454, or 5654 mg/kg/day). The dosage levels were determined based on the results of a range-finding study. Maternal body weight and water consumption were observed and recorded every 3 or 4 days.

All females of every group became pregnant and there was no death found in female rats of any group. At the highest dose level, significant decrease in maternal body weight accompanied by reduced food and water consumption was found; fetal weight was lowered; and there was an increase in the incidence of fetuses with skeletal variations and decreased degree of ossification. Maternal toxicity is described in Table 7.

However, there was no increase in the incidence of fetuses with external, skeletal, and internal abnormalities at any dose level, and there was no significant increase in the incidence of preimplantation and postimplantation embryonic loss at any dose level. Reproductive findings are described in Table 8. The authors concluded that *n*-Butyl Alcohol is a developmental

TABLE 7
Maternal toxicity in rats given *n*-Butyl Alcohol on days 0 to 20 of pregnancy (Ema et al. 2005).

Parameter	Dose (%)			
	0 (control)	0.2	1.0	5.0
No. of rats	20	20	20	20
No. of pregnant rats	20	20	20	20
No. of dead rats	0	0	0	0
Initial body weight	245 ± 14	247 ± 13	245 ± 11	244 ± 12
Body weight gain during pregnancy (g)[a]				
Days 0–7	44 ± 7	45 ± 7	40 ± 6	20 ± 28[c]
Days 7–14	40 ± 6	41 ± 5	41 ± 7	42 ± 10
Days 14–20	78 ± 14	82 ± 8	84 ± 7	75 ± 11
Days 0–20	162 ± 19	168 ± 16	165 ± 15	146 ± 16[c]
Food consumption during pregnancy (g)[a]				
Days 0–7	179 ± 12	180 ± 16	164 ± 12[b]	138 ± 21[c]
Days 7–14	40 ± 6	41 ± 5	41 ± 7	42 ± 10
Days 14–20	78 ± 14	82 ± 8	84 ± 7	75 ± 11
Days 0–20	162 ± 19	168 ± 16	165 ± 15	146 ± 16[c]
Water consumption during pregnancy (ml)[a]				
Days 0–7	284 ± 28	305 ± 37	258 ± 29[b]	175 ± 34[c]
Days 7–14	318 ± 35	337 ± 48	299 ± 40	239 ± 80[c]
Days 14–20	328 ± 47	342 ± 47	334 ± 46	256 ± 85[c]
Days 0–20	930 ± 105	983 ± 126	890 ± 106	669 ± 182[c]

[a]Values are given as the mean ± *SD*.
[b]Significantly different from the control, $p < .05$.
[c]Significantly different from the control, $p < .01$.

toxicant only at maternally toxic doses. Based on the significant decreases in maternal body weight gain and fetal weight, authors reported no observed adverse effect levels (NOAELs) of *n*-Butyl Alcohol for both dams and fetuses are 1.0% (1454 mg/kg/day) in rats (Ema et al. 1994).

GENOTOXICITY

Elder (1987) reported that *n*-Butyl Alcohol was found to be nonmutagenic in the *Salmonella/* mammalian-microsome mutagenicity test. A 15% aqueous *n*-Butyl Alcohol solution did not induce sister chromatid exchanges or chromosome breakage in the "chick embryo cytogenetic test." Treatment of Chinese hamster ovary cells for 7 days with 0.1% *n*-Butyl Alcohol (*v*/*v*) resulted in no increase in the number of sister-chromatid exchanges observed per mitosis. *n*-Butyl Alcohol did not induce micronuclei formation in V79 Chinese hamster ovary cells.

Muller et al. (1993) reported on *Salmonella typhimurium* TA102 as a screen for mutagenicity of 30 chemical compounds of various chemical classes, performed in three laboratories. Aromatic amines often produce poor results in standard Ames tests. *n*-Butyl Alcohol was not mutagenic in any of the tests.

Engelhardt et al. (1998) examined chromosome-damage and damage of the mitotic apparatus in NMRI mice after a single oral administration of *n*-Butyl Alcohol using the micronucleus test method. The mice had mean weights of 26.9 g (with an age range of about 5 to 8 weeks). Olive oil was chosen as the vehicle because of the limited solubility of *n*-Butyl Alcohol in water. The test substance was dissolved in oil and administered once orally to male and female animals at dose levels of 500, 1000, and 2000 mg/kg body weight in a concentration of 10 ml/kg body weight in each case.

As a negative control, both male and female mice were orally administered just olive oil. Control frequencies of micronucleated polychromatic erythrocytes were within the historical control range. Both positive control chemicals (cyclophosphamide for chromosome aberrations and vincristine for mitotic spindle effects) led to the expected increase in the rate of polychromatic erythrocytes containing small or large micronuclei.

n-Butyl Alcohol did not lead to any increase in the rate of micronuclei. Animals that were given the vehicle or the positive control substances (cyclophosphamide or vincristine) did not show any clinical signs of toxicity, but there were signs of toxicity in the highest *n*-Butyl Alcohol dose group, including irregular respiration, abdominal position, piloerection and squatting posture after about 30 to 60 min; the general state of the animals was poor. Piloerection had been observed in the 1000 mg/kg dose group as well.

TABLE 8
Reproductive Findings in Rats Given *n*- Butyl Alcohol on Days 0–20 of Pregnancy (Ema et al. 2005).

Parameter	Dose (%)			
	0 (control)	0.2	1.0	5.0
No. of litters	20	20	20	20
No. of litters totally resorbed	0	0	0	0
No. of corpora lutea per litter[a]	16.4 ± 3.6	16.7 ± 3.0[d]	16.1 ± 2.1	16.3 ± 2.6
No. of implantations per litter[a]	14.3 ± 2.8	15.1 ± 1.7	15.2 ± 1.2	14.7 ± 2.5
% preimplantation loss per litter[b]	9.0	9.0[d]	4.4	9.2
% postimplantation loss per litter[c]	6.0	5.4	3.7	8.0
No. of live fetuses per litter[a]	13.4 ± 2.6	14.3 ± 1.4	14.7 ± 1.5	13.5 ± 2.5
Sex ratio of live fetuses (male/female)	128/139	145/140	149/144	131/139
Body weight of live fetuses (g)[a]				
Male	4.18 ± 0.27	4.00± 0.24	4.04 ± 0.25	3.83 ± 0.18[e]
Female	3.97± 0.25	3.86 ± 0.20	3.83 ± 0.16	3.59 ± 0.17[e]
Fetal crown-rump length (mm)[a]				
Male	40.5 ±1.2	40.3 ± 1.4	40.2 ± 1.2	39.7 ± 1.3
Female	39.4 ± 1.2	39.4 ± 1.2	39.3 ± 1.1	38.5 ± 1.4
Placental weight (g)				
Male	0.50 ± 0.05	0.49 ± 0.05	0.48 ± 0.06	0.50 ± 0.06
Female	0.49 ± 0.05	0.48 ± 0.05	0.47 ± 0.05	0.49 ± 0.06

[a] Values are given as the mean ± *SD*.
[b] (No. of preimplantation embryonic loss/no. of corpora lutea) × 100.
[c] (No. of resorptions and dead fetuses/no. implantations) × 100.
[d] Value was obtained from 19 pregnant rats.
[e] Significantly different from the control, $p < .01$.

The authors concluded that the single oral administration of *n*-Butyl Alcohol did not lead to any increase in the number of polychromatic erythrocytes containing either small or large micronuclei, and no inhibition of erythropoiesis determined from the ratio of polychromatic to normochromatic erythrocytes was detected (Engelhardt et al. 1998).

CLINICAL ASSESSMENT OF SAFETY

According to Elder (1987), 105 dermatological patients were tested with *n*-Butyl Alcohol using a chamber test on the upper back for non-immunological contact urticaria. No redness was observed in any patient, but four patients were positive for edema.

A nail color containing 3% *n*-Butyl Alcohol was studied in repeat-insult patch tests (RIPTs). In one study, 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; this finding, however, was not attributed to *n*-Butyl Alcohol exposure. In a second study of 173 female and 37 male subjects, no clinical response was noted at challenge. In the third study, a moderately intense erythema was observed at the second challenge in 115 female and 41 male subjects. Overall, the nail color was not considered to be a significant irritant or sensitizer.

Two additional RIPTs were performed using a nail enamel containing 3% *n*-Butyl Alcohol. In the first, a strong, infiltrated erythema and accompanying vesicles were noted at challenge in 182 female and 34 male subjects, but on further testing, the positive reaction was attributed to residual solvent (not *n*-Butyl Alcohol "solvent"). In the other study, only a faint erythema was noted in 144 female and 59 male subjects during induction. Overall, the nail enamel was not considered to be a significant irritant or sensitizer.

A photopatch test was conducted with the nail enamel containing 3.0% *n*-Butyl Alcohol in 30 subjects. No reactions were observed in any of the subjects. Under these test conditions, the nail enamel product was not considered a phototoxin and photoallergen (Elder 1987).

Nasal Irritation

Wysocki et al. (1996) examined the odor and irritation thresholds for *n*-Butyl Alcohol in 64 human subjects (49 females). The average age of the subjects was 37.5 years with an age range from 25 to 65. A total of 36 subjects were smokers. The study consisted of two experiments: (1) olfactory and chemesthetic sensitivities to *n*-Butyl Alcohol were evaluated in 32 acetone-exposed workers in a cellulose acetate production facility and (2) 32 nonexposed residents from the Philadelphia metropolitan

area. One individual (36-year-old female) withdrew from the study after completing the olfactory thresholds, which remained in the data set. Quantitative and qualitative measurements were performed.

Analytical grade *n*-Butyl Alcohol (99.8% pure) was used in this study. Mineral oil served as the diluent. The *n*-Butyl Alcohol was diluted in a tertiary series (each step was 33.3% as concentrated as the previous) from neat. The dilution series was made up of 26 steps ranging from 100% to 1.1802×10^{-10}% v/v. Direct measurements of vapor-phase concentrations were made. Immediately after completion of detection trials, intranasal irritation thresholds were obtained by using a similar, two-alternative, forced-choice, modified, staircase method. Unlike the detection trials, each irritation trial required that subjects sniff only from a single pair of bottles; one bottle was a blank and the other contained either acetone or *n*-Butyl Alcohol.

Results of the threshold tests indicated that the median olfactory detection threshold for *n*-Butyl Alcohol was 0.17 ppm, significantly lower than the lateralization threshold of 2400 ppm. The average overall rated intensity increased with increasing concentrations of *n*-Butyl Alcohol. Responses to the categorical probes differed between acetone-exposed factory workers and nonexposed Philadelphia residents. Individuals in the two study groups experienced different perceptions of irritation at a concentration of *n*-Butyl Alcohol that was below the individual's irritation threshold but well above the individual's detection threshold. Overall, factory workers treated *n*-Butyl Alcohol as a non-irritating odorant, whereas the non–acetone-exposed population ascribed irritating properties to *n*-Butyl Alcohol.

These authors extended this work by performing the sensitivity portion of the testing on a group of 142 individuals ranging in age from 20 to 89 years of age to determine the effects of age. Each decade of age included at least 10 males and 10 females. The results indicated a reduced olfactory sensitivity to *n*-Butyl Alcohol and a reduction in intranasal chemesthesis with age (Wysocki et al.1996).

Cometto-Muniz et al. (1998) reported a study of homologous alcohols of increasing chain length to track sensitivity for human nasal irritation using a detection procedure that required the subject to indicate whether a vapor has stimulated the right or left nostril. An anosmic group (having an impaired sense of smell) comprised five subjects: three men and two women. The normosmic group (normal sense of smell) comprised four subjects: three men and one woman. The homologous n-alcohols tested included 1-propanol, *n*-Butyl Alcohol, 1-hexanol, and 1-octanol.

Odor, nasal pungency, and eye irritation thresholds were measured using the two-alternative, forced-choice procedure with an ascending-concentration method of limits. The method required the participant to choose the stronger odor (odor, nasal pungency, or eye irritation) of the two stimuli. One stimulus was a blank, i.e., diluent, and the other was a certain dilution step in a series. Testing began with the highest dilution step (i.e., the lowest concentration) and progressed to stronger levels whenever the subject chose incorrectly. The first step chosen correctly five times in a row was taken as the threshold.

The two-alternative forced-choice procedure with presentation of progressively higher concentrations was also used to measure thresholds for nasal localization in normosmics and anosmics. Five correct choices in a row for a given nostril was the criterion for the localization threshold.

The results indicated that the nasal pungency, the odor detection, nasal localization and ocular irritation thresholds decreased as chain length increased. Within the limits of resolution, the authors stated that detection thresholds and nasal localization thresholds yielded comparable indices of the potency of the volatile organic compounds to evoke nasal irritation (Cometto-Muniz et al. 1998).

Ocular Irritation

Hempel-Jorgenson (1999) reported the time course of sensory eye irritation in humans exposed to *n*-Butyl Alcohol and 1-octene. There were a total of 16 participants in the study (7 males, 9 females). All were healthy, did not wear contact lenses, and had not smoked for more than 6 months. The participants were all told not to wear any cosmetics on the days of the study.

The subjects were randomly exposed to *n*-Butyl Alcohol or 1-octene. The average ages of the groups exposed to *n*-Butyl Alcohol and 1-octene were 31.9 ± 16.3 and 33.5 ± 19.1 years, respectively. Target concentrations for *n*-Butyl Alcohol were 300, 950, and 3000 ppm. Measured values were 363 ± 26, 1033 ± 20, and 2731 ± 213 ppm. The authors concluded that the threshold for irritation was clearly exceeded for 1-octene exposures, but not *n*-Butyl Alcohol (Hempel-Jorgenson 1999).

Audiologic Impairment

Velazquez et al. (1969) reported audiologic impairment in workers in a small, noisy cellulose acetate ribbon factory, where *n*-Butyl Alcohol was the only solvent used. Twenty-three of the 47 individuals exposed to intense factory noise had audiologic impairment and the magnitude of the impairment was directly related to exposure duration. Nine of 11 individuals exposed to both noise and *n*-Butyl Alcohol had audiologic impairment and the magnitude of the impairment also was directly related to exposure duration. Absent any explanation of the high proportion of individuals with audiologic impairment among workers exposed to both noise and *n*-Butyl Alcohol, the authors hypothesized that *n*-Butyl Alcohol may be an etiologic agent.

In an unpublished review of this study, Royster (1993) was critical of these findings, noting among other factors that noise induced hearing loss is not seen in direct relationship to exposure time, but rather is more pronounced in the first 10 years of a working lifetime and incrementally changes less over the remainder of an individual's working lifetime.

Occupational Exposure

Elder (1987) reported that workers who used *n*-Butyl Alcohol alone or in combination with other solvents at six plants complained of ocular irritation, disagreeable odor, slight headache and vertigo, slight irritation of nose and throat, and dermatitis of the fingers and hands, when the air concentration of *n*-Butyl Alcohol was greater than 50 ppm. At several plants, the use of *n*-Butyl Alcohol was discontinued and the complaints ceased.

Corneal lesions have been described in workers exposed to *n*-Butyl Alcohol and diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) and denatured alcohol. Some workers complained of ocular irritation, foreign body sensation, epiphora, and burning of the eyes. Blurring of vision, itching and swelling of lids, and redness of the eyes were described less often.

A 10-year study was conducted on men exposed to *n*-Butyl Alcohol vapors in an industrial setting. An initial group of 16 workers was increased to 100. The initial 200 ppm *n*-Butyl Alcohol vapor concentration in the breathing zone was reduced so that the mean value for most of the 10 years was 10 ppm. No eye injuries or symptoms were observed in workers exposed to levels up to 100 ppm. Complaints were rare. There was only one transfer among several hundred workers; this single person disliked the odor of *n*-Butyl Alcohol. At 200 ppm, some workers described transient corneal inflammation with associated burning feeling, lacrimation, and photophobia. No systemic effects were observed (Elder 1987).

Exposure Limits

The American Conference of Governmental Industrial Hygienists (ACGIH 2007) gives a time-weighted average (TWA) allowable as 20 ppm for *n*-Butyl Alcohol stating that this concentration should not be exceeded even instantaneously. NIOSH (2007) gives a ceiling exposure of 50 ppm and lists OSHA's permitted exposure level (PEL) as a TWA of 100 ppm.

According to the European Agency for the Evaluation of Medicinal Products (EAEMP), *n*-Butyl Alcohol may be considered to be less toxic and of lower risk to human health than other solvents. Although there are no long-term toxicity or carcinogenicity studies for many of the solvents considered to have low toxic potential, many of the available data show that they are less toxic in acute or short-term studies and negative in genotoxicity studies. This source states that exposure to residual amounts of *n*-Butyl Alcohol of 50 mg/day or less (5000 ppm or 0.5%) would be acceptable (EAEMP 1997).

SUMMARY

n-Butyl Alcohol is a primary aliphatic alcohol generally used as a solvent in cosmetics. In 1981, *n*-Butyl Alcohol was reported as an ingredient in 112 cosmetic formulations at concentrations ranging from ≤0.1% to 10% only in nail care products, but new concentration of use data indicate that *n*-Butyl Alcohol is also being used at low concentrations in eye makeup, personal hygiene, and shaving products. The highest current reported concentration for 2005 is 4% in nail polish and enamel products; outside of this category, the highest use concentration is 0.002% in makeup foundations.

n-Butyl Alcohol has been generally recognized as safe for use as a flavoring substance in food and appears on the 1982 FDA list of inactive ingredients for approved prescription drug products.

n-Butyl Alcohol can be absorbed through the skin, lungs, and the gastrointestinal tract. Dogs given intravenous *n*-Butyl Alcohol 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*-Butyl Alcohol was detected in the breath. It may be formed in vitro by hydrolysis of butyl acetate in the blood. In the blood, *n*-Butyl Alcohol is rapidly oxidized in vivo; it leaves animal blood quickly and oxidation products are undetectable. *n*-Butyl Alcohol is oxidized more rapidly than ethanol, probably due to the high substrate affinity of *n*-Butyl Alcohol to alcohol dehydrogenase. *n*-Butyl Alcohol is a hydroxyl radical scavenger. *n*-Butyl Alcohol can be oxidized nonenzymatically to *n*-butyraldehyde by ascorbic acid.

The single oral dose LD_{50} of *n*-Butyl Alcohol for rats ranged from 0.79 to 4.36 g/kg. The dermal LD_{50} for rabbits was reported as 4.2 g/kg.

Exposure to *n*-Butyl Alcohol can result in intoxication of laboratory animals, restlessness, irritation of mucous membranes, ataxia, prostration, and narcosis. High concentrations of *n*-Butyl Alcohol vapors can be fatal. At 1268 ppm, *n*-Butyl Alcohol caused a 50% decrease in the respiratory rate of mice.

Ocular irritation was observed for *n*-Butyl Alcohol at 0.005 ml of a 40% solution.

Inhalation toxicity studies in humans demonstrate sensory irritation of the upper respiratory tract, but only at levels above 3000 mg/m^3. Animal studies demonstrate intoxication, restlessness, ataxia, prostration, and narcosis in animals, but exposures of rats to levels up to 4000 ppm failed to produce hearing defects. High concentrations of *n*-Butyl Alcohol vapors can be fatal. Laboratory animals have been reported to adapt to low concentrations of *n*-Butyl Alcohol vapors during chronic exposure.

The behavioral no-effect dose for *n*-Butyl Alcohol injected s.c. was 120 mg/kg.

Fetotoxicity has been demonstrated, but only at maternally toxic levels (1000 mg/kg). No significant behavioral or neurochemical effects were seen in offspring following either maternal or paternal exposure to 3000 or 6000 ppm.

n-Butyl Alcohol was not mutagenic in Ames tests, did not induce sister-chromatid exchange or chromosome breakage in chick embryos or Chinese hamster ovary cells, did not induce micronuclei formation in V79 Chinese hamster cells, did not have any chromosome-damaging effects in a mouse micronucleus test, and did not impair chromosome distribution in the course of mitosis.

Clinical testing of *n*-Butyl Alcohol for nonimmunological contact urticaria were negative in 105 subjects. RIPT studies of

nail colors and enamels containing 3% *n*-Butyl Alcohol in one study produced reactions on challenge, but further study linked significant positive reactions to another solvent. In other RIPT studies, only minimal reactions were reported. A photopatch test demonstrated that a nail enamel containing 3% *n*-Butyl Alcohol resulted in no reactions.

Workers complained of ocular irritation (when the air concentration of *n*-Butyl Alcohol 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*-Butyl Alcohol was discontinued, and the complaints ceased. One study of workers suggested hearing loss may be linked to *n*-Butyl Alcohol exposure, but the methodology may have been flawed.

The ACGIH TWA is 20 ppm, the NIOSH ceiling level is 50 ppm, and the OSHA TWA is 100 ppm.

DISCUSSION

When the CIR Expert Panel previously reviewed the safety of *n*-Butyl Alcohol, the only reported uses were in nail care products. The original safety assessment was specific in limiting the conclusion only to the use of *n*-Butyl Alcohol in nail products. Since then, additional cosmetic uses have been reported in bath soaps and detergents, eye makeup, foundations, lipstick, underarm deodorants, and aftershave lotions, all at low concentrations. Of these non-nail uses, the highest use concentration is 0.002% in makeup foundations.

The CIR Expert Panel recognizes that there are data gaps regarding use and concentration of this ingredient. However, the overall information available on the types of products in which this ingredient is used and at what concentration indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

Since the original safety assessment was completed, new safety test data have become available. The Panel noted that new studies including: in vitro inhibition of cell growth, behavioral toxicity and neurotoxicity in rats, inhalation toxicity, ototoxicity in animals, genotoxicity, reproductive and developmental toxicity, and one occupational study of hearing loss. An in vivo study in mice, for example, found no chromosome damage at dose levels up to 2 g/kg.

In reproductive and developmental toxicity studies, *n*-Butyl Alcohol was fetotoxic only at maternally toxic doses (~1 g/kg or higher) and no significant behavioral or neurochemical effects were seen in offspring following either maternal or paternal exposure to 3000 or 6000 ppm. The ototoxicity study failed to demonstrate an adverse effect of *n*-Butyl Alcohol and inhalation toxicity data were consistent with findings in the earlier safety assessment. Likewise, the new genotoxicity data did not suggest any risk, confirming the data in the earlier safety assessment.

The Panel did note that the summary of the original safety assessment describes RIPT studies of nail colors and enamels in such a way to suggest that virtually none of the subjects studied had any reaction. In the text, it is correctly noted that reactions in subjects were seen widely on challenge, but that those reactions were either indicative of a minimal reaction or were subsequently linked to another component of the product tested, not *n*-Butyl Alcohol.

Taken together, neither the original safety assessment data nor the new data suggest any concern about the use of *n*-Butyl Alcohol in nail care products (at concentrations up to 15%) or in other product categories (at concentrations up to 0.002%). Although these other exposure categories do present routes of exposure not found with nail care products, the Panel noted that the uses outside of nail products have been reported at extremely low concentrations. And as noted above, there are no toxicity concerns at these use levels described for the several new uses.

CONCLUSION

The CIR Expert Panel concluded that *n*-Butyl Alcohol is safe as a cosmetic ingredient in the practices of use and concentration as described in this safety assessment.

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