Amended Safety Assessment of Butoxyethanol as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (i.e., by, **November 25, 2025**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

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ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ATP	adenosine trisphosphate
BEI	Biological Exposure Index
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
EC	European Commission
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
G-6-PDH	glucose-6-phosphate dehydrogenase
HET-CAM	hen's eye test-chorioallantoic membrane
HRIPT	human repeated insult patch test
IARC	International Agency for Research on Cancer
IRIS	integrated risk information system
LOAEL	lowest-observed-adverse-effect level
MDA	malondialdehyde
MOE	margin of exposure
MOS	margin of safety
MoCRA	Modernization of Cosmetics Regulation Act
MRI	magnetic resonance imaging
MTT	3-[4,5-dimethylthiazol-2-yl]2,5-diphenyl tetrazolium bromide
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NA	not applicable
NR	not reported
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OH8dG	8-hydroxy-2'-deoxyguanosine
Panel	Expert Panel for Cosmetic Ingredient Safety
RLD	Registration and Listing Data
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCCP	Scientific Committee on Consumer Products
SED	systemic exposure dose
SHE	Syrian hamster embryo
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Butoxyethanol, which is reported to function as a fragrance ingredient, solvent, and viscosity decreasing agent in cosmetic products. The Panel reviewed the available data to determine the safety of this ingredient. The Panel issued an amended report with a revised conclusion stating that the available data are insufficient to make a determination of safety for Butoxyethanol under the intended conditions of use as a cosmetic ingredient.

INTRODUCTION

This assessment reviews the safety of Butoxyethanol as used in cosmetic formulations. According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), Butoxyethanol functions as a fragrance ingredient, solvent, and viscosity decreasing agent in cosmetic products.[1]

In the Cosmetic Ingredient Review (CIR) report published in 1996, on the basis of the animal and clinical data included in the report, the Expert Panel for Cosmetic Ingredient Safety (Panel) concluded that "Butoxyethanol is safe in hair and nail products at concentrations up to 10.0%."[2] Subsequently, at the February 2002 meeting, the Panel discussed the need to reassess safety in cosmetics because of questionable evidence of carcinogenicity (in mice and rats) in a two-year National Toxicology Program (NTP) inhalation carcinogenicity study on Butoxyethanol that was published in 2000. However, the Panel determined that the results were not relevant to humans, and thus reaffirmed this conclusion, as published in 2005.[3]

In June 2024, the Panel determined that this safety assessment should be re-opened for re-evaluation due to reported restrictions by the European Commission (EC) on the use of Butoxyethanol. Excerpts from the summaries of the 1996 report are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized* text.

This report includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted July 2025. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some chemical and toxicological data on Butoxyethanol included in this safety assessment were obtained from robust summaries of data submitted to the European Chemicals Agency (ECHA) by companies as part of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) chemical registration process.[4] Additionally, data were obtained from opinions produced by the Scientific Committee on Consumer Products (SCCP) of the EC.[5] These data summaries are available on the databases for ECHA and the EC, respectively, and when deemed appropriate, information from the summaries has been included in this report.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, Butoxyethanol (CAS No. 111-76-2) is the ether alcohol that conforms to the structure depicted in Figure 1.[1]

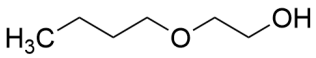

Figure 1. Butoxyethanol

Chemical Properties

Chemical properties for Butoxyethanol are summarized in Table 1. Butoxyethanol is a colorless liquid with a molecular weight of 118.2 g/mol.[2] The log P_{ow} at 25ºC is 0.81.[4]

Method of Manufacture

Butoxyethanol is usually prepared by the reaction of ethylene oxide with butyl alcohol and may also be prepared by the direct alkylation of ethylene glycol with an agent such as dibutyl sulfate. [2] *Another method for the production of Butoxyethanol is the reaction of butyl alcohol with ethylene carbonate or 2-chloroethanol. Butoxyethanol may also be produced through reacting ethylene glycol with butyl bromide.*

Composition and Impurities

Water accounts for not more than 0.2% of the composition of Butoxyethanol.[2] *The purity of technical-grade Butoxyethanol ranges from 98 - 99.5%. Commercial samples of glycol ethers invariably contain small quantities of peroxides. A supplier reported impurities as follows: acidity (0.001 mEq/g), carbonyl (210 - 276 ppm), peroxide (66 - 169 ppm), dioxane (0.35 ppm), ethylene oxide (0.015 ppm), ethylene glycol (0.32%), butanol (420 - 450 ppm), butyraldehyde (210 - 330 ppm), diethylene glycol (100 ppm), butyl carbitol (< 100 ppm), and "heavies" (0.1%).*

The SCCP reported that Butoxyethanol is ≥ 99% pure.[5] Impurities are as follows: 2-butoxyethoxyethanol (≤ 0.3% w/w), ethylene glycol (≤ 0.5% w/w), 1-butanol (≤ 0.2% w/w), and water (< 0.2% w/w). Butylated hydroxytoluene (0.008 - 0.012% w/w) may be added to prevent the formation of peroxides.

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of Butoxyethanol in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption.[6] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to RLD that CIR received in 2024, Butoxyethanol is used in 81 formulations, with 79 uses reported in hair dyes and colors (Table 2).[7] A single use each was reported in perfumes and makeup fixatives. VCRP survey data received in 2023 reported Butoxyethanol was used in 3 hair dyes and colors.[8] When comparing the VCRP data received in 2023 to that received in 2001, the frequencies of use for Butoxyethanol have greatly decreased since the first re-review was considered; in 2001, Butoxyethanol was reported to have 110 uses, with the majority in hair coloring formulations.[3,8] No uses were reported in the concentration of use survey conducted by the Council in 2025.[9] In 2001, the maximum concentration of use range for Butoxyethanol was 3% in leave-on products (that resulted in dermal contact) and 50% in rinse-off products (nail polish and enamel removers).[3] Of note, concentrations of use were not reported for hair coloring products at the time of the first re-review (2001 data).

The RLD reported that this ingredient may be used in cosmetic sprays and powders, and could possibly be inhaled; for example, Butoxyethanol is reported to be used in a perfume (concentration not reported).[7,9] In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Some products containing Butoxyethanol may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available in some instances. None of the reported product categories for Butoxyethanol as listed in the RLD include a designation using airbrush application, so it is possible that this ingredient is used with airbrush delivery systems, but not reported as such. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available when submitted. Nevertheless, no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

In the European Union (EU), Butoxyethanol is categorized in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down.[10] For this ingredient, the regulation states that Butoxyethanol may only be used as a solvent in oxidative hair dye products at up to 4%, a solvent in non-oxidative hair dye products at up to 2%, and must not be used in aerosol dispensers (sprays). The SCCP opinion gives these same restrictions on use in hair dye formulations, as related to direct application to the hair/scalp.[5] The opinion does not include any other cosmetic exposure, such as exposure to other types of cosmetics or possible aerosol/spray products.

Non-Cosmetic

Butoxyethanol is used as an industrial solvent for resins and varnishes, in hydraulic fluids, and in the formulation of floor polishes, floor waxes, and cleaning compositions for leather, upholstery, and glass.[2] *Food-related uses of Butoxyethanol described in the Code of Federal Regulations (CFR) are as follows: component of adhesives (21 CFR 175.105), use in flume water (concentration not to exceed 1 ppm) for washing sugar beets prior to slicing (21 CFR 173.315), defoaming agent used in the manufacture of paper and paperboard (21 CFR 176.210), solvent in polysulfide polymer/ polyepoxy resins for contact with dry food (21 CFR 177.1650), and use in sanitizing solutions (21 CFR 178.1010).*

In addition to the regulations described above, residue of Butoxyethanol is exempted from the requirement of a tolerance when used in accordance with good manufacturing practices as an ingredient in an antimicrobial pesticide formulation, provided it is applied on a semi-permanent or permanent food-contact surface (other than being applied on food packaging) with adequate draining before contact with food (40 CFR 180.940).

TOXICOKINETIC STUDIES

The results of rat and human studies indicated that ^{14}C-Butoxyethanol was percutaneously absorbed and metabolized to butoxyacetic acid, with excretion in urine, after oral, dermal, or inhalation exposure.[2] *The in vitro percutaneous absorption of Butoxyethanol was demonstrated using rat, guinea pig, and human skin samples. When ^{14}C-Butoxyethanol was administered orally to rats, the major route of excretion was via the urine, and butoxyacetic acid was the major urinary metabolite. In one study, an analysis of tissues excised subsequent to oral administration indicated that the greatest specific activity was detected in the thymus, followed by the spleen and liver.*

Dermal Penetration

Dermal penetration studies for Butoxyethanol are summarized in Table 3. In human skin samples, Butoxyethanol absorbed more rapidly through damaged skin than undamaged skin (3.39 mg/cm^2/h vs 1.19 mg/cm^2/h).[5] In solution, a steady state flux of 544 ± 64 nmol·cm^{-2}/h (0.064 mg/cm^2/h) was found with human dermatomed skin.[11] In a study with oxidative hair dye formulations, the dermal absorbance for formulations with 5 and 10% Butoxyethanol was 61 ± 29 µg/cm^2 (12.1 ± 5.9%) and 125 ± 73 µg/cm^2 (12.5 ± 7.3%), respectively.[5] Butoxyethanol penetrated human skin up to 6-fold more rapidly from aqueous solution (50%, 450 mg/ml) than from the neat solvent (900 mg/ml); a corresponding increase in apparent permeability coefficient was observed as Butoxyethanol concentration in water decreased.[12] Permeation rates of Butoxyethanol through unoccluded rat dermatomed skin (16%) were greater than rat whole skin (8%), while absorption through human dermatomed skin (4%) was lower than the rat.[13] Absorption of undiluted Butoxyethanol through occluded rat dermatomed skin in vitro was 18%. This same study found that Butoxyethanol absorption was enhanced by application in methanol to 23%. In a study with full-thickness human skin with undiluted Butoxyethanol, approximately 0.16% of the absorbed Butoxyethanol was metabolized to butoxyacetic acid.[14]

Following topical application of undiluted Butoxyethanol in rats, 28% of the dose was absorbed after 24 h.[13] The major routes of excretion included the urine (19%), expiration as carbon dioxide (6%) and feces (0.4%): little of the dose remained in the carcass (1.3%). In a study with human volunteers exposed to Butoxyethanol vapors (for 8 of the 9 exposures, volunteers wore air-fed half masks to supply clean air), urinalysis results showed that baseline dermal absorption of Butoxyethanol vapor was 11% of the total absorbed dose. [15] Higher temperatures and greater humidity increased dermal absorption. The rate of percutaneous absorption of Butoxyethanol is greater in aqueous solutions than when it is applied neat or diluted in ethanol.[16,17]

Absorption, Distribution, Metabolism, and Excretion

Human

Dermal

Six male volunteers were dermally exposed for 4 h to 50% aq. Butoxyethanol on the arm for 30 min.[18] Butoxyethanol in blood and total and free 2-butoxyacetic acid in the urine were measured. After dermal exposure, 147.1 and 346 mg of free and total 2-butoxyacetic acid, respectively, were excreted in the urine at up to 48 h after exposure. The proportion of conjugated 2-butoxyacetic acid in single urine samples increased after dermal exposure from 45% in the first collection period to 92% after 48 h. The elimination half-life of total 2-butoxyacetic acid following dermal exposure was longer than that of free butoxyacetic acid (5.1 h and 3.8 h, respectively).

Inhalation

Six male volunteers were exposed via inhalation by mouth to 93 mg/m^3 Butoxyethanol for 30 min.[18] Butoxyethanol in blood and total and free 2-butoxyacetic acid in the urine were measured. After exposure, the 24-h cumulative excretion of free and total 2-butoxyacetic acid in urine was 5.5 and 12.8 mg, respectively. The interindividual variation in the cumulative excreted amount after inhalation exposure was higher (49%) for free 2-butoxyacetic acid than for total 2-butoxyacetic acid (31%).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Butoxyethanol was slightly toxic (mean LD_{50} = 0.58 g/kg) when administered dermally to rabbits.[2] *In dermal toxicity studies with rats and guinea pigs, mean LD_{50} values of 2.52 and 0.23 ml/kg, respectively, have been reported. Butoxyethanol was slightly toxic (mean LD_{50} = 2.8 g/kg) in an acute oral toxicity study involving rats. In oral toxicity studies with guinea pigs and rabbits, LD_{50} values of 1.20 and 0.35 g/kg, respectively, have been reported. In acute inhalation toxicity studies, animal mortality rates were related to both the concentration of Butoxyethanol and the duration of exposure.*[2] *In mice, 7- and 32-h exposure to 770 ppm Butoxyethanol caused 12.5 and 81.25% mortality, respectively. Exposures of 7 and 32 h to 1220 ppm Butoxyethanol caused 68.75 and 100% mortality, respectively. At a concentration of 800 ppm Butoxyethanol, none of 6 rats exposed died at 4 h, but 3 animals died at 8 h.*

Additional acute toxicity studies are summarized in Table 4. In dermal studies, the LD_{50} for Butoxyethanol was greater than 2000 mg/kg in rats and guinea pigs.[4,5] The dermal LD_{50} in rabbits ranged from 307 to greater than 2000 mg/kg. The oral LD_{50} for mice was 1519 mg/kg in fasted animals and 2005 mg/kg in fed animals; LD_{50} in rats ranged from 880 to 2100 mg/kg. All rabbits that received 695 or 1500 mg/kg orally died, and the oral LD_{50} for Beagle dogs was greater than 695. In inhalation studies, no deaths were observed in rats that were exposed up to 2.25 mg/l for 3 h, but all rats died after being exposed to 4.25 mg/l for 8 h.[5] In guinea pigs, the LC_{50} was greater than 2.25 mg/l Butoxyethanol following a 4-h exposure.[19] The LC_{50} was less than 2.0 mg/l in rabbits that were exposed to Butoxyethanol for 7 h.[5]

Repeated Dose Toxicity Studies

Rabbits that received 50 or 100% Butoxyethanol topically had necrosis and hemoglobinuria after 9 d of treatment while rabbits that received 5 or 25% Butoxyethanol had erythema and no systemic effects.[2] *In a 13-wk dermal study, rabbits that received up to 42.8% (150 mg/kg) had no test substance-induced adverse effects.*

In mice that received 500 - 2000 mg/kg Butoxyethanol via gavage for 5 wk, reduced erythrocyte counts were observed in the 500 and 1000 mg/kg groups; all mice in the 2000 mg/kg group died. In rats that received 500 or 1000 mg/kg Butoxyethanol in water for 4 d, increases in relative weights of the spleen, liver, and kidneys, reduced thymic weights, and reduction in erythrocyte and leukocyte counts were observed in both treatment groups, in addition to reduced packed cell volume and hemoglobin and increased mean corpuscular volume, reticulocyte counts and mean corpuscular hemoglobin in the high dose group. Similar effects were observed in a 6-wk oral study in rats that received 222, 443, or 885 mg/kg Butoxyethanol undiluted. In a 14-d oral study in mice and rats at up to 650 mg/kg/d Butoxyethanol in drinking water performed by the NTP, no clinical signs of toxicity or test substance-induced gross lesions were observed in mice or rats, and non-significant changes in absolute and relative thymus weights were observed in the rats. However, absolute and relative thymus weights were significantly lower ($p \leq 0.05$) in 400 and 650 mg/kg male mice only. In a 90-d dietary study in rats that received up to 2% (1540 mg/kg/d) Butoxyethanol, the no-observed-effect level (NOEL) was determined to be between 0.125 and 0.5% (76 and 310 mg/kg/d). Liver weight was significantly increased in the 0.5 and 2% groups and kidney weight was increased in the 2% group. In a similar study with Butoxyethanol at up to 1.25% in the diet, rats had a statistically significant reduction in weight gain starting at 0.25% in males and 1.25% in females. In a 13-wk drinking water study in mice and rats at 750 - 6000 ppm Butoxyethanol performed by the NTP, no adverse effects were observed in the mice. However, hematological alterations were noted at doses of 3000 ppm and higher in males and in most dose groups in females, significant changes to thymus weights were observed in male rats starting at 4500 ppm and in female rats starting at 6000 ppm, and histopathologic lesions were seen in the liver, spleen, and bone marrow in rats of both sexes in all dose groups.

Observations made in rats (20 - 500 ppm, 6 - 7 h/d, 5 d/wk) and dogs (~385 ppm, 7 h/d) subjected to repeated inhalations (up to 30 d) of Butoxyethanol included increased erythrocyte fragility, decreased hemoglobin concentration and erythrocyte count, and pathological changes in the kidneys, liver, and lungs. Increased kidney weight was observed in guinea pigs subjected to repeated inhalation of Butoxyethanol concentrations ranging from 203 to 495 ppm 7 h/d, 5 d/wk for 30 d. One of 2 monkeys died prior to the completion of 10 d of exposure to 104 ppm Butoxyethanol for 7h/d with multiple splenic neoplasms. The surviving monkey had its exposure regimen changed to 210 ppm Butoxyethanol for 30 d when no significant hematological alterations were initially observed; after 30 d, erythrocyte count had decreased to a value less than half of the original count and a similar pattern was observed with hemoglobin concentrations. Congestion was observed in the lungs, liver, and kidneys. Mice that inhaled up to 400 ppm 7h/d for 90 d had no significant increases in mortality rates or occurrence of gross lesions, nor were there significant tissue changes at microscopic examination of the kidneys; however, increased erythrocyte fragility was observed. In 90 d studies in rats exposed 6 h/d for 5 d/wk, erythrocyte and hemoglobin counts were decreased significantly at the highest dose level tested (77 ppm) in females; only a decrease in erythrocyte count was observed in males at this dose level. In a 13-wk inhalation study (6 h/d, 5 d/wk) in mice at up to 500 ppm Butoxyethanol performed by the NTP, the hematopoietic NOEL was 62.5 ppm in male and female mice and the histopathological NOEL was 31 ppm for females and 62.5 ppm for males. A similar NTP study performed in rats at the same duration and same concentrations of Butoxyethanol yielded a hematopoietic NOEL of 62.5 ppm in males (no NOEL could be established for females) and a NOEL for hepatic lesions was 62.5 ppm for males and 31 ppm for females. Dogs that inhaled up to 415 ppm Butoxyethanol 7 h/d, 5 d/wk for 12 wk experienced mild irritation during exposure, a maximal decrease in erythrocyte count and hemoglobin concentration which was observed after 4 - 6 wk of exposure, and elevated urea concentrations throughout

the course of exposure starting after 1 wk. Leukocyte counts were increased in dogs that were exposed to 100 ppm Butoxyethanol vapor 7 h/d for 90 d.

Additional repeated-dose toxicity studies are summarized in Table 5. In an oral 6-wk toxicity study in rats that received up to 885 mg/kg/d Butoxyethanol, the no-observed-adverse-effect level (NOAEL) was less than 222 mg/kg/d.[4,5] Significant toxicity was observed at 885 mg/kg/d. Adverse effects observed included changes to red blood cells, splenic congestion, and liver anisokaryosis starting at 222 mg/kg/d. In inhalation studies, no adverse effects were observed in studies in male guinea pigs and male Beagle dogs that were exposed for 7 h/d for 2 wk to approximately 400 - 411 ppm (2.02 mg/l) Butoxyethanol.[5] A no-observed-adverse-effect concentration (NOAEC) could not be established in studies with mice, rats, rabbits, and cats exposed to 537 ppm (2.63 mg/l) Butoxyethanol for 6 h/d for 15 d; a NOAEC was determined to be 537 ppm for guinea pigs following this exposure.[4] In a 90-d inhalation study in rats, the NOAEC was less than 50 ppm for rats exposed to Butoxyethanol 7 h/d for 5 d/wk. Adverse effects included an increase in erythrocyte osmotic fragility and an increase in relative kidney to bodyweight ratio.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In an in vitro study in rat embryos, 100% embryo lethality was induced at Butoxyethanol concentrations greater than 12.5 mM.[2] Dermal applications of Butoxyethanol did not cause embryotoxicity or fetotoxicity in rats that received the test material on gestation days 7 - 16, and there were no significant differences in visceral or skeletal defects.

In oral teratogenicity studies, the only significant finding in mice dosed on gestation days 8 - 14 with Butoxyethanol (up to 2000 mg/kg/d) was a significant difference in the number of resorptions between experimental and control groups. A study was performed to determine the effects to cardiovascular development during critical periods of pregnancy in rats that received 30 to 200 mg/kg/d Butoxyethanol on gestation days 9 - 11 or 30 - 300 mg/kg/d Butoxyethanol on gestation days 11 - 13. Oral administration of Butoxyethanol did not result in any increase in the incidence of fetal malformations, particularly cardiovascular malformations, over that noted in the control group. Embryo/fetal effects included increased resorptions and non-live implants in the 200 mg/kg/d dose group dosed on gestation days 9-11 and a decreased platelet count in the 300 mg/kg/d dose group dosed on gestations days 11-13. Maternal body weights, organ weights, and hematology were altered at the top doses in the different gestation day dose groups. A separate study also analyzed the effects these doses and dosing days (up to 200 mg/kg/d on gestation days 9 - 11 and up to 300 mg/kg/d on gestation days 11 - 13) had on cardiovascular development. Doses $\geq$ 100 mg/kg/d induced maternal toxicity on gestation days 9 - 13. The viability of embryos was markedly reduced at doses of 200 mg/kg on gestation days 9 - 11, but not at 300 mg/kg on gestation days 11 - 13.

In an inhalation teratogenicity study involving rats on gestation days 6 - 15, ventricular septal defects and absent or severely shortened innominate arteries were noted in fetuses; results of fetal skeletal examinations and statistical analyses were not available. The results of other inhalation teratogenicity studies involving rats on gestation days 7 - 15 or 6 - 15 included mixed results regarding significant differences in the number of resorptions. In the latter of these studies, there were no statistically significant increases in the incidence of external, visceral, skeletal, or total malformations. The inhalation of Butoxyethanol in rabbits on gestation days 6 - 18 caused a significant reduction in unossified sternebra 6, rudimentary rib (first lumbar vertebra), and the number of viable implants per litter. However, there were no statistically significant increases in the number of litters with one or more fetuses with external, visceral, skeletal, or total malformations.

Neither oral (up to 2000 mg/kg/d; up to 25 d in male mice and rats) nor inhaled doses (undiluted; up to 4-h duration in male rats) of Butoxyethanol caused testicular atrophy or other testicular effects. A 3-part, 2-generation drinking water study of up to 2% Butoxyethanol in male and female mice resulted in a significant decrease in the number of viable litters at 1 and 2% Butoxyethanol. The study found that Butoxyethanol affected the reproductive capacity of female mice more than that of male mice in the same exposure conditions.

Oral

In a two-generation reproductive toxicity study, male and female CD-1 mice were exposed for a period of 14 wk to 0.5, 1, or 2% (equivalent to 720, 1340 or 2050 mg/kg bw) Butoxyethanol in drinking water.[4,5] Significant adverse reproductive effects were observed in the females at very high dose levels which also caused severe general toxicity, including death (6/20 deaths in the 1340 mg/kg group; 13/20 deaths in the 2050 mg/kg group). An insufficient number of pups from 1340 mg/kg group were available to mate in the F_1 generation, so only pups from the 720 mg/kg dose group were used for the next mating cycle. At 720 mg/kg, the only adverse finding was a marginal, statistically significant reduction in pup weight in the F_1 generation. This reduction was only 3% compared to controls and was not repeated in the F_2 generation, so it was not considered a significant adverse finding. Thus, the conservative lowest-observed-adverse-effect level (LOAEL) was determined to be 720 mg/kg/d. The reproductive NOAEL for Butoxyethanol was determined to be 720 mg/kg/d. A NOAEL for developmental toxicity could not be derived.

The SCCP noted that two NOAELs were identified in a rat study that was reported on in the original CIR safety assessment:[2,5] a fetal NOAEL of 100 mg/kg bw/d and a maternal NOAEL of 30 mg/kg bw/d. The fetal NOAEL was based on increased fetal lethality without malformations observed at 200 mg/kg bw/d. The maternal NOAEL of 30 mg/kg bw/d

was derived from observations of retarded body weight gain and hematological effects (e.g., hemolytic anemia) after a 3-d exposure to 100 mg/kg bw/d.

GENOTOXICITY STUDIES

Butoxyethanol was not mutagenic in the Ames test (up to 10,000 µg/plate)or in point mutation (up to 1%), forward mutation (up to 1%), and chromosomal aberration (up to 5000 µg/ml) assays involving Chinese hamster ovary (CHO) cells.[2] *Butoxyethanol (up to 0.25%) also did not induce sister chromatid exchanges in non-metabolically activated cultures of CHO cells. However, positive and negative results were noted with metabolic activation at 0.0312% only. Butoxyethanol (at up to 0.1% by volume) was weakly mutagenic at 0.0001 and 0.001% in an unscheduled DNA synthesis assay.*

Additional genotoxicity data are summarized in Table 6. In Syrian hamster embryo (SHE) cells, Butoxyethanol (0.5 - 20 mM) did not induce cellular transformation.[20] No increase in DNA damage was observed in a comet assay using SVEC4-10 mouse endothelial cells following exposure of up to 10 mM Butoxyethanol or 10 mM butoxyacetic acid (a metabolite).[21] Genotoxicity was not observed in an in vivo micronucleus induction test in mice at up to 1100 mg/kg Butoxyethanol via intraperitoneal injection or in a *Pig-a* assay in rats at up to 450 mg/kg Butoxyethanol via gavage.[4,22]

CARCINOGENICITY STUDIES

In dermal carcinogenicity studies with rats, a hair dye containing Butoxyethanol (10%) was not carcinogenic, but a rust-preventive product containing Butoxyethanol (2.5%) was carcinogenic.[2] *It should be noted that the latter product contained 90.9% Stoddard solvent (a refined petroleum distillate).*

In 2000, the NTP published the results of 2-yr inhalation studies of Butoxyethanol in male and female B6C3F1 mice and male and female F344/N rats.[23] *The mice were exposed to 0, 62.5, 125, or 250 ppm for 6 h/d, 5 d/wk, for 104 wk, and the rats were exposed to 0, 31.2, 62.5, or 125 ppm for the same time period. In male mice of the 250 ppm group, increased incidences of hemangiosarcoma of the liver, a marginal increase in the incidences of forestomach squamous cell papilloma, and an increase in the incidences of hepatocellular carcinoma were observed. In female mice of the 250 ppm, increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma) were observed. Increased incidences of forestomach neoplasms in the mice occurred in groups in which ulceration and hyperplasia were also present. No evidence of carcinogenic activity from exposure to Butoxyethanol was observed in male rats; however, there was equivocal evidence of carcinogenic activity in female rats exposed to 125 ppm Butoxyethanol based on the increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla. In both species of animals, exposure to Butoxyethanol caused a mild regenerative anemia and effects secondary to the anemia.*

Although forestomach tumors and hemangiosarcomas have been observed in rodent studies with Butoxyethanol, extensive mechanistic evidence indicates that these tumor types are of limited or no relevance to humans. Forestomach tumors arise in a rodent-specific anatomical structure that is absent in humans and are typically linked to local irritation or high-dose bolus exposure via oral gavage, with tumor formation driven by sustained cytotoxicity and regenerative epithelial proliferation rather than a genotoxic mechanism.[24,25] Similarly, hemangiosarcomas induced in mice–often by nongenotoxic agents–are associated with mouse-specific responses such as hemolysis-induced hypoxia, dysregulated erythropoiesis, macrophage activation, and increased angiogenic signaling, a mode of action that lacks biological plausibility in humans.[26-31] The species-specific nature of these mechanisms suggests that tumor findings observed in rodents are of limited relevance to human cancer risk assessment.

Overall, the International Agency for Research on Cancer (IARC) determined that Butoxyethanol is not classifiable as to its carcinogenicity to humans (Group 3).[32] In the evaluation, there was inadequate evidence in humans and limited evidence in experimental animals for carcinogenicity of Butoxyethanol. The US Environmental Protection Agency (EPA) integrated risk information system (IRIS) assessment of Butoxyethanol published in 2005 determined that the human carcinogenicity of this ingredient could not be determined at the time the assessment was performed, but "suggestive evidence" for cancer exists from laboratory animal studies performed on mice and rats by the NTP.[33]

Mechanism

In Vitro

In a study examining the mode of action for Butoxyethanol-induced hemangiosarcomas,.[21] hemolyzed red blood cells activated macrophages, producing a marked induction of tumor necrosis factor (TNF)-α in macrophages. However, neither Butoxyethanol nor butoxyacetic acid (a metabolite) did not directly activate macrophages, as evidenced by a lack of TNF-α production from macrophages. The effect of activated macrophages on endothelial cell DNA damage and DNA synthesis was also studied. Co-culture of endothelial cells with activated macrophages increased endothelial cell DNA damage after 4 or 24 h and increased endothelial cell DNA synthesis after 24 h. These data demonstrate that Butoxyethanol and related metabolites (butoxyacetic acid and butoxyacetaldehyde) do not directly cause DNA damage. Supportive evidence also demonstrated that damaged red blood cells, iron, and/or products from macrophage activation (possibly reactive oxygen species) produce DNA damage in endothelial cells and that activated macrophages stimulate endothelial cell proliferation.

Oral

Gene expression data from the bone marrow, liver, and spleen of B6C3F1 male mice (10 animals per group) exposed via gavage to a single dose (4 h) or 7 daily doses of 900 mg/kg Butoxyethanol in deionized water were used to develop a mechanistic model of hemangiosarcoma.[34] The resulting mechanistic model confirmed previous work proposing that Butoxyethanol induced macrophage activation and inflammation in the liver. In addition, the model supported local tissue hypoxia in the liver and spleen, coupled with increased erythropoietin signaling and erythropoiesis in the spleen and bone marrow, and suppression of mechanisms that contribute to genomic stability, events that could be contributing factors to hemangiosarcoma formation. Finally, an immunohistochemistry method demonstrated that tissue hypoxia was present in the spleen and bone marrow.

OTHER RELEVANT STUDIES

Cytotoxicity

In a study that investigated the effects of Butoxyethanol (0.1 - 25 mM) on cell viability and on the hydrogen peroxide-induced damage in the human neuroblastoma (SH-SY5Y) cells, Butoxyethanol alone did not affect lactate dehydrogenase release and 3-[4,5-dimethylthiazol-2-yl]2,5-diphenyl tetrazolium bromide (MTT) reduction.[35] A concentration-dependently enhanced cytotoxic effect of hydrogen peroxide (0.5 mM) was observed with Butoxyethanol.

Immunotoxicity

Butoxyethanol did not induce immunotoxicity in rats that received a single intravenous injection of trinitrophenyl-lipopolysaccaride followed by 50, 100, 200, or 400 mg/kg Butoxyethanol via gavage for 2 d.[2] *All rats that received 400 mg/kg/d died. A significant reduction ($p < 0.05$) in serum hemagglutination titer was reported at 200 mg/kg/d, but this was probably due to overt toxicity of Butoxyethanol at doses of 200 mg/kg/d and higher. Butoxyethanol in deionized water at up to 506 mg/kg/d (6000 ppm) administered orally to rats for 20 d did not affect antibody production or cause delayed-type hypersensitivity reactions.*

Nephrotoxicity

In studies with rats, Butoxyethanol was nephrotoxic when administered once intravenously (0.034 mg/kg bw in physiological saline).[2] *However, Butoxyethanol was not nephrotoxic when administered 5 times/wk for 2 wk intraperitoneally (0.055 g/kg in olive oil or water).*

Hematotoxicity

Hemolytic effects of Butoxyethanol were observed in a number of in vitro hematotoxicity studies.[2] *At 20 mM Butoxyethanol, a significant increase in packed cell volume and hemolysis was observed in blood samples from rats incubated with the test material. In mice bone marrow cells, the hematopoietic microenvironment was destroyed at doses > 30 mM. Lysis of dog erythrocytes was observed at concentrations of 0.05 - 0.5% Butoxyethanol, but only at concentrations $\geq$ 0.25% in rats, rabbits, and humans. Hematopoietic toxicity was observed in different human cell lines at concentrations ranging from 80 µM to 0.1 M.*

In animal studies, hemolytic effects were observed in rats that received single dermal doses > 200 mg/kg Butoxyethanol.[2] *Increased erythrocyte fragility was observed in rats that received a single oral dose of 10% Butoxyethanol (1.48 g/kg) and in rats that inhaled up to 200 ppm for 9 d, but this effect was not observed in dogs that inhaled up to 665 ppm for 3 d.*

Groups of 4 male and 4 female F344 rats were exposed orally to single daily doses of Butoxyethanol at 250 mg/kg bw for 2, 3, or 4 d.[36] The rats were examined for hemolysis and histopathological evidence of disseminated thrombosis on days 2, 3, 4, and 29 (the latter in an additional group that was dosed for 4 d). Time-course Butoxyethanol-related erythrocytic changes were statistically significant in both sexes. Evidence of thrombosis and infarction was seen mainly in females dosed more than once with widespread thrombotic crisis after 2 or 3 doses, likely explicable by the more significant morphological changes in erythrocytes and hemolysis observed in this gender. Thrombosis and infarction in the heart, brain, lungs, eyes, and bones were observed.

In another study employing similar protocol as above, groups of male and female F344 rats were exposed orally to single daily doses of Butoxyethanol at 250 mg/kg bw for 2, 3, or 4 d.[37] Blood was taken before the rats were killed on days 2, 3, 4, and 29 (the latter in an additional group that was dosed for 4 d). The administration of Butoxyethanol did not affect red blood cells aggregability but markedly enhanced their adherence to extracellular matrix; such enhancement was correlated with adherence to cultured endothelial cells. Red blood cell/endothelial cell interaction has been shown to be a potent catalyst of vascular occlusion in hemolytic hemoglobinopathies; thus, the enhanced red blood cell adherence to endothelial cell is a likely mechanism by which thrombosis and organ infarct are induced in Butoxyethanol-treated rats.

Age and dose-related differences in sensitivity to Butoxyethanol were investigated in groups of five 6- and 12-week-old female F344 rats at 62.5, 125, or 250 mg/kg/d of Butoxyethanol via oral gavage for up to 4 d.[38] The maximum hemolytic response, resulting in decreased erythrocyte count and higher mean cell volume, occurred in the 12-wk-old rats treated with

the 250 mg/kg/d dose of Butoxyethanol. The highest increase in intracellular adhesion molecule-1 levels occurred in the 12-wk-old rats treated with 125 and 250 mg/kg Butoxyethanol. No intravascular thrombi were noted in the 6-wk-old Butoxyethanol-treated animals. The majority of intravascular thrombi occurred in the 12-wk-old rats treated with 250 mg/kg Butoxyethanol.

The nature of hemolytic effects induced by Butoxyethanol was studied by analyzing glucose-6-phosphate dehydrogenase (G-6-PDH) activity, adenosine triphosphate (ATP), pyruvate and thiols levels in peripheral blood of male Wistar rats.[39] In addition, the susceptibility to autoxidation of rat erythrocyte lipids was evaluated. Groups of 5 rats were treated with single doses of 0.625, 1.25, or 5.0 mM/kg Butoxyethanol. Analyses were performed 24 h after dosing. A decrease of ATP level in a dose-dependent manner and an increase in protein- and nonprotein-bound sulfhydryl groups were observed. These results indicate that an acute hemolytic effect of Butoxyethanol is not associated with alterations in G-6-PDH activity and the susceptibility of erythrocyte lipids to autoxidation. Increases in protein- and nonprotein-bound sulfhydryl groups seem to indicate the selective hemolysis of the aged erythrocytes. The increase in pyruvate and thiol levels may protect erythrocytes against the appearance of oxidative stress.

Hepatotoxicity

The hepatic effects of Butoxyethanol were studied in male B6C3F1 mice and male F344 rats.[40] Via daily gavage, the mice received 0, 225, 450, and 900 mg/kg/d and rats received 0, 225, and 450 mg/kg/d, 5 times per wk. Following treatment for up to 90 d, hematocrit was measured from blood collected by cardiac puncture and DNA synthesis, oxidative damage, , and iron deposition were measured in the livers. An increase in hemolysis was observed in Butoxyethanol-treated rats and mice in a dose-dependent manner. An increase in the percentage of iron-stained Kupffer cells was observed following treatment with 450 and 900 mg/kg in mice and 225 and 450 mg/kg in rats. A biphasic increase in oxidative damage was seen in mouse liver after 7 and 90 d of treatment with Butoxyethanol, whereas no increases were observed in treated rat liver. Vitamin E levels were reduced by Butoxyethanol treatment in both mouse and rat livers; however, the basal level of vitamin E was approximately 2.5-fold higher in rat than in mouse liver. A similar biphasic induction of DNA synthesis was seen following in the mouse. In the mouse liver, increased DNA synthesis was observed in hepatocytes at 90 d and in endothelial cells at 7 and 14 d at all doses. No change in DNA synthesis was seen in Butoxyethanol-treated rat liver. No apparent differences in apoptosis and mitosis in the liver were observed in mouse and rat liver between Butoxyethanol treatment groups and untreated controls.

Butoxyethanol induced oxidative stress in the liver of male B6C3F1 mice (groups of 5) following 7-d treatment by gavage at 0, 450, or 900 mg/kg.[41] The study also examined whether Butoxyethanol (at 1 and 5 mM), 2-butoxyacetic acid, or iron ($FeSO_4$) produced oxidative stress in B6C3F1 mouse and F344 rat hepatocytes. Oxidative stress was examined by measuring oxidative DNA damage (8-hydroxy-2'-deoxyguanosine; OH8dG), lipid peroxidation (malondialdehyde (MDA) formation), and cellular vitamin E concentrations. Neither Butoxyethanol or 2-butoxyacetic acid induced changes in the oxidative stress parameters examined in either rat or mouse hepatocytes. In contrast, iron produced a dose-related increase in OH8dG and MDA and a decrease in vitamin E levels following 24 h treatment. Mouse hepatocytes were more sensitive than rat hepatocytes to the oxidative damage induced by the iron. Iron-induced oxidative stress was not increased by co-treatment of iron with either Butoxyethanol or 2-butoxyacetic acid. These results support the proposal that the induction of hepatic oxidative stress by Butoxyethanol in vivo occurs secondary to induction of hemolysis and iron deposition in the liver rather than as a direct action of Butoxyethanol or 2-butoxyacetic acid.

Cardiovascular Effects

Atrial thrombosis was evaluated in 2-yr bioassays of more than 500 chemicals reported on by the NTP.[42] Incidences of atrial thrombosis were increased in high-dose groups involving 13 compounds, including Butoxyethanol. One of 5 female F344 rats that inhaled 500 ppm Butoxyethanol for 14 wk experienced left atrium thrombosis, hemolytic anemia, thrombocytosis, and systemic thrombosis.

Osteotoxic Effects

In a study of bone injury associated with thrombosis from hemolytic disorders, groups of 4 male and 4 female F344 rats were given 4 daily doses of 250 mg Butoxyethanol/5 ml water/kg bw via gavage.[43] Tail vertebrae were studied by histopathology and magnetic resonance imaging (MRI). Thrombosis and infarction were seen in both sexes, but females were more severely affected. Lesions were characterized by extensive medullary fat necrosis, granulomatous inflammation, fibroplasia, growth plate degeneration, and new woven bone formation adjacent to necrotic bone trabeculae. MRI mean and standard deviation tissue-density data for both sexes indicated a significant ($p \leq 0.05$) decrease following 4-d treatment and a significant increase ($p \leq 0.05$) following an additional 24 d without treatment.

A second study with a similar protocol as above utilized only female F344 rats.[44] The rats were given 0, 250, or 300 mg of Butoxyethanol/kg bw/d via gavage for 4 consecutive days. The rats were then killed 2 h or 26 d after the final treatment. The treated animals displayed a darkened purple-red discoloration on the distal tail. Histopathological evaluation, including phosphotungstic acid-hematoxylin staining of animals killed 2 h after the final treatment, revealed disseminated thrombosis and infarction in multiple organs, including bones. X-ray analysis found premature thinning of the growth plate occurred in the calcaneus, lumbar and coccygeal vertebrae, femur, and ilium of the treated animals. Areas of decreased radiographic densities were seen in the diaphysis of the femur of all treated animals. The bones were then examined histologically and

showed a range of changes, including loss or damage to growth plates and necrosis of cortical bone. No thrombi were seen in the animals sacrificed at 30 d, but bone and growth plate changes consistent with prior ischemia were noted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation potential of Butoxyethanol was evaluated in 4 studies in rabbits.[2] *The material was tested undiluted or in sweet almond oil at concentrations of 5, 10, 25, or 50%. Butoxyethanol was, at most, moderately irritating to rabbit skin, when tested undiluted.*

The skin sensitization potential of 10% Butoxyethanol (aqueous) was evaluated in a human repeated insult patch test (HRIPT) involving 201 healthy subjects.[2] *During induction, 9 consecutive occlusive patch applications of the test material were made on the back of each subject. The subjects removed the patches ~ 24 h post-application and had the patches reapplied at 48-h intervals following evaluation of the test sites. The challenge phase was initiated after a 14-d rest period. Patches were applied to naïve sites and removed 24 h later; reactions were scored at 48 and 72 h post-application. Challenge reactions were observed in 14 subjects. Definite erythema with no edema was observed in 1 subject at 72 h and doubtful (barely perceptible erythema) responses were observed in 13 subjects: 6 subjects at 48 and 72 h, 6 subjects at 72 h, and 1 subject at 48 h. Eleven of the 14 subjects with challenge reactions also had reactions ranging from doubtful to definite erythema, but with no edema, during the induction phase. Additionally, a total of 52 subjects had reactions only during the induction phase; 35 subjects had doubtful reactions and 17 subjects had reactions ranging from doubtful to definite erythema, but with no edema.*

Irritation

Animal

In a study using 5 New Zealand White rabbits, undiluted Butoxyethanol (0.5 ml) was applied under occlusion to an area of 6 cm^2 shaved skin for 4 h.[4] The application site was then rinsed. Slight to moderate erythema and very slight edema were observed. The effects were persistent and still very slightly visible at the end of the 14-d observation period. The mean erythema score was 1.7 out of 4 and the mean edema score was 0.

In another irritation study, 6 albino rabbits received undiluted Butoxyethanol (0.5 ml) under occlusive conditions to an area of 2.54 cm^2 for 24 h.[4,5] Test sites were not rinsed. Very slight edema and erythema were observed at the 72-h observation period. The mean primary dermal irritation index was 1.5 out of 8.

Sensitization

Animal

The sensitization potential of Butoxyethanol was assessed in a guinea pig maximization study in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 406.[4,5] Ten Dunkin-Hartley guinea pigs were used in the study. During the induction phase, 0.5% Butoxyethanol in 0.9% saline was injected intradermally and 25% Butoxyethanol in saline was applied topically under occlusion (2 x 4 cm^2 area) for 48 h. After an ~2-wk rest, the challenge phase was performed topically under occlusion (8 mm diameter patch) for 24 h with 10% Butoxyethanol in saline. A rechallenge application was performed 1 wk after the initial challenge. Skin irritancy was observed, but it was determined the Butoxyethanol was not a skin sensitizer in this study.

OCULAR IRRITATION STUDIES

Undiluted Butoxyethanol was an ocular irritant in rabbits.[2] *Additional testing in rabbits found Butoxyethanol at 5% caused no corneal injury, while 15% Butoxyethanol caused moderate corneal injury.*

Additional ocular irritation data are summarized in Table 7. Butoxyethanol tested undiluted and in 10% solution was irritating in a hen's eye test-chorioallantoic membrane (HET-CAM) assay and a corneal swelling test.[4] In several in vivo rabbit studies, undiluted Butoxyethanol was irritating to eyes.[4,5]

CLINICAL STUDIES

Case Reports

A 53-yr-old male patient accidentally co-ingested ethanol and 150 - 250 ml of pure Butoxyethanol.[45] The patient developed rapid obtundation, severe airway edema, hypotension, and prolonged acidosis. The patient recovered without sequelae.

Occupational Exposure

The application of an ink wash solvent, diluted to a concentration of 0.5 - 2.5% Butoxyethanol, did not induce sensitization or photosensitization reactions in 5 workers who had been exposed to Butoxyethanol in the workplace.[2]

An assessment was performed with 34 screen-printing workers exposed to Butoxyethanol and 37 non-exposed clerical workers.[46] The exposed group of workers usually worked 8 h/d for 5 d/wk. A Chi-square test showed the reticulocyte percentages and corrected reticulocyte counts to be significantly higher in the exposed group. T-tests showed a significant

increase in white blood cell counts, reticulocyte percentages, and corrected reticulocyte count (i.e., reticulocyte index) in the exposed group, with *p*-values of 0.002, 0.004, and 0.002, respectively. Multivariate analysis showed the odds ratio for the corrected reticulocyte counts to be 16.30 for the exposed group, when compared with that of the control group.

Firefighter exposure to ingredients in firefighting foam, including Butoxyethanol, was assessed by biomonitoring methods during 3 consecutive firefighting training sessions in Finland.[47] The short-term exposure of firefighters to Butoxyethanol was analyzed by urinalysis of 2-butoxyacetic acid. In 2 of the training sessions, the average urinary excretions of 2-butoxyacetic acid (1.4 mmol/mol creatinine) exceeded the reference limit of the occupationally unexposed population (0.5 mmol/mol creatinine; no further details available). In the third session, the average urinary excretion of 2-butoxyacetic acid was 0.8 mmol/mol creatinine.

In a 5-d work week, 31 decal transfer workers with direct contact (hands) with a 10% dilute aqueous solution of Butoxyethanol were exposed to an average of 1.7 ppm of Butoxyethanol in the air.[48] Correlation of Butoxyethanol in the air and post-shift urinary 2-butoxyacetic acid (a Butoxyethanol metabolite) levels was poor. Post-shift total 2-butoxyacetic acid levels in urine on Monday and Friday (446.8 and 619.4 mg/g creatinine, respectively) were around 223 and 310% of the American Conference of Governmental Industrial Hygienists (ACGIH) proposed Biological Exposure Index (BEI; 200 mg/g creatinine). Higher levels of total 2-butoxyacetic acid were observed in the urine of subjects exposed to low-level 2-butoxy-acetic acid in air, likely because of direct dermal contact.

RISK ASSESSMENT

Margin of exposure (MOE) is a quantitative factor calculated for cosmetic ingredients by dividing the NOAEL obtained for an ingredient in an animal experiment by the estimated systemic exposure dose (SED) for the ingredient in humans, generally according to US EPA and EC SCCS guidelines. The MOE is sometimes referred to as margin of safety (MOS), despite the parameters being definitionally different.

In 2007, the SCCP calculated an MOE value for Butoxyethanol as a solvent in hair dye preparations (2% in non-oxidative hair dyes and 4% in oxidative hair dyes) to be 27.[5] This calculation is based on the NOAEL of 30 mg/kg bw/d (from a rat maternal toxicity study) and a SED of 1.11 mg/kg bw (skin area surface of 700 cm^2 x absorption through skin of 95 $\mu g/cm^2$ x 0.001 (unit conversion)/typical human bw of 60 kg). The SCCP determined that the inter-species dynamics uncertainty factor should be 0.01, rather than the default value of 2.5, due to the significantly higher resistance of humans to hemolysis compared to rodents. To ensure a cautious and conservative assessment, the SCCP further adjusted this factor to 0.1. Taking toxicokinetics and toxicodynamics into account, the minimal protective MOE was set at 4, calculated as follows: 4 (inter-species kinetics) × 0.1 (inter-species dynamics) × 3.2 (intra-species kinetics) × 3.2 (intra-species dynamics) = 4. Since the derived MOE is 27, which exceeds the minimum requirement of 4, it is considered to provide sufficient protection for the use of Butoxyethanol as a solvent in hair dye formulations. However, the endpoint used for the NOAEL value employed in this MOE calculation was red blood cell hemolysis in rats. Humans, relative to rats, are resistant to red blood cell hemolysis,[49] so extrapolating risk from rats to humans using this endpoint is questionable.

SUMMARY

Butoxyethanol is reported to function as a fragrance ingredient, solvent, and viscosity decreasing agent in cosmetics, according to the *Dictionary*. The Panel first reviewed the safety of Butoxyethanol in a report published in 1996 with the conclusion that "Butoxyethanol is safe in hair and nail products at concentrations up to 10.0%." The Panel reaffirmed this conclusion after determining that the questionable evidence of carcinogenicity (in mice and rats) observed in a two-year NTP inhalation carcinogenicity study was not relevant to humans, as published in 2005. In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2024, the Panel determined that this safety assessment should be re-opened for re-evaluation due to reported restrictions by the EC on the use of Butoxyethanol.

According to RLD that CIR receive in 2024, Butoxyethanol is used in 81 formulations, with 79 uses reported in hair dyes and colors. A single use each was reported in perfumes and makeup fixatives. VCRP survey data received in 2023 reported Butoxyethanol was used in 3 hair dyes and colors. When comparing the VCRP data received in 2023 to that received in 2001, the frequencies of use for Butoxyethanol greatly decreased since the original re-review was considered; in 2001, Butoxyethanol was reported to have 110 uses, with the majority in hair coloring formulations. No uses were reported in the concentration of use survey conducted by the Council in 2025. In 2001, the maximum concentration of use range for Butoxyethanol was 3% in leave-on products and 50% in rinse-off products; concentrations of use were not reported for hair coloring products at the time of the first re-review.

In the EU, Butoxyethanol is categorized in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. For this ingredient, the regulation states that Butoxyethanol may only be used as a solvent in oxidative hair dye products at up to 4%, a solvent in non-oxidative hair dye products at up to 2%, and must not be used in aerosol dispensers (sprays). The SCCP opinion gives these same restrictions on use in hair dye formulations, as

related to direct application to the hair/scalp. The opinion does not include any other cosmetic exposure, such as exposure to other types of cosmetics or possible aerosol/spray products.

In human skin samples, Butoxyethanol absorbed more rapidly through damaged skin than undamaged skin (3.39 $mg/cm^2/h$ vs 1.19 $mg/cm^2/h$). In solution, a steady state flux of 544 ± 64 $nmol \cdot cm^{-2}/h$ (0.064 $mg/cm^2/h$) was found with human dermatomed skin. In a study with oxidative hair dye formulations, the dermal absorbance for formulations with 5 and 10% Butoxyethanol was 61 ± 29 $\mu g/cm^2$ (12.1 ± 5.9%) and 125 ± 73 $\mu g/cm^2$ (12.5 ± 7.3%), respectively. Butoxyethanol penetrated human skin up to 6-fold more rapidly from aqueous solution (50%, 450 mg/ml) than from the neat solvent (900 mg/ml); a corresponding increase in apparent permeability coefficient was observed as Butoxyethanol concentration in water decreased. Permeation rates of Butoxyethanol through non-occluded rat dermatomed skin (16%) were greater than rat whole skin (8%), while absorption through human dermatomed skin (4%) was lower than the rat. Absorption of undiluted Butoxyethanol through occluded rat dermatomed skin in vitro was 18%. This same study found that Butoxyethanol absorption was enhanced by application in methanol to 23%. In a study with full-thickness human skin with undiluted Butoxyethanol, approximately 0.16% of the absorbed Butoxyethanol was metabolized to butoxyacetic acid.

Following topical application of undiluted Butoxyethanol in rats in vivo, 28% of the dose was absorbed after 24 h. The major routes of excretion included the urine (19%), expiration as carbon dioxide (6%) and feces (0.4%): little of the dose remained in the carcass (1.3%). In a study with human volunteers exposed to Butoxyethanol vapors (for 8 of the 9 exposures, volunteers wore air-fed half masks to supply clean air), urinalysis results showed that baseline dermal absorption of Butoxyethanol vapor was 11% of the total absorbed dose. Higher temperatures and greater humidity increased dermal absorption. The rate of percutaneous absorption of Butoxyethanol is greater in aqueous solutions than when it is applied neat or diluted in ethanol.

Volunteers were dermally exposed for 4 h to 50% aq. Butoxyethanol or exposed via inhalation to 93 mg/m^3 Butoxyethanol for 30 min. After dermal exposure, 147.1 and 346 mg of free and total 2-butoxyacetic acid, respectively, were excreted in the urine at up to 48 h after exposure. After inhalation exposure, the 24-h cumulative excretion of free and total 2-butoxyacetic acid in urine was 5.5 and 12.8 mg, respectively.

In acute dermal studies, the LD_{50} for Butoxyethanol was greater than 2000 mg/kg in rats and guinea pigs. The dermal LD_{50} in rabbits ranged from 307 to greater than 2000 mg/kg. The oral LD_{50} for mice was 1519 mg/kg in fasted animals and 2005 mg/kg in fed animals; the LD_{50} in rats ranged from 880 to 2100 mg/kg. All rabbits that received 695 or 1500 mg/kg orally died, and the oral LD_{50} for Beagle dogs was greater than 695. In acute inhalation studies, no deaths were observed in rats that were exposed up to 2.25 mg/l for 3 h, but all rats died after being exposed to 4.25 mg/l for 8 h. In guinea pigs, the LC_{50} was greater than 2.25 mg/l Butoxyethanol following a 4 h exposure. The LC_{50} was less than 2.0 mg/l in rabbits that were exposed to Butoxyethanol for 7 h.

In an oral 6-wk toxicity study in rats that received up to 885 mg/kg/d Butoxyethanol, the NOAEL was less than 222 mg/kg/d. Significant toxicity was observed at 885 mg/kg/d. Adverse effects observed included changes to red blood cells, splenic congestion, and liver anisokaryosis starting at 222 mg/kg/d. In inhalation studies, no adverse effects were observed in studies in male guinea pigs and male Beagle dogs that were exposed for 7 h/d for 2 wk to approximately 400-411 ppm (2.02 mg/l) Butoxyethanol. A NOAEC could not be established in studies with mice, rats, rabbits, and cats exposed to 537 ppm (2.63 mg/l) Butoxyethanol for 6 h/d for 15 d; a NOAEC was determined to be 537 ppm for guinea pigs. In a 90-d inhalation study in rats, the NOAEC was less than 50 ppm exposed to Butoxyethanol 7 h/d for 5 d/wk. Adverse effects included an increase in erythrocyte osmotic fragility and an increase in relative kidney to bodyweight ratio.

In an oral two-generation reproductive toxicity study, the conservative LOAEL for Butoxyethanol was determined to be 720 mg/kg/d based on a statistically significant reduction in pup weights in the F_1 generation. The reproductive NOAEL for Butoxyethanol was determined to be 720 mg/kg/d. An NOAEL for developmental toxicity could not be derived. The SCCP noted that the lowest fetal NOAEL was 100 mg/kg bw/d in a rat study that was reported on in the original CIR safety assessment. It was based on effects observed at 200 mg/kg bw/d: increased fetal lethality without malformations. These effects were observed with maternal toxicity (hemolytic anemia) and reduced body weight gain observed at 100 mg/kg bw/d. The maternal NOAEL was 30 mg/kg bw/d in this study.

In SHE cells, Butoxyethanol (0.5 - 20 mM) did not induce cellular transformation. No increase in DNA damage was observed in a comet assay using SVEC4-10 mouse endothelial cells following exposure of up to 10 mM Butoxyethanol. Genotoxicity was not observed in an in vivo micronucleus induction test in mice at up to 1100 mg/kg Butoxyethanol via intraperitoneal injection or in a *Pig-a* assay in rats at up to 450 mg/kg Butoxyethanol via gavage.

Although forestomach tumors and hemangiosarcomas have been observed in rodent studies, extensive mechanistic evidence indicates that these tumor types are of limited or no relevance to humans. Forestomach tumors arise in a rodent-specific anatomical structure absent in humans and are typically linked to local irritation or high-dose bolus exposure via oral gavage, with tumor formation driven by sustained cytotoxicity and regenerative epithelial proliferation rather than a genotoxic mechanism. Similarly, hemangiosarcomas induced in mice–often by nongenotoxic agents–are associated with mouse-specific responses such as hemolysis-induced hypoxia, dysregulated erythropoiesis, macrophage activation, and

increased angiogenic signaling, a mode of action that lacks biological plausibility in humans. The species-specific nature of these mechanisms suggests that tumor findings observed in rodents are of limited relevance to human cancer risk assessment.

Overall, IARC determined that Butoxyethanol is not classifiable as to its carcinogenicity to humans (Group 3). In the evaluation, there was inadequate evidence in humans and limited evidence in experimental animals for carcinogenicity of Butoxyethanol. The US EPA IRIS assessment of Butoxyethanol published in 2005 determined that the human carcinogenicity of this ingredient could not be determined at the time the assessment was performed, but "suggestive evidence" for cancer exists from laboratory animal studies performed on mice and rats by the NTP. In a study of the mechanism of carcinogenicity using mice exposed to a single dose or 7 daily doses of 900 mg/kg Butoxyethanol in water, Butoxyethanol induced macrophage activation and inflammation in the liver. In addition, the model supported local tissue hypoxia in the liver and spleen, coupled with increased erythropoietin signaling and erythropoiesis in the spleen and bone marrow, and suppression of mechanisms that contribute to genomic stability, events that could be contributing factors to hemangiosarcoma formation.

Butoxyethanol (0.1 - 25 mM) enhanced the cytotoxic effect of hydrogen peroxide in a concentration-dependent manner. In a study examining the involvement of hemolysis and macrophage activation in Butoxyethanol carcinogenesis, DNA damage was produced by hemolyzed red blood cells, ferrous sulfate, and hydrogen peroxide in mouse endothelial cells. Butoxyethanol and related metabolites did not directly cause the DNA damage. Supportive evidence demonstrated that damaged red blood cells, iron, and/or products from macrophage activation (possibly reactive oxygen species) produce DNA damage in endothelial cells and that activated macrophages stimulate endothelial cell proliferation. In studies with rats that received up to 250 mg/kg/d Butoxyethanol, thrombosis and infarction of the organs were observed. A decrease of ATP level in a dose-dependent manner and an increase in protein- and nonprotein-bound sulfhydryl groups were observed following treatment with singled dose of up to 5.0 mM/kg Butoxyethanol.

Following treatment for up to 90 d with Butoxyethanol in mice (up to 900 mg/kg/d) and rats (up to 450 mg/kg/d, an increase in hemolysis was observed in Butoxyethanol-treated rats and mice in a dose-dependent manner. A biphasic increase in oxidative damage was seen in mouse liver after 7 and 90 d of treatment with Butoxyethanol, whereas no increases were observed in livers from treated rats. In the mouse liver, increased DNA synthesis was observed in hepatocytes at 90 d and in endothelial cells at 7 and 14 d at all doses. No change in DNA synthesis was seen in Butoxyethanol-treated rat liver. No apparent differences in apoptosis and mitosis in the liver were observed in mouse and rat liver between Butoxyethanol treatment groups and untreated controls. Butoxyethanol induced oxidative stress in the liver of male mice following 7-d treatment by gavage of up to 900 mg/kg. Neither Butoxyethanol or 2-butoxyacetic acid induced changes in the oxidative stress parameters examined in either rat or mouse hepatocytes. Mouse hepatocytes were more sensitive than rat hepatocytes to the oxidative damage induced by the iron. Iron-induced oxidative stress was not increased by co-treatment of iron with either Butoxyethanol or 2-butoxyacetic acid.

In studies of bone injury associated with thrombosis from hemolytic disorders in rats that received up to 300 mg/kg/d Butoxyethanol via gavage, lesions were characterized by extensive medullary fat necrosis, granulomatous inflammation, fibroplasia, growth plate degeneration, and new woven bone formation adjacent to necrotic bone trabeculae. Bones examined histologically showed a range of changes, including loss or damage to growth plates and necrosis of cortical bone.

In dermal irritation studies in rabbits with undiluted Butoxyethanol under occlusive conditions, slight erythema and edema were observed. Butoxyethanol was determined not to be a skin sensitizer, but produced irritation, in a guinea pig maximization study that used induction concentrations of 0.5% (intradermally) and 25% (topically) and a challenge concentration of 10%.

Butoxyethanol tested undiluted and in 10% solution was irritating in a HET-CAM assay and a corneal swelling test. In several in vivo rabbit studies, undiluted Butoxyethanol was irritating to eyes.

A 53-yr-old male patient developed rapid obtundation, severe airway edema, hypotension, and prolonged acidosis following accidental co-ingestion of ethanol and pure Butoxyethanol. Occupational exposure studies have been performed on workers exposed to Butoxyethanol in screen-printing, decal transfer, and firefighting foam.

In 2007, the SCCP calculated an MOE value for Butoxyethanol as a solvent in hair dye preparations (2% in non-oxidative hair dyes and 4% in oxidative hair dyes) to be 27. This calculation is based on the NOAEL of 30 mg/kg bw/d (from a rat maternal toxicity study) and an SED of 1.11 mg/kg bw (skin area surface of 700 cm^2 x absorption through skin of 95 $\mu g/cm^2$ x 0.001 (unit conversion)/typical human bw of 60 kg). The SCCP determined that the inter-species dynamics uncertainty factor should be 0.01, rather than the default value of 2.5, due to the significantly higher resistance of humans to hemolysis compared to rodents. To ensure a cautious and conservative assessment, the SCCP further adjusted this factor to 0.1. Taking toxicokinetics and toxicodynamics into account, the minimal protective MOE was set at 4. Since the derived MOE is 27, which exceeds the minimum requirement of 4, it is considered to provide sufficient protection for the use of Butoxyethanol as a solvent in hair dye formulations. However, given the relative resistance of humans to red blood cell hemolysis when compared to rats, application of this model to estimate human risk is questionable.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 1996, the Panel published a final report on Butoxyethanol and concluded that the available data supported the safety of this ingredient as used in hair and nail products at concentrations up to 10%. In 2002, because a new NTP study became available, the report was reconsidered; however, the conclusion was reaffirmed, as published in 2005. Accordingly, in June 2024, the Panel considered whether the safety of Butoxyethanol should be reassessed since it was at least 15 years since the last review, and the report was reopened due to reported restrictions by the EC on the use of Butoxyethanol.

This amended report reviews the safety of Butoxyethanol as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel concluded that the available data are insufficient for determining the safety of this ingredient under the intended conditions of use as a cosmetic ingredient. The Panel noted a lack of relevant safety data and determined that the data needs from the Insufficient Data Announcement following the March 2025 Panel meeting remain unmet. In order to come to a conclusion of safety for this ingredient, the following additional data are needed:

- Maximum concentration of use in hair dye formulations
- Maximum concentration of use in non-hair dye formulations

The Panel was concerned about the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities from Butoxyethanol before blending them into cosmetic formulations.

The Panel also discussed the issue of incidental inhalation resulting from exposure to this ingredient; for example, Butoxyethanol is reported to be used in a perfume (concentration not provided) and could possibly be inhaled. Data are available from multiple inhalation studies, including acute and chronic exposure data, developmental and reproductive toxicity data, and carcinogenicity data. Although effects were observed in 2-yr inhalation studies in mice and rats, the Panel noted that rodents are more susceptible than humans to developing hemangiosarcomas and that tumors in the forestomach, a rodent-specific organ, are typically due to local irritation or high-dose exposure via gavage. Given the species-specific differences in mode-of-action, the Panel concluded that these findings in rodents have limited relevance for human risk assessment. Coupled with the small actual exposure in the breathing zone and the low concentrations at which this ingredient is used (or is expected to be used) in potentially inhaled products, the available information indicates that the incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination of safety for Butoxyethanol under the intended conditions of use as a cosmetic ingredient.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	Clear, thin liquid	[2]
Color	Colorless	[5]
Odor	Mild, sweet ester/ether	[4]
Molecular Weight (g/mol)	118.2	[2]
Specific Gravity	0.89 - 0.91	[2]
Viscosity (kg/(s x m @ 20 ºC)	336.5	[4]
Vapor pressure (mmHg @ 140 ºC) (mmHg @ 25 ºC)	300 0.88	[2]
Melting Point (ºC)	< -40 -77 -74.8	[2] [5]
Boiling Point (ºC)	171 - 172	[2]
Water Solubility	Miscible with water	[2]
Other Solubility	Miscible with methanol and ether in all proportions	[2]
log P_{ow} (@ 25 ºC & pH 7)	0.81	[4]
Disassociation constant (pKa @ 20 ºC)	15 (QSAR estimation)	[4]

Table 2. Frequency (RLD/VCRP) and concentration of use of Butoxyethanol according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*	
	RLD (2024)[7]	**VCRP (2023)[8]**	**VCRP (2001)[3]**	**% (2025)[9]**	**% (2001)[3]**
Totals*	**81**	**3**	**110**	**NR**	**3-50**
summarized by likely duration and exposure**					
Duration of Use					
Leave-On	***	*NR*	*3*	*NR*	*3*
Rinse-Off	***	*3*	*107*	*NR*	*50*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*
Exposure Type					
Eye Area	***	NR	NR	NR	3
Incidental Ingestion	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	2[a]	NR	NR
Incidental Inhalation-Powder	***	NR	NR	NR	NR
Dermal Contact	***	NR	NR	NR	3
Deodorant (underarm)	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	2	NR	NR
Hair-Coloring	***	3	107	NR	NR
Nail	***	NR	1	NR	3-50
Mucous Membrane	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR
as reported by product category					
Eye Makeup Preparations (not children's)					
Eye Shadow	NR	NR	NR	NR	3
Fragrance Preparations	***1***				
Perfumes	1	NR	NR	NR	NR
Hair Preparations (non-coloring)					
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	2	NR	NR
Hair Coloring Preparations	***79***				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	79	3	94	NR	NR
Hair Tints	NR	NR	3	NR	NR
Hair Shampoos (coloring)	NR	NR	8	NR	NR
Hair Bleaches	NR	NR	2	NR	NR
Makeup Preparations (not eye; not children's)	***1***				
Blushers and Rouges (all types)	NR	NR	NR	NR	3
Makeup Fixatives	1	NR	NR	NR	NR
Manicuring Preparations					
Nail Polish and Enamel	NR	NR	1	NR	3
Nail Polish and Enamel Removers	NR	NR	NR	NR	50

NR – not reported

*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.

**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

***In the RLD, each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

Table 3. Dermal penetration studies on Butoxyethanol

Vehicle	Test System	Concentration/Dose	Protocol	Results	Reference
			IN VITRO		
not reported	human abdominal skin; damaged (n = 4) and undamaged (n = 8)	not reported	Dermal penetration study performed as 2 experiments using liquid Butoxyethanol; skin was exposed to the test material in Franz-type diffusion cells; absorption results were measured twice due to high variability in the first experiment	Mean absorption rates were: 0.857 ± 0.282 mg/cm^2/h in the first experiment and 1.52 ± 0.37 mg/cm^2/h in the second experiment. The damage ratio (permeability constant after contact with Butoxyethanol/permeability constant before contact with Butoxyethanol) was 3.25 ± 3.33 in the first experiment and 5.14 ± 4.99 in the second experiment. Due to the high variability in each experiment, mean absorption rates were calculated separately for the undamaged and damaged skin. The results from the damaged skin specimens were about 3 times higher than the undamaged skin (3.39 mg/cm^2/h vs 1.19 mg/cm^2/h). When the results from the four cells showing the high damage ratio are excluded from the calculation of the overall mean result, the mean damage ratio is 1.66 ± 1.31.	[5]
tested neat and in water	full thickness or dermatomed human breast skin	100 or 200 µl in aq. solution; 10 µl neat	Dermal absorption study of liquid Butoxyethanol using flow-through diffusion cells; measured for 24 h	In solution, a steady state flux of 544 ± 64 nmol·cm^{-2}/h (0.064 mg/cm^2/h) was found with dermatomed skin. Reducing the dose to 100 µl decreased the steady state flux by about 55%. With full thickness skin, the time to steady state increased and the steady state flux decreased. Absorption rates of undiluted Butoxyethanol in finite dose exceeded those measured with aqueous solutions, though the apparent permeability coefficient was higher with the aqueous doses.	[11]
oxidative hair dye formulations, mixed 50/50 w/w with developer containing hydrogen peroxide	human skin	20, 500, or 1000 µg/cm^2; formulation contained 5 or 10% butoxyethanol (final on-skin concentrations were 2.5 and 5% butoxyethanol, respectively)	Dermal absorption study performed in accordance with OECD TG 428; 2 different formulations containing 5 or 10% ^{14}C-Butoxyethanol were mixed with equal volume of developer and applied to skin for 30 min; skin surface was 1.76 cm^2; at end of exposure, skin was washed; diffusion was monitored during the 24 h following application and receptor fluid was collected 2, 4, 6, 10, 21, and 24 after the beginning of exposure.	Total recovery for the formulation containing 5% Butoxyethanol was 84 ± 4%; for the 10% formulation, total recovery was 81 ± 4%. Dermal absorbance for formulation with 5% Butoxyethanol was 61 ± 29 µg/cm^2 (12.1 ± 5.9%); for the 10% formulation, dermal absorbance was 125 ± 73 µg/cm^2 (12.5 ± 7.3%).	[5]
tested neat and in water	synthetic polydimethylsiloxane membrane, rat skin, and human skin	900 mg/ml neat and 0.9 -810 mg/ml in aq. solution	Dermal absorption study using in vitro diffusion system that assessed the influence of water mixtures on the absorption of ^{14}C-Butoxyethanol in a synthetic membrane (400 µm thickness), dermatomed rat skin (280 µm thickness), and dermatomed human skin (320 µm thickness); Scoot Dick-Newcastle cells and Eagles minimum essential medium receptor fluid were utilized in this study; study performed under partially occluded conditions	Butoxyethanol penetrated human skin up to 6-fold more rapidly from aqueous solution (50%, 450 mg/ml) than from the neat solvent; a corresponding increase in apparent permeability coefficient was observed as Butoxyethanol concentration in water decreased. The maximum penetration rate of water also increased in the presence of Butoxyethanol. Absorption through a synthetic membrane obeyed Fick's Law and absorption through rat skin showed a similar profile to human skin but with a lesser effect.	[12]

Table 3. Dermal penetration studies on Butoxyethanol

Vehicle	Test System	Concentration/Dose	Protocol	Results	Reference
undiluted or prepared in methanol	rat whole and dermatomed skin (280 µm); human dermatomed skin (330 µm)	aliquots of 10 µl	Percutaneous absorption test of ^{14}C-Butoxyethanol using in vitro flow through diffusion cell technique, results compared with the in vivo absorption in rat skin (described below); some samples of skin were occluded with parafilm; absorption was measured for up to 24 h after application	Permeation rates of Butoxyethanol through unoccluded rat dermatomed skin (16%) were greater than rat whole skin (8%), while absorption through human dermatomed skin (4%) was lower than the rat. Absorption of undiluted Butoxyethanol through occluded rat dermatomed skin was 18%. Butoxyethanol absorption (23%) was enhanced by application in methanol. Distribution analysis and microautoradiography demonstrated the lack of Butoxyethanol accumulation within the skin in vitro. This was reflected in the absence of first-pass metabolism of Butoxyethanol during percutaneous penetration through viable human or rat skin in vitro, despite rat skin cytosol having the potential to metabolize Butoxyethanol.	13
undiluted	full-thickness excised human skin	200 µl/cm^2; 115.2 mg	Dermal absorption and metabolism study of ^{14}C-Butoxyethanol; skin samples were placed on transwell supports and placed with the underside of the skin in contact with receptor fluid; absorption and metabolism of Butoxyethanol to butoxyacetic acid was monitored for 24 h	In total 64.94 ± 0.04 mg of Butoxyethanol or its metabolites were removed from the surface of the skin at 24 h, representing the equivalent of 56% of the applied dose, the equivalent of 17.5% of the applied dose was recovered from the receiver fluid, 3% from within the skin and the remaining 23.5% of the dose was lost to the atmosphere through evaporation. After 24 h, a total of 31.5 µg of butoxyacetic acid had been produced representing approximately 0.03% of the applied dose. Approximately 0.16% (31.5 µg as a percentage of the total amount of Butoxyethanol reaching the receiver fluid (20.17 mg)) of the absorbed Butoxyethanol was metabolized to butoxyacetic acid.	14
			ANIMAL		
undiluted	male Wistar rats; number not reported	100 µl	Percutaneous absorption test of ^{14}C-Butoxyethanol in rats; results compared with the in vitro absorption in rat skin (described above); animals received test material on clipped skin, test sites were occluded; blood was drawn at 1, 4, 7, and 24 h post dosing; animals were placed in sealed metabolism cages to message radioactivity in expired air; urine was collected; animals were killed for tissue distribution studies	Following topical application, 28% of the dose was absorbed after 24 h. The major routes of excretion included the urine (19%), expiration as carbon dioxide (6%) and feces (0.4%): little of the dose remained in the carcass (1.3%). Free Butoxyethanol (0.5%), butoxyacetic acid (8%), glucuronide conjugate (3%), sulfate conjugates (0.7%) and ethylene glycol (0.6%) were detected in urine. Distribution analysis and microautoradiography demonstrated the lack of Butoxyethanol accumulation within the skin in vivo. This was reflected in the absence of first pass metabolism of Butoxyethanol during percutaneous penetration through rat skin in vivo, despite rat skin cytosol having the potential to metabolize Butoxyethanol.	13
			HUMAN		
none	4 volunteers, 2 males and 2 females	50 ppm for 2 h	Study to investigate the influence of temperature, humidity, and clothing on dermal absorption of Butoxyethanol vapors; volunteers were exposed to Butoxyethanol vapors on 9 occasions; for 8/9 exposures, volunteers wore air-fed half masks to supply clean air; absorption was measured through urinalysis for 2-butoxyacetic acid; urine was collected before and after each exposure at 0, 4, 6, 8, 10, 12, 22, 26, 30 and 34 h; baseline conditions were 25°C, 40% relative humidity, shorts and T-shirt	Urinalysis results showed that baseline dermal absorption of Butoxyethanol vapor was 11% of the total absorbed dose. Higher temperature (30°C) and greater humidity (65%) increased dermal absorption. Wearing whole-body overalls did not attenuate absorption. By combining several factors together in the occupation scenario, dermal absorption of vapors was significantly increased with a mean of 39% of the total absorbed dose.	15

Table 3. Dermal penetration studies on Butoxyethanol

Vehicle	Test System	Concentration/Dose	Protocol	Results	Reference
diluted in water (17%) or diluted in ethanol (17%)	3 volunteers, 2 males and 1 female	10 µl	Butoxyethanol (≥ 99.4% pure) was applied diluted in water or diluted in ethanol on the skin of healthy volunteers and occluded with Finn Chambers to prevent evaporation. Confocal Raman micro-spectroscopy measurements were done following application after 15 min and 3 h. The concentration of Butoxyethanol as a function of distance to the skin surface was calculated and further analyzed with regard to mass transport into the stratum corneum and the flux through the stratum corneum.	Butoxyethanol penetrated markedly faster when dissolved in water as compared to ethanol (after 15 min: 104 µg/cm^2 compared to 22.3 µg/cm^2; after 3 h: 321 µg/cm^2 compared to 23.3 µg/cm^2).	[16]
aqueous solution	6 male volunteers	50%, 90%, or 100% w/w	Volunteers were dermally exposed (8 ml) to Butoxyethanol for 4 h on the arm over an area of 40 cm^2. Each volunteer was exposed twice to the 50% solution, and once each to the 90% solution and to Butoxyethanol neat. Dermal absorption parameters were calculated from 24-h excretion of total butoxyacetic acid in urine and Butoxyethanol in blood. The time-weighted average dermal fluxes were calculated from the urine and blood data.	The dermal absorption of Butoxyethanol from aqueous solutions was markedly higher than that of neat Butoxyethanol. The dermal fluxes obtained from cumulative 24-h excretion of 2-butoxyacetic acid amounted to 1.34, 0.92, and 0.26 mg/cm^2/h for 50, 90 and 100% Butoxyethanol, respectively. The dermal fluxes calculated from the Butoxyethanol blood data amounted to 0.92 and 0.74 mg/cm^2/h for 50 and 90% Butoxyethanol, respectively. The permeation rates into the blood reached a plateau between 60 and 120 min after the start of exposure, indicating achievement of steady-state permeation. The apparent permeability coefficient K(p), was 1.75 x 10^{-3} and 0.88 x 10^{-3} cm/h for 50 and 90% Butoxyethanol, respectively.	[17]

Table 4. Acute toxicity studies on Butoxyethanol

Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
			DERMAL		
none	groups of 5 male and 5 female Sprague-Dawley rats	2000 mg/kg	Acute dermal toxicity study in accordance with OECD TG 402; rats received test material under semi-occlusive patch; test site wiped clean with cotton wool moisten with water after 24 h and animals were observed for 14 d after administration	LD_{50} > 2000 mg/kg; no clinical signs of toxicity during observation period and no deaths were observed	[4,5]
none	groups of 5 male and 5 female Sprague-Dawley rats	2000 mg/kg	Acute dermal toxicity study in accordance with OECD TG 402; rats received test material under occlusive patch for 24 h; animals were observed for 14 d after administration	LD_{50} > 2000 mg/kg; 1 female found dead 2 d after dosing; clinical signs of toxicity in 2 females included ataxia, pallor of the extremities, emaciation, lethargy, decreased respiratory rate, labored respiration, and tiptoe gait with incidents of ptosis and red/brown staining around the eyes; hunched posture was observed in most animals at end of exposure period; no abnormalities observed at necropsy in surviving animals; in animal that died during the study, hemorrhagic lungs, dark liver, dark kidneys, sloughing of the non-glandular epithelium of the stomach, and hemorrhage of the small and large intestines were observed	[4,5]
none	Groups of 5 male and 5 female Hartley guinea pigs	2000 mg/kg	Acute dermal toxicity study; guinea pigs received test material under occlusive patch; test sites were washed after 24 h and animals were observed for 14 d after administration	LD_{50} > 2000 mg/kg; no clinical signs of toxicity during observation period and no deaths were observed; all animals gained weight and no signs of organ toxicity at necropsy	[4,5]
none	groups for 4 male and female rabbits, strain not specified	3 doses, not specified	Acute dermal toxicity study; rabbits received test material under occlusive patch for 24 h; no further details provided	LD_{50} = 612 mg/kg (680 ml/kg); no further details provided	[4]

Table 4. Acute toxicity studies on Butoxyethanol

Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
none	groups of 5 male New Zealand White rabbits	153, 307, 614, or 1239 mg/kg	Acute dermal toxicity study in accordance with OECD TG 402; rabbits received test material under occlusive patch for 24 h; test site wiped with cotton wool; animals observed for 14 d after administration	LD_{50} = 307 mg/kg; at lower doses, clinical effects included anorexia, slight depression, cyanosis, ataxia, and soft feces; at higher doses, clinical effects included salivation, nasal discharge, iritis, significant depression, labored breathing and prostration	[4]
none	groups of 5 male and 5 female New Zealand White rabbits	1000 and 2000 mg/kg, tested sequentially	Acute dermal toxicity study in accordance with OECD TG 402; rabbits received test material under semi-occlusive patch; test site wiped clean with cotton wool moisten with water after 24 h; animals were observed for 14 d after administration	LD_{50} > 2000 mg/kg; no deaths at 1000 mg/kg; at 2000 m/kg, 1 female died on day 2 and 1 male and 1 female were killed *in extremis* on day 1; no signs of systemic toxicity noted in 1000 mg/kg dose group, very slight to well-defined erythema/slight edema at test stie; in 2000 mg/kg dose group, lethargy, stained urine, decreased respiratory rate, hunched posture, yellow skin and eyes observed along with isolated incidents of righting reflex, hypothermia, ataxia, and diarrhea, test site had very slight to well defined erythema/slight edema; no abnormalities observed at necropsy in the 1000 mg/kg dose group, animals that died in the 2000 mg/kg dose group before study end had pale kidneys, dark liver, hemorrhage of the gastric mucosa, and red fluid in the bladder, no abnormalities noted in surviving animals	[4,5]
none	groups of 5 male and 5 female New Zealand White rabbits	500, 707, or 1000 mg/kg	Acute dermal toxicity study in accordance with OECD TG 402; rabbits received test material under occlusive patch; test site wiped clean with cotton wool moisten with water after 24 h; animals were observed for 14 d after administration	LD_{50} = 841 mg/kg for all animals (LD_{50} males = 1060 mg/kg and LD_{50} females = 667 mg/kg); clinical signs of toxicity in all groups were lethargy, ataxia, red stained urine, diuresis, decreased respiratory rate, hunched posture, and yellow skin and eyes; no adverse effects were observed at necropsy in animals that survived until study end; in animals that died during the study, hemorrhagic lungs, dark kidneys, dark or pale liver or patchy liver pallor, and red fluid in the bladder were observed	[4,5]
			ORAL		
none	groups of 5 male CD-1 mice	not specified, but within 2.6 - 168 mM/kg	Acute oral toxicity study in accordance with OECD TG 401; mice received a single oral dose via gavage; study conducted with fed and fasted groups	LD_{50} = 1519 mg/kg in fasted mice and 2005 mg/kg in fed mice; clinical signs in both fed and fasted mice were inactivity, labored breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, proration, and death; animals that died exhibited bloody urine, and/or blood in the stomach and intestines (fasted animals); these conditions were not noted in animals that survived until study termination; hematuria was noted in the intermediate dose fed group at necropsy and was blood noted in the stomach of some fed mice which died before study end	[4,5]
none	groups of 5 male CD/BR rats	not specified, but within 2.6 - 168 mM/kg	Acute oral toxicity study in accordance with OECD TG 401; rats received a single oral dose via gavage; study conducted with fed and fasted groups	LD_{50} = 1746 mg/kg in both fed and fasted rats; clinical signs in both fed and fasted animals were inactivity, labored breathing, rapid respiration, anorexia, slight-to-moderate weakness, tremors, prostration, and death; animals that died had bloody urine and/or blood in the stomach and intestines (fasted animals), these conditions were not noted in animals that survived until study termination; hematuria was noted in high dose fasted and fed animals at necropsy	[4,5]
water	groups of 10 male and 10 female rats, strain not specified	200 - 1600 mg/kg	Acute oral toxicity study in accordance with OECD TG 401; rats received a single oral dose via gavage	LD_{50}= 880 mg/kg in males and 615 mg/kg in females; signs of toxicity in the 1000 – 1600 mg/kg dose groups included staggering, reduced general state, atony, abdominal and lateral position, irregular respiration, dyspnea, and hemolytic urine; surviving animals had squatting posture and scrubby fur 4 d after administration, but these animals were without findings after 6 d. Signs of toxicity in the 200 - 800 mg/kg dose groups included slight staggering, accelerated respiration, and hemolytic urine; 1 d after administration, squatting posture, straight fur, and reddened eyes occurred; surviving animals rebounded with no abnormalities at study end; animals that died during the study had anemic musculature, hemoglobinuric nephrosis, blood-colored urine, adipose, livers, and blurred snouts at necropsy; no remarkable abnormalities were observed at necropsy in animals that survived until study end	[4]
none	groups of 3 female CDF rats	130 - 2000 mg/kg	Acute oral toxicity study; rats received a single oral dose via gavage	LD_{50} = 1900 mg/kg; clinical signs included staining of perineal region (130 - 1000 mg/kg), rough hair coats (1000, 2000 mg/kg), lethargy, rapid shallow breathing, palpebral closure (2000 mg/kg), and necrosis of tails in all surviving animals in the 1000 and 2000 mg/kg dose groups	[4]

Table 4. Acute toxicity studies on Butoxyethanol

Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
water	groups of male and female Wistar rats, number not reported	test material given as a 5 or 10% (vol/wt) solution, or in one case, undiluted	Acute oral toxicity study; route not specified	LD_{50} = 2100 mg/kg in males and 1850 mg/kg in females; clinical signs included sluggishness, ruffling of coats, prostration, and narcosis at doses at or above the LD_{50}; necropsy on rats that died revealed congestion of hemorrhaged lungs, mottled livers, severely congested kidneys, and hemoglobinuria	[4]
water	groups of 3 male and 3 female rabbits	695 and 1500 mg/kg	Acute oral toxicity study; rabbits received a single oral dose via gavage	All animals died during the observation period (up to 48 h) in both dose groups; clinical signs in the high-dose group included atonia, lateral position, hyperpnea, staggering gait, and hyperemia; bloody red coloration of the eye occurred in 2 animals in the lower dose group; at necropsy, the high-dose animals had hyperemia and edema of the lung, hematuria and tubular necrosis of the kidney, hemorrhagia in the interstitial tissues of the adrenal gland, and follicular hemorrhagia in the spleen; lower dose animals had hyperemia, heart muscle adiposis, acute hemolytic nephrosis, pulmonary edema, and acute lymphocytopenia	[4]
water	1 male and 1 female Beagle dog	695 mg/kg	Acute oral toxicity study; dogs received a single oral dose via gavage	LD_{50} > 695; no remarkable clinical signs or abnormalities at necropsy were observed	[4]
INHALATION					
none	groups of 3 male 3 and female rats, strain not specified	1.44 mg/l for 3 h or 4.25 mg/l for 8 h	Acute inhalation toxicity study; rats were exposed to test material via whole body exposure for 3 or 8 h followed by a 7-d observation period	No deaths were observed to 1.44 mg/l exposure for 3 h, but all animals died after an 8 h exposure to 4.25 mg/l; clinical signs of toxicity included acute bloody urine, apathy, scrubby fur, intermittent respiration, mucous membrane irritation, and slight anemia; at necropsy, bloody nether regions, hematuria, liver anemia, and blood clotting the bladder were observed in the 8 h exposure group and chronic bronchitis was observed in the 3 h exposure group	[4]
none	groups of 3 male and 3 female Sprague-Dawley rats	2.25 mg/l for 3 h or 4.26 mg/lg for 7 h	Acute inhalation toxicity study; rats were exposed to test material via whole body exposure for 3 or 7 h followed by a 14-d observation period	LC_{50} > 4.26 mg/ml; no deaths were observed after 3 h exposure, 2/6 animals died after 7-h exposure; clinical signs of toxicity included eyelid closure, slight salivation, accelerated respiration, hemorrhagic urine, apathy, crouch position, unstable gait, scrubby and contaminated fur, and anemic ears; at necropsy, animals that died during the observation period had acute dilation of the right side of the heart and sallow left ventricle, moderate acute exhalation of the lungs, clay-gray toned liver, bloody ulcerations of the glandular stomach, and hematinic intestinal contents	[4]
not reported	groups of 6 male and female Dunkin-Hartley guinea pigs	not fully described, at minimum 2.25 mg/l	Acute inhalation toxicity study in accordance with OECD TG 433; guinea pigs were exposed to test material via snout-only, single exposure for 4 h followed by a 14-d observation period	LC_{50} > 2.25 mg/l; no deaths occurred attributable to exposure to test material; no clinical signs of toxicity or adverse gross pathology observed	[19]
air	groups of 4 male albino rabbits	~2.02 mg/l (400 - 411 ppm)	Acute inhalation toxicity study; rabbits were exposed to test material via whole body exposure for 7 h followed by a 7-d observation period; study was repeated with fresh animals 2 more times	LC_{50} < 2.0 mg/l; mortality rate was 75%; clinical signs included poor coordination of extremities and loss of equilibrium; at necropsy, rabbits that died during the study had reddish ocular and nasal discharges, yellow discoloration of the sclera, congested kidneys, hematuria, hemorrhagic ulcers in the gastric mucosa, mottled or yellow discoloration of the liver, slight congestion of the lungs and nasal turbinates	[4]

Table 5. Repeated-dose toxicity studies on Butoxyethanol

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
			ORAL			
water	male CR, COBS, CD, BR albino rats	6 wk	0, 222, 443, or 885 mg/kg/d	Repeated dose oral toxicity study performed in accordance with OECD TG 407; rats received test material 5 d/wk via gavage	NOAEL $\leq$ 222 mg/kg/d; significant toxicity was seen in the 885 mg/kg/d dose group, most significant adverse effects were changes to the red blood cells (reduced count, decreased hemoglobin and increased mean corpuscular hemoglobin) from the 222 mg/kg/d dose group upwards; other effects in the low dose group were equivocal changes in the kidney (proteinaceous casts and hemosiderin) and changes attributed to the dosing method (stomach hyperkeratosis); splenic congestion and stomach hyperkeratosis observed in virtually all animals at all doses, the latter is likely to be at least partly related to the dosing method, so the findings are uncertain in terms of relevance and extramedullary hematopoiesis was evident in the spleens of treated animals; liver anisokaryosis was also seen at 222 mg/kg/d.	[4,5]
			INHALATION			
air	male and female mice (20 total, strain not specified),	15 d	2.63 mg/l (537 ppm)	Animals were exposed to test material via whole-body exposure for 6 h/d	NOAEC could not be established; adverse effects aside from death included general anemia, deep blue concrement in urinary bladder, adipose liver, and discolored liver and lung	[4]
air	male and female rats (10 total, strain not specified) (strain not specified)	15 d	2.63 mg/l (537 ppm)	Animals were exposed to test material via whole-body exposure for 6 h/d	NOAEC could not be established; adverse effects aside from death included hematuria, anemic and adipose liver, and edematous soft tissue of the lung.	[4]
air	32 Carworth E strain male rats	90 d	0 or 50 ppm	Rats were exposed to test material via whole-body exposure for 7 h/d, 5 d/wk	NOAEC < 50 ppm; adverse effects included an increase in erythrocyte osmotic fragility and an increase in relative kidney-to-bw ratio, but not the absolute weight ratio	[4]
air	groups of 8 male guinea pigs, strain not specified	~2 wk	~2.02 mg/l (400 - 411 ppm)	Guinea pigs were exposed to test material via whole body exposure for 7 h followed by a 7-d observation period; 7-h was then repeated, and then for half the animals, the exposure was repeated for 5 consecutive days	LC_{50} > 2.0 mg/l; no adverse effects observed	[5]
air	male guinea pigs (10 total, strain not specified)	15 d	2.63 mg/l (537 ppm)	Animals were exposed to test material via whole-body exposure for 6 h/d	NOAEC was determined to be 537 ppm	[4]
air	1 male and 1 female Himalayan rabbit	15 d	2.63 mg/l (537 ppm)	Animals were exposed to test material via whole-body exposure for 6 h/d	NOAEC could not be established; adverse effects aside from death included lung edema, anemic liver, and deep blue-purple kidneys.	[4]
air	1 male and 1 female cat (strain not specified)	15 d	2.63 mg/l (537 ppm)	Animals were exposed to test material via whole-body exposure for 6 h/d	NOAEC could not be established; adverse effects aside from death included liver adiposis	[4]
air	2 male Beagle dogs	~ 2 wk	~2.02 mg/l (400 - 411 ppm)	Dogs were exposed to test material via whole-body exposure for 7 h followed by a 7-d observation period; 7 h exposure was then repeated, and for half the animals, the exposure was repeated for 5 consecutive days	LC_{50} > 2.0 mg/l; salivation occurred, no other adverse effects observed	[5]

Table 6. **Genotoxicity studies on Butoxyethanol**

Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
			IN VITRO		
DMSO	0.5 - 20 mM	Syrian hamster embryo (SHE) cells	SHE cell transformation study; cells were treated with test material for 7 d	Butoxyethanol did not induce cellular transformation.	[20]
not reported	1, 5 or 10 mM	SVEC4-10 mouse endothelial cells	Comet assay; Butoxyethanol and its metabolites, 2-butoxyacetaldehyde (0.1 - 1.0 mM) and 2-butoxyacetic acid (1 - 10 mM) were tested; exposure duration was 2, 4, or 24 h	No increase in DNA damage was observed following Butoxyethanol exposure	[21]
			IN VIVO		
phosphate-buffered saline	0,17.19, 34.38, 68.78, 137.5, 550, or 1100 mg/kg	groups of 5 male B6C3F1 mice	Micronucleus induction test; mice injected intraperitoneally 3 times at 24 h intervals	Butoxyethanol did not cause an increase in polychromatic erythrocytes; a statistically significant increase in the number of micronucleated polychromatic erythrocytes observed in the 138 mg/mg dose group when compared to control but not observed in any other dose group; all mice died in the 1100 mg/kg dose group	[4]
not reported	0, 10, 35, 100, 250, or 450 mg/kg	groups of 6 male Wistan-Han IGS rats	*Pig-a* assay; rats received test material via gavage using both single administration and 28-d treatment regimens; mutant frequencies were assessed on days 15 and ~30 for both treatment protocols and also on days 43 and 57 for the 28-d protocol	Not mutagenic; in single dose, a statistically significant increase in the percentage of reticulocytes on day 15 at doses of 100 - 450 mg/kg was observed, but there was no effect on either mutant reticulocytes or erythrocyte frequences at any doses test. In 28-d dosing, a statistically significant increase in percentage of reticulocytes on day 15 and 29 at doses of 100 - 450 mg/kg was observed; on day 43 there was slight but statistically significant decreasing trend in percentage of reticulocytes compared with controls at 250 and 450 mg/kg.; on day 57, reticulocyte values were comparable with controls; no increase in mutant reticulocyte or erythrocyte frequency was observed at any doses on days 15, 29, or 43 or on mutant erythrocyte frequency on day 57	[22]

Table 7. Ocular irritation studies on Butoxyethanol

Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
			IN VITRO/EX VIVO		
doubly distilled water	undiluted and in 10% solution	3 eggs from White Leghorn hens	HET-CAM assay; observed for 3.5 min after application	Irritating; with undiluted test material, slight hemorrhagia was observed in all eggs after 8 - 15 sec, moderate intra- and extravascular coagulation in all eggs after 24 - 47 sec; with 10% solution, slight hemorrhagia in all eggs after 26 - 36 sec, moderate intra- and extravascular coagulation observed in all eggs after 40 51 sec	[4]
none	undiluted	enucleated eyes from New Zealand White rabbits	Corneal swelling test; treatment duration was 5 h	Irritating to eyes; corneal swelling of over 100% with no sign of recovery observed	[4]
			ANIMAL		
none	undiluted; 0.1 ml applied	3 New Zealand White rabbits, sex not specified	Ocular irritation study performed in accordance with OECD TG 405; eyes were instilled with test material and washed 24 h after treatment, prior to 24-h reading; observations made at 1, 24, 48, and 72 h and 7, 14, and 21 d	Irritating to eyes; 1 rabbit had slight corneal opacity that was reversible in 21 d; signs of a slight iris injury observed that was reversible in 7 d; a medium to severe irritation of the conjunctivae also observed and was reversible in 21 d	[4,5]
none	undiluted; 0.1 ml applied	6 albino rabbits, sex not specified	Ocular irritation study; eyes instilled with test material and were not rinsed; observations made at 24, 48, and 72 h and 7 d	Irritating to eyes; mild effects to the cornea and severe effects to the conjunctivae were observed in all animals at all time points; mild iritis was observed in the majority of the animals at most time points and was not reversed after the 72-h observation period	[4,5]
none	undiluted; 0.1 ml applied	6 New Zealand White rabbits, sex not specified	Ocular irritation study performed in accordance with OECD TG 405; eyes instilled with test material and were not rinsed; observations made at 24, 48, and 72 h	Irritating to eyes; negligible iritis and corneal effects observed; very mild chemosis and moderate to significant redness/conjunctivitis observed, which persisted until the end of observation but showed signs of recovery	[4,5]
none	undiluted; 0.1 ml applied	3 New Zealand White rabbits, sex not specified	Ocular irritation study performed in accordance with OECD TG 405; not specified if eyes were rinsed after instillation of the test material; observations made at 24, 48, and 72 h	Irritating to eyes; conjunctival effects were persistent, lasting until within 21 d in 2 animals; corneal and iridial effects were fully reversible within 14 d	[4]
none	undiluted; “one drop” applied	2 Vienna White rabbits, sex not specified	Ocular irritation study; one drop of test material applied to conjunctival sac of the right eye, left eye received physiological solution of sodium chloride and served as control; animal observed several times on treatment day and 14 d afterward; not reported if eyes were rinsed	Irritating to eyes; conjunctival and corneal effects were marked; corneal effects disappeared within 8 d	[4]

REFERENCES

1. Nikitakis J, Kowcz A. 2025. Web-Based International Cosmetic Ingredient Dictionary and Handbook. https://incipedia.personalcarecouncil.org/winci/.

2. Andersen FA. Final Report on the Safety Assessment of Butoxyethanol. *J Am Coll Toxicol*. 1996;15(6):462–526.

3. Andersen FA (ed.). Annual Review of Cosmetic Ingredient Safety Assessments - 2002/2003. Butoxyethanol. *Int J Toxicol*. 2005;24(Suppl 1):18–20.

4. European Chemicals Agency. 2024. 2-Butoxyethanol. https://chem.echa.europa.eu/100.003.550/dossier-view/57c85aa7-f198-4012-9d0f-9dbcc25424e0/6904173c-d8a4-49e9-afd0-47e025ee496e_6904173c-d8a4-49e9-afd0-47e025ee496e?searchText=butoxyethanol. Date Accessed: January 13, 2025.

5. Scientific Committee on Consumer Products. 2007. Opinion on Ethylene Glycol Monobutyl Ether (EGBE). SCCP/1045/06. https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_095.pdf. Date Accessed: January 15, 2025.

6. U.S. Food and Drug Administration. Federal Food, Drug, and Cosmetic Act Section 612 Title 21.

7. U.S. Food and Drug Administration Office of the Chief Scientist. 2024. Registration and Listing Data - Frequency of Use of Cosmetic Products. College Park, MD [Obtained under the Freedom of Information Act from the Division of Freedom of Information; requested as "Frequency of Use Data" July 17; 2024; received July 30, 2024].

8. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). 2023. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD [Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023.].

9. Personal Care Products Council. 2025. Concentration of Use by FDA Product Category: Butoxyethanol. [Unpublished data submitted by the Personal Care Products Council on March 27, 2025.].

10. EUR-Lex. 2009. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast). (Text with EEA relevance). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1223-20240424.

11. Wilkinson SC, Williams FM. Effects of experimental conditions on absorption of glycol ethers through human skin in vitro. *Int Arch Occup Environ Health*. 2002;75(8):519–527.

12. Traynor MJ, Wilkinson SC, Williams FM. The influence of water mixtures on the dermal absorption of glycol ethers. *Toxicol Appl Pharmacol*. 2007;219(2):128–134.

13. Lockley DJ, Howes D, Williams FM. Percutaneous penetration and metabolism of 2-butoxyethanol. *Arch Toxicol*. 2004;78(11):617–628.

14. Traynor MJ, Wilkinson SC, Williams FM. Metabolism of butoxyethanol in excised human skin in vitro. *Toxicol Lett*. 2008;177(3):151–155.

15. Jones K, Cocker J, Dodd LJ, Fraser I. Factors affecting the extent of dermal absorption of solvent vapours: A human volunteer study. *Ann Occup Hyg*. 2003;47(2):145–150.

16. Broding HC, van der Pol A, de Sterke J, et al. In vivo monitoring of epidermal absorption of hazardous substances by confocal Raman micro-spectroscopy. *J Dtsch Dermatol Ges*. 2011;9(8):618–627.

17. Jakasa I, Mohammadi N, Kruse J, et al. Percutaneous absorption of neat and aqueous solutions of 2-butoxyethanol in volunteers. *Int Arch Occup Environ Health*. 2004;77:79–84.

18. Kezic S, Meuling W, Jakasa I. Free and total urinary 2-butoxyacetic acid following dermal and inhalation exposure to 2-butoxyethanol in human volunteers. *Int Arch Occup Environ Health*. 2004;77(8):580–586.

19. Kelsey JR, Otter R, Rogers E, Salthammer T. The acute vapour inhalation toxicity of 2-butoxyethanol. Points considered when designing and conducting a study in guinea pigs and evaluating existing inhalation toxicity data on low volatility solvents. *Regul Toxicol Pharamcol*. 2023;144:105492.

20. Park J, Kamendulis LM, Klaunig JE. Mechanisms of 2-butoxyethanol carcinogenicity: Studies on Syrian hamster embryo (SHE) cell transformation. *Toxicol Sci*. 2002;68(1):43–50.

21. Corthals SM, Kamendulis LM, Klaunig JE. Mechanisms of 2-butoxyethanol-induced hemangiosarcomas. *Toxicol Sci*. 2006;92(2):378–386.

22. Kenyon MO, Coffing SL, Ackerman JI, et al. Compensatory erythropoiesis has no impact on the outcome of the in vivo Pig-a mutation assay in rats following treatment with the haemolytic agent 2-butoxyethanol. *Mutagenesis*. 2015;30(3):325–334.

23. National Toxicology Program. 2000. NTP Technical Repot on the Toxicology and Carcinogenesis Studies of 2-Butoxyethanol (CAS No. 111-76-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 484. NIH Publication No. 00-3974. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr484.pdf.

24. Proctor DM, Suh M, Chappell G, et al. An adverse outcome pathway (AOP) for forestomach tumors induced by non-genotoxic initiating events. *Regul Toxicol Pharamcol*. 2018;96:30–40.

25. Proctor DM, Gatto NM, Hong SJ, Allamneni KP. Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment. *Toxicol Sci*. 2007;98(2):313–326.

26. Cohen SM, Storer RD, Criswell KA, Doerrer NG, Dellarco VL, et al. Hemangiosarcoma in rodents: Mode-of-action evaluation and human relevance. *Toxicol Sci*. 2009;111(1):4–18.

27. Criswell KA, Cook JC, Morse D, et al. Pregabalin induces hepatic hypoxia and increases endothelial cell proliferation in mice, a process inhibited by dietary vitamin E supplementation. *Toxicol Sci*. 2012;128(1):42–56.

28. Criswell KA, Cook JC, Wojcinski Z, et al. Mode of action associated with development of hemangiosarcoma in mice given pregabalin and assessment of human relevance. *Toxicol Sci*. 2012;128(1):57–71.

29. Criswell KA, Wojcinski Z, Pegg D, Albassam M, Duddy S, et al. Key components of the mode of action for hemangiosarcoma induction in pregabalin-treated mice: Evidence of increased bicarbonate, dysregulated erythropoiesis, macrophage activation, and increased angiogenic growth factors in mice but not in rats. *Toxicol Sci*. 2012;128(1):22–41.

30. Kakiuchi-Kiyota S, Vetro JA, Suzuki S, Varney ML, Han J, et al. Effects of the PPARγ agonist troglitazone on endothelial cells in vivo and in vitro: Differences between human and mouse. *Toxicol Appl Pharmacol*. 2009;237(1):83–90.

31. Liu L, Kakiuchi-Kiyota S, Arnold LL, Johansson SL, Wert D, Cohen SM. Pathogenesis of human hemangiosarcomas and hemangiomas. *Hum Pathol*. 2013;44(10):2302–2311.

32. International Agency for Research on Cancer. 2006. Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. Volume 88. https://publications.iarc.fr/_publications/media/download/2757/c6a9fc1529ff03f196d3595caf6e198cb9b104ce.pdf.

33. Gift JS. U.S. EPA's IRIS assessment of 2-butoxyethanol: The relationship of noncancer to cancer effects. *Toxicol Lett*. 2005;156(1):163–178.

34. Laifenfeld D, Gilchrist A, Drubin D, et al. The role of hypoxia in 2-butoxyethanol-induced hemangiosarcoma. *Toxicol Sci*. 2010;113(1):254–266.

35. Regulska M, Pomeirny B, Basta-Kaim A, Starek A, et al. Effects of ethylene glycol ethers on cell viability in the human neuroblastoma SH-SY5Y cell line. *Pharmacol Rep*. 2010;62(2):1243–1249.

36. Ezov N, Levin-Harrus T, Mittelman M, et al. A chemically induced rat model of hemolysis with disseminated thrombosis. *Cardiovasc Toxicol*. 2002;2(3):181–194.

37. Koshkaryev A, Barshtein G, Nyska A, et al. 2-Butoxyethanol enhances the adherence of red blood cells. *Arch Toxicol*. 2003;77(8):465–469.

38. Ramot Y, Lewis DA, Ortel TL, et al. Age and dose sensitivities in the 2-butoxyethanol F344 rat model of hemolytic anemia and disseminated thrombosis. *Exp Toxicol Pathol*. 2007;58(5):311–322.

39. Starek A. Studies on the nature of hemolytic effect induced by ethylene glycol alkyl ethers. *Acta Pol Pharm*. 2008;65(4):421–425.

40. Siesky AM, Kamendulis LM, Klaunig JE. Hepatic effects of 2-Butoxyethanol in rodents. *Toxicol Sci*. 2002;70(2):252–260.

41. Park J, Kamendulis LM, Klaunig JE. Effects of 2-butoxyethanol on hepatic oxidative damage. *Toxicol Lett*. 2002;126(1):19–29.

42. Yoshizawa K, Kissling GE, Johnson JA, et al. Chemical-induced atrial thrombosis in NTP rodent studies. *Toxicol Pathol*. 2005;33(5):517–532.

43. Shabat S, Nyska A, Long PH, et al. Osteonecrosis in a chemically induced rat model of human hemolytic disorders associated with thrombosis – A new model for avascular necrosis of bone. *Calcif TIssue Int*. 2004;74(3):220–228.

44. Lewis DN, Nyskka A, Johnson K, et al. 2-Butoxyethanol female-rat model of hemolysis and disseminated thrombosis: X-ray characterization of osteonecrosis and growth-plate suppression. *Toxicol Pathol*. 2005;33(2):272–282.

45. Hung T, Dewitt CR, Martz W, Schreiber W, Holmes DT. Fomepizole fails to prevent progression of acidosis in 2-butoxyethanol and ethanol coingestion. *Clin Toxicol*. 2010;48:569–571.

46. Song S, Kang S, Choi W, et al. Reticulocytosis in screen-printing workers exposed to 2-butoxyethanol and 2-ethoxyethanol. *Ann Occup Environ Med*. 2017;29:54.

47. Laitinen JA, Koponen J, Kokkalainen J, Kiviranta H. Firefighters' exposure to perfluoroalkyl acids and 2-butoxyethanol present in firefighting foam. *Toxicol Lett*. 2014;231:227–232.

48. Hung P, Cheng S, Liou S, Tsai S. Biological monitoring of low-level 2-butoxyethanol exposure in decal transfer workers in bicycle manufacturing factories. *Occup Environ Med*. 2011;68:777–782.

49. Ghanayem BI, Sullivan CA. Assessment of the haemolytic activity of 2-butoxyethanol and its major metabolite, butoxyacetic acid, in various mammals including humans. *Hum Exp Toxicol*. 1993;12(4):305–311.