Final Report on the Safety Assessment of Phenethyl Alcohol

Phenethyl Alcohol (PEA) is an aromatic alcohol that is used as a fragrance and an antimicrobial preservative in cosmetic formulations. PEA is metabolized to phenylacetic acid in mammals. In humans, it is excreted in urine as the conjugate phenylacetylglutamine.

The acute oral LD₅₀ of PEA to rats ranged from 2.5 to 3.1 ml/kg, and for mice and guinea pigs was 0.8 to 1.5 g/kg and 0.4 to 0.8 g/kg, respectively. The dermal LD₅₀ for rabbits and guinea pigs were 0.8 g/kg and 5 g/kg, respectively. PEA was slightly to moderately irritating to the skin of rabbits and guinea pigs and was not a guinea pig sensitizer. PEA, in concentrations of 1% or greater, was irritating to the eyes of rabbits. PEA was neither an irritant nor a sensitizer in human studies.

PEA was not mutagenic in the Ames test or in an Escherichia coli DNA-polymerase-deficient assay system. PEA did inhibit the repair of radiation-induced breaks in the DNA of E. coli. PEA did not increase the number of sister chromatid exchanges in human lymphocytes.

Maternal exposure to PEA, microencapsulated in the feed, at concentrations of 1000, 3000, and 10,000 ppm had no effect on embryo-fetal loss, or embryo-fetal development and morphology. There was an increased incidence of incomplete ossification in the 10,000 ppm PEA group litters. Doses of 0.14, 0.43, and 1.40 ml/kg of PEA were applied to the skin of pregnant rats. Maternal toxicity was marked at the highest dose. Morphological abnormalities in fetuses in the 1.40 ml/kg PEA group were observed. The number of fetuses with moderate degrees of reduced ossification and with cervical rib(s) was significantly greater in the 0.43 ml/kg PEA group than in the controls. The incidence of structural changes was slightly greater in 0.14 ml/kg PEA-treated rats than in control rats. Dermal doses of 0.07, 0.14, 0.28, 0.43, and 0.70 ml/kg/day PEA to pregnant rats significantly increased cervical ribs in the 0.70 ml/kg/day group litters.

The highest no observed adverse effect level (NOAEL) was 0.43 ml/kg/day for cervical rib malformation (teratogenic effect). The dermal applied teratogenicity NOAEL of 0.43 ml/kg/day was used to estimate a safe use level of 1.0% PEA in cosmetic products.¹
CHEMICALS AND PHYSICAL PROPERTIES

Phenethyl Alcohol (PEA) (CAS No. 60-12-8) is the aromatic alcohol with the following chemical formula:

\[
\begin{align*}
&\text{CH}_3\text{CH}_2\text{OH} \\
&\text{phenethyl alcohol (PEA)}
\end{align*}
\]

PEA is also called β-phenethyl alcohol, β-phenyl ethyl alcohol, 2-phenyl ethanol, benzeneethanol, benzyl carbinol, and β-hydroxyethylbenzene.\(^{(2-5)}\)

PEA is a colorless, transparent, slightly viscous liquid with a sharp, burning taste. It has a floral odor with a rose character.\(^{(2,5,6)}\)

The molecular weight of PEA is 122.17. It has a specific gravity of 1.0202 at 20°C (compared with water at 4°C) and a specific gravity of 1.017 to 1.019 at 25°C (compared with water at 25°C). The boiling point of PEA at 750 mm Hg is 219 to 221°C, at 14 mm Hg is 104°C, at 12 mm Hg is 98 to 100°C, and at 10 mm Hg is 97.4°C. The freezing point of PEA is -27°C. The alcohol is combustible, and its flash point is 102.2°C. The index of refraction for PEA at 20°C for sodium light is 1.530 to 1.534.\(^{(2,4-6)}\)

PEA is very soluble in alcohol and ether. It is also soluble in fixed oils, glycerol, and propylene glycol and is slightly soluble in mineral oil. A 2-ml sample of PEA will dissolve in 100 ml of water after thorough shaking.\(^{(4-7)}\)

Exposure to air may cause a slight oxidation of PEA. PEA can be oxidized by acids and other oxidants, and oxidation in the presence of air is accelerated by heat. It is stable in colorless glass ampules at room temperature or in full opaque containers stored at 4 to 27°C for up to 1 year. PEA is absorbed by polyethylene containers.\(^{(2,8,9)}\)

PEA occurs naturally in the environment. It is produced by microorganisms, plants, and animals.\(^{(10)}\) It has been found as the free alcohol or esterified in a number of natural essential oils, and in food, spices, and tobacco. PEA has been found in undistilled alcoholic beverages, beers, and wines at concentrations of 10 to 50 mg/L, and in whiskey, at a concentration greater than 15 mg/L.\(^{(5,11-13)}\)

PEA has been isolated from the fungus, Gibberella fujikuroi.\(^{(5)}\) Commercial quantities of PEA have been produced by reduction of various phenylacetic acid esters, by hydrogenation of phenylacetaldehyde in the presence of a nickel catalyst, by the action of ethylene oxide on phenylmagnesium bromide or phenylmagnesium chloride, by catalytic hydrogenation using styrene oxide, and by the Friedel-Crafts reaction of benzene and ethylene oxide.\(^{(2,5,6,14)}\) PEA can be purified by distillation.\(^{(5)}\)

Researchers have reported that the concentration of PEA in technical and perfumery grade PEA is 72.9 to 76% and 89.9 to 90.9%, respectively.\(^{(16)}\) However, it has been stated by other researchers that PEA for cosmetic use should contain not less than 98% PEA\(^{(17)}\) and that PEA containing 0.01 to 0.03% impurities is suitable for perfumery use.\(^{(15)}\)

Qualitative and quantitative determinations of PEA are made by colorimetry,\(^{(17)}\) thin-layer chromatography,\(^{(18)}\) gas chromatography,\(^{(9)}\) gas-liquid chromatography,\(^{(2,18,19)}\) mass spectrometry,\(^{(20)}\) gas chromatography-mass spectrometry,\(^{(21)}\) ultraviolet spectroscopy,\(^{(22)}\) and infrared spectroscopy.\(^{(7,19)}\) Positive identification of PEA can be made by comparison of an infrared absorption spectrum with a published
infrared absorption spectrum for PEA. An unpublished ultraviolet absorption spectrum is also available for PEA. Maximum absorption occurs at a wavelength of 258 nm.

USE

Cosmetic Use

PEA is used as an antimicrobial preservative in cosmetics. It is active at pH 6 or less and is inactivated by nonionic detergents including polysorbate-80. PEA is also a widely used fragrance material that imparts a rose character to perfume compositions. Almost all rose fragrances and other floral-type perfumes contain PEA, and PEA is used extensively for many other fragrance applications because it blends well.

Product types and the number of product formulations containing PEA and reported voluntarily to the Food and Drug Administration (FDA) in 1984 and 1987 are presented in Tables 1 and 2. Voluntary filing of this information by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations. Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Data

<table>
<thead>
<tr>
<th>TABLE 1. Product Formulation Data for Phenethyl Alcohol</th>
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<tbody>
<tr>
<td><strong>Product category</strong></td>
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<tr>
<td></td>
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<tr>
<td>Bubble baths</td>
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<tr>
<td>Eyeliner</td>
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<tr>
<td>Eye makeup remover</td>
</tr>
<tr>
<td>Mascara</td>
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<tr>
<td>Other eye makeup preparations</td>
</tr>
<tr>
<td>Colognes and toilet waters</td>
</tr>
<tr>
<td>Perfumes</td>
</tr>
<tr>
<td>Shampoos (noncoloring)</td>
</tr>
<tr>
<td>Hair shampoos (coloring)</td>
</tr>
<tr>
<td>Lipstick</td>
</tr>
<tr>
<td>Makeup bases</td>
</tr>
<tr>
<td>Skin cleansing products (cold creams, lotions, liquids, and pads)</td>
</tr>
<tr>
<td>Depilatories</td>
</tr>
<tr>
<td>Face, body, and hand (excluding shaving preparations)</td>
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<tr>
<td>Hormone products</td>
</tr>
<tr>
<td>Moisturizing products</td>
</tr>
<tr>
<td>Paste masks (mud packs)</td>
</tr>
<tr>
<td>1984 Totals</td>
</tr>
</tbody>
</table>
submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration. In 1984, PEA was reported to be an ingredient in 36 cosmetic formulations at concentrations ranging from ≤0.1% to between 0.1 and 1% (Table 1).\(^{26}\) In 1987, PEA was reported to be an ingredient in 45 cosmetic formulations at concentrations of ≤1% (Table 2).\(^{27}\) FDA has reported that PEA was used as a preservative in 6 cosmetic formulations in 1977, 6 in 1980, 9 in 1984, and 8 in 1987.\(^{28}\)

Another source reported that PEA is used in perfume at a maximum concentration of 2.0%, in creams and lotions at a maximum concentration of 0.2%, in soap at a maximum concentration of 0.5%, and in detergent at a maximum concentration of 0.05%.\(^{12}\) The odor stability of PEA in toilet soap is good to very good.\(^{29}\)

Cosmetic products containing PEA may be applied to, or come in contact with, skin, eyes, hair, and mucous membranes (Tables 1 and 2).\(^{26,27}\)

Product formulations containing PEA may be applied as many as several times a day and may remain in contact with the skin for variable periods following application. Daily or occasional use may extend over many years (Tables 1 and 2).\(^{26,27}\)

**Noncosmetic Use**

PEA was given GRAS, or generally recognized as safe, status by the Flavoring Extract Manufacturers’ Association (FEMA) (FEMA No. 2858) and is approved by the FDA for food use.\(^{12}\) PEA may be safely used as a synthetic flavoring substance or adjuvant in the minimum quantity required to produce its intended effect, and otherwise in accordance with all the principles of good manufacturing practice.\(^{25}\)

In 1965, the average maximum use concentration of PEA as a flavoring substance in beverages was 1.5 ppm, in ice cream and ices was 8.3 ppm, in candy was 12 ppm, in baked goods was 16 ppm, in gelatins and puddings was 0.15 ppm, and in chewing gum was 21 to 80 ppm.\(^{30}\) In 1970, the average maximum use concentration of PEA as a flavoring substance in baked goods was 32.8 ppm, in fats and oils was 0.1 ppm, in frozen dairy products was 23.4 ppm, in soft candy was 30.0 ppm, in hard candy was 2.45 ppm, in chewing gum was 78.8 ppm, in gelatins and puddings was 9.87 ppm, and

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**TABLE 2. Product Formulation Data**\(^{27}\)

<table>
<thead>
<tr>
<th>Product category</th>
<th>Total no. of formulations in category</th>
<th>Total no. containing ingredient</th>
<th>No. of product formulations within each concentration range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye area preparations</td>
<td>692</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Perfumes, toilet waters, colognes</td>
<td>1333</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hair shampoos (noncoloring)</td>
<td>798</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Makeup preparations</td>
<td>1709</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depilatories</td>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin care preparations</td>
<td>3121</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>1987 Totals</td>
<td></td>
<td>45</td>
<td>45</td>
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</tbody>
</table>
in beverages was 6.6 to 17.8 ppm. The estimated daily per capita intake of PEA in 1970
was 74.3 μg. The total annual consumption of PEA, in 1983 to 1984 in the United
States, natural and added as a flavoring substance, in apples, apple juice, beer, roasted
coffee, cranberries, orange juice, and strawberries was 630,850 kg. Only 638 kg of PEA
were consumed as an added flavor in these foods in 1982.

PEA is on the FDA list of inactive ingredients for approved prescription drug
products. PEA has been used as a preservative in eyedrops, usually at a concentra-
tion of 0.5%. In the FDA Over-the-Counter (OTC) Drug Review for ophthalmic
drug products as preservatives, PEA is in Category III; there are insufficient data to
determine safety and effectiveness or the substance is not yet categorized.

PEA is also used as an intermediate in the preparation of dyestuffs and photographic
materials.

**ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION**

The log octanol/water partition coefficient for PEA was 1.34 to 1.36, and the
n-heptane/water partition coefficient was 0.518.

Doses of 0.14 and 0.7 ml/kg [14C]PEA were applied to the skin on the backs of rats
one time or repeatedly, and excretion and plasma concentration data were
collected. After single administration of 0.14 ml/kg [14C]PEA, 77.2% of the
radioactivity was excreted in the urine within 24 h; by 120 h the urinary excretion
reached 80.7%. After a dose of 0.7 ml/kg [14C]PEA, 35.8% was excreted within 24 h,
39.0% by 120 h. The excretion of radioactivity in the urine of rats given a daily dose of
0.14 or 0.7 ml/kg for 5 days was 68.6% and 40.2%, respectively, over a 216 h period
after the first dose; most of the urinary radioactivity was excreted within 24 h of
application. Most of the radioactivity not recovered from the urine was retained in
dressings or lost by evaporation. Radioactivity was eliminated rapidly from the tissues.
After exposure to 0.14 ml/kg [14C]PEA dose for 6 h, the highest concentrations of
radioactivity detected when the rats were sacrificed at 120 h were found in the treated
skin, the fat, and the pancreas. After 10 doses of 0.14 or 0.7 ml/kg [14C]PEA,
radioactivity was detected in the fetuses of dams sacrificed at peak plasma concentra-
tions. Phenaceturic acid, the glycine conjugate of phenylacetic acid, was the major PEA
metabolite detected in rat urine and plasma. Phenylacetic acid was detected in both
urine and plasma. Hippuric acid, the glycine conjugate of benzoic acid, was detected
in urine but not in plasma. PEA was detected in urine and plasma in small quantities.
The researchers concluded that, following dermal application, PEA was absorbed
rapidly and excreted rapidly in the urine of the rat. PEA was oxidized rapidly and
primarily to phenylacetic acid, which was conjugated as phenylaceturic acid.

Plasma concentrations of PEA and phenylacetic acid were measured after the
dermal application of single doses of 0.7 and 1.4 ml/kg PEA. Peak PEA plasma
concentrations were reached 0.5 h after PEA application. Peak phenylacetic acid
plasma concentrations were reached 4 h after PEA application and declined to almost
background concentrations by 24 h. The mean plasma concentrations of phenylacetic
acid were greater than those of PEA for most of the sampling period at both doses of PEA,
and the phenylacetic acid plasma concentration was not linear with PEA dose.

Six to 8% of PEA administered by stomach tube to chinchilla rabbits was excreted in
the urine as the glucuronide. The major metabolite of PEA was phenylacetic acid;
this oxidation product accounted for 61 to 76% of the dose. Phenylaceturic acid was extracted readily from the urine. A dose of 0.3 g/kg of PEA was administered by stomach tube to 3 to 6 rabbits.\textsuperscript{42} No signs of toxicity were observed. Within 24 h, 42% of the original PEA dose was excreted in the urine as a glycine conjugate and 5% was excreted as a glucuronide. Three chinchilla rabbits were given 2 mmol/kg PEA via stomach tube.\textsuperscript{43} Within 24 h, 3% of the original PEA dose was excreted as hippuric acid. Phenylaceturic acid was also detected in the urine.

A 1.0 g dose of PEA was administered orally to one dog each day for 14 consecutive days.\textsuperscript{44} Phenylaceturic acid, at 44.5% of the theoretical yield, was recovered from the urine of the dog.

Permeability chambers were prepared with human cadaver abdominal skin. PEA, both as a liquid and as a vapor, was absorbed through the skin. The liquid flux of 650 $\mu$g/cm²/h was 24 times greater than the vapor flux of 27 $\mu$g/cm²/h.\textsuperscript{37}

$[{}^{14}\text{C}]$PEA in ethanol was applied to the skin of the upper chest of two male volunteers at a dose of 0.1 mg/cm².\textsuperscript{45} After 6 h, the treatment sites were washed. Neither subject experienced adverse reactions attributable to PEA exposure. A mean of 7.55% of the initial radioactivity applied was absorbed through the skin and excreted in the urine. Radioactivity was detected in the urine only during the first 48 h after treatment. No radioactivity was detected in the feces. Radioactivity was recovered in the dressings at 2.60% of the initial dose and in the treated skin washes at 6 h at 0.64% of the initial dose. Most of the radioactivity was lost, probably by evaporation, from the skin during the 6-h treatment period. Radioactivity was detected in the plasma 15 min after treatment (mean dose of 3.5 ng/ml), reached a peak of 13.8 ng/ml at 1.5 h, and, after 4 h, was below the limit of accurate detection (3.0 ng/ml). Radioactivity in whole blood was always below the limit of accurate detection (between 7 and 15 ng/ml). The researchers concluded that, following dermal administration, PEA was absorbed rapidly and excreted rapidly in the urine of man. Two metabolites were detected in the urine of the two subjects. Phenylacetylglutamine was the major metabolite and was present at 4.1% of the initial dose. The second metabolite was a glucuronide or ethereal sulfate and was present at 2.7% of the initial dose.

PEA is metabolized almost entirely to phenylacetic acid in mammals, and, in man, is excreted in the urine as the conjugate, phenylacetylglutamine.\textsuperscript{12,46,47} A 4.0 g dose of PEA was administered orally to one adult male human.\textsuperscript{44} Phenylacetylglutamine, at 26% (2.25 g) of the theoretical yield, was recovered from the urine of the man. PEA has also been isolated from the urine of man following exposure to chemicals, such as styrene.\textsuperscript{48}

**ANIMAL TOXICOLOGY**

**Oral Studies**

The acute oral LD₅₀ of PEA for rats was 2.46 ml/kg.\textsuperscript{49} Groups of Osborne-Mendel rats were given PEA by intubation and were observed for 14 days.\textsuperscript{50} The acute oral LD₅₀ was 1.79 g/kg. With large doses of PEA, coma ensued within 15 min. Gross lesions included those consistent with irritation of the lower half of the stomach. The time to death was 4 to 18 h.

Doses of 1.0, 2.0, 3.0, and 4.0 ml/kg PEA were given to groups of 5 female rats by intubation, and the rats were observed for 24 h.\textsuperscript{51} The acute oral LD₅₀ was 3.1 ml/kg. One rat given 3.0 ml/kg died at 25 h. All other rats were alive at 72 h.
Six groups of four rats were given PEA by stomach tube. Females received 0.16 to 2.5 g/kg PEA, and males received 0.10 to 5.0 g/kg PEA. The LD₅₀s for female and male rats were 0.65 g/kg and 1.43 g/kg, respectively. Degeneration of the liver and kidneys was observed. In the liver, hyperemia and a slight fatty change were observed. In the kidneys, tubular necrosis was found in the renal medulla, and tubular cell cloudy swelling and cast formation were found in the renal cortex.

A 10% (v/v) aqueous PEA solution was administered by oral intubation to groups of 12 mice in doses of 0.3, 0.6, and 0.9 g/kg. The intoxicating effects of the PEA were determined by evaluating the performance of the mice on a tilting plane. The doses of 0.3, 0.6, and 0.9 g/kg PEA resulted in performances at 15 min of 91.3, 80.3, and 65.4% of control values, respectively. Groups of 10 to 40 mice received 1.0 to 2.0 mg/kg PEA as a 5% solution in 10% propylene glycol orally. Narcosis was effected in most mice within 1 and 5 min. The oral LD₅₀ of PEA was approximately 1.5 g/kg.

The acute oral LD₅₀s of PEA in mice and guinea pigs was 0.8 to 1.5 g/kg and 0.4 to 0.8 g/kg, respectively.

The average LD₅₀ of a 20–45% PEA solution in sunflower oil administered orally to rats, mice, and guinea pigs at doses of 2.0 to 5.0 ml/kg was 2.54 g/kg for the three species. When administered at approximately 0.02 times the LD₅₀ (51 mg/kg) orally to rats for 4 months, PEA increased the activity of alanine aminotransferase and the concentration of sulfhydryl groups and decreased the activity of cholinesterase in the serum. There were no changes in serum fructose diphosphaldolase, asparaginase, and amylase activities. Blood serum proteins decreased slightly, and galactose utilization by the liver increased. Few or no signs of toxicity were observed.

Rats were fed diets containing 0.0625 to 2 g/kg PEA for 14 days. No adverse effects were observed.

An eye makeup remover, containing 0.05% PEA, was given by gavage at a dose of 5 ml/kg to 5 male and 5 female Sprague-Dawley rats. The rats were observed for 14 days; no toxic effects were observed.

**Dermal Studies**

The dermal LD₅₀ for rabbits was 790 mg/kg and for guinea pigs it was 5 g/kg. The acute dermal LD₅₀ of PEA for rabbits was 0.79 ml/kg in another report. Another source reported that the dermal LD₅₀ for guinea pigs was 5 to 10 ml/kg. All treated rats (number unspecified) died within 24 h after the percutaneous application of 6 to 8 ml/kg PEA to the shaved dorsum. A 3 ml/kg dose of PEA was applied daily to the skin of two rats for up to 28 days; one of the 2 rats died after 7 days of treatment.

PEA was applied by inunction to the shaved dorsa of groups of 15 male and 15 female Charles River CD rats at doses of 0.25, 0.50, 1.00, and 2.00 ml/kg for 90 days. Thirty each of untreated male and untreated female rats served as controls. Animals were observed for changes in appearance and behavior, body weights and feed consumption were measured, and funduscopic and biomicroscopic examinations were performed on the eyes. Blood biochemical and urinary analyses were performed. At the end of the study, the rats were necropsied, organs were weighed, and adrenal glands, brain, heart, kidneys, liver, lungs and bronchi, mesenteric lymph node, pituitary, sternum, spinal cord, testes with epididymides, ovaries, spleen, urinary bladder, and nerve with muscle from all control rats and those given the highest dose
were microscopically examined. Bone marrow smears from these groups were also examined. No deaths occurred during the study, and treated and control animals did not differ in appearance or behavior. The mean body weight gains were decreased in a dose-dependent manner, and these decreases were statistically significant at 1.00 and 2.00 ml/kg. All treated and control rats consumed the same amount of feed. Results of eye examinations and urinary analyses were within the normal range. There was a statistically significant decrease in the hemoglobin concentration and leukocyte count in male rats that received 2.00 ml/kg. Some organ weights were increased, and some were decreased. No other treatment-related effects were observed.

PEA was tested for skin irritation in rabbits, guinea pigs, and miniature swine.\(^{56}\) Hair was clipped from the dorsal surface of groups of 6 albino angora rabbits and male Hartley guinea pigs, and 0.1 g PEA was applied to the skin and spread. After 24 h, the sites were scored, and the PEA was reapplied. The sites were scored again after 48 h, and Evans blue in saline was injected intravenously into the animals. One hour later, the animals were sacrificed, and the dorsal skin was removed and evaluated for degree of dilation of blood vessels, the amount of swelling, the degree of bluing, and the amount of bleeding. A total irritation score for PEA was determined with scores from the living skin and the removed skin. A 48-h patch with 0.05 g PEA was applied to the clipped dorsal skin of 6 miniature swine, and the sites were scored at patch removal. The skin of the rabbits, guinea pigs, and miniature swine was histopathologically evaluated. PEA was moderately irritating to the skin of rabbits and guinea pigs; the percent of positive or ± reactions on a 4+ scale was between 40 and 70%. PEA was not irritating to the skin of miniature swine; the percentage of positive or ± reactions on a 4+ scale was 10% or less.

In other studies, PEA was slightly irritating to the skin of guinea pigs\(^{12}\) and to the abdominal skin of rabbits.\(^{49}\)

PEA was not a sensitizer for guinea pig skin in concentrations of 1 to 2%.\(^{9}\)

An eye makeup remover containing 0.05% PEA was applied to the clipped skin of 6 female New Zealand white rabbits at a dose of 0.5 ml.\(^{57}\) The application sites were left open to the air. The product was removed and reapplied 24 and 48 h after the initial application. The application sites were observed at 24, 48, 72, and 96 h. There were no positive reactions.

### Ocular Studies

A 0.005 ml dose of 100% PEA or a 0.5 ml dose of 5 or 15% PEA in propylene glycol instilled into rabbit eyes caused severe corneal irritation and iritis.\(^{49}\)

Irritation of the conjunctiva and transient clouding of the cornea were observed following the instillation of 1% PEA into rabbit eyes.\(^{55}\)

PEA, at concentrations of up to 2% in saline, induced a loss of touch response in the cornea of rabbits.\(^{56}\)

No ocular redness, discharge, or other sign of irritation were observed when two drops of a 0.3% PEA in saline solution were instilled into the left eyes of 2 rabbits three times a day, 5 days a week for 2 weeks.\(^{51}\)

Ophthalmic preparations containing PEA as a preservative were irritating to rabbit eyes.\(^{59}\)

An eye makeup remover, containing 0.05% PEA, was instilled into the conjunctival sac of one eye of 9 female New Zealand white rabbits at a dose of 0.1 ml.\(^{60}\) The product was not irritating to the eyes of rabbits.
Intraperitoneal Studies

The intraperitoneal LD₅₀ of PEA for mice has been reported to be 0.2 to 0.4 g/kg and for guinea pigs, 0.4 to 0.8 g/kg, respectively. Another source reported that the intraperitoneal LD₅₀ of PEA for mice was 0.8 mg/kg. Other researchers have reported that intraperitoneal doses of greater than 0.3 g/kg PEA were usually lethal to mice.

Male Sprague-Dawley rats were injected intraperitoneally with several doses of PEA, and the dose necessary to produce an intoxication score of 3, or the ED₃, on a scale of 0 to 7 was calculated. A score of 3 was defined as the presence of impairment of gait and motor coordination but with the abdomen and pelvis still elevated. The ED₃ was 2.3 mmol/kg (281 mg/kg). The maximum intoxication response was obtained in 5 to 15 min.

Ten of 20 mice received 1.47 mmol/kg pyrazole intraperitoneally. Thirty minutes later, all 20 mice received 300 mg/kg PEA intraperitoneally. A sleeping time of 10 min was induced by PEA alone, and of 45 min by PEA and pyrazole. The researchers concluded that pyrazole had an inhibitory effect on the oxidation of PEA by liver alcohol dehydrogenase.

Subcutaneous Studies

PEA in saline was injected subcutaneously into white mice that weighed 20 to 30 g. The minimum lethal dose of PEA was 0.041 ml or 0.041 g. A general anesthesia was observed for about 1 h in one mouse. At the end of the hour, the mouse “moved about voluntarily and gradually became normal.” In other mice, muscular incoordination, weakness, and exophthalmos were observed. Mice that died were in a coma for several hours before death. There were no “constant” respiratory changes, and there were no signs of irritation at the site of injection.

PEA in peanut oil was administered subcutaneously at doses of 30 mmol/kg (3065 mg/kg) each day for 7 days to partially hepatectomized Holtzman or Charles River (unspecified) rats, and the rats were sacrificed at the end of the study. PEA had no effect on liver regeneration.

Intravenous Studies

PEA in saline was administered intravenously at a dose of 1.83 g to a fox terrier dog that weighed 9 kg. The pulse rate of the dog doubled within a few minutes but quickly returned to normal. Although the pupils reacted to light, they were markedly enlarged. “Extreme” salivation was observed. After the injection, the dog was observed to be depressed and made no attempt to move when urged. Later, the dog attempted to walk, but lacked muscular coordination. Finally, the dog was excited and ran around the room aimlessly. Retching movements were observed several hours after the injection, but these disappeared in about two hours. No effects were evident 12 hours after the injection.

Groups of 20 female A/He mice were given 50 or 250 mg of 2-phenethyl acetate in tricaprylin intraperitoneally 3 times a week for 8 weeks. The mice received total doses of 1.20 and 6.00 g/kg 2-phenethyl acetate and were sacrificed at 20 weeks due to infection with Pseudomonas. Experimental controls included untreated mice, mice treated with distilled water, and mice treated with tricaprylin. Positive controls were given urethan. All controls were sacrificed at 24 weeks. At the end of the study, the
lungs, liver, kidneys, spleen, thymus, intestine, and salivary and endocrine glands of the mice were examined. Seventeen of 20 mice at the low dose survived for 20 weeks. There were no lung tumors in the high-dose mice, and there was one lung tumor in the low-dose mice. Forty-five percent of the vehicle control mice had lung tumors. The frequencies of lung tumors in the treated mice were significantly lower than in the vehicle control mice. No other tumors occurred at a statistically significant frequency.

**Animal Reproduction and Teratology**

Aqueous suspensions of PEA were given by gavage in daily doses of 20 ml/kg to groups of pregnant Long-Evans rats on days 6 to 15 of gestation.\(^{66,67}\) Five pregnant rats received 432 mg/kg PEA, 7 received 43 mg/kg, 7 received 4.3 mg/kg, and 19 control rats received distilled water. These doses were 0.24, 2.4, and 24% of the LD\(_{50}\) for PEA, respectively. The pregnant rats were sacrificed with an overdose of ether on day 20, and the fetuses were examined. Severe maternal intoxication was observed immediately following administration of 432 mg/kg PEA. This condition persisted overnight and was observed each day. No signs of maternal intoxication were observed at the two lower doses of PEA. One rat given 432 mg/kg PEA died from intratracheal intubation. All pups from rats given 432 mg/kg PEA, 97% of pups from rats given 43 mg/kg PEA, and 55% of pups from rats given 4.3 mg/kg PEA were either dead or malformed. Intrauterine growth retardation occurred in both the low- and high-dose groups; average pup weight and crown–rump length were decreased on a per litter basis, and numbers of grossly runted live pups were increased. Embryolethality was not observed in the high-dose group. Mean litter size was decreased in the 43 mg/kg and 4.3 mg/kg dose groups, but the decrease was not significant in the 43 mg/kg group due to the large variability; mean litter size was 9 in these groups and 12 in the control group. The fetal death rate of 18% in the 43 mg/kg group was significantly increased in comparison with the 6% rate in the controls. The increase in malformations caused by PEA was dose related; all live pups in the 432 mg/kg group were grossly malformed, and 93% in the 43 mg/kg group and 50% in the 4.3 mg/kg group were malformed. High-dose group pups had malformed eyes, malformed limbs, hydronephrosis, neural tube defects, and malformed digits. The 43 mg/kg group pups had malformed eyes, hydronephrosis, and limb defects. Low-dose group pups had eye defects and hydronephrosis. Reduced ossification was observed in the skull, limbs, vertebrae, sternum, rib, or tail of treatment groups.

Oral doses of 508 mg/kg PEA in sunflower oil were given to female rats on either day 4 or days 10 to 12 of pregnancy.\(^{68}\) Control rats received sunflower oil orally. On the gestation day 20, the rats were sacrificed, and the fetuses were examined. No differences in size or number of fetuses and no developmental anomalies were observed in the treated rats. The embryos from the rats given PEA on days 10 to 12 of pregnancy were examined histologically; the size of the ossification sites on the extremities of the fetuses were smaller than those of the controls. There were no ossification sites for the pubic bone or the second phalanx of the left and right extremities in 10 to 15% of the embryos from the treated rats. The sagittal sections were also examined; no abnormalities were observed in palatal structure, eyes, brain, or internal organs.

Pregnant female rats were given 1000, 3000, or 10,000 ppm microencapsulated PEA in feed on days 6 to 15 of gestation.\(^{69}\) Actual intake of PEA was 83, 266, and 799
mg/kg/day, respectively. On day 20, the rats were sacrificed, and the fetuses were examined. Reduced maternal feed consumption and a slight weight loss in dams were observed in the 10,000 ppm PEA group only during the first 2 days of treatment. Exposure to PEA had no effect on embryo-fetal development and morphology; incidence, type, and distribution of malformations, anomalies, and skeletal variants in treated and control fetuses were comparable. There was an increased incidence of incomplete ossification in the 10,000 ppm PEA group only; a delay in ossification is usually considered to be transient and self-correcting during the growth and maturation of pups. There was no evidence that exposure to PEA had a detrimental effect on litter size, embryo-fetal loss, litter weight, mean fetal weight, or sex ratio.

Doses of 0.14, 0.43, and 1.40 ml/kg of undiluted PEA were applied under occlusion to the skin of pregnant female rats 24 h per day on days 6 to 15 of gestation. The rats were sacrificed on day 20, and the fetuses were examined. Maternal toxicity was observed at the 1.40 ml/kg PEA dose; 3 of 35 dams died, and clinical signs of toxicity were marked. Mean feed intake and growth rate were decreased. There was resorption of 5 of 23 litters, and 50% or more embryo-fetal wastage in an additional 4 of 18 litters. However, 7 of 18 dams carrying to term had less than 10% early resorptions. Rats had marked differences in response to PEA treatment. Mean litter size was reduced, and fetal weight was decreased. Morphological abnormalities observed in fetuses in the 1.40 ml/kg PEA group included soft tissue and skeletal changes and incomplete ossification. No clear evidence of adverse PEA-related effects on parent and litter parameters was observed in the 0.43 ml/kg group. Although the number of fetuses with soft tissue structural changes was greater than in the controls, there was no obvious pattern to the changes. The number of fetuses with moderate degrees of reduced ossification and with cervical rib(s) was significantly less than in the 1.40 ml/kg PEA group, but was significantly greater than in the controls. The cervical ribs observed were extremely small, and the persistence and functional significance of these ribs is unknown. At the 0.14 ml/kg PEA dose, there was no evidence of maternal toxicity or adverse effects on litter parameters. Although the number of fetuses with soft tissue structural changes was greater than in control rats, the incidence and distribution of such changes were not conclusively associated with PEA treatment.

Doses of 0.07, 0.14, 0.28, 0.43, and 0.70 ml/kg/day of undiluted PEA were applied to the skin of groups of 8 presumed pregnant female rats on days 6 to 15 of gestation. Deionized water was applied to the skin of control rats. Application areas were covered with dressings for 24 h following each application. The animals were sacrificed on gestation day 20. Dermal erythema and/or desquamation was observed in increased incidence in dams following administration of all doses of PEA, and the onset, duration, and severity of these reactions were dose dependent. Atonia and eschar formation were observed only at the highest PEA dose. Small skin lesions were observed at necropsy in one animal that received 0.28 ml/kg/day PEA and in three given 0.70 ml/kg/day PEA. No dams died during the study. There were significantly increased incidences of dams with ptosis and/or urine-stained abdominal fur in the 0.70 ml/kg/day PEA group in comparison with the control group. PEA administration did not reduce average maternal body weight or body weight gain or affect average maternal feed consumption or feed utilization values in a consistent dose-dependent pattern. The averages for corpora lutea, implantations, litter sizes, or resorptions were not adversely affected by PEA administration. The average percentages of resorbed conceptuses and live male fetuses per litter were not different for treated and control groups. Live fetal body
weights were decreased significantly in litters from dams given PEA at doses of 0.14 ml/kg/day and greater, as compared with litters from control dams. The incidence of fetuses with cervical ribs was increased significantly only in the 0.70 ml/kg/day PEA group litters. All other fetal alterations were considered reversible delays in ossification. Delayed sternal and/or pelvic ossification was observed in fetuses from all treated groups, although there was no clear dose-dependent pattern. The incidence of fetuses with delayed pelvic ossification was significantly increased in all treatment groups. In the 0.43 and 0.70 ml/kg/day PEA groups, the incidence of fetuses with incompletely ossified ribs and/or wavy ribs was significantly increased and was dose dependent. Dose-dependent decreases were observed in the litter averages for specific fetal ossification sites in all treatment groups, as compared with the control group. The decreases were statistically significant for metacarpals and hindpaw phalanges in the 0.14 ml/kg/day PEA and greater groups, for caudal vertebrae in the 0.28 ml/kg/day PEA and greater groups, for forepaw phalanges in the 0.43 ml/kg/day PEA and greater groups, and for sternal centers in the 0.70 ml/kg/day PEA group.

MUTAGENICITY

PEA was not mutagenic to Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 with or without metabolic activation in the Ames Salmonella/ mammalian microsome mutagenicity test conducted as a spot test with 3 μmol/plate of PEA.¹⁷²

PEA was negative in an Escherichia coli DNA–polymerase-deficient assay system without metabolic activation. A disk diffusion procedure was used for the test.¹⁷³

PEA at a concentration of 0.25% inhibited the repair of radiation-induced single-strand breaks in the DNA of E. coli.¹⁷⁴

PEA at concentrations of 0.1 to 1.5 mM did not increase the number of sister chromatid exchanges observed in lymphocytes from human whole blood lymphocyte cultures. The highest concentration of PEA used in the study was toxic to the cultures.¹⁷⁵

CLINICAL ASSESSMENT OF SAFETY

Dermal Studies

Undiluted PEA was applied to the inner aspects of the forearms of 20 male and female subjects, and the sites were covered with adhesive bandages for 24 h.¹⁷⁶ The application sites were observed at 24-h intervals for 5 days. No positive reactions for irritation were observed.

Aliquots of 0.05 ml of a 32% solution of PEA in acetone were applied to patches, and the patches were applied for 48 h to the backs of 50 male subjects with no known allergic reactions.¹⁵⁶ Sites were evaluated for irritation 30 minutes after patch removal. PEA was negative for skin irritation; the percentage of positive or ± reactions on a 4+ scale was 10% or less.

PEA had an anesthetic effect upon skin, in some cases, when injected intradermally at concentrations of 0.02 to 0.033% into wheals on the volar surface of the upper part of the forearm of three humans.¹⁵₆
One hundred and eight subjects completed a repeated insult patch test (RIPT) with 8% PEA in diethyl phthalate. The negative control was a patch containing 20% ethylene brassylate in diethyl phthalate, and the vehicle control was diethyl phthalate. Nine 24-h occlusive induction patches per sample tested were applied to the upper arm, and one 24-h occlusive challenge patch per sample tested was applied to the lower back. The challenge patch sites were observed at 48 and 96 h. One subject had mild erythema following all three patches at the 48-h challenge reading, and a definite papular response to all three samples at 96 h. This subject also had a definite edema and a papular response to all three samples at the fifth induction. This subject was sensitized to PEA and the negative control and the vehicle. Another subject had moderate to strong reactions to all three samples during induction but not at challenge. PEA, the negative control, and the vehicle were irritants for this subject. No other evidence of skin irritation or sensitization was observed.

The skin sensitization potential of PEA was evaluated in 25 subjects. For induction, a patch containing 1.0 ml of a 5% sodium lauryl sulfate solution was applied to the skin for 24 h to produce a moderate inflammatory reaction and make the skin more permeable to the PEA. After removal of this patch, a patch containing 8% PEA was applied for 48 h to the same site. The sodium lauryl sulfate and PEA patches were alternated for a total of five exposures each over a 15-day period. Following a 10-day nontreatment period, a 10% sodium lauryl sulfate solution was applied to an untreated site for 1 h. Afterward, a 48-h 8% PEA challenge patch was applied to the same new site. The site was scored at patch removal and each day for two further days. There were no positive reactions; PEA was a nonsensitizer in this RIPT.

An eye makeup remover containing 0.05% PEA was tested in a repeat insult patch test with 54 male and 101 female volunteers. The induction phase consisted of three 48-h occlusive patches on the back each week for three weeks. Following a 2-week nontreatment period, the subjects were challenged with two consecutive 48-h occlusive patches on an untreated site on the upper back. Reactions were observed at 48 and 96 h. There were no allergic responses. The product was “not a clinically significant irritant or sensitizer.”

An eye makeup remover containing 0.05% PEA was tested in a use test with 53 female volunteers. The subjects used the product at least once daily for 4 weeks. Four subjects had transient, insignificant subjective complaints. Excessive dryness of the eyelids and some swelling was observed in one subject; this was believed to be due to the surfactant content of the product. No other reactions were reported or observed.

**Other Studies and Observations**

The probable oral lethal dose of PEA in humans is between 0.5 and 5 g/kg or between 1 ounce and 1 pint for a 70-kg person. PEA, at a concentration of 0.5% in 0.9% saline, applied as eyedrops caused a smarting sensation in 3 of 4 patients. It caused only occasional slight conjunctival hyperemia. A 0.75% solution of PEA was irritating to the human eye. PEA caused transient stinging at the time of use of a commercial ophthalmic solution. Another source reported that concentrations of PEA greater than 1 g/L in eyedrops may be irritating to the human eye.

The use of PEA and benzalkonium chloride as preservatives in a 2% disodium cromoglycate nasal spray induced a chemical rhinitis.
PEA is an aromatic alcohol that occurs naturally in many plants. It has a floral odor with a rose character. Contaminants in PEA may include β-phenethyl chloride, diethylene glycol chlorohydrin, α-Phenethyl Alcohol, benzyl alcohol, and dibenzyl.

PEA is used as an antimicrobial preservative in cosmetics. It is also a widely used fragrance material that imparts a rose character to perfume compositions. Almost all rose fragrances and other floral-type perfumes contain PEA.

PEA is used in a wide variety of cosmetic products. In 1984, PEA was reported to be an ingredient in 36 cosmetic formulations at concentrations ranging from ≤0.1% to between 0.1 and 1%. In 1987, PEA was reported to be an ingredient in 45 cosmetic formulations at concentrations of ≤0.1%. The FDA has reported that PEA was used as a preservative in 6 cosmetic formulations in 1977, 6 in 1980, 9 in 1984, and 8 in 1987.

PEA was granted GRAS status by FEMA, and it is approved by the FDA for food use. It is used widely as a flavoring agent. PEA is on the FDA list of inactive ingredients for approved prescription drug products. PEA has been used as a preservative in eyedrops.

PEA is metabolized almost entirely to phenylacetic acid in mammals, and, in humans, is excreted in urine as the conjugate, phenylacetylglutamine.

The acute oral LD₅₀ of PEA to rats ranged from 2.46 to 3.1 ml/kg and 0.65 to 1.79 g/kg in several studies. The acute oral LD₅₀ of PEA to mice was 0.8 to 1.5 g/kg and to guinea pigs, 0.4 to 0.8 g/kg. No toxic effects were observed when rats were fed diets containing 0.0625 to 2 g/kg PEA for 14 days or when eye makeup remover containing 0.05% PEA was given by gavage to rats in a dose of 5 ml/kg.

The dermal LD₅₀ for rabbits was 790 mg/kg and for guinea pigs it was 5 g/kg. In another report, the acute dermal LD₅₀ of PEA for rabbits was 0.79 ml/kg. Another source reported that the dermal LD₅₀ for guinea pigs was 5 to 10 ml/kg. Doses of 0.25 to 2.00 ml/kg PEA were applied by inunction to the skin of rats for 90 days; no deaths occurred during the study, and treated and control animals did not differ in appearance or behavior. Mean body weight gains were decreased in a dose-dependent manner.

PEA was slightly to moderately irritating to the skin of rabbits and guinea pigs, and it was not irritating to the skin of miniature swine. PEA was not a sensitizer when tested using guinea pig skin. No positive reactions were observed when an eye makeup remover containing 0.05% PEA was applied to the skin of rabbits.

PEA, in concentrations of 1% or greater, was irritating to the eyes of rabbits. A 0.3% PEA in saline solution was not irritating to the eyes of rabbits. An eye makeup remover containing 0.05% PEA was not irritating to the eyes of rabbits.

Several reproductive studies have been conducted with PEA. In the first study, aqueous suspensions of 4.3, 43, and 432 mg/kg PEA were given by gavage to pregnant rats on days 6 to 15 of gestation. Severe maternal intoxication was observed in the high-dose group. All pups from rats given 432 mg/kg PEA, 97% of pups from rats given 43 mg/kg PEA, and 55% of pups from rats given 4.3 mg/kg were either dead or malformed. Embryolethality was not observed in the high-dose group. The fetal death rate was significantly increased in the mid-dose group. The increase in malformations caused by PEA was dose related: all live pups in the 432 mg/kg group were grossly malformed, and 93% in the 43 mg/kg group and 50% in the 4.3 mg/kg group were malformed. Malformations included eye defects, limb defects, and hydronephrosis. Reduced ossification was observed in all the treatment groups.

In a second study, oral doses of 508 mg/kg PEA in sunflower oil were given to pregnant rats on either day 4 or days 10 to 12 of pregnancy. No developmental
anomalies were observed in pups from treated rats. The sizes of the ossification sites on the extremities of the pups were smaller than those of the controls.

Pregnant rats were given 1000, 3000, or 10,000 ppm microencapsulated PEA in feed on days 6 to 15 of gestation. Exposure to PEA had no effect on embryo-fetal loss, or embryo-fetal development and morphology. There was an increased incidence of incomplete ossification in the 10,000 ppm PEA group only.

Doses of 0.14, 0.43, and 1.40 ml/kg of PEA were applied to the skin of pregnant rats on gestation days 6 to 15. Maternal toxicity was marked at the highest dose. Morphological abnormalities observed in fetuses in the 1.40 ml/kg PEA group included soft tissue and skeletal changes and incomplete ossification. There was no clear evidence of adverse PEA-related effects in the maternal rats given 0.43 ml/kg. The number of fetuses with moderate degrees of reduced ossification and with cervical rib(s) was significantly greater in the 0.43 ml/kg PEA group than in the controls. At the 0.14 ml/kg PEA dose, there was no evidence of maternal toxicity. Although the incidence of structural changes was slightly greater in 0.14 ml/kg PEA-treated rats than in control rats, the incidence and distribution of such changes were not conclusively associated with PEA treatment.

Doses of 0.07, 0.14, 0.28, 0.43, and 0.70 ml/kg/day PEA were applied to the skin of pregnant rats on days 6 to 15 of gestation. PEA administration did not affect the maternal rats in a dose-dependent manner. The incidence of fetuses with cervical ribs was increased significantly only in the 0.70 ml/kg/day group litters. All other fetal alterations were considered reversible delays in ossification; reduced ossification at some sites was dose dependent.

PEA was not mutagenic in the Ames test or in an E. coli DNA—polymerase-deficient assay system. PEA did inhibit the repair of radiation-induced breaks in the DNA of E. coli, but PEA did not increase the number of sister chromatid exchanges in human lymphocytes.

PEA, under occlusive patches, was not irritating to the skin of the forearms of 20 subjects or the backs of 50 subjects with no known allergic reactions. PEA was not a sensitizer in an RIPT test with 108 subjects or in an RIPT test with sodium lauryl sulfate with 25 subjects. An eye makeup remover containing 0.05% PEA was not an irritant or a sensitizer in an RIPT test with 156 subjects. The same eye makeup remover was tested in a use test for 4 weeks with 53 subjects; excessive dryness of the eyelids and some swelling was observed in one subject. No other reactions were observed.

DISCUSSION

Two dermal studies demonstrated the teratogenicity of PEA in rats. The first study suggested a teratogenic effect but significant maternal toxicity prevented a clear interpretation of the results. In the second study, statistically significant dose-dependent increases in the incidence of fetuses with incompletely ossified (hypoplastic) ribs and/or wavy ribs occurred at doses of 0.43 and 0.70 ml/kg/day in the absence of observable maternal toxicity; increases in the incidence of fetuses with cervical rib occurred at the highest dose tested, and delayed ossification of the sternum and/or pelvis occurred in some fetuses from all treated, but not control animals. The highest no observed adverse effect level (NOAEL) was 0.43 ml/kg/day for cervical rib malformation (teratogenic effect); since the lowest dose tested, 0.07 ml/kg/day, resulted in statistically significant incidences of delayed ossification (embryo-development toxic-
ity), a NOAEL for this effect cannot be determined. The teratogenicity NOAEL of 0.43 ml/kg/day can be used to estimate a safe use level of PEA in a cosmetic product; this NOAEL is divided by an uncertainty factor (safety factor) of 100 to reflect the availability of valid results from a teratogenicity study in one experimental animal species but no available human teratogenicity data.

An oral study on the teratogenicity of PEA in rats determined a dose-related response (malformed eyes, hydronephrosis, and limb defects); the lowest dose tested, 4.3 mg/kg, was still teratogenic. If this exposure is obtained in the daily application of a product, then that product could be expected to be teratogenic if it contained a level equivalent to the estimated NOAEL for PEA in a product applied to the skin. This difference in potency of PEA as a teratogen between the two routes of administration apparently lies in the incomplete absorption of PEA from the skin due to loss by evaporation. Since it is not known how much of the PEA evaporated from a cosmetic product is inhaled during use, the Panel increases by one order of magnitude the safety factor used to calculate the NOAEL for PEA applied to the skin. The resulting NOAEL for PEA supports the safe use of PEA in cosmetics.

CONCLUSION

On the basis of the available data, the Expert Panel concludes that Phenethyl Alcohol is safe in cosmetic products in the present practices of use at concentrations of up to 1%.

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REFERENCES


*Available for review: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., NW, Suite 810, Washington, DC 20005.


