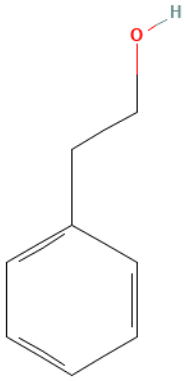
PHENYLETHYL ALCOHOL

CAS number: 60-12-8

Synonyms: 2-Phenylethyl alcohol; 2-phenyl ethanol; β-phenyl ethanol; 2-PEA; PEA; 1-phenyl-2-ethanol; benzene ethanol; benzyl carbinol; benzyl methanol; β-hydroxyethylbenzene

Molecular formula: $C_8H_{10}O$

Chemical structure[1]:



TLV®–TWA, 0.5 ppm

Skin

TLV Recommendation

A TLV®–TWA of 0.5 ppm is recommended for phenylethyl alcohol (PEA) to minimize the potential for adverse effects to fetal development.

The available human information for PEA is limited to studies on olfaction, irritation, and sensitization, which are insufficient to characterize toxicity and dose-response effects, therefore the TLV–TWA is based on animal studies.

In pregnant rats and rabbits, PEA produced embryolethality, fetal toxicity, and fetal malformations and alterations at relatively low dosages. The most serious effects (fetal death, malformations) were observed following oral gavage and dermal exposure at dosages that generally produced significant maternal toxicity,[2] whereas following oral dietary and dermal exposures, at dosages at which maternal toxicity was low to absent, developmental effects were generally limited to reduction in fetal body weight along with some skeletal variations and delayed ossification.[3,4] (See unnamed report, 2019, in ECHA.[4]) The NOAEL of 50 mg/kg per day derived from the rabbit oral gavage study and the LOAEL of 70 mg/kg/day derived from a rat dermal study are the basis for the TLV–TWA value.[3,4] (See unnamed report, 2019, in ECHA.[4]) Converting the oral dose, by first assuming total absorption, a pharmacokinetic study showed that most of an oral dose to rats was absorbed and excreted in urine,[5] and with the exchange of 10 m^3 of air by a 70-kg worker in an 8-hour work shift, a human inhalation equivalent dose of 350 mg/m^3 (70 ppm) is

calculated. For the dermal dose, this value adjusted for rat dermal uptake of 77%,[5] and for the exchange of 10 m^3 of air by a 70-kg worker in an 8-hour work shift, a similar human inhalation equivalent dose of 380 mg/m^3 (75 ppm) is obtained. Thus, the TLV–TWA of 0.5 ppm should protect against the developmental effects of PEA.

Data are not sufficient to support a TLV–STEL. The rat and rabbit oral gavage and rat dermal studies contributed peak exposures to PEA that may occur with short-term occupational exposures. However, the findings from these studies were the result of multiple exposure days and hence do not represent true short-term exposures. Ocular irritation has been reported in humans following vapor exposures but at concentrations 40 times higher than the recommended TLV–TWA value. Thus, a TLV–STEL is not warranted.

A skin notation is recommended for PEA. Although PEA uptake through human skin appears to be relatively low (7.6%) compared with uptake through rat skin (77%),[5] this substance is, however, demonstrated to produce developmental toxicity in rats at low dermal dosages.

No animal cancer data are available for PEA to evaluate the human carcinogenic potential; hence no cancer notation is assigned. Results of a mouse local lymph node assay were negative so a DSEN notation is not recommended.[6,7] (See unnamed study, 2004, in ECHA,[6] and Central Toxicology Laboratory, 2004, in ECHA.[7]) Data were not sufficient to recommend an RSEN or an OTO notation.

TLV Basis

Embryo/fetal damage.

Chemical and Physical Properties

PEA is a colorless, slightly viscous liquid with high water solubility and moderate vapor pressure.[8] It has a floral rose odor with a reported odor threshold between 20 and 50 ppb.[8-10] Chemical and physical properties are shown in Table 1.[8,11,12]

Table 1. Chemical and Physical Properties of Phenylethyl Alcohol (PEA)

Property	PEA
Molecular weight	122.2
Specific gravity	1.017 to 1.019 at 25°C (77°F)
Melting point	−27°C (−17°F)
Boiling point	218°C (425°F)
Vapor pressure	0.087 mm Hg @ 25°C (77°F)
Saturated vapor concentration	1,114 ppm @ 25°C
Flash point	102 °C (216°F) method not specified
Flammable limits	No information
Autoignition temperature	442°C (828°F)
Solubility	22,200 mg/L (water at 25°C [77°F])
Octanol/water partition coefficients	1.36
Conversion factors at 25°C and 760 torr	1 ppm = 5 mg/m^3; 1 mg/m^3 = 0.2 ppm

Sources: CIR,[8] Flavor and Fragrance Consortia.[11,12]

Major Sources of Occupational Exposure

PEA is a synthetic as well as natural substance. Commercial PEA has been manufactured using various processes such as reduction of various phenyl acetic acid esters, hydrogenation of phenylacetaldehyde in the presence of a nickel catalyst, the action of ethylene oxide on phenylmagnesium bromide or phenyl magnesium chloride, catalytic hydrogenation using styrene oxide, and the Friedel-Crafts reaction of benzene and ethylene oxide.[1,8] The US national aggregate production volume of PEA reported in 2015 was 1 to 10 million lbs.[13] PEA is produced by microorganisms, plants, and animals; is present in fungal species; and has been found as the free alcohol or esterified in natural essential oils, and in food, spices, and tobacco.[8] It 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, and is an ingredient in e-cigarette liquids.[8,14] (See NICNAS, 2019, in NICNAS.[14])

PEA has industrial, commercial, and consumer uses.[8,14] Reported industrial uses are generally site-limited and include chemical product and preparation manufacturing and other basic organic chemical manufacturing.[14] Commercial uses include use in softeners and as an absorbant.[14] PEA has numerous uses in consumer products. A major use is in cosmetics as an antimicrobial preservative.[8] In 2005, PEA was reportedly used in 28 cosmetic products.[15] (See Food and Drug Administration (FDA), 2006, in CIR.[15]) Reported concentrations of PEA in cosmetic products are typically below 1% (up to 0.5% in soap, 0.2% in creams and lotions, and 0.8% in eye makeup products.[8] (See Opdyke, 1975, in CIR.[8]) It is also a widely used fragrance material that imparts a rose character to perfume compositions.[8] PEA is present in almost all rose fragrances and other floral-type perfumes, and it is used extensively for many other fragrance applications because it blends well.[8] It is currently permitted by the FDA for direct addition to food for human consumption as a flavoring substance and is considered by the Flavor and Extract Manufacturers' Association (FEMA) Expert Panel to be "generally recognized as safe" (GRAS) for its intended use as a flavoring substance (See Hall, 1960, in Flavor and Fragrance Consortia.[12]) In addition, a group of 42 phenethyl alcohol, phenylacetaldehyde, phenylacetic acid, and related phenethyl esters and acetals have been approved for use as flavoring agents by both the FDA (CFR 172.515) and the World Health Organization's Joint Expert Committee on Food Additives (JECFA; see JECFA, 2003, in Flavor and Fragrance Consortia.[12]). Concentrations of up to 15% are reported in numerous household products including cleaning products; as an odor agent in paints, lacquers, and varnishes; in surface treatment; in paper products; in room and car deodorizers; and in polishes and waxes.[14] Additional uses are as a feed additive for animals, in nonagricultural pesticides, and in pharmaceutical products and as an antibacterial agent in ophthalmic solutions.[14] (See European Food Safety Authority [EFSA], 2012, in NICNAS.[14]) PEA was assessed by EFSA for use in the feed of food-producing animals and the maximum safe concentration was calculated to be 1 to 1.5 mg/kg feed.[14] (See EFSA, 2012, in NICNAS.[14])

Occupational exposure to PEA is expected to occur by inhalation and dermal contact. No recent information on occupational exposures to PEA were identified.

Animal Studies

Acute/Subacute

PEA has low acute toxicity for skin and inhalation exposures but moderate toxicity by oral exposure.

ORAL

PEA has been evaluated for acute toxicity and lethality in rats, mice, and guinea pigs. Oral LD_{50} values are reported to range from 1,500 to 2,540 mg/kg for rats; 800 to 2,540 mg/kg for mice, and 400 to 2,540 mg/kg for guinea pigs.[8,11] (See Carpenter et al., 1974, CTFA, 1980a, Opdyke, 1975, and Zaitsev and Rakhmanina, 1974, in CIR[8]; and Jenner et al., 1964, International Flavors & Fragrances, Inc., 1982,

Moreno, 1982a, in Flavor and Fragrance Consortia.[11]) Reported clinical signs of acute toxicity in rats included diarrhea, exophthalmos, chromodacryorrhea, wheezing, and various neurologic signs of hypersensitivity, tremors, prostration, ataxia, and decreased activity (International Flavors & Fragrances, Inc., 1982, in Flavor and Fragrance Consortia.[12]) Gross pathology changes found in rats were distended stomachs with hemorrhages of the glandular mucosa, red foci on the thymus, discolored adrenals, and fluid-filled bladders, and reported histologic changes included degeneration of the liver and kidneys with hyperemia and a slight fatty change observed in the liver; 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.[8,12] (See Purchase, 1969, in CIR,[8] and International Flavors & Fragrances, Inc., 1982, in Flavor and Fragrance Consortia[12]) In a subacute study, no adverse effects were observed in rats fed diets containing 0.06 to 2 g/kg PEA for 14 days.[16]

DERMAL

Acute dermal toxicity studies for PEA reported LD_{50} values greater than 5,000 mg/kg for rats, 790 to 2,535 mg/kg for rabbits, and 6,000 to 12,000 mg/kg for guinea pigs.[8,12] (See Carpenter et al., 1974, and Opdyke, 1975, in CIR;[8] and Moreno, 1982b, and International Flavors & Fragrances,1983, in Flavor and Fragrance Consortia.[12]) No clinical signs of toxicity were reported in these studies, but one rabbit study reported pathology findings that included hemorrhages in the muscle at the application site, dark fluid in the bladder, distended stomachs and intestines, fluid in the abdominal cavity, and hemorrhages of the cecum and pale kidneys.[12] (See International Flavors & Fragrances,1983, in Flavor and Fragrance Consortia.[12])

INHALATION

One acute inhalation study in rats is reported for PEA.[12] (See Breckenridge et al., 1980, in Flavor and Fragrance Consortia.[12]) This study exposed a group of 5 male and female rats for 4 hours to an aerosol concentration of 4.63 mg/L and found no clinical signs of toxicity or deaths (LC_{50} > 4.63 mg/L).

SENSITIZATION

PEA has been assessed for skin sensitization potential using the mouse local lymph node assay.[6,7] (See unnamed study, 2004, in ECHA,[6] and Central Toxicology Laboratory, 2004, in ECHA.[7]) In this study, PEA concentrations of 2.5%, 5%, 10%, 25%, or 50% w/v were prepared in a solution of 25% ethanol/75% diethylphthlate and applied to the dorsal surface of each ear of groups of 4 female mice for 3 consecutive days. The study resulted in stimulation index values of approximately 1.06, 1.01, 0.87, 0.95, and 0.84 for the tested concentrations, 2.5%, 5%, 10%, 25%, and 50%, respectively. As these stimulation index values were less than 3, the study was concluded to be negative for skin sensitization. The EC3 value (concentration giving rise to a 3-fold increase in lymphocyte proliferation) was not specifically reported, however, the authors concluded that the EC3 was greater than 50% w/v (>12,500 µg/cm^2). PEA was not found to be a sensitizer for guinea pig skin at tested concentrations of 1% to 2%, however, no detailed information on this study is reported.[8] (See Kabara, 1984, in CIR.[8])

OTHER STUDIES

PEA is slightly to moderately irritating to skin and severely irritating to the eye.

Skin irritation studies on PEA have been conducted in rabbits, guinea pigs, and miniature swine. Two rabbit studies that tested groups of 3 and 4 females with 0.5 mL PEA for 4 hours under semiocclusive conditions found slight to moderate skin irritation responses that were diminished or absent

168 hours after exposures.[17-19] (See Toxicology Laboratory report 1984, 1985, and unnamed study, 1984, in ECHA.[17-19]) The mean irritation scores reported in one study at 24, 48, and 72 hours were 1, 0.75, and 0.5 for erythema and 0.25, 0.25, and 0 for edema, respectively (maximum scores of 4)[6,7,17,18] (See Toxicology Laboratory report 1984, 1985, in ECHA[17,18]); the second study reported mean scores at 24, 48, 72, and 168 hours of 2, 1.3, 1.3, and 0.33 for erythema and 0.7, 0.7, 0.7, and 0 for edema, respectively (maximum scores of 4).[6,7,18,19] (See Toxicology Laboratory report 1984, 1985.[18,19]) An earlier study tested 0.05 g PEA applied topically once for 48 hours to a group of 6 miniature swine and 0.1 g PEA applied to the skin of 6 rabbits and 6 guinea pigs followed by a second application 24 hours later, after which the animals were sacrificed and histopathological examination of the skin performed.[8] (See Motoyoshi et al., 1979, in CIR.[8]) This study reported moderate irritation to the skin of rabbits and guinea pigs and no irritation to the skin of swine.

PEA concentrations of 1% or greater have been reported to produce severe eye irritation, whereas concentrations lower than 1% were nonirritating to rabbit eyes. Severe corneal irritation and iritis was observed in rabbit eyes following instillation of a 0.005 mL dose of 100% PEA or a 0.5 mL dose of 5% or 15% PEA in propylene glycol.[8] (See Carpenter et al., 1974, in CIR.[8]). A concentration of 1% PEA instilled into rabbit eyes produced conjunctival irritation and corneal clouding, and a 2% concentration induced a loss of touch response in the cornea of rabbits.[8] (See Grant, 1974, and Hjort and Eagen, 1920, in CIR.[8]) Two drops of a 0.3% solution of PEA that was instilled into rabbit eyes 3 times per day, 5 days per week for 2 weeks produced no signs of eye irritation and an eye makeup remover containing 0.05% PEA applied at a dose of 0.1 mL was also not irritating to the eyes of rabbits.[8] (See Grote and Woods, 1955, and CTFA, 1980b, in CIR.[8])

PEA toxicity has also been studied for intraperitoneal, subcutaneous, and intravenous exposures,[8] however, this information has less relevance for potential occupational exposures.

Subchronic

PEA has been evaluated for repeated exposure toxicity following dermal and oral exposure and a PEA precursor substance has been evaluated for oral exposure. These studies did not find evidence of significant or specific target organ toxicity but there was limited evidence for liver changes (weight and enzymes) and nonspecific toxicity (body weight decreases).

In a dermal study, Sprague Dawley rats (groups of 15 per sex per dosage for treatment groups and 30 per sex for controls) received daily topical exposures (occlusion not specified) of 0, 0.25, 0.5, 1, or 2 mL/kg per day (approximately 0, 255, 510, 1,020 or 2,040 mg/kg per day) for 90 days and were evaluated for mortality, clinical signs, body weights, hematology, organ weights, and pathology changes.[16] The study found no treatment-related mortality effects or clinical signs of toxicity. Body weights and body weight gains were noted to be significantly decreased in males and females at greater than or equal to 1,020 mg/kg per day that were not accompanied by changes in feed consumption. Among the rats that received 2,040 mg/kg per day, males exhibited significant decreases in hemoglobin concentration and white blood cell counts and both males and females had significant increases in relative brain, kidney, and gonad weights. Absolute and relative liver weights were decreased only in the 1,020 mg/kg per day males and relative liver weights were increased in females at all doses; however, no histopathologic effects were observed in the liver or any other tissues that were associated with PEA treatment. The study NOAEL was 510 mg/kg per day. These authors also reported an earlier dermal study in rats in which 3 mL/kg were applied daily for 28 days that resulted in the death of 1 of 2 rats after 7 days of treatment.[16]

A limited oral gavage subchronic study was conducted for PEA in male rats.[8] (See Zaitsev and Rakhmanina, 1974, in CIR.[8]) A dosage of 51 mg/kg per day was administered daily for 4 months, and only liver function tests were evaluated, which showed evidence (not specified) of enzyme induction.

Another study conducted a more thorough evaluation of subchronic oral toxicity for phenethyl phenylacetate.[11,12] (See Hagan et al., 1967, in Flavor and Fragrance Consortia.[11,12]) This substance hydrolyzes to PEA and phenylacetic acid (PAA) before absorption.[11] (See Longland et al., 1977, and Grundschober, 1977, in Flavor and Fragrance Consortia.[11]) In this study, groups of 10 male and 10 female Osborne Mendel rats were exposed every day for 17 weeks to diets containing 1,000, 2,500, or 10,000 ppm of phenethyl phenylacetate (estimated daily intakes of 50, 125, or 500 mg/kg per day). No treatment effects were found on body weights, hematology parameters, organ weights, or gross or histopathologic findings (NOAEL = 500 mg/kg per day).

Chronic/Carcinogenicity

No long-term animal studies have specifically evaluated PEA for chronic toxicity or carcinogenicity, but 1 long-term study is reported for a PEA mixture. In a 56-week oral drinking water study, a group of 20 male and 20 female Wistar rats were administered a mixture of 6,000 mg/kg ethyl alcohol (6%), 120 mg/kg isoamyl alcohol (0.12%), 120 mg/kg phenethyl alcohol (0.12%), 200 mg/kg isobutyl alcohol (0.2%), 200 mg/kg acetic acid (0.2%), and 4 mg/kg ethyl acetate (0.004%).[11,12] (See Johannsen and Purchase, 1969, in Flavor and Fragrance Consortia.[11,12]) The study found no treatment-related effects on absolute or relative liver weights or histopathologic changes in the liver, kidney, heart, spleen, and lung. This study is not an adequate test of PEA chronic toxicity due to the single exposure and low concentration tested.

Genotoxicity

PEA has been tested for genotoxicity *in vitro* and overall, the evidence indicates this substance is not mutagenic toward bacterial or mammalian systems or clastogenic toward mammalian cell lines.

PEA was not mutagenic in a reverse mutation assay performed with *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2uvrA both in the absence or presence of metabolic activation.[8,20,21] (See Florin et al., 1980, in CIR;[8] unnamed study, 2012, in ECHA;[20] and Harlan Laboratories, 2012a, in ECHA.[21]) In an *in vitro* study for the detection of structural chromosomal aberrations, culture specimens of human lymphocytes were treated with PEA. The result showed that this substance did not induce any statistically significant increases in the frequency of cells with chromosome aberrations in either the absence or presence of metabolic activation.[21,22] (See Harlan Laboratories, 2012, in ECHA.[21]) In a mammalian cell mutation study, no increase in mutation at the TK +/- locus was recorded after incubation of PEA with L5178Y mouse lymphoma cells in the presence or absence of metabolic activation.[23] (See Harlan Laboratories, 2012c, in ECHA,[21] and unnamed study, 2012, in ECHA,[23]) A study of sister chromatid exchanges found that PEA concentrations of 0.1 to 1.5 mL did not increase the number of exchanges in human whole blood lymphocytes on culture specimens.[8] (See Norppa and Vainio, 1983, in CIR.[8]) One positive finding was reported in a study of single strand breaks.[8] (See Nair et al., 1975, in CIR.[8]) PEA at a concentration of 0.25% inhibited the repair of radiation-induced single strand breaks in the DNA of *Escherichia coli*.

Reproductive/Developmental Toxicity

No reproductive toxicity studies were identified for PEA, however, a subchronic dermal study in rats provided some information on the effects of PEA in reproductive tissue (as discussed in the Subchronic Toxicity section).[16] This study found increases in gonadal weights, but no histopathologic changes were observed in the testes, epididymides, or ovaries at a dermal PEA dosage of 2,040 mg/kg per day.

Seven studies, 4 by oral exposure and 3 by dermal exposure, have investigated PEA for developmental toxicity. In the earliest oral study, a single dosage of 508 mg/kg PEA in sunflower oil was given to female rats (strain and number not specified) on either day 4 or days 10 to 12 of pregnancy, and

the dams were sacrificed on gestation day 20 and the fetuses examined.[8] (See Maganova and Zaitsev, 1973, in CIR.[8]) No information on maternal toxicity was reported. The size and number of fetuses were not different from the sunflower oil control group and no developmental anomalies were observed in the treated rats. Histologic examination of the fetuses from the rats given PEA on days 10 to 12 of pregnancy found that the size of the ossification sites on the extremities of the fetuses were smaller than those of the controls. No ossification of the pubic bone or the second phalanx of the left and right extremities was observed in 10% to 15% of the fetuses from the treated rats. The sagittal sections were also examined, and no abnormalities were observed in palatal structure, eyes, brain, or internal organs.

In a study performed to investigate PEA's potential fetotoxic and teratogenic properties, groups of 7, 7, and 5 pregnant Long Evans rats were administered PEA through oral gavage at doses of 4.3, 43, and 432 mg/kg per day, respectively, from gestation day 6 to 15, and the fetuses were assessed on day 20.[2] A group of 19 pregnant rats that received distilled water served as the controls. The dams that received 432 mg/kg per day exhibited maternal toxicity (intoxication not further specified) and no clinical signs of toxicity were observed at the lower dosages. Mean litter size was decreased and embryolethality was increased in the 43 and 4.3 mg/kg per day groups, but not in the 432 mg/kg per day group. Dose-related increased fetal malformations were reported in all treatment groups. All live pups in the 432 mg/kg per day group were grossly malformed, and 93% in the 43 mg/kg per day group and 50% in the 4.3 mg/kg per day group were malformed. These percentages were statistically significantly higher than in controls, which showed 4% of offspring with abnormalities (percentage of litters not stated). The malformations identified in the high-dose group included malformed eyes, malformed limbs, hydronephrosis, neural tube defects, and malformed digits; the 43 mg/kg per day pups had malformed eyes, hydronephrosis, and limb defects; and the 4.3 mg/kg per day pups had eye defects and hydronephrosis. However, the pups that received 4.3 mg/kg per day showed a notably higher incidence of the eye defect microphthalmia than the higher dosage groups, and hence was not dose-responsive (pup incidence of 2, 9, 7, and 6 in the control, 4.3, 43, and 432 mg/kg per day groups, respectively); the incidence of hydronephrosis in the 4.3 mg/kg per day group was just above that of the control pups (pup incidence of 3, 5, 19, and 15 in the control, 4.3, 43, and 432 mg/kg per day groups, respectively). Importantly, the malformation incidence and all of the pup effects are reported on an individual pup basis and not in the appropriate litter basis, therefore these findings cannot be interpreted as such. Decreases in pup weight and pup size at birth and increases in skeletal variations were also observed; however, there was no clear dose-response relationship for these effects. The NOAEL for maternal toxicity was 43 mg/kg per day, and the LOAEL for fetal effects (malformations, reduced live litter size) was 4.3 mg/kg per day. In abstracts of subsequent studies, all PEA doses equivalent to 0.02% and 24% of the oral LD_{50} administered to pregnant Long Evans rats produced intrauterine growth restriction (birth weight reductions) and embryolethality.[11] (See Mankes et al., 1984, 1985, in Flavor and Fragrance Consortia.[11]) Maternal toxicity was not reported for these studies and their observations were not consistent with the findings of their original study.

In response to the findings of Mankes et al.,[2] a follow-up study was performed to study the effects of dietary administration of microencapsulated PEA on developmental toxicity in the rat.[3,8,11,12] (See Bottomley et al., 1987, in CIR[8]) This study tested groups of 28 pregnant Sprague Dawley rats that were administered PEA via the diet at 1,000, 3,000, or 10,000 ppm (equivalent to calculated daily intakes of 83, 266, or 799 mg/kg) on gestation days 6 through 16. The PEA doses were microencapsulated in gum arabic to increase food palatability. No clinical signs of toxicity or mortality were observed in any of the treatment groups dams. Reduced maternal feed consumption and a slight body weight loss in dams were observed in the 10,000 ppm group only during the first 2 days of treatment. Litter parameters (embryo-fetal loss, litter sizes, sex ratios, and litter and mean fetal weights) were unaffected by PEA. The incidence, type, and distribution of fetal malformations, anomalies, and skeletal variants were statistically unaffected by maternal exposure to PEA, though at the highest dosage level (10,000 ppm), a marginal delay in fetal ossification might have occurred, as a slightly higher incidence of fetuses with incomplete ossification of some skeletal elements, particularly the sacrocaudal vertebral arches, was observed

(NOAEL for maternal and developmental toxicity = 799 mg/kg per day). This study did not replicate the significant malformations that had been observed in the Mankes et al. study.[2] These 2 studies used different strains of rats and oral exposure routes. Mankes et al[2] used oral gavage dosages that delivered bolus exposures that likely produced spike serum concentrations of PEA, whereas the dietary study provided for continuous exposures with lower but more prolonged serum levels.

One oral developmental toxicity study is reported in rabbits.[4] (See unnamed report, 2019, in ECHA.[4]) In this study, groups of 22 pregnant New Zealand white rabbits received PEA (in a 0.5% aqueous carboxymethyl cellulose + 1.25% Tween 80 vehicle) through oral gavage at dosage levels of 0, 15, 50, and 150 mg/kg per day once daily, 7 days a week, from gestation days 6 through 28. There were a few deaths in the controls and treatment groups, but the deaths were not considered to be related to treatment. In all groups including controls, feces production was reduced (severe in some), though persistence/severity was higher at 150 mg/kg per day. Other maternal effects and fetal effects were limited to the 150 mg/kg per day group. These females exhibited a reduction in mean body weight (loss of 3%) over gestation days 6 to 9, and this decrease in body weight gain resulted in up to 6% lower mean body weights compared with the controls throughout the study period. They also exhibited significant reduction in mean food consumption (up to 53%) compared with concurrent mean consumption in the control animals during the first week of treatment, followed by a recovery from gestation day 15 onwards. Fetal effects at 150 mg/kg per day consisted of lower mean combined fetal body weight (in both males and females), and an increase in the litter incidence of vertebral anomaly was observed in 4 fetuses; the litters also exhibited an increased incidence of several skeletal variations as well as an increase in the incidence of the skeletal variation 13th full ribs and caudal shift of pelvic girdle. The NOAEL for maternal and developmental toxicity was 50 mg/kg per day.

The earliest developmental toxicity study performed in rats using the dermal route examined dosages of PEA approximately equivalent to the oral dosages tested by Mankes et al.[2,3,8,11,12] (See Palmer et al. 1986, in CIR.[8]) In this study, PEA was applied to the skin of groups of 25 to 35 pregnant Sprague Dawley rats at doses of 0, 0.14, 0.43, and 1.40 mL/kg per day (equivalent to approximately 0, 143, 439, and 1,430 mg/kg per day) on days 6 through 15 of gestation. The developmental status of the fetuses was assessed on day 20 of pregnancy. The results showed significant maternal and fetal toxicity at the highest dose tested. At 1,430 mg/kg per day, 3 of 35 dams died; dams in this group exhibited decreased food consumption, marked decrease in body weight gain, clinical signs of toxicity (irritability, hunched posture, walking on toes, piloerection, periorbital staining), and slight edema at the dose site. In the high-dose 1,430 mg/kg group animals, developmental effects evident were resorption of 5 of 23 litters, reductions in litter size and weight, and skeletal and soft tissue changes (including anophthalmia/microphthalmia, ventricular septal defects, thoracic and lumbar vertebral defects, kinky tail, thoracic and cervical rib changes) in nearly all (160 of 161). The 439 mg/kg per day dams showed no clear maternal toxicity effects, but their fetuses exhibited an increased incidence of cervical ribs and thoracic vertebrae defects. Treatment with 143 mg/kg per day was associated with only equivocal evidence of effects on fetal skeletal development as the incidences of rudimentary cervical ribs and thoracic vertebral irregularities were only marginally increased. The NOAEL for maternal toxicity was 438 mg/kg per day and for developmental toxicity was 143 mg/kg per day.

A second dermal developmental toxicity study was performed to corroborate the findings from the first study and to better characterize the dose-response curve for the rudimentary cervical rib findings.[3,8,11,12] (See Christian and Hoberman, 1988, in CIR.[8]) The same strain of rats was used, 10 pregnant rats were assigned to each dosage group, and 5 treatment dosages of 70, 140, 280, 430, and 700 mg/kg per day PEA were applied on gestation days 6 through 15 of pregnancy with fetal and litter parameters assessed on day 20. No deaths occurred in the study, but all dosages of PEA produced localized, low levels of erythema and/or desquamation at the intrascapular application sites, the severity of which was dose related. Additional signs of toxicity present only in the 700 mg/kg per day dams included ptosis and/or urine-stained abdominal fur. Classic signs of maternal toxicity, such as reduced

feed intake and body weight gains, did not occur in a consistent manner. There were no treatment-related effects on average litter sizes, numbers of implantations, live fetuses, or postimplantation loss (resorptions). No soft tissue changes were identified in fetuses, but fetal skeletal alterations were reported with PEA dosages greater than or equal to 70 mg/kg per day. Fetal effects included dose-dependent reductions in mean live fetal body weights for the litter, which were statistically significant at greater than or equal to 140 mg/kg per day but not at the lowest dosage of 70 mg/kg per day. A significantly increased incidence of rudimentary cervical ribs was observed at 700 mg/kg per day and minimal increases of reversible delays in ossification were observed at greater than or equal to 70 mg/kg per day. The incidences of the reversible delays in ossification, however, were reported to be within the historical ranges of the testing facility. The specific delays identified included delayed sternal and/or pelvic ossification (all dosage levels); incompletely ossified (hypoplastic) ribs and/or wavy ribs at 70 and greater than or equal to 430 mg/kg per day; and delays in ossification of the metacarpals and hindpaw phalanges (≥140 mg/kg per day), caudal vertebrae (≥280 mg/kg per day), forepaw phalanges (≥430 mg/kg per day), and sternal centers (≥700 mg/kg per day). Interpretation of the study developmental findings is difficult in view of the dermal irritation that was present at all tested dosage levels, which may have confounded the results. However, based on the reported information, the LOAEL for maternal toxicity (local effects) was 70 mg/kg per day, NOAEL for maternal toxicity (systemic effects) was 700 mg/kg per day, and the LOAEL for developmental toxicity was 70 mg/kg per day.

The most recent dermal developmental toxicity study was designed to evaluate the reversibility of the effects in pups euthanized on postnatal day 21.[24] (See Belsito et al., 2012, in Health Canada.[24]) In this study, pregnant female rats (strain not specified; 40/group) were exposed dermally to PEA at dosages of 0, 140, 430, or 1,400 mg/kg on gestation days 7 through 20. Half of the dams (20/group) had cesarean sections on gestation day 21 and the remaining dams/group were allowed to naturally deliver their litters, and were euthanized on postnatal day 21. Dermal irritation, as indicated by flaking and/or erythema, was observed in female rats administered 430 and 1,400 mg/kg per day during the gestation period. In general, the onset and severity of skin reactions were dose dependent. The developmental NOAEL was 140 mg/kg per day based on reductions in fetal body weight, with corresponding delays in fetal skeletal ossification and an increase in the incidence of cervical ribs in fetuses from the rats selected for cesarean delivery at maternal dosages of greater than or equal to 430 mg/kg per day. These changes, however, were not found in pups from rats exposed to the same dose for the same duration and selected for natural delivery by postnatal day 21 and hence appeared to have resolved. The study identified a NOAEL for maternal and developmental toxicity of 430 mg/kg per day.

Overall, the available developmental toxicity studies indicate that PEA is toxic to rat and rabbit development at relatively low dose levels. The lowest reported effect level for developmental toxicity for PEA was oral exposure at 4.3 mg/kg/day (Mankes et al., 1984, 1985 in Flavor and Fragrance Consortia[11]) and 70 mg/kg/day for dermal exposure.[3] The lowest identified oral effect level, however, was for an oral gavage study that is questionably reliable.[2] This study used significantly smaller numbers of dams in the treatment groups (5 dams in the 432 mg/kg per day group and 7 dams each in the 4.3 and 43 mg/kg per day groups, respectively) than specified in current standardized test guidelines (n = 20); therefore results were based on small numbers of total pups per group (60, 65, and 41 pups in the 4.3, 43, and 432 mg/kg per day groups, respectively). The study reported results only as total pup basis and not as the more appropriate litter basis (pups within a litter are related and do not represent individual treatment units). Although the malformation incidence was high and reported to be dose responsive, other developmental parameters, including embryonic deaths and pup size and weight did not show dose-related effects. Also, no information was reported on the laboratory's historical incidence of malformations in control animals to confirm the in-study control animal responses. With these limitations and inconsistent findings, it is not possible to derive confident interpretations of this study's results. The only other developmental toxicity study that reported increases in PEA-related soft tissue and skeletal malformations (excludes skeletal variations) was the rat dermal study that tested PEA dosages up to 1,430 mg/kg per day.[3,8,11,12] (See

Palmer et al., 1986, in CIR.[8]) At 430 mg/kg per day, a dosage comparable to the high dosage in the oral gavage study, only occasional fetuses displayed these changes but only the skeletal variations exceeded the control incidence. Findings in the lowest dosage, 140 mg/kg per day, were equivocal, with skeletal variations only marginally higher than in controls. Therefore, although soft tissue and skeletal malformations were observed in this dermal study, the dosage that produced these effects was significantly higher than the oral gavage dosage that produced malformations, with this high dermal dosage also leading to dam deaths. Thus, the LOAEL of 4.3 mg/kg per day for developmental effects in the rat oral gavage study is not supported by the developmental toxicity NOAEL of 140 mg/kg per day in the rat dermal study. Of note, as discussed in the Absorption, Distribution, Metabolism, and Excretion section, in rats, a dermal dosage of 430 mg/kg of PEA produced higher plasma concentrations than a comparable dosage given through oral gavage.[3] PEA maximum concentrations (C_{max}) and area under curve (AUC) concentrations were 23.6 µg/mL and 33.3 µg hour/mL, respectively, for dermal exposure, and 2.14 µg/mL and 2.7 µg hour/mL, respectively, for oral gavage exposure. Therefore, the PEA exposure in the rat dermal developmental toxicity study likely produced higher PEA levels than achieved in the rat oral gavage study, yet did not replicate the developmental effects reported at 4.3 mg/kg per day. Increases in soft tissue and skeletal malformations were not found in the rat oral dietary study at dosages up to 799 mg/kg per day, the second rat dermal study at dosages up to 700 mg/kg per day, and the rabbit oral study at dosages up to 150 mg/kg per day.[3,4,8,11,12] (See Bottomley et al., 1987, and Christian and Hoberman, 1988, in CIR;[8] and unnamed report, 2019, in ECHA.[4]) The primary developmental effects observed in most PEA studies are a dose-related reduction in fetal body weight along with some skeletal variations and delayed ossification, which are questionably adverse.[25] These results are reminiscent of those reported for high plasma levels of carboxylic acids such as PAA, the main metabolite of PEA (as discussed in the Absorption, Distribution, Metabolism, and Excretion section).[11] (Brown, 1987, and Magnova and Seitzer, 1973, in Flavor and Fragrance Consortia.[11]) An evaluation of PAA developmental toxicity is available in a reproductive/developmental screening study conducted using groups of 10 virgin Sprague Dawley rats that were administered oral dosages of 0, 250, 500, or 1,000 mg/kg of PAA by gavage once daily, 7 days before cohabitation, through cohabitation (mating with treated males for a maximum of 7 days), gestation, delivery, and a 4-day postparturition period.[8] (See Vollmuth et al., 1995, in CIR.[8]). The only developmental effects reported occurred at the 1,000 mg/kg per day dosage as indicated by a statistically significant decrease in viability, a nonsignificant decrease in body weight gain, and slight skeletal variations. Thus, this study with high gavage doses of PAA also did not find evidence of the severe fetal malformations that were observed in the PEA oral gavage study.[2] In the dermal studies, skin irritation is a confounder in interpreting these results. Skin irritation was likely associated with maternal stress, which affected fetal development; however, some similar effects were also observed in oral studies. From the available studies, the key studies and developmental toxicity levels are the rabbit oral gavage study, with a NOAEL of 50 mg/kg per day, and the rat dermal study that produced a LOAEL of 70 mg/kg per day.[3,4] (See unnamed report, 2019, in ECHA.[4])

Absorption, Distribution, Metabolism, and Excretion

The absorption and disposition of PEA after oral exposure has been investigated in rats, rabbits, dogs, and humans using dermal or oral exposures. Absorption, distribution, metabolism, and excretion were compared after oral and topical application of 14C-labeled PEA to rats and topical applications to rabbits and humans (specific activities of topical dosing solutions: 58-580, 164, and 50 mCi/mL, respectively).[5]

PEA is readily and significantly absorbed via oral and dermal exposure. In a study of female CD rats using radiolabeled PEA, peak plasma concentrations of unchanged PEA were reached within 0.25 hours on average after oral administration (gavage) and 0.5 hours on average after dermal application of a dose of 0.43 mL/kg (430 mg/kg) PEA.[5] For oral dietary exposure, when rats were fed for up to 24 hours an *ad libitum* diet containing encapsulated PEA in a gum arabic matrix providing a nominal dose of 430 mg/kg

(normalized for a mean administered dosage of 261 mg/kg), peak PEA plasma concentrations were reached within 4 hours. Plasma concentrations of PEA were higher after the dermal route compared with oral administration, whereas plasma concentrations of the metabolite PAA were higher after oral exposure compared with dermal exposure. PEA C_{max} and AUC concentrations were 23.6 µg/mL and 33.3 µg hour/mL, respectively, for dermal exposure; 2.14 µg/mL and 2.7 µg hour/mL, respectively, for oral gavage exposure; and 0.387 µg/mL and 3.8 µg hour/mL, respectively, for estimated normalized mean oral dietary exposures. PAA C_{max} and AUC concentrations were 572 µg/mL and 6,333 µg hour/mL, respectively, for oral gavage exposure; 281 µg/mL and 1,965 µg per hour/mL, respectively, for dermal exposure; and 34.7 µg/mL and 346 µg hour/mL, respectively, for estimated normalized mean oral dietary exposures. Absorption through rat skin was higher than through human skin. In a study of 2 human volunteers in which radiolabeled PEA was applied to the chest, an average of only 7.6% of the total dosage was absorbed, compared with 77% in rats and 50% in rabbits.[5] The human study results indicated that most of the dose (~ 90%) was lost from the surface of the skin due to evaporation, but differences among the species may have also contributed to the absorption differences.

The results from rat, rabbit, and human studies indicate that once absorbed, PEA is rapidly and widely distributed through the body and excreted primarily in the urine.[5] In a quantitative tissue distribution study, male rats were administered a single topical application of 140 mg/kg radiolabeled PEA for 6 hours. The study found that the greatest concentration of radioactivity was in tissues at 3 hours.[5] By 24, 48, and 72 hours after exposure, all tissues, except the treated skin and fat, had concentrations less than 1.0 µg/mL, indicating that PEA was rapidly absorbed and eliminated from most tissues.

PEA is metabolized almost entirely to PAA in mammals.[5,8] Rats that received 0.43 mL/kg (430 mg/kg) of PEA through oral gavage excreted 74% of the dose in the urine as PAA within 24 hours.[5] Similarly, the feeding of microencapsulated PEA at a nominal dose of 430 mg/kg resulted in the excretion of 70% of the dose in the urine as PAA within 24 hours. When the rats were treated dermally with 0.43 mL/kg (430 mg/kg) of PEA, the urinary elimination of PAA was only 27% after 24 hours. The glycine conjugate of PAA was the major metabolite detected in rat urine and plasma after 10 dermal applications of PEA at levels of 0.14 and 0.7 mL/kg.[5] Unconjugated PAA was also detected in urine and plasma along with a small amount of the parent compound. The glycine conjugate of benzoic acid, hippuric acid, was only detected in the urine. In rabbits that were given a 300 mg/kg dose of PEA, 42% of the dose was recovered in the urine as the glycine conjugate and 5% as the glucuronide by 24 hours. In an early study, a single human male received an oral dose of 4 g PEA and phenylacetylglutamine at 26% (2.25 g) of the theoretical yield was recovered from the urine of the man.[8] (See Thierfelder and Schempp, 1917, in CIR.[8]) These authors also described a study of 1 dog given a 1.0 g/kg dose of PEA for 14 consecutive days that found that 44.5% of the total dose was excreted as PAA.[8] (See Thierfelder and Schempp, 1917, in CIR.[8]).

No information on PEA adsorption and disposition was identified for inhalation exposure.

Human Studies

PEA has been evaluated in humans for odor and sensory responses, eye, skin, and respiratory irritation, and skin sensitization.

PEA has been used to assess olfactory function in humans. PEA vapor has a sweet rose-like scent and does not cause intranasal stimulation of the trigeminal nerve; therefore, the substance makes for an ideal control for response bias in studies that assess the sensory irritation of vapors or gases.[26] It has also become the odorant of choice for assessing both olfactory response and olfactory thresholds in various chemosensory assays.[27,28] As a result of these properties, numerous human olfactory threshold values are now available for PEA. Over the years, odor thresholds for PEA have been determined to range from 6.5 to 7,500 ppb; however, a more reasonable estimate using modern methodologies supports a

threshold in the range of 20 to 50 ppb for normal human volunteers.[9,10] PEA vapor was not an upper respiratory tract irritant in human volunteer studies[29]; however, PEA as a neat liquid was able to elicit a trigeminal response and cause intranasal irritation in a group of test subjects.[30] Undiluted PEA applied to the nasal septae of 4 male and female volunteers resulted in a slight burning, itching, or stinging sensation experienced by all volunteers.

PEA was found not to be irritating or sensitizing to the skin in human studies. Undiluted PEA applied to the forearms of 20 male and female volunteers for 24 hours failed to illicit any sign of irritation over a 5-day observation period.[8] (See Katz, 1946, in CIR.[8]). In a study of 50 male subjects treated for 48 hours with an occlusive patch containing a 32% solution of PEA, fewer than 10% responded with a positive or equivocal irritation response 30 minutes after patch removal.[8] A study of 179 subjects showed no irritation and only 1 positive allergic reaction with a 25% solution of PEA in petrolatum that was applied to the skin for up to 72 hours.[31] In a repeated insult study, 25 volunteers who had their skin treated with sodium laurel sulfate (to produce skin inflammation), failed to show any sign of sensitization when a patch containing 8% PEA was applied 5 times for 48 hours over a 15-day period.[8] (See Grief, 1967, in CIR.[8]). These same subjects also failed to react after a 10-day rest period, after which they were challenged again with 8% PEA for 48 hours. PEA was also not a sensitizer in a repeated insult patch test performed on a group of 108 subjects.[8] (See Research Institute for Fragrance Materials, Inc., 1988, in CIR.[8]) The induction phase involved the forearm application of 9 patches containing 8% PEA for 24 hours. A challenge patch containing the same amount of PEA was applied to the back and the reactions were scored at 24 and 48 hours.

Although PEA is not a dermal irritant in humans, several studies indicate that PEA as a liquid or vapor can be a potent ocular irritant in humans. A PEA solution of 0.5% in normal saline caused a smarting sensation and slight conjunctival redness in 3 or 4 subjects who were tested.[8] (See Grant, 1974, in CIR.[8]) Eye irritation in humans was also reported for a 0.75% solution of PEA and a concentration of 1 g/L PEA present in eyedrops.[8] (See Kabara, 1984, and Boer, 1981, in CIR.[8]) Transient stinging was reported for an unspecified concentration of PEA in a commercial ophthalmic solution.[8] (See Lee et al., 1983, in CIR.[8])

The ocular irritancy of PEA vapor was examined in 2 groups of 12 male and female volunteers.[32] The first group was a naive control population with no previous occupational exposure to organic solvents, whereas the second group included professional phlebotomists exposed to isopropanol in the course of their work drawing blood samples. Ocular hyperemia was assessed by a trained panel of judges who examined conjunctival photographs taken before, during, and after (0, 2, and 4 hours) each whole-body exposure session. Compared with sessions involving clean air exposures, in both groups, PEA vapor caused an appreciable increase in the degree of ocular redness after 4 hours of exposure, but not after 2 hours. The differences in ocular irritation for the PEA-exposed groups were not statistically different from their respective clean air control groups, however, the results showed a consistent trend that was repeatable across both control groups and directly dependent on exposure duration. At the time of the study, a suitable analytic method was not available to directly measure the PEA exposure concentration in the chamber; therefore, ethanol was added as an easily detectable tracer chemical to ensure that the PEA exposure concentration did not vary excessively. The added ethanol resulted in a coexposure chamber of concentration of about 40 ppm, which is well below the ocular irritation threshold of 1,000 ppm or more.[33] Therefore, it is highly unlikely that the ethanol coexposure contributed to the ocular hyperemia observed in the PEA-exposed volunteers. As follow-up on the PEA exposures in this study, the senior author of the study re-created the exposure scenarios and applied a more sensitive analytic method to assess the actual PEA exposure concentrations attained (personal communication, Pamela Dalton, PhD, MPH, Monell Chemical Senses Center, March 23, 2022). This analysis revealed that the exposures resulting in an increased incidence and severity of ocular hyperemia occurred at a PEA chamber concentration of 20 ppm (± 2 ppm).

Another study that evaluated human ocular irritation with chemical vapors found irritation to be associated with the longest unfolded length of the molecule.[34] An examination of the ocular irritation from a series of alkyl alcohols and acetates revealed that chemicals with carbon chain lengths less than 18 to 19 angstroms could act as ocular irritants. Subsequent analysis indicated that PEA had a chain length of 10.2 angstroms, which was less than the cutoff value for abolishing ocular irritation.[29]

TLV Chronology

Table 2. TLV Chronology: *Phenylethyl Alcohol*

Date	Determinant	Action	TLV
2022	TLV–TWA Skin	Proposed	0.5 ppm

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