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Final Report on the Safety Assessment of Phenoxyethanol

Phenoxyethanol is an aromatic ether which is used in cosmetics as a preservative at concentrations below 1% and as a fixative for perfumes.

According to the classification scheme of Hodge and Sterner,[1] Phenoxyethanol is practically nontoxic when administered orally or dermally to rats.

In a subchronic oral toxicity study in rats of Phenoxyethanol, signs of toxicity included reduced body weights and an impaired ability to utilize feed. Increased liver, kidney, and thyroid weights were noted at necropsy in surviving rats.

Undiluted Phenoxyethanol was a strong eye irritant, but was nonirritating when tested at 2.2%. Phenoxyethanol at 2.0% was a slight irritant to rabbit skin, but was neither an irritant nor sensitizer to guinea pig skin.

In dermal treatment studies, Phenoxyethanol was neither teratogenic, embryotoxic, or fetotoxic at doses which were maternally toxic. Phenoxyethanol was nonmutagenic in the Ames test, with and without metabolic activition, and in the mouse micronucleus test.

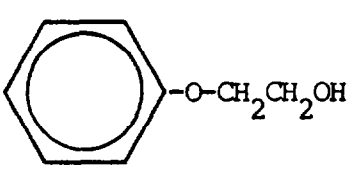
In clinical studies, Phenoxyethanol was neither a primary irritant nor sensitizer. Phenoxyethanol was not phototoxic in clinical studies.

It is concluded that Phenoxyethanol is safe as a cosmetic ingredient in the present practices of use and concentration.

CHEMISTRY

Definition and Structure

Phenoxyethanol is an aromatic ether alcohol which conforms to the structure:[2]



Phenoxyethanol (CAS No. 122-99-6) is also known was 2-phenoxyethanol,[2–5] phenoxetol,[2,4,6] ethylene glycol monophenyl ether,[3,5–8] and phenyl cellosolve.[3,5,6,8,9]

Properties

Phenoxyethanol is an oily,[6] slightly viscous liquid,[10] colorless[3,7,9] to off-white[7] in appearance. It has a faint aromatic[3,6] or rose-like[7] odor.

Phenoxyethanol is practically insoluble in mineral oil,[11] slightly soluble in water,[3,6,7] and soluble in alcohol and ether,[6,8] and in alkaline solutions.[3,6,7] Phenoxyethanol is miscible with glycerine, propylene glycol, and benzene.[11] It is also stable in acid solutions.[3] Partition coefficients for Phenoxyethanol are as follows: 2.9 in isopropyl palmitate-water, 2.6 in peanut oil-water, and 0.3 in mineral oil-water.[11]

Phenoxyethanol has a molecular weight of 138.17.[8] The boiling point for Phenoxyethanol has been reported as 237,[8] 242,[9] 244.9,[3] and 245.2°C.[6] Absolute Phenoxyethanol has a melting point of 14°C,[3,6,8,9] while the cosmetic grade material is a heavy syrup or glass at −10°C due to the presence of the diethoxylate.[11] The flash point of Phenoxyethanol is 121°C.[3,6,9] Its specific gravity is 1.1094 (20/20°C),[3,6] and its vapor pressure is < 0.01 mm (at 20°C).[3]

Phenoxyethanol has a density at 20°C of 1.105–1.110. Its refractive index at 25°C is 1.535–1.539. A 2.5% solution of Phenoxyethanol has a pH of 6.3–6.6.[12]

Method of Manufacture

Industrial-grade Phenoxyethanol is made by reacting phenol with ethylene oxide in the presence of a basic catalyst under pressure and with heating; the resulting product is neutralized, and purified to some extent.[11] Though the product is mainly Phenoxyethanol, the impurities may cause discoloration and unpleasant odors, making it unsuitable for cosmetic or fragrance use. In addition, this process results in a residual free phenol content of under one percent, another undesirable impurity for cosmetic formulation purposes.

In order to make the cosmetic-grade material, the reaction is continued to the point where 4–8% of the Phenoxyethanol is converted to the diethoxylate, thereby reducing the free phenol content. It is not desirable to obtain too much of the diethoxylated product as it does not have the antimicrobial properties of the Phenoxyethanol and thus serves only as a diluent. Finally, the end product must be handled and stored with care, as any contamination may result in undesirable colors or odors.[11]

Impurities

As previously mentioned, Phenoxyethanol may contain free phenol (less than 1%), or the diethoxylate of Phenoxyethanol.[11] Cosmetic-grade Phenoxyethanol is generally 98% pure[13] and is free of ethylene oxide (<1ppm).[14]

Analytical Methods

Analytical methods for the separation/determination of Phenoxyethanol include: infrared and ultraviolet spectrophotometry, nuclear magnetic resonance spectrometry, mass spectrometry,[15] and high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection.[16]

Chemical Reactions

The chemical reactions of Phenoxyethanol are basically those of an alcohol. It can be oxidized to form an aldehyde and a carboxylic acid; it can undergo condensation to form esters or ethers, and, in the presence of very strong acids, the ether bond may be hydrolyzed. The aromatic ring of Phenoxyethanol may undergo substitution reactions, but otherwise it behaves like an aliphatic chain.[11]

There is some evidence that sorption of preservatives (including Phenoxyethanol) from solutions to their containers may occur. This phenomenon was especially prevalent in bottles made of polyethylene, though the author noted that the phenomenon may not be as noticeable when the jars are full (test were performed with 20 ml of test solution in a 120 ml bottle).[17]

No inactivation of the preservative effects of Phenoxyethanol occurred due to adsorption of Phenoxyethanol to commonly used powder adjuvants in solution with the preservative.[18]

USE

Cosmetic

Phenoxyethanol is used in cosmetics as a preservative.[11] It is also used as a fixative for perfumes[6] and soaps.[3] It may be used in the synthesis of fragrance materials.[3]

Data submitted to the Food and Drug Administration in 1987 by cosmetic firms participating in the voluntary registration program indicated that Phenoxyethanol was used in 253 cosmetic products (Table 1). Product types containing Phenoxyethanol include eye makeup preparations, fragrance preparations, all types of blushers, face, body, and foot powders, foundations and makeup bases, lipstick, cuticle softeners, bath soaps, bath detergents and other bath preparations, skin care preparations

TABLE 1. Product Formulation Data for Phenoxyethanol[19]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*			
			>1–5	*≤1*	*>0.1–1*	*≤0.1*
Eye makeup preparations	1550	23	1		21	1
Fragrance preparations	853	4			3	1
Hair preparations including hair coloring	3008	54			42	12
Blushers (all types)	451	7			6	1
Face, body, and foot powders	698	10			7	3
Foundations and makeup bases	645	20			19	1
Lipstick	1494	7			3	4
Cuticle softeners	23	1		1		
Bath soaps, detergents and other bath preparations	665	8			5	3
Skin care preparations (including baby products)	3684	109	1		90	18
Suntan products	240	10			9	1
1987 Totals		253	2	1	205	45

(including baby care products), and suntan products.[19] The greatest use of Phenoxyethanol is in the category of skin care preparations (109 products). A majority of the formulations contained concentrations of Phenoxyethanol ranging from ≤ 0.1% (45 products) to 0.1–1% (205 products). One product contained Phenoxyethanol at a concentration of ≤1%, and two products, one bath preparation and one skin care preparation, contained Phenoxyethanol at concentrations of >1–5%.

The FDA cosmetic product formulation computer printout[20] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[21] Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges 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 two- to tenfold error in the assumed ingredient concentration.

Phenoxyethanol is listed as an approved cosmetic preservative in the European Economic Community (EEC) Cosmetics Directive in concentrations up to 1%, with the provision that the concentration used may be other than that listed in the Annex for specific purposes that may require a different concentration.[22]

Phenoxyethanol is listed with the Japanese Ministry of Health and Welfare (MHW) as an approved traditional cosmetic ingredient.[23]

Cosmetic products containing Phenoxyethanol may be used on all parts of the body, including the ocular region, may be applied repeatedly throughout the day or over an extended period of time, and may remain in contact with the skin or be rinsed off.

Noncosmetic

Phenoxyethanol may be used as a topical antiseptic,[4,6] especially in the case of wounds and burns being prepared for skin grafts.[24] Phenoxyethanol is used in ophthalmic solutions at concentrations of 0.3 and 2%.[12] It may also be used as a preservative in combination with formalin for DPT and DPT-polio vaccines,[25] and as a preservative for long- and short-term storage of animal tissues as a nontoxic substitute for formaldehyde.[26,27] In addition, Phenoxyethanol may be used as an anesthetic for fish.[4,28]

Phenoxyethanol may also be used in insect repellents,[6] as a solvent for cellulose acetate, dyes, inks, and resins, and in the organic synthesis of plasticizers and pharmaceuticals.[3]

Phenoxyethanol is approved without limitations for use as a component of adhesives in articles used in packaging, transporting, or holding food.[29]

Phenoxyethanol is also present in natural products such as green tea, Gyokuro.[30]

GENERAL BIOLOGY

Antimicrobial Activity

Phenoxyethanol has a broad range of antimicrobial activity, but the greatest activity is against gram-negative organisms. It is particularly effective against *Pseudomonas aeruginosa* (minimum inhibitory concentration [MIC], 0.32%).[11] At higher concentrations, it is effective against gram-positive organisms (MIC, *Staphylococcus aureus,* 0.85%) and yeasts (MIC, *Candida albicans,* 0.54%).[10]

Phenoxyethanol is also effective as a broad-spectrum preservative when used in combination with other preservatives such as neomycin and streptomycin,[31] hexachlorophane or tribromosalicylanilide or aminacrine hydrochloride,[32] and with the parabens.[33]

Mechanism of Action

The mechanism by which Phenoxyethanol inhibited the growth of *Escherichia coli* was studied by Gilbert et al.[34] The researchers found that Phenoxyethanol (in sub-bactericidal concentrations) uncoupled oxidative phosphorylation from respiration and inhibited malate dehydrogenase by competing for the active site of the enzyme.

Studies have indicated that the site of the bactericidal action of Phenoxyethanol was at the cell membrane.[35–37] Phenoxyethanol caused increased permeability of the cell membrane to potassium ions.[35,36]

Gilbert et al.[38,39] examined the inhibition of the biosynthesis of macromolecules in the cell by Phenoxyethanol, using *E. coli* and [^{14}C]glucose, thymidine, uracil, and phenylalanine. It was found that Phenoxyethanol inhibited the synthesis of DNA and RNA while, at lower Phenoxyethanol concentrations, protein synthesis remained unaffected. It was concluded that Phenoxyethanol had a direct inhibitory effect on the synthesis of DNA and RNA rather than an indirect effect on adenine triphosphate (ATP) supplies or metabolic precursors.

In studies using *P. aeruginosa,* the bacterial cells were similarly sensitive to potassium efflux, proton translocation, and inhibition of exogenous substrate respiration.[40] Unlike *E. coli, P. aeruginosa* sustained little gross cytoplasmic membrane damage, even at Phenoxyethanol concentrations which were highly bactericidal, but its respiratory cytochrome chain underwent total and irreversible oxidation at Phenoxyethanol concentrations of 1% (w/v) and higher. The authors concluded that this could be due to a greater resistance of *P. aeruginosa* to penetration by Phenoxyethanol or to different sites of action in the different cells.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The oral LD_{50} for Phenoxyethanol in male and female rats was 1.4 and 1.9 g/kg, respectively.[41] The oral LD_{50} for Phenoxyethanol was 1.3 g/kg for rats.[42]

Undiluted Phenoxyethanol (cosmetic grade, minimum 92% 2-Phenoxyethanol, maximum 8% diethylene glycol monophenyl ether) was administered by intubation to five groups of ten Sprague-Dawley albino rats, five rats of each sex per group.[43] The doses of Phenoxyethanol administered were 0.464, 1.00, 2.15, 4.64, and 10.0 ml/kg. The rats were fasted for 18 h prior to dosing, and were allowed feed and water *ad libitum* following intubation. The rats were observed for signs of systemic toxicity frequently on the day of Phenoxyethanol administration and at least twice daily for 14 days. The rats were weighed on the day of intubation, and on days 7 and 14 of observation. Necropsy was performed on all of the rats in the study; all major organs were examined.

All of the rats of the lowest dosage group survived the 14-day observation period. One male rat of the 1.00 ml/kg group died 4 1/2 h after intubation; the other rats of the group survived the 14 days. Of the rats of the 2.15 ml/kg group, none of the male rats survived beyond day 1 of the observation period, whereas three of the female rats survived the study. Of the male rats of the two high-dose groups, no rats survived beyond 4 1/2 h. None of the female rats of the 4.64 ml/kg group survived beyond 5 h, and none of the females of the 10.0 dose group survived beyond an hour. All of the rats that survived the study gained weight.

Signs noted in the low-dose group rats included slight to severe reduction of spontaneous activity, severely decreased reflexes, and labored respiration. All of the rats appeared normal after 24 h. The signs noted in the 1.00 ml/kg group were essentially the same, though slightly longer in duration; the male rats appeared normal after 24 h, and the female rats appeared normal after 48 h. The male rats in the 2.15 ml/kg group had severe reduction of spontaneous activity, severely decreased reflexes, and labored respiration, and all had died by 24 h. The female rats of this group all had varying degrees of decreased activity, and all had labored respiration at some point during the observation period. The four rats that survived beyond 1 h were comatose with rapid heart rates by 5 h. Three of those rats recovered and appeared normal after 48 h. The systemic effects in the male rats of the two high-dose groups were the same as those of the males in the 2.15 ml/kg group, with mortality occurring earlier in the study. In addition to the effects noted in the male rats of the group, the females of the 4.64 ml/kg group had excessive salivation. The female rats of the high-dose group were moderately inactive following intubation, and were comatose 10 min later. Death of these rats occurred within 1 h. No lesions were found at necropsy in the rats which survived the study.

The acute LD_{50} of Phenoxyethanol in male Sprague-Dawley rats was 1.26 ml/kg and in female Sprague-Dawley rats it was 2.33 ml/kg.[43]

In a preliminary range-finding study to determine the maximum tolerated doses (MTD) in mice for a mutagenicity study, groups of male and female Swiss CD-1 mice were administered Phenoxyethanol in 1% methylcellulose.[44] The study consisted of two phases. In the first phase, groups of four mice, equally divided by sex, were administered in two equal doses 24 h apart, a total of 500, 1000, 1500, 2000, 2500, or 3000 mg/kg of the test material. The mice were observed for any signs of toxicity or adverse reactions for 24 h after the last dose. Phase two of the study was performed to obtain a more accurate MTD. The dosage schedule was the same as in phase one; five female mice received a total dose of 600 mg/kg, another five female mice received a total dose of 750 mg/kg; 10 mice, 5 of each sex, received a total dose of 900 mg/kg; 5 male mice received a total of 2000 mg/kg; and a group of 5 male mice received a total of 4000 mg/kg. In the first phase of the study, the mice that received doses of 2000,

2500, or 3000 mg/kg of Phenoxyethanol in 1% methylcellulose had lethargy, ataxia, and body tremors 6 h after the first dose. Nine of the mice in these dosage groups died within 8 h after dosing. The mice of the 1000 and 1500 mg/kg groups were also lethargic, and deaths occurred in both groups. Deaths in each dosage group of phase one were as follows: 500 mg/kg, 0/4; 1000 mg/kg, 1/4; 1500 mg/kg, 3/4; 2000 mg/kg, 4/4; 2500 mg/kg, 4/4; and 3000 mg/kg 1/4. In phase two of the study, all of the mice of the 4000 mg/kg group died within 8 h of dosing. Lethargy and ataxia were noted in the mice of the 2000 mg/kg group following dosing; the mice were normal within 2 1/2 h. Other than those in the 4000 mg/kg group, no deaths occurred.

Groups of 10 rats, equally divided by sex, received undiluted Phenoxyethanol at doses of 1.0, 1.2, 3.2, 5, and 10 ml/kg in an acute oral toxicity range-finding study.[45] The doses used in the actual test were 1, 1.25, 1.6, 2, and 3.2 ml/kg. The researchers noted the following reactions: lethargy, ataxia, hyperpnoea, and coma. Death, when occurring, was within 24 h of dosing. The oral LD_{50} was 1.30 (range 1.16–1.46) ml/kg for undiluted Phenoxyethanol.

Dermal

The acute dermal toxicity of undiluted Phenoxyethanol was evaluated using 10 CFY strain rats, five of each sex.[46] The Phenoxyethanol was applied to the dorsolumbar region under an occlusive patch such that 10% of the total body surface was covered. Doses ranged from 1–22.2 ml/kg. The Phenoxyethanol remained in contact with the skin for 24 h. Death occurred 21–48 h after dosing. Hemorrhagic lungs were found at necropsy. The dermal LD_{50} for undiluted Phenoxyethanol was 13.0 (range 10.3–15.4) ml/kg.

When 2.0 ml/kg undiluted Phenoxyethanol (cosmetic grade) was applied to the shaved and abraded skin of four New Zealand White rabbits, remaining in place for 24 h, followed by a 14-day observation period and necropsy, no systemic toxicity or adverse effects were noted.[43] All of the rabbits gained weight during the study.

Short-Term Toxicity

Oral

Three groups of five male rats each were administered Phenoxyethanol by gavage at doses of 100, 300, or 1000 mg/kg per dose for a total of 11 doses over a 15-day period.[41] The Phenoxyethanol was 96.3% pure as determined by gel chromatography (GC) analysis. The rats of the high-dose group had reduced body weight gains, though feed consumption was not affected. The rats of the high-dose group also had depression of the nervous system (requiring the euthanasia of one rat of the group), but the depression did not last beyond the fifth dose of Phenoxyethanol. The liver and kidney weights as well as the hematologic values of the rats of all three dosage groups were comparable to those of the controls. Of the clinical chemistry values, the rats of the high-dose group had significantly increased activities of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase; however, the values for these two clinical chemistry parameters were within the normal range of historical controls for the laboratory. No treatment-related abnormalities were noted upon microscopic evaluation.

Dermal

Phenoxyethanol was applied dermally to 10 female New Zealand White rabbits at a dose of 1000 mg/kg/day for 14 days. The five control rabbits received distilled water daily. Seven of the rabbits died or were sacrificed in a moribund condition between days 5 and 8 of treatment. The prominent hematologic change noted in these rabbits was indicative of the breakdown of erythrocytes. There were no hematologic changes noted in the three surviving rabbits.[47]

Subchronic Oral Toxicity

Groups of 30 CD rats, divided equally by sex, were used to determine the subchronic oral toxicity of Phenoxyethanol.[48] Doses of 0, 80, 400, and 2000 mg/kg/day of Phenoxyethanol in 0.5% gum tragacanth were administered by gavage daily for 13 weeks. The rats were observed for signs of toxicity throughout the study. Nine rats (four females of the high-dose group were the only rats specified) died during the study. Body weights were reduced in the rats of the high-dose groups; males had the lower body weights. Male rats in the high-dose group had a 6% reduction in feed consumption as compared to controls; all of the rats in the high-dose group had an impaired ability to utilize the feed which was consumed. Water intake was increased in the rats of the high-dose group at weeks 6 and 12. Lack of grooming was observed in the rats of the high-dose group during the first 8 weeks of the study, and in the female rats of the 400 mg/kg group during the first 6 weeks of the study. The rats of the high-dose group were occasionally lethargic 10–30 min after dosing, the lethargy was followed by prostration lasting for 2–18 h, and the female rats were more often affected.

Treatment with Phenoxyethanol was the cause of death in the four female rats of the high-dose group, no abnormalities were found at necropsy or after microscopic examination. Clinical biochemical changes noted in the rats of the high-dose group included elevated urea and glucose and increased activities of alkaline phosphatase and glutamate-pyruvate transaminase at week 4. The alkaline phosphatase activities remained elevated at week 12. The urinary volume of the high-dose rats was increased at weeks 4 and 12, but the specific gravity was not decreased. In addition, large amounts of epithelial cells and polymorphonuclear leukocytes were found in the urinary sediment. There was an increase in the alkaline phosphatase activities of the 400 mg/kg male rats at 4 weeks; no other clinical pathologic effects were noted in the rats in dosage groups of 400 mg/kg and below.

At necropsy, changes noted in the high-dose rats were increased liver, kidney, and thyroid weights. Microscopic changes considered related to treatment with Phenoxyethanol at 2000 mg/kg/day, and at 400 mg/kg/day in the male rats, were "prominent groups of distended tubules with associated basophilic staining tubules and chronic inflammatory cell infiltration in the kidneys." Minor changes of low incidence in the testes of the high-dose males were noted but were considered of equivocal toxicological significance.[48]

Ocular Irritation

Undiluted Phenoxyethanol (cosmetic grade, minimum 92% 2-Phenoxyethanol, maximum 8% diethylene glycol monophenyl ether), 0.1 ml, was applied to the left eye of each of 12 New Zealand White rabbits; the right eyes served as controls.[43] The eyes

of six of the rabbits remained unrinsed, the eyes of three rabbits were rinsed after 4 s for 5 min with water, and the eyes of three rabbits were rinsed after 30 s for 5 min with water. The eyes were examined for irritation at 1, 24, 48, and 72 h, and daily for an additional 11 days. Irritation was scored according to the method of Draize.[49]

Of the rabbits receiving no rinse (rabbits no. 1–6), all had slight corneal opacity, minimal iritis, moderate to severe redness of the conjunctivae with blisters under the eyelids, and moderate swelling and discharge. The time required for the reactions to subside varied with the individual rabbits, the highest total Draize score was 46 at 1 h, and all rabbits had scores of 0 by day 14. The ocular reactions of the three rabbits receiving a rinse 4 s after instillation of the test material were slight opacity of the cornea, slight iritis, and severe erythema with blisters under the lids in two of the rabbits. A score of 0 was noted on day 8 for two of the rabbits, and on day 11 for the third rabbit. The three rabbits which received a rinse 30 s after instillation had slight corneal opacity over varying areas of the cornea, slight iritis, and severe erythema with blisters under the eyelids, and swelling with minimal discharge. These reactions persisted for varying lengths of time, and all were cleared by day 12. The rabbits received scores of 0 on days 7, 8, and 12; no maximum score was greater than 2 after 72 h. Undiluted Phenoxyethanol was an eye irritant under the conditions of the study.

Undiluted Phenoxyethanol, 96.3% pure, was instilled into the conjunctival sacs of the eyes of three rabbits.[41] One eye of each rabbit was rinsed. The unrinsed eyes had moderate to severe erythema and edema, injected irides, and slight corneal opacities. The three unrinsed eyes also had fluorescein staining of the cornea and adnexa. The rinsed eyes had slight (two eyes) to moderate (one eye) irritation. The rinsed eyes had fluorescein staining of the adnexa. Undiluted Phenoxyethanol was a strong eye irritant under the conditions of the study.

In an acute ocular irritation screen study, a 2.2% aqueous solution of Phenoxyethanol, 0.1 ml, was instilled into the right conjunctival sac of three New Zealand White rabbits; the left eyes served as controls.[50] The eyes were observed for irritation at 19, 43 1/2, and 66 3/4 h after instillation. The signs of irritation were scored according to the method of Draize.[49] No irritative effects were noted in any of the rabbits.

In an acute ocular irritation study following the previously mentioned screening study, 0.1 ml of a 2.2% aqueous Phenoxyethanol solution was instilled into the conjunctival sac of each of six New Zealand White rabbits with the contralateral eye serving as a control.[51] The eyes had been examined with sodium fluorescein dye 24 h before application of the test material. The eyes were examined for signs of irritation at 23, 51 1/4, and 72 1/2 h postinstillation. Eye irritation was scored according to the method of Draize.[49] One rabbit had slight conjunctival erythema at the 72 1/2 h reading; all other scores were 0. It was concluded that the 2.2% aqueous solution of Phenoxyethanol was not an ocular irritant.

Phenoxyethanol applied to the conjunctival sac of rabbits, in undiluted form, caused severe damage; when diluted to 5%, there was a mild irritation of the conjunctivae.[52]

Dermal Irritation and Sensitization

The irritant potential of Phenoxyethanol was evaluated using six rabbits.[53] A single occlusive patch of 2% or 10% Phenoxyethanol in acetone/water (10/90) was applied to the clipped and intact or abraded skin on the flanks of the rabbits. The patches remained in place for 24 h, and the patch sites were examined upon patch removal and at 72 h.

Slight transient erythema was observed in two of the rabbits at the 10% Phenoxyethanol site at the 24 h reading, and in one rabbit at the 2% Phenoxyethanol site at 24 h.

The dermal sensitization potential of Phenoxyethanol was evaluated using six albino guinea pigs.[54] The induction phase of the study consisted of five applications at 24 h intervals of 0.1 ml of 10% Phenoxyethanol to the outer surface of the ears. Five days after the last application to the ear, 0.2 ml of 0.1, 1.0, and 10% solutions of Phenoxyethanol were applied to the shaved flanks of the guinea pigs. No reactions were noted during either the induction or challenge phases of the study.

Undiluted Phenoxyethanol (cosmetic grade, minimum 92% 2-Phenoxyethanol, maximum 8% diethylene glycol monophenyl ether), 2.0 ml/kg, was applied to the shaved and abraded dorsal skin of four New Zealand White rabbits.[43] The test material remained in contact with the skin for 24 h, after which the unabsorbed material was removed. The rabbits were examined upon removal of the test material for signs of systemic toxicity and dermal irritation. The rabbits were examined twice daily for 14 d following exposure to Phenoxyethanol. The rabbits were weighed prior to exposure, and on days 7 and 14. At the end of the observation period, the rabbits were sacrificed for necropsy. At bandage removal, two rabbits had erythema; the erythema persisted in one rabbit through day 3. This rabbit also had desquamation on days 3–14. No other adverse effects were noted.

Undiluted Phenoxyethanol, 96.3% pure, was applied under an occlusive patch to the depilated abdomens of three guinea pigs.[41] The patches remained in place for 24 h, and the skin was examined upon patch removal. Phenoxyethanol produced slight irritation of the skin of all three guinea pigs.

When Phenoxyethanol was applied daily to the shaved backs of five guinea pigs for a total of ten applications, it was noted that all of the test animals had slight erythema, which was not worsened with the repeated applications.[41]

In an "open irritation test," a 500-mg dose of Phenoxyethanol caused mild skin irritation in rabbits.[55]

Teratogenicity/Reproduction Studies

A feeding study to determine the reproductive and fertility effects of Phenoxyethanol (92–94% pure) using CD-1 mice was performed by the National Toxicology Program (NTP).[56] In a preliminary range-finding study, groups of 16 mice, divided evenly by sex, were given 0, 1.0, 2.5, 5.0, 7.5, and 10.0% Phenoxyethanol in the diet for 14 days. Analysis of the mortality led to the calculation of an LD_{10} of 8.2%. Weight gains of the combined sexes in the two highest dose groups were significantly lowered. A decreased percent weight gain was noted in the 5.0% Phenoxyethanol group.

The test groups, 40 mice each, evenly divided by sex, were given 0.25, 1.25, and 2.50% Phenoxyethanol in the diet. The control group consisted of 40 mice of each sex. The mice were administered the test substance in the feed for 7 days prior to mating, and throughout the remainder of the study. Pairs of mice were then housed together for 98 days with feed and water available *ad libitum*; reproduction records were kept during this continuous breeding phase of the study. For the following 20 days, the mice were separated and housed individually; the mice of the litters prior to this 20-day period were sacrificed; eight to ten of the litters obtained during this 20-day period were maintained for use in another phase of the study. Exposure to Phenoxyethanol had no effect on the number of mouse pairs that produced at least one litter and no effect on the

number of male pups per total number of pups born alive. Mice in the high-dose group produced fewer litters per pair, had smaller litters, and produced fewer live pups per litter. The decrease in weight of live pups was dose dependent.

In the next phase of the study, a crossover mating trial, with a seven-day mating period, was performed to determine which sex was affected by the administration of Phenoxyethanol. This phase of the study was a continuation of the previous phase, using control males and females, control females and high-dose males, and control males and high dose females as the mating pairs. The only significant difference noted among the three groups was that the live pup weight was lower in the control male × high-dose female group compared to the other two groups. Live pup weight adjusted for total pups per litter was also significantly lower for this same group. This indicated that the Phenoxyethanol was fetotoxic in the F_0 females.

Mice involved in the crossover mating test were necropsied 3 weeks after their 7-day mating period. No significant differences were found in the sperm viability and in brain, pituitary, left testis/epididymis, right testis, and prostate weights. Body and seminal vesicle weights were significantly lowered and liver weights were significantly increased in the high-dose males compared with control males. The differences in seminal vesicle weights were not significant when adjusted for body weights and then compared with the seminal vesicle weight for the combined controls. The only significant difference noted in the female mice was an increased liver weight in the high-dose females.

In another phase of the study, the final litters obtained from the continuous breeding phase of the study were weaned at 21 days of age. Eight to ten of these litters remained on study to an age of 74 ± 10 days, at which time one to three mice of each sex from each litter were selected for breeding within their feeding group. Dose-dependent decreases were found in body weight at birth, weaning day, and breeding day in these mice, suggesting that Phenoxyethanol was toxic throughout lactation and postweaning. Pup lethality was increased during these same periods in the two highest dose groups (1.25 and 2.5%). At 74 ± 10 days of age, one mouse of each sex from different litters in the same dose group were mated for 7 days. Only three mating pairs were available from the high-dose group, and because of the small sample size, the data obtained from these mice were not included in the statistical analyses. No significant differences in reproductive/fertility parameters were noted for the F_1 mice; again live pup weights were reduced in a dose-dependent manner.

The control and the high-dose mice (in this case, the 1.25% dose group) were necropsied 3 weeks after the 7-day mating period. No significant differences were noted in the sperm viability. Decreases in body weights, left testis/epididymis, and seminal vesicle weights of the high-dose mice were significant. The seminal vesicle weights remained significantly lower after adjustment for body weight. In the high-dose mice, the adjusted liver and pituitary weights were significantly greater; the same was true for the adjusted liver weights of the high-dose females. There were no significant differences in the reproductive organ weights between control and high-dose females. Brain and body weights were also significantly lower in high-dose females, but the difference in brain weight was not significant when adjusted for body weight.

The conclusions from this study were that 2.5% Phenoxyethanol in the diet was a reproductive toxicant in F_0 mice and produced a dose-dependent decrease in live pup weight during exposure of the F_0 mice. Phenoxyethanol was selectively fetotoxic to F_0 females. Continuous exposure to Phenoxyethanol reduced the body weights of the F_1 mice in a dose-dependent manner, and produced mortalities of 39% (33/84) in the mice

of the 1.25% dose group and 87% (66/76) in the mice of the 2.5% dose group. The weights of the F_2 generation were also decreased in a dose-dependent manner. Phenoxyethanol in the diet was toxic to newborn and young mice. Seminal vesicle weights were decreased in the mice of the two highest dose groups, and adjusted pituitary weights were increased for F_1 males of the 1.25% dose group. Generalized effects noted in the F_0 and F_1 mice were decreased body weights and increased liver weights. Body weight gain and reproductivity/fertility were not adversely affected by Phenoxyethanol in the diet at doses of 0.25 and 1.25%. The authors noted that the reproductive effects of Phenoxyethanol may have been secondary to its toxic effects.

A teratogenicity study using New Zealand White (NZW) rabbits was performed by Scortichini et al.[57] Phenoxyethanol, greater than 99% pure and undiluted, was applied to the clipped skin of the backs of groups of 25 pregnant rabbits at doses of 300, 600, or 1000 mg/kg/day from day 6 through day 18 of gestation. The treated skin was covered with an occlusive bandage which remained in place for 24 h. After removal of the bandage, and prior to the next application of Phenoxyethanol, the skin was examined for signs of irritation and regrowth of hair. On day 19 of gestation, the bandages were removed, and the treated skin was washed in order to prevent ingestion of the test material.

The animals were observed daily for signs of treatment-related effects, and they were weighed daily on days 6–19, and on day 28 of gestation. Blood samples were collected from approximately 10 animals from each dose group, except the highest dose group, on day 19 of gestation; in addition, two rabbits of the 600 mg/kg/day group and one of the 1000 mg/kg/day group were sacrificed *in extremis* and blood samples were collected. Urinalyses were performed on samples taken from two moribund rabbits, one each from the two highest dose groups, at the time of necropsy. When caesarian sections were performed on day 28 of gestation, the maternal liver weights were recorded.

There was a slight to moderate reddening of the skin at the site of application of Phenoxyethanol in some of the rabbits in each dose group. The skin of four rabbits in the 600 mg/kg/day group, and of three rabbits in the high dose group had darkened at the site of application. There was also staining of the perineal region and dark urine in some of the rabbits of these two groups.

Fourteen rabbits (5 and 9 in the 600 and 1000 mg/kg/day groups, respectively) died or were sacrificed *in extremis* during the study, most between days 11 and 18 of gestation. At necropsy, the urine and kidneys were dark and the body was jaundiced. Blood samples taken from some of these animals indicated a regenerative hemolytic anemia. No intact erythrocytic cells were found in the urine; the only other hematologic findings were those due to intravascular hemolysis.

Treatment with 1000 mg/kg/day was terminated after only five rabbits had reached day 28 of gestation; this group was eliminated due to the excessive mortality. Of the five rabbits that completed the dose regimen, none had signs of adverse effects (the same was true for the surviving rabbits of the 600 mg/kg/day group), and the fetuses appeared normal.

Of the remaining dosage groups, no differences were seen in body weight gains, liver weights, pregnancy rates, numbers of resorptions, or fetal body measurements. No malformations of the internal organs were observed in the fetuses of either the treated groups or the controls. The authors concluded that dermal treatment of NZW rabbits with Phenoxyethanol did not result in teratogenicity, embryotoxicity, or fetotoxicity even at doses that were maternally toxic (600 mg/kg/day).[57]

A study to determine the effects of several ethylene glycol alkyl ethers, including Phenoxyethanol, on the testes was undertaken using JCL-ICR mice.[58] Mice were dosed with Phenoxyethanol by oral intubation at 62.5, 125, 250, 500, 1000, and 2000 mg/kg 5 days per week for 5 weeks. Controls received water in the same manner. The mice were sacrificed on the day after the last dose was administered, and the testes were weighed, as were the seminal vesicles and coagulating gland. Tissue specimens and blood samples were obtained at the time of necropsy. No statistically significant differences were seen in the weights of the testes in the treated and control groups. The authors concluded that oral treatment with Phenoxyethanol produced no significant testicular atrophy in mice.

Phenoxyethanol was assessed for developmental toxicity potential in a predictive assay using adult *Hydra attenuata* polyps.[59] The adult polyps were mechanically dissociated, pelleted, and allowed to randomly reassociate. During reassociation, the *Hydra* cells underwent a differentiation and organogenesis that simulated the developmental biology which occurs in the embryo of any species. The reassociating cells as well as the adult polyps were exposed to the test substance. With Phenoxyethanol, toxicity to adult polyps occurred at a concentration of 1.0 ml/L, and toxicity to the developing "embryo" occurred at 0.3 ml/L. These values gave an A/D (lowest concentration toxic to adults/lowest concentration disruptive to "embryo" development) ratio of 3.3 for Phenoxyethanol. The conclusion reached by the authors was that Phenoxyethanol would be toxic to the developing embryo at concentrations below those which were toxic to the adults. For comparison, the *Hydra* test results for ethylene glycol monoethyl ether were similar to data from published animal studies, A/D = 5 (five times more toxic to embryo than adult), and the results for ethylene glycol (A/D = 1.7) and ethylene glycol monomethyl ether (A/D = 1.3) indicated that these would be toxic to the developing embryo at concentrations which were maternally toxic, a conclusion also substantiated by other published studies.

MUTAGENICITY

Phenoxyethanol was evaluated for mutagenicity (Ames test) at concentrations of 50, 150, 500, 1500, and 5000 μg/plate in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100.[60] No significant increases in the numbers of revertants were found in any of the test strains at any of the Phenoxyethanol concentrations, with or without metabolic activation.

Phenoxyethanol was also tested for mutagenicity in a micronucleus test using Swiss CD-1 mice.[44] The mice were administered two equal doses of Phenoxyethanol in a methylcellulose vehicle at 24-h intervals for total doses of 300, 600, or 1200 mg/kg. The methylcellulose vehicle was used as a negative control and mitomycin C was used as a positive control. The mice were observed for either 24 or 48 h, after which time five mice of each sex from each dosage group were sacrificed and bone marrow cells were removed. The cells were examined for the number of micronucleated cells per 1000 polychromatic erythrocytes per mouse and for the ratio of normochromatic to polychromatic erythrocytes. The numbers of micronucleated cells and the ratio of normochromatic to polychromatic cells were comparable for both the Phenoxyethanol-treated mice and the control mice. Phenoxyethanol was nonmutagenic under the conditions of the study.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Phenoxyethanol, 10% (v/v) in mineral oil was tested for irritation and sensitization potential in a repeated insult patch test using a panel of 51 subjects, male and female, aged 16–>60.[61] The Phenoxyethanol, 0.3 ml, was applied to a patch which was then applied to the skin of the upper arm of the panelist. The patches were applied every Monday, Wednesday, and Friday for 3 weeks. The patches were removed 24 h after application, and the sites were scored before application of the next patch, or in the case of the last patch, 72 h after removal. Any panelist who missed an induction patch received a final patch in the fourth week of the study. After 10 days to 2 weeks, a challenge patch was applied (beginning of the sixth week of the study). The challenge patch included both the induction site and an adjacent previously untreated site. The challenge patch remained in place for 24 h, and challenge sites were scored 24 and 72 h later. A vehicle control was also tested.

During the induction phase of the study, two panelists had reaction scores of 1 (reaction visible but mild), one after induction 3 and one after induction 5 (reactions noted before application of induction patches 4 and 6, respectively). In both cases, the reaction had cleared by the application of the next patch. No other reactions were recorded during either the induction or challenge phases of the study. Phenoxyethanol, at the concentration tested, was neither a primary nor a cumulative irritant, nor was there any evidence of delayed contact hypersensitivity.

Of 2736 patients patch-tested with 1% Phenoxyethanol in petrolatum, none had signs of irritant or allergic reactions 2 and 4 days after application.[62] Patch testing of 130 patients with 1, 5, and 10% Phenoxyethanol in petrolatum resulted in no irritant or allergic reactions. Allergic contact dermatitis to 1% Phenoxyethanol could be a rare possibility in patients having an adverse reaction to aqueous creams. An adverse reaction occurred in a patient with a 6-month history of hand eczema and a childhood history of flexural eczema; an aqueous cream containing 1% Phenoxyethanol used in place of soap caused the disease to worsen, and the patient subsequently had a positive reaction to the patch test using Phenoxyethanol.

In a study to determine the necessity of including common preservatives in the Dutch standard series, 14 preservatives were used in patch tests on 501 patients who were undergoing routine patch testing for suspected contact dermatitis.[63] Phenoxyethanol, 5% in petrolatum, was tested according to ICDRG guidelines. There was one positive reaction to the preservative, for a 0.2% positive reaction rate.

Phenoxyethanol was evaluated for sensitization potential in a modified repeated insult patch test using a panel of 138 male and female subjects.[64] A 10% solution of Phenoxyethanol in petrolatum was applied under an occlusive patch to the backs of the test subjects. The first patch remained in place for 48 h, and subsequent patches, applied every other day for a total of eight applications, remained in place for 24 h. Three weeks after the last (ninth) patch application, the subjects were challenged with 10% Phenoxyethanol at a previously unpatched site. No skin reactions consistent with allergic sensitization were observed.

Phototoxicity

A phototoxicity study of Phenoxyethanol was performed using 28 panelists, male and female, aged 18–50.[65] The Phenoxyethanol, 0.3 ml, was applied undiluted to

patches which were then applied in duplicate to the volar surface of the forearm of each panelist. One patch was removed after 24 h. The site was rinsed and dried, and was then exposed for 10 min to 16–20 J/cm of UVA light. After the completion of the irradiation of the first patch site, the second patch on each panelist was removed, and the site was rinsed and dried. All sites were evaluated 1, 24, 48, and 72 h after irradiation.

Following UVA exposure, 12 panelists had reactions of varying duration. Five of the panelists had readily visible but mild reactions (a score of 1) at 1 h and were clear for the remainder of the study. Three panelists had scores of 1 at 24 h and were clear for the remainder of the study. One panelist had a score of 1 at both 1 and 24 h; the reaction had diminished by 48 h. Another panelist had scores of 1 at 1 and 72 h. The final two panelists had reactions at 1, 24, and 48 h and at 1, 48, and 72 h, respectively. All of these reactions were readily visible but mild. One panelist also had a mild reaction at 72 h at the unexposed patch site. This panelist had no reactions at the irradiated site. It was concluded that Phenoxyethanol was not phototoxic under the conditions of the study. Occasional incidences of slight erythema were observed at the irradiated sites, but these were not considered significant since erythema was occasionally observed at both nonirradiated sites and blank control patch sites.

SUMMARY

Phenoxyethanol is an aromatic ether with an alcohol moiety. It is used in cosmetics as a preservative and as a fixative for perfumes. Most cosmetic products contain Phenoxyethanol at concentrations below 1%. Phenoxyethanol is approved by the European Economic Community in cosmetics at concentrations up to 1%, and by the Japanese Ministry of Health as a traditional cosmetic ingredient.

Phenoxyethanol is also used as an antiseptic, tissue preservative, and solvent. It is used in the synthesis of plastics and pharmaceuticals, and as a component of adhesives. It is also a natural component of green tea.

Phenoxyethanol has a wide range of antimicrobial activity, especially against gram-negative organisms. At higher concentrations, it is also effective against yeasts. Phenoxyethanol was bactericidal to *E. coli* by the action of proton conduction and uncoupling of oxidative phosphorylation. Treatment with Phenoxyethanol also caused increased permeability of cellular membranes to potassium ions. Results of certain studies indicated that Phenoxyethanol probably exerted a direct effect on the synthesis of DNA and RNA. In studies using *P. aeruginosa*, similar effects of potassium efflux, proton translocation, and inhibition of exogenous substrate respiration were noted after treatment with Phenoxyethanol.

According to the classification scheme of Hodge and Sterner,[1] Phenoxyethanol is practically nontoxic to slightly toxic when orally administered to rats and mice and practically nontoxic when administered dermally to rats.

When Phenoxyethanol was administered at varying doses by intubation to albino rats, no treatment-related lesions were found at necropsy of rats that died during the study. In mice that were administered varying doses of Phenoxyethanol, signs of toxicity included lethargy and ataxia, and in some cases, body tremors.

Systemic toxicity was produced when Phenoxyethanol was applied to the skin of CFY rats, but was not produced when Phenoxyethanol was applied to the skin of New Zealand White rabbits.

No treatment-related abnormalities were noted in a short-term oral toxicity study of Phenoxyethanol in rats. In a short-term dermal study using NZW rabbits, hemolysis was noted in the rabbits that did not survive the study; no hematologic changes were noted in the rabbits that survived the study.

In a subchronic oral toxicity study of Phenoxyethanol using rats, signs of toxicity during the study included reduced body weights, reduced feed consumption, and an impaired ability to utilize feed in the rats receiving the higher doses of Phenoxyethanol. Other signs included increased water intake, occasional lethargy which was sometimes followed by prostration, and occasional changes in hematologic values and in the results of urinalyses. Treatment with Phenoxyethanol was determined to be the cause of death of four female rats in the high-dose group, though no abnormalities were found at necropsy and at microscopic examination of those rats. Increased liver, kidney, and thyroid weights were recorded in surviving rats of the high-dose group and microscopic examination revealed abnormalities in the kidneys.

Undiluted Phenoxyethanol was strongly irritating to rabbit eyes, while diluted Phenoxyethanol was either nonirritating or mildly irritating.

Diluted Phenoxyethanol caused slight transient irritation to rabbit skin and undiluted Phenoxyethanol caused slight irritation and desquamation of rabbit skin. Diluted Phenoxyethanol was neither an irritant nor a sensitizer to guinea pig skin, while the undiluted chemical was slightly irritating to guinea pig skin.

Phenoxyethanol, when administered in the feed to mice, was a reproductive toxicant to F_0 mice. In addition, there was a dose-dependent decrease in live pup weight. Continuous exposure of the F_1 mice to Phenoxyethanol resulted in reduced body weights and in mortality in the mid- and high-dose groups. Phenoxyethanol in the diet was toxic to newborn and young mice. Seminal vesicle weights were reduced in the males of the mid- and high-dose groups. Body weight gain and reproductivity/fertility were not adversely affected by Phenoxyethanol at low- and mid-dose dietary concentrations. Dermal treatment of pregnant New Zealand White rabbits with Phenoxyethanol did not result in teratogenicity, embryotoxicity, or fetotoxicity at doses up to those which were maternally toxic. No significant testicular atrophy was seen in mice after oral treatment with Phenoxyethanol.

In a developmental toxicity assay using *Hydra attenuata,* it was determined that Phenoxyethanol would be toxic to the developing embryo at concentrations below those which were toxic to the adults.

Phenoxyethanol was nonmutagenic in the Ames test (with and without metabolic activation) and in the mouse micronucleus test.

In clinical studies, Phenoxyethanol was neither a primary nor a cumulative irritant, and it did not cause delayed hypersensitivity. Phenoxyethanol was also nonphototoxic.

CONCLUSION

On the basis of the available information presented in this report, the Expert Panel concludes the Phenoxyethanol is safe as a cosmetic ingredient in the present practices of use and concentration.

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