

Are phenoxyethanol products safe for babies? – A review of current evidences

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ABSTRACT

Phenoxyethanol is used at concentrations below 1% as a preservative in cosmetic products and fixative in perfumes. Some people have reported adverse responses to phenoxyethanol on their skin. Some suggest that the test subjects' negative reactions are the result of allergies. Nevertheless, there are claims that it's simply a skin irritant that has varying degrees of effect on various people. In 2012, the ANSM (French National Agency of Medicine and Health Products Safety) advised against using phenoxyethanol in cosmetics for babies' bottoms. On a European level, this advice had not been confirmed. The purpose of this article is to discuss the potential negative effects of phenoxyethanol on newborns and infants.

Key words: Phenoxyethanol, Preservatives, Newborns, Hematotoxicity

The skin of the newborn plays an important role in the transition from the aqueous intrauterine environment to extrauterine life. It is also a vital organ as it provides mechanical protection, helps in thermoregulation and cutaneous immunosurveillance, and prevents insensible water loss by maintaining a barrier.

Human skin comprises three layers: Epidermis, dermis, and subcutaneous fat. The skin of a newborn is similar to that of older individuals histologically. On the other hand, a premature baby's skin has several unique features. The skin of newborns and infants is still at a functionally developing stage, and the poor barrier function of the skin of newborns makes it more prone to chemical irritation and infections as compared to adults [1]. Epidermal fragility is marked in preterm infants because the skin barrier is not completely matured [2].

An effective skin barrier is present in infants of 37 weeks gestation or more as shown by low skin water loss and little or no drug absorption. By contrast, significant skin water loss and drug absorption occur in infants of 32 weeks gestation or less in the early neonatal period because of the defective skin barrier. The skin of most preterm infant's shows less drug absorption and water loss at about 2 weeks of age and functions like that of mature infants. These varying barrier properties are due to the poor development of the stratum corneum in premature infants at birth and its rapid maturation in postnatal life [3].


Agents that are applied topically may get absorbed and leads to toxic systemic effects such as neurotoxicity, structural damage, and sometimes even death [4]. Repeated use of isopropyl alcohol can be absorbed and cause systemic intoxication. In preterm newborns, it can cause severe hemorrhagic necrosis of the skin [5]. In more than 2 months of age infants, the recommended topical antiseptic is chlorhexidine as an alternative to alcohol but there safety data are limited in newborns [6]. Topical iodine solutions can cause iodine overload and lead to transient hypothyroidism. Therefore, it should be avoided especially in preterm neonates [7]. Systemic toxicity can be caused by topical keratolytic agents, such as lactic acid or salicylic acid [8,9]. Methemoglobinemia can occur after absorption of aniline dye, which is used to stamp the name [10].

The detoxification system of the skin is not completely developed in preterm newborns which is responsible for the absorption of topical substances without chemical modifications [11]. Therefore, only those topical agents should be used which are not associated with toxicity after systemic administration. Newborns and infants require particular attention when selecting a topical agent. Particular care is required for cleansing infants and newborns to avoid irritation of the skin or eye which can lead to infections. The use of liquid, skin cleansers is recommended for infant cleansing because emollients are often present in a cleansing bar [12].

Phenoxyethanol belongs to ether and aromatic alcohol group. It is also known as 2-phenoxyethanol, ethylene glycol monophenyl ether, phenoxytol, 1-hydroxy-2-phenoxyethane,

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Access this article online	
Received - 07 May 2022 Initial Review - 10 May 2022 Accepted - 12 May 2022	Quick Response code 
DOI: 10.32677/ijch.v9i5.3465	

and (2-hydroxyethoxyl) benzene. It has antimicrobial properties and is effective against both Gram-negative and Gram-positive *Staphylococcus aureus* bacteria, and against yeasts [13,14]. It has been used for many years as a preservative in several products such as vaccines and hand disinfecting products up to a concentration of 5% because of its broad-spectrum antimicrobial properties [15]. It is also used as a preservative in many leave-on and rinse-off products. Phenoxyethanol was present in 23.9% of the products as per the recent study which analyzed the full ingredient information found in the American Contact Dermatitis Society database – the Contact Allergen Management Program – for a large group of commonly used cosmetic products marketed in the USA [16]. A recent study done in Spain found that 43.09% of sold cosmetics in pharmacies, 23.29% sold in supermarkets, and 14.1% sold in herbal shops, consisting of phenoxyethanol [17].

Some concerns about the safety of phenoxyethanol were heightened due to its similarity to the glycol ether family. Further controversial claims were made that it affects the liver and blood, and also disrupts endocrinal functions. The French National Agency for the Safety of Medicines and Health Products (ANSM) advocated that phenoxyethanol should be avoided in cosmetics as a preservative particularly in those products which are used in the nappy area (diaper rash cream) of children less than 3 years of age [18]. The various effects of phenoxyethanol in newborns and infants are discussed in details in the present article.

EFFECTS OF PHENOXYETHANOL IN INFANTS

Systemic Absorption through Dermal Route

According to the findings of an unpublished study by Vincent and Marty in 2002 (cited by the SCCS) [19], phenoxyethanol absorption after topical application is rapid and high regardless of its concentration. After 24 h, the majority of the absorbed phenoxyethanol was identified in the receptor fluid. After 24 h of application, the absorption of the formulation containing 1% phenoxyethanol was higher in leave-on products ($78\% \pm 7\%$) than in rinse-off products ($37\% \pm 10\%$). After topical administration, phenoxyethanol is eliminated in the urine, mostly as 2-phenoxyacetic acid, in a clinical trial on preterm newborns [20]. Therefore, to sum up the above details, dermal absorption of phenoxyethanol (the total quantity of phenoxyethanol in the receptor fluid, dermis, and epidermis) was $37\% \pm 10\%$ for rinse-off products and $78\% \pm 7\%$ for leave-on products over a 24 h for a formulation containing 1% phenoxyethanol. Phenoxyethanol was found to be almost entirely absorbed after topical administration ($78\% \pm 7\%$ for leave-on formulations) and converted into its primary metabolite 2-phenoxyacetic acid, which is primarily eliminated in urine.

Toxicity Due to Repeated Application of Phenoxyethanol and Products Containing It

Various animal models have been used to investigate the toxic potential of phenoxyethanol following exposure to various

routes. The inhalation (rat models), oral (mice and rat models), and cutaneous routes (rabbit models) of phenoxyethanol toxicity have all been thoroughly examined in animals.

Inhalation route

There were no treatment-related systemic effects in rats (five animals per sex per dose) treated to phenoxyethanol concentrations of 0, 40, 200, and 1000 mg/m³ by inhalation for 6 h/day and 5 days/week for 14 days. The sole side effect identified was local irritation of the respiratory system (BASF AG [2007], Report No.: 3610498/01187) [19].

Oral route

Signs of hematotoxicity were reported at doses of 100 mg/kg body weight (bw)/day and above in a rabbit trial (six females in the control group and three females per dose group) treated with a 10-day oral therapy. At high doses, that is, the lowest observed adverse effect level of 687 mg/kg bw/day for males and 1000 mg/kg bw/day for females, exposure through the oral route had effects on red blood cell parameters and led to histopathological changes in the kidney and urinary bladder in a 90-day repeated dose toxicity study in rats (10 animals per sex per dose) (MHLW Japan Bioassay Research Centre [2003], Study No. 459) [19,21].

At phenoxyethanol doses of 765 mg/kg bw/day for males and 948 mg/kg bw/day for females, results of a 90-day repeated dose toxicity study carried out through the oral route in mice (10 animals per sex per dose) showed some changes in red blood cell parameters suggestive of mild anemia, as well as some effects on the liver such as decreases in cholesterol and phospholipid concentrations (MHLW Japan Bioassay Research Centre [2003], Study No. 460, unpublished study as cited by the SCCS) [19].

Topical route

Two published studies and one unpublished study utilized the rabbit models to expose them to phenoxyethanol through the topical method. 90-day topical route toxicity assessment in rabbits, 500 mg/kg bw/day exposure to phenoxyethanol, showed no treatment-related effects on bw or organ weight, hematological or clinical parameters, or gross or histological features (even up to the maximum dose tested) [13]. Similarly, no systemic effects were identified in a developmental toxicity pilot investigation up to a maximum tested dose of 1000 mg/kg bw/day (Source: SCCS3, Dow Chemical USA, Report No. K-000111011, unpublished study).

Another developmental toxicity research, on the other hand, found evidence of hematotoxicity at 600 mg/kg bw/day and higher [18]. Finally, the systemic effects reported in these animal investigations such as hematological and hepatic abnormalities occurred after oral administration to high doses of phenoxyethanol. The oral mode of administration and high doses used in these animal trials, however, is irrelevant for assessing the toxicity of

phenoxyethanol as a cosmetic element. In one rabbit investigation, hematological effects were also identified after treatment through the topical method. These effects were also seen at high doses (600 mg/kg bw/day and above), which are not relevant for phenoxyethanol toxicity tests in cosmetic settings.

Indeed, according to the SCCS report, the aggregate value for phenoxyethanol at a maximum concentration of 1% is 2.69 mg/kg bw/day when a customer uses a collection of cosmetic goods containing the same preservative, such as rinse-off and leave-on products. As a result, the hematological effects documented in the rabbit developmental study were found at a dose 200 times higher than that utilized by the corresponding human consumers. Furthermore, rabbit skin is known to be more permeable than human skin [22,23], and rabbits have a slower rate of phenoxyethanol metabolism than other species, particularly humans (human > rat > mouse > rabbit; Dow Chemical USA, Report No.: K-000111011, unpublished study as reported by the SCCS) [19].

To summarize, the systemic consequences of phenoxyethanol, such as hematological and liver damage following oral or topical administration, are a cause for worry, as demonstrated in these animal experiments. However, because of its susceptibility to hematotoxic effects, the rabbit is the most susceptible species studied, according to the available data. This greater sensitivity can be explained in part by this species' poor ability to metabolize phenoxyethanol in comparison to other species, including humans. *In vitro* investigations have also revealed that rabbit red blood cells are more sensitive to phenoxyethanol than red blood cells from other species, including humans. As a result, the hematological effects observed in rabbits should not be used to make toxicity determinations in humans [19]. Further long-term studies are required to confirm, if the findings of these animal studies are suitable and applicable in humans as well.

EFFECTS ON GENETICS

Phenoxyethanol was presumed to possess mutagenicity and genotoxicity. Therefore, few researches focused on identifying if this agent has any genotoxic effect. The Ames test was used to determine the mutagenic potential of 2-phenoxyethanol *in vitro*. With or without rat liver microsomal activation, phenoxyethanol had no carcinogenic effect in bacteria at doses up to 5000 µg/plate (an unpublished study cited by the SCCS) [19]. When phenoxyethanol, up to a maximum concentration of approximately 10 mmol/L, was evaluated for its ability to cause gene alterations at the Hprt locus in mammalian cells, negative results were observed [19]. *In vitro* structural chromosome aberration assays revealed no clastogenic effect (Dow Chemical USA, Report No.: K000111-018, unpublished study cited by the SCCS) [19].

In the above-mentioned *in vivo* investigation, micronucleus and chromosomal aberration assays were also done, but no evidence of clastogenic potential was found [19]. Finally, in a UDS test in rats, phenoxyethanol caused no DNA damage and exhibited no signs of genotoxicity. Therefore, the SCCS suggested that 2-phenoxyethanol showed no carcinogenic potential *in vivo* and was not genotoxic to people based on these findings.

CARCINOGENIC PROPERTY

Every day, we use enormous amounts of beauty products and are exposed to a wide range of chemicals found in these products. Because these chemicals reach the human body through various channels, they are a particularly insidious form of pollution. They are simple to consume, inhale, and absorb through the mucous membranes of the eyes, mouth, and nose. Our skin absorbs about 60% of the chemical compounds and transports them to the bloodstream, where they can reach every organ in the body within seconds after absorption [24]. Similarly, baby products also contain various amounts of chemical products that might have carcinogenic potential.

The carcinogenic potential of phenoxyethanol was studied in rats (MHLW Japan Bioassay Research Centre [2007], Research No. 0497, unpublished study as referenced by the SCCS) [19] and mice (MHLW Japan Bioassay Research Centre [2007], Study No. 0498, unpublished study as cited by the SCCS) [19]. Mild-to-moderate toxic effects on the kidneys were identified in males at the high dose of 510 mg/kg bw/day in rat research (50 animals each sex per dose). Females did not have these side effects at any of the levels studied.

Reduced gains in bw, as well as decreases in some chemical parameters (phospholipids and cholesterol), were observed at intermediate and high doses (>898 mg/kg bw/day) in mice (50 animals per sex per dose), but the differences compared to controls were in part minor, showed no clear dose-response relationship, and were not clearly related to the administration of phenoxyethanol. These two investigations found no evidence of carcinogenic consequences, such as the existence of neoplastic tumors [15]. Although there were some changes in the cellular level due to phenoxyethanol, the carcinogenic property of this agent is still not clearly understood and is debated.

EFFECT ON ENDOCRINAL SYSTEM

At high doses, phenoxyethanol is suspected of disrupting the endocrine system and having negative effects on the blood and liver. Allergies have been linked to phenoxyethanol, although just a few cases have been reported.

A study done by Garlantézec *et al.* through a self-administered questionnaire found a statistically significant relation between glycol ether exposure and a longer duration of pregnancy in 519 women [25]. Phenoxyethanol metabolites were associated with lower levels of SHBG in boys and higher levels of SHBG in girls as observed in a study done to find the changes in hormone levels in cord blood of in utero exposure to glycol ethers [26]. These two studies provide evidence for the association between the metabolite of phenoxyethanol (phenoxyacetic acid) and changes in endocrinal activity in the form of alteration of SHBG levels in newborns.

EFFECTS ON THE NERVOUS SYSTEM

In an observational occupational study, symptoms of intoxication such as headache followed by diminished sensation

and strength of hands were observed in women who were exposed to Phenoxyethanol. After 1–2 years of exposure, neuropsychologic testing revealed focal cognitive impairment that manifested as an inability to work due to cognitive impairment. The effect of phenoxyethanol exposure both immediate and delayed on the central nervous system is similar to other organic solvents [26].

Children of mothers who had high levels of phenoxyethanol metabolite phenoxyacetic acid in urine during pregnancy performed significantly low on Wechsler Intelligence Scale for Children IV – Verbal Comprehension Index score [27]. The SCCS published the results of an observational occupational research involving three women who worked in a fish hatchery and anesthetized fish with phenoxyethanol. Headaches and grogginess were among the neurological side effects encountered by these women [19].

LOCAL EFFECTS

Irritation of Eye

Signs of irritation of the eye have been observed in an unpublished study cited by SCCS, (BASF AG (1983), Report No.: 83/143, after exposure to undiluted phenoxyethanol *in vivo*, in three rabbits [19]. However, more evidence to confirm this finding is presently unavailable.

Irritation of Skin

As found in a retrospective study conducted in Germany over premature and extremely low birthweight infants, signs of irritation of the skin, such as erosion or erythema occurred after topical application of antiseptic solution which contained phenoxyethanol [28].

Allergy

An allergic reaction of the skin in the form of contact urticaria and contact dermatitis was associated with phenoxyethanol after topical application of medicines, cosmetic products, and metal-working fluids [29–36]. Application of ultrasound gel that contained phenoxyethanol was also found to be associated with Contact dermatitis and contact urticaria [37–39]. These findings suggest phenoxyethanol as a possible allergen.

CONCLUSION

Phenoxyethanol can be regarded safe when used as a preservative in cosmetic goods at a concentration of up to 1% based on currently available safety data. However, in sub-chronic and chronic tests in different species, phenoxyethanol has been shown to cause hemotoxicity, hepatotoxicity, renal toxicity, and hemolysis at higher dosages. Furthermore, only at levels of exposure that was exponentially higher than those that people would be exposed to when using cosmetics containing phenoxyethanol were adverse systemic effects identified in animal tests. Because the use of

phenoxyethanol-containing cosmetics in newborn babies may cause the above-mentioned detrimental effect, it is recommended that products having phenoxyethanol not be used in newborn babies.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Agrawal A, Pandwar U, Pandya N. Are phenoxyethanol products safe for babies? – A review of current evidences. *Indian J Child Health*. 2022; 9(5):63-67.