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REVIEW ARTICLE

Safety review of phenoxyethanol when used as a preservative in cosmetics

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Abstract

Phenoxyethanol, or 2-phenoxyethanol, has a large spectrum of antimicrobial activity and has been widely used as a preservative in cosmetic products for decades. It is effective against various Gram-negative and Gram-positive bacteria, as well as against yeasts, and has only a weak inhibitory effect on resident skin flora. According to the European Scientific Committee on Consumer Safety, phenoxyethanol is safe for all consumers – including children of all ages – when used as a preservative in cosmetic products at a maximum concentration of 1%. Adverse systemic effects have been observed in toxicological studies on animals but only when the levels of exposure were many magnitudes higher (around 200-fold higher) than those to which consumers are exposed when using phenoxyethanol-containing cosmetic products. Despite its widespread use in cosmetic products, phenoxyethanol is a rare sensitizer. It can be considered as one of the most well-tolerated preservatives used in cosmetic products.

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Conflict of interest

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Introduction

Phenoxyethanol (CAS n. 122-99-6) is an ether and aromatic alcohol, which is also known as 2-phenoxyethanol, ethylene glycol monophenyl ether, phenoxytol, 1-hydroxy-2-phenoxyethane and (2-hydroxyethoxy) benzene.

It has a large spectrum of antimicrobial activity and is effective against various Gram-negative (e.g. *Pseudomonas aeruginosa*) and Gram-positive (e.g. *Staphylococcus aureus*)[1] bacteria, as well as against yeasts (e.g. *Candida albicans*).[2,3] Phenoxyethanol exerts its antimicrobial activity by uncoupling oxidative phosphorylation from respiration and by competitively inhibiting malate dehydrogenase.[4] It also acts as a bactericidal agent by increasing the permeability of the cell membrane to potassium ions and exerts a direct inhibitory effect on microbial DNA and RNA synthesis.[4] Due to its broad antimicrobial activity, phenoxyethanol has been used for decades as a preservative in various products such as medicines (e.g. in vaccines) and hand disinfecting biocidal products up to a concentration of 5%, including products for toddlers.[5]

Phenoxyethanol exhibits a weaker inhibitory effect on normal skin-resident bacteria than other cosmetic chemical preservatives (e.g. methylisothiazolinone, iodopropynyl butylcarbamate, ethylhexylglycerin and methylparaben[6]) and is used as a preservative in a large range of rinse-off and leave-on cosmetic products. It is also a fragrance ingredient used in many fragrance mixtures.[3] In a recent study analysing the full ingredient information contained in the American Contact Dermatitis Society database – the Contact Allergen Management Program – for a large panel of common cosmetic products marketed in the USA (n = 4737), phenoxyethanol was found in 23.9% (n = 1132) of the products.[7] Moreover, a recent study conducted in Spain reported that 43.09% of cosmetics sold exclusively in pharmacies, 23.29% of cosmetics sold in supermarkets and 14.1% of cosmetics from herbal shops, contained phenoxyethanol.[8]

Some glycol ethers, such as ethylene glycol ethyl ether or ethylene glycol methyl ether, have been shown to have toxic effects on reproduction and have been banned in Europe [see

European Regulation (EC) No 1272/2008]. However, the chemical and physical properties of phenoxyethanol differ from those of these glycol ethers (e.g. it is not volatile) and phenoxyethanol was not classified as a reproductive toxicant in EC No 1272/2008 unlike some other glycol ethers. Nevertheless, some concerns about its safety were raised due to its assimilation to the whole glycol ether family. Furthermore, controversial claims that phenoxyethanol has an effect on the blood and liver, and that it disrupts endocrine activity, have been a matter of public debate and received media attention. According to Commission Regulation 2018/605 amending Plant Protection Regulation No. 1107/2009, a substance should be considered as having endocrine disrupting activity in humans if: it shows an adverse effect in an intact organism or its progeny leading to functional changes; it has an endocrine mode of action (anti-oestrogenic, androgenic or anti-androgenic activity, alters steroidogenesis or has thyroid and anti-thyroid hormone activity); or the adverse effect is a consequence of the endocrine mode of action. In June 2015, the high-throughput Endocrine Disruptor Screening Program of the U.S. Environmental Protection Agency (US-EPA) determined that phenoxyethanol had no oestrogenic activity.[9] In addition, although phenoxyethanol may be a rare sensitizer, it has not been classified as a skin sensitizer by the European Chemicals Agency (ECHA).

In Europe, preservatives allowed for use in cosmetic products are regulated by Annex V of Cosmetics Regulation (EC) No. 1223/2009.[10] According to this regulation, phenoxyethanol is authorized as a preservative in cosmetic formulations at a maximum concentration of 1% (Annex V/29). The safety profile of phenoxyethanol as a preservative in cosmetic products was assessed at the European level by the Scientific Committee on Consumer Safety (SCCS) in 2016.[3] This assessment led the committee to conclude that phenoxyethanol was safe for consumers – including children of all ages – when used as a preservative in cosmetic products at a maximum concentration of 1%. However, the French National Agency for the Safety of Medicines and Health Products (ANSM) recommended that phenoxyethanol should not be used as a preservative in cosmetic products intended for application on the nappy area (including wipes) of children aged under 3 years.[11] This recommendation was based on a worst-case aggregate exposure calculation covering the five most used cosmetic products in French children. When wipes and cosmetic products intended for application to the nappy area were excluded from exposure calculation, the risk assessment conducted by the ANSM indicated that phenoxyethanol used at a maximum concentration of 1% in cosmetic products was also safe for children aged under 3 years.

The objective of this report was to review the safety of phenoxyethanol, taking into account the opinion of the SCCS and published scientific literature.

Data searching methods

The SCCS conducted a review of available safety data on phenoxyethanol, which included both data from peer-reviewed scientific journals and safety data from unpublished studies carried out by cosmetic product manufacturers, often at the request of the SCCS. These data, as well as other data from ANSM assessments, were used in the current review. In addition, an updated search of safety data on phenoxyethanol was performed using PubMed. The following search terms were used: 'phenoxyethanol' OR 'Ethylene glycol monophenyl ether' OR '(2-hydroxyethoxy) benzene' OR 'glycol ether' OR 'phenoxyacetic acid'. As the most recent publication used in the SCCS opinion study was dated November 2015, the date limits for publications used in our review were set as 1 November 2015 to 31 May 2019. Articles were screened by two reviewers based on titles and abstracts, and only those dealing with the safety of phenoxyethanol were selected.

Review of safety data

Dermal/percutaneous absorption

The percutaneous absorption of phenoxyethanol at concentrations of 0.2 and 1% was evaluated *in vitro* using rat and human skin samples in two studies.[3,12] The study of Roper *et al.*[12] contained some deficiencies and was not considered as relevant by the SCCS.

The results of an unpublished study (Vincent CM and Marty JP (2002), as cited by the SCCS [3]) showed that *in vitro* dermal absorption of phenoxyethanol in humans was high and rapid, regardless of its concentration in the formulation tested. After 24 h of exposure, very small amounts (<0.1%) remained in the various layers of the skin and most of the phenoxyethanol was recovered in the receptor fluid, indicating that phenoxyethanol does not bind to or accumulate in the skin. The dermal absorption of phenoxyethanol (i.e. the total amount of phenoxyethanol in the receptor fluid, dermis and epidermis) after a 24-h period for a formulation containing 1% phenoxyethanol was 37% ± 10% for the rinse-off products and 78% ± 7% for the leave-on products.

Bioavailability

Numerous *in vivo* kinetic studies using oral and topical routes have been conducted in animals,[3,12–15] as well as in humans.[14] These studies showed that phenoxyethanol is rapidly absorbed, distributed, metabolized and excreted. It can be metabolized either in the skin or in the liver; however, its metabolism rate is higher in the liver. The major metabolite of phenoxyethanol, 2-phenoxyacetic acid, is formed in a two-step oxidation process by cytosolic alcohol dehydrogenase and aldehyde dehydrogenase.[12]

In humans, regardless of the route of exposure – i.e. after topical exposure in clinical trials with adults[14] or preterm babies,[16] or after oral administration in a study conducted in an adult male[14] – phenoxyethanol is excreted in urine, primarily as

2-phenoxyacetic acid. This metabolite was found in higher concentrations in *in vitro* experiments using liver S9 homogenates of human donors than in other species (human > rat > mouse > rabbit).[3,12] None of these studies allowed the systemic bioavailability of phenoxyethanol to be determined in humans.[3]

In 2015, a research team[17] used a physiologically based pharmacokinetic (PBPK) model to predict the systemic availability of phenoxyethanol in rats and humans. However, the results of this PBPK model were not considered to be relevant by the SCCS[3] due to the following reasons:

- Results for rats obtained using the PBPK model were underestimated compared to those obtained from a 'real' study conducted in rats[15];
- Results in humans could not be compared with 'real' data [observed area under the curve (AUC) of either phenoxyethanol or 2-phenoxyacetic acid compared to their predicted AUC], thus limiting the validity of this PBPK model.

In conclusion, phenoxyethanol is almost completely absorbed through skin (78% ± 7% for the leave-on products) and metabolized either by the skin or by the liver into its major metabolite 2-phenoxyacetic acid. This metabolite is primarily found in human urine. The systemic availability of phenoxyethanol, and its metabolite, cannot be determined in humans from the data that are currently available.

Repeated dose toxicity

The repeated dose toxicity of phenoxyethanol has been extensively studied in animals via the inhalation (rats), oral (mice and rats) and dermal routes (rabbits).[3] A brief review of the results of the studies considered as relevant in terms of their methodological approach by the SCCS (i.e. OECD guidelines and Good Laboratory Practices compliant studies) is reported below (summarized in Table 1).

Inhaled route Rats (five animals per sex per dose) exposed to phenoxyethanol concentrations of 0, 40, 200 and 1000 mg/m³ via the inhaled route for 6 h/day and 5 days/week for 14 days showed no treatment-related systemic effects (Table 1). Local irritation of the respiratory system was the only effect reported (BASF AG (2007), Report No.: 3610498/01187, unpublished study as cited by the SCCS[3]).

Oral route In a study conducted in rabbits (six females in the control group and three females per dose group) exposed to a 10-day treatment via the oral route, signs of haematotoxicity were reported at doses of 100 mg/kg bodyweight (bw)/day and above[13] (Table 1).

In a 90-day repeated dose toxicity study conducted in rats (10 animals per sex per dose), exposure via the oral route had effects on red blood cell parameters and led to histopathological changes in the kidney and urinary bladder at high doses, i.e. the lowest observed adverse effect level of 687 mg/kg bw/day for males and 1000 mg/kg bw/day for females [MHLW Japan Bioassay Research Centre (2003), Study No. 459, unpublished study as cited by the SCCS[3]] (Table 1).

In mice (10 animals per sex per dose), results of a 90-day repeated dose toxicity study carried out via the oral route showed some changes in red blood cell parameters suggestive of mild anaemia, and some effects on the liver such as decreases in cholesterol and phospholipid concentrations at phenoxyethanol doses of 765 mg/kg bw/day for males and 948 mg/kg bw/day for females [MHLW Japan Bioassay Research Centre (2003), Study No. 460, unpublished study as cited by the SCCS[3]] (Table 1).

Topical route Three studies conducted in rabbits exposed via the topical route were identified: two published and one unpublished (Table 1). In a 90-day topical route toxicity study in rabbits, no treatment-related effects were observed on bodyweight or organ weight, on haematological or clinical parameters, or on gross or histopathological features up to the highest dose tested of 500 mg/kg bw/day.[13] Similarly, in a developmental toxicity pilot study, no systemic effects were reported up to a maximum tested dose of 1000 mg/kg bw/day (Dow Chemical USA, Report No.: K-000111011, unpublished study as cited by the SCCS[3]). In contrast, another developmental toxicity study reported signs of haematotoxicity at 600 mg/kg bw/day and above.[18]

In conclusion, the systemic effects – such as haematological and liver effects – observed in these animal studies occurred after oral exposure to high doses of phenoxyethanol. However, the oral route of administration and the high doses used in these animal studies are not relevant for evaluation of the toxicity of phenoxyethanol used as a cosmetic ingredient.

Haematological effects were also reported after exposure through the topical route in one study conducted in rabbits. These effects were also observed at high doses (600 mg/kg bw/day and above), which are not relevant for toxicity evaluations of phenoxyethanol used under cosmetic conditions. Indeed, based on the SCCS report and considering that a consumer may use a set of cosmetic products containing the same preservative, such as rinse-off and leave-on products, the aggregate value for phenoxyethanol at a maximum concentration of 1% is 2.69 mg/kg bw/day. Therefore, the haematological effects reported in the developmental study conducted in rabbits were observed at a dose approximately 200-fold higher than that used by consumers.

Additionally, the skin of rabbits is known to be more permeable than that of humans[19] and the rate of metabolism of phenoxyethanol in rabbits is lower than that of other species, particularly humans (human > rat > mouse > rabbit; Dow Chemical USA, Report No.: K-000111011, unpublished study as cited by the SCCS[3]). Phenoxyethanol (and not its metabolite 2-phenoxyacetic acid) is responsible for the haematotoxicity

Table 1 Summary of the main repeated dose toxicity studies on phenoxyethanol considered as relevant by the SCCS[3]

References	Species, strain and number of animals	Route of exposure	Doses	Duration of exposure	Dose descriptor (mg/kg bw/day)	Main findings
BASF AG (2007), Report No.: 3610498/01187, unpublished study in the SCCS[3]	Rat Wistar 5 animals per sex per dose	Inhalation	0, 40, 200 and 1000 mg/m³ corresponding to 0, 48.2, 246 and 1070 mg/m³	6 h per day, 5 days per week for 14 days	NOAEC: 48.2 × 5/7 = 34.4 mg/m³	Local irritation effects of the respiratory system
Breslin *et al.*, 1991[13]	Rabbit New Zealand White 6 females in the control group and 3 females per other dose group	Oral	100, 300, 600 and 1000 mg/kg bw/day	10 days	Lowest observed adverse effect level: 100	Occurrence of some deaths above 100 mg/kg bw/day Decreased bodyweight Decreased RBC count, Hb concentration and PCV, with concurrent increases in nucleated and polychromatophilic red blood cells Haemolytic anaemia including enlarged and dark kidneys and spleen, dark urine in the urinary bladder and dark urine staining the perineal region at 600 and 1000 mg/kg bw/day
MHLW Japan Bioassay Research Centre (2003), Study No. 459, unpublished study in the SCCS[3]	Rat F344 DuCrj 10 animals per sex per dose	Oral	0, 1250, 2500, 5000, 10 000 and 20 000 ppm in drinking water corresponding to 96, 185, 369, 687 and 1514 mg/kg bw/day in males 163, 313, 652, 1000 and 1702 mg/kg bw/day in females	90 days	NOAEL: 369	Reductions in red blood cells (at ≥10 000 ppm in males and females) and Hb (at ≥10 000 ppm in females and at 20 000 ppm in males) Increases in MCV and MCHC (at ≥10 000 ppm in males and at 20.000 ppm in females) Mild-to-moderate urothelial hyperplasia of the renal pelvis at 10 000 ppm in males and females and at 20 000 ppm in males Mild-to-moderate urinary bladder transitional epithelial hyperplasia at 10 000 ppm in females and at 20 000 ppm in females Mild urinary bladder transitional epithelial hyperplasia at 20 000 ppm
MHLW Japan Bioassay Research Centre (2003), Study No. 460, unpublished study as cited by the SCCS[3]	Mouse Cru:BDF1 (B6D2F1) 10 animals per sex per dose	Oral	0, 1250, 2500, 5000, 10 000 and 20 000 ppm in drinking water; corresponding to 182, 390, 765, 1178 and 2135 mg/kg bw/day in males and 236, 478, 948, 1514, 2483 mg/kg bw/day in females	90 days	NOAEL: 390	Reductions in Hb and MCHC and an increase in MCV at 20 000 ppm in females Increases in reticulocytes at 20 000 ppm in males Decreases in plasma total protein (at 1250, 5000 and 20 000 ppm), total cholesterol (at 5000 and 20 000 ppm), phospholipid (at ≥5000 ppm), calcium (at 5000 and 20 000 ppm) and phosphorus (at 5000 and 20 000 ppm) in males Increase in ALP at 20 000 ppm in males

Table 1 *Continued*

References	Species, strain and number of animals	Route of exposure	Doses	Duration of exposure	Dose descriptor (mg/kg bw/day)	Main findings
Breslin *et al.*[13]	Rabbit New Zealand White 10 animals/sex/dose	Topical	0, 50, 150 and 500 mg/kg bw/day	90 days	NOAEL: 500	No treatment-related effects on bodyweight, organ weight, haematological and clinical parameters, and gross and histopathological features
Dow Chemical USA (1985), Report No. K-000111011, unpublished study in the SCCS[3]	Rabbit New Zealand White 10 females (developmental toxicity pilot study)	Topical	0, 300, 600 and 1000 mg/kg bw/day	Days 6–18 of gestation	NOAEL: 1000	No treatment-related effects on bodyweight, organ weight, haematological and clinical, and gross and histopathological features
Scortichini *et al.*[18]	Rabbit New Zealand White 25 females (developmental toxicity main study)	Topical	0, 300, 600 and 1000 mg/kg bw/day	Days 6–18 of gestation	NOAEL for maternal toxicity: 300 NOAEL for developmental toxicity: 600	Intravascular haemolysis of red blood cells (decreased RBC counts and PCV values, as well as elevated reticulocytes and increased red blood cell fragility) and death at 600 and 1000 mg/kg bw/day

ALP, alkaline phosphatase; bw, bodyweight; Hb, haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; PCV, packed cell volume; RBC, red blood cells.

observed in animal studies.[3] Overall, the available data indicate that the rabbit is the most sensitive species tested due to its susceptibility to haematotoxic effects. This increased sensitivity may be explained, for the most part, by the limited capacity of this species for metabolizing phenoxyethanol compared to other species, including humans. In addition, *in vitro* studies have shown that rabbit red blood cells are more sensitive to phenoxyethanol than those of other species, including humans.[3,13] Consequently, the haematological effects reported in rabbits should not be considered as relevant for toxicity assessments in humans.

Mutagenicity/genotoxicity

The mutagenic potential of 2-phenoxyethanol was first tested *in vitro* using the Ames test. Phenoxyethanol did not show any mutagenic activity in bacteria at concentrations up to 5000 µg/plate, with or without rat liver microsomal activation (BASF AG, 2002, Report No.: 712402, unpublished study as cited by the SCCS[3]). Similarly, negative results were obtained in mammalian cells when phenoxyethanol, up to a maximum concentration of approximately 10 mmol/L, was tested for its ability to induce gene mutations at the Hprt locus (BASF AG, 2002, Report No.: 712401, unpublished study as cited by the SCCS[3]). Furthermore, no clastogenic effect was observed in structural chromosome aberration tests *in vitro* (Dow Chemical USA, Report No.: K-000111-018, unpublished study as cited by the SCCS[3]).

Micronucleus and chromosome aberration tests performed *in vivo* in mice did not provide evidence of any clastogenic potential (BASF AG, 2002, Report No.: 712403, unpublished study as cited by the SCCS[3]). Finally, phenoxyethanol induced no DNA damage in an UDS test in rats and also showed no evidence of genotoxicity (BASF AG, 2002, Report No.: 712404, unpublished study as cited by the SCCS[3]).

Based on these studies, the SCCS considered that 2-phenoxyethanol had no mutagenic potential *in vivo* and was not genotoxic to humans.

Long-term toxicity and carcinogenicity studies

The carcinogenic potential of phenoxyethanol was assessed in two carcinogenicity studies conducted using the oral route in rats [MHLW Japan Bioassay Research Centre (2007), Study No. 0497, unpublished study as cited by the SCCS[3]] and mice [MHLW Japan Bioassay Research Centre (2007), Study No. 0498, unpublished study as cited by the SCCS[3]]. In the study carried out in rats (50 animals per sex per dose), mild-to-moderate toxic effects were reported on the kidneys in males at the high dose of 510 mg/kgbw/day. These effects were not reported in females at any of the doses tested.

In the study conducted in mice (50 animals per sex per dose), reduced gains in bodyweight, as well as decreases in some chemical parameters (phospholipids and cholesterol), were observed at intermediate and high doses (>898 mg/kg bw/day), but the changes relative to controls were in part slight and showed no

clear dose–response relationship and were not clearly related to the administration of phenoxyethanol.

No carcinogenic effects, such as the presence of neoplastic lesions, were reported in these two studies (Table 2).

Reproductive effects in animals

As stated in the introduction, phenoxyethanol is not classified as a reproductive toxic substance in EC No 1272/2008. In the animal studies reported by the SCCS – a two-generation reproductive toxicity study conducted in mice and two developmental toxicity studies carried out in rabbits – no effects on reproductive and developmental parameters were observed.[3]

Endocrine disruption potential

There were no data included in the SCCS opinion on the endocrine activity of phenoxyethanol.[3] However, the June 2015 high-throughput Endocrine Disruptor Screening Program conducted by the US-EPA determined that phenoxyethanol has no oestrogenic activity.[9] Moreover, a systematic review has been recently published studying the association between exposure to non-persistent chemicals in consumer products and fecundability.[20] Amongst the 12 studies included in this review, only one observational study conducted by Garlantézec *et al.*[21] in 2013 dealt with glycol ethers, including phenoxyethanol (Table 3). More recently, the same team also recently published two other observational studies on glycol ethers, including phenoxyethanol.[22,23]

The three original articles cited above[21–23] report the results of observational longitudinal French studies in two large mother–child cohorts, the PELAGIE cohort and the Eden cohort, aiming to determine the relationship between occupational and non-occupational exposure to several glycol ethers, including phenoxyethanol, and specific outcomes related to ovarian function in a random sample of women. The PELAGIE cohort included 3421 pregnant women recruited before 19 weeks of gestation between 2002 and 2006 and followed up to the end of pregnancy. The EDEN cohort included 2002 pregnant women, before their 24th week of amenorrhoea, from 2003 to 2006 (Table 3). Time to pregnancy was assessed using a self-administered questionnaire, and exposure to glycol ethers was assessed by measuring metabolite levels, including phenoxyacetic acid the primary metabolite of phenoxyethanol, in a random sample of urine specimens.

Garlantézec *et al.*[21] first evaluated the relationship between exposure to glycol ethers and time to pregnancy in 519 women through a self-administered questionnaire filled in at inclusion. The results showed a statistically significant association between high urine phenoxyacetic acid concentrations and a longer time to pregnancy (Table 3). With the exception of phenoxyacetic acid, no associations between other glycol ether metabolites and a longer time to pregnancy were observed. As the study of Garlantézec *et al.*[21] is the only study that showed such results, Hipwell *et al.*[20] concluded in their review that it was not possible to draw a final conclusion without additional data. Furthermore, this kind of observational epidemiological study is prone to considerable scientific inconsistencies and weaknesses. Firstly, these studies are susceptible to recall bias and the self-reported information may be incomplete or inaccurate. Moreover, the measured endpoint 'time to pregnancy' is a so-called fickle endpoint

Table 2 Summary of carcinogenic studies of phenoxyethanol based on SCCS[3]

References	Species, strain and number of animals	Route of exposure	Doses	Duration of exposure	Main findings
MHLW Japan Bioassay Research Centre (2007), Study No. 0497, unpublished study as cited by the SCCS[3]	Rat F344 DuCrlCrlj 50 animals per sex per dose	Oral	0, 2500, 5000 and 10 000 ppm in drinking water corresponding to 124, 249 and 510 mg/kg bw/day in males and 191, 380 and 795 mg/kg bw/day in females	104 days	Increased incidence of mild-to-moderate urothelial hyperplasia and mild papillary mineralization and necrosis in the kidneys in males at 10 000 ppm No histopathological findings in the kidney in females Increases in liver enzymes (AST, ALT) in males at 10 000 ppm Increased bilirubin and decreased triglycerides in females at 10 000 ppm, without any histopathology findings in the liver
MHLW Japan Bioassay Research Centre (2007), Study No. 0498, unpublished study as cited by the SCCS[3]	Mouse B6D2F1 Crlj 50 animals per sex per dose	Oral	0, 5000, 10 000 and 20 000 ppm in drinking water corresponding to 468, 898 and 1701 mg/kg bw/day in males and 586, 1072 and 2058 mg/kg bw/day in females	104 days	Decreases in cholesterol and phospholipids at ≥10 000 ppm and decreases in triglycerides at 20 000 ppm in males Decreases in bodyweight gain at ≥10 000 ppm in males and at 20 000 ppm in females

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bw, bodyweight.

Table 3 Summary of endocrine disruption effects assessed in human studies

Author, year	Study design	Number of women	Outcome	Results
Garlantézec *et al.*, 2013[21]	Residential retrospective	519	Time to pregnancy assessed using a self-administered questionnaire	Statistically significant association between high urine phenoxyacetic acid concentrations (≥ 1.38 mg/L with a fOR = 0.70; 95%; CI = 0.52–0.95, compared to the lowest concentration < 0.14 mg/L) and a longer time to pregnancy
Warembourg *et al.*, 2018a[22]	Residential prospective	338	Concentrations of 13 sex steroid hormones and SHBG in cord blood samples collected after delivery	Lower levels of SHBG and some other steroid hormones assessed in boys Association between phenoxyacetic acid and significant linear decreases in DHEA levels [β (95% CI) = −0.09 (−0.16; −0.01)], 17-Preg levels [β (95% CI) = −0.10 (−0.18; −0.02)] and D5 levels ('small departures from linearity') in boys Association between phenoxyacetic acid and small increases in the levels of SHBG, as well as 16-alpha-hydroxy-DHEA (16-DHEA), in girls
Warembourg *et al.*, 2018b[23]	Nested case–control study	115	Cryptorchidism or hypospadias reported in forms of routine clinical examination for congenital anomalies	No association between urinary concentrations of phenoxyacetic acid and cryptorchidism or hypospadias

Note: Measurement mode of phenoxyethanol exposure in all these studies was performed by dosing its metabolite, phenoxyacetic acid, in a single urine sample.

16-DHEA, 16-alpha-hydroxy-DHEA; 17-Preg, 17-alpha-hydroxy-Pregnenolone; CI, confidence interval; D5, delta-5-androstenediol; DHEA, dehydroepiandrosterone; OR, odds ratio; SHBG, sex hormone-binding globulin.

and the baseline was not clear, making it impossible to interpret any changes. Also, the risk cannot be estimated directly and the odds ratio (OR) is only an approximation of the relative risk in the underlying population. Only one urine sample was collected, and this unique sample would not have been representative of the all-day exposure to glycol ethers as they are cleared very rapidly from the body. Finally, as stated by the authors,[21] it could not be excluded that phenoxyacetic acid exposure was actually a proxy marker to exposure to other chemicals, or even that their results were due to chance or to uncontrolled confounding factors that need to be evaluated in future studies.

In a second publication,[22] the same team studied the association between *in utero* exposure to glycol ethers and hormone levels in the cord blood of 338 women included in the PELAGIE cohort. Cord blood samples were collected after delivery, and the levels of 13 sex steroid hormones and the sex hormone-binding globulin (SHBG) were evaluated. The results showed that phenoxyacetic acid was associated with lower levels of SHBG and of some other steroid hormones assessed in boys: significant linear decreases in dehydroepiandrosterone [DHEA; β (95% CI) = −0.09 (−0.16; −0.01)] and 17-alpha-hydroxy-pregnenolone [17-Preg; β (95% CI) = −0.10 (−0.18; −0.02)] levels, as well as 'small departures from linearity' for delta-5-androstenediol (D5), were reported. Furthermore, an association between phenoxyacetic acid and small increases in the levels of SHBG and 16-alpha-hydroxy-DHEA (16-DHEA) was observed amongst girls. However, this study was prone to similar scientific inconsistencies and weaknesses as those reported for the study of Garlantézec *et al.*[21] The ANSM assessed this study in its recent opinion[11] and concluded that further research is needed to reach a conclusion on these results.

The third study was a case–control study nested in the two joint PELAGIE and EDEN cohorts. Its results showed that there was no association between urinary concentrations of phenoxyacetic acid and cryptorchidism or hypospadias.[23]

In conclusion, only three publications were identified and all were part of the same cohort study. These three reports did not reveal that phenoxyethanol had any endocrine disrupting potential. The first study did not show any association between phenoxyacetic acid, the primary metabolite of phenoxyethanol, and cryptorchidism or hypospadias. The two other studies did not provide any evidence for a plausible association between phenoxyacetic acid and changes in SHBG, androgenic and oestrogenic activities in newborns. Concerning the thyroid effects, there are no indications from the animal studies of any effect involving the thyroid hormone pathway. Furthermore, the ANSM concluded that these data cannot be used to assess the endocrine disruption potential of phenoxyethanol.[11]

Neurological effects

Phenoxyethanol was not reported to have any neurotoxic effects in subchronic animal studies, irrespective of the administration route used (see section on repeated dose toxicity). The SCCS reported an observational occupational study conducted in three women working in a fish hatchery and using phenoxyethanol to anaesthetize fish.[24] These women experienced neurological

effects such as headaches or grogginess. However, no conclusions can be drawn from this study because of its numerous limitations: the low number of participants (only three women), a failure to report the concentration of phenoxyethanol used to anaesthetize the fish, the lack of measurements of the dosage of phenoxyethanol or its metabolite in blood or urine, and the absence of a description of the neuropsychological test used to assess cognitive impairment.

A recent ancillary study of the PELAGIE cohort[25] (see section Reproductive effects in animals for more details) assessed the neurocognitive abilities of the 6-year-old children of a random sample of mothers using the Wechsler Intelligence Scale for Children IV (WISC) and the Developmental Neuropsychological Assessment (NEPSY). The results showed no association between NEPSY and WISC – Working Memory Index scores and exposure to phenoxyacetic acid. A significantly lower WISC – Verbal Comprehension Index (VCI) score – was observed for children whose mothers were in the highest tertile of the urinary phenoxyacetic acid concentrations measured. Nevertheless, the relationship between prenatal urinary phenoxyacetic acid concentrations and lower WISC – VCI scores – was not linear as an inverse correlation was observed when participants with urinary phenoxyacetic acid concentrations below the median were considered. Additionally, the same limitations as those reported for the three studies discussed above[21–23] can be applied to this study – i.e., these results may be due to chance or to uncontrolled confounding factors.

Local effects

Eye irritation Phenoxyethanol has been shown to produce signs of eye irritation *in vivo*, when administered undiluted in three rabbits, with a maximal irritation 72 h after instillation of the test substance (BASF AG (1983), Report No.: 83/143, unpublished study as cited by SCCS).[3]

Skin irritation Undiluted phenoxyethanol, which is never used in cosmetics, has been shown to induce mild-to-moderate irritation in animals studies conducted in rabbits and guinea pigs.[3,26] In humans, no local or systemic effects were observed after the use of phenoxyethanol on injured skin: patients with superficial wounds or with burns.[27,28] Additionally, phenoxyethanol was well tolerated in a study where the skin of premature neonatal infants was disinfected with an aqueous solution containing 0.1% octenidine and 2% phenoxyethanol.[16] However, a recent retrospective study conducted in premature infants with extremely low birthweights in Germany found that some signs of skin irritation, such as erythema or skin erosion, occurred with a topical antiseptic solution containing both 0.1% octenidine and phenoxyethanol. However, the concentrations in this antiseptic were not reported and it is difficult to link these effects exclusively to phenoxyethanol, because octenidine may also cause serious cutaneous complications.[29] Nevertheless, premature infants are at higher risk of developing skin irritation due to their immature skin barrier.

The ANSM described other studies in its assessment and no irritation reactions were observed in humans.[26]

Allergy Sensitization animal studies (maximization tests) conducted in Guinea pigs did not show any sensitization reactions following skin exposure to phenoxyethanol.[3,26] In humans, the overall frequency of sensitization reactions attributed to phenoxyethanol is very low (0.1–0.24%). The SCCS reported the studies described below[3,26,30] (summarized in Table 4).

In a large surveillance study conducted between 1996 and 2009 in Germany, Switzerland and Austria, the frequency of sensitization to phenoxyethanol tested at a concentration of 1% in a patch-test population of 6932 subjects was 0.24%.[31] The authors concluded that phenoxyethanol could be regarded as an extremely rare allergen, if as an allergen at all.[31] The same authors had also conducted a previous study, between 1990 and 1994, and showed that the frequency of positive patch tests to phenoxyethanol was 0.1% of the 11 120 patients patch-tested.[32] The SCCS also reported a small study carried out in Spain,[33] which showed that 0.2% of patch-tested patients showed a positive reaction to 1% 2-phenoxyethanol.

Recently, in 2012, Scognamiglio *et al.* reviewed patch test studies with phenoxyethanol and found that positive reactions ranged from zero to 0.2%.[34]

The SCCS and the ANSM reported a small number of cases (n = 8) of skin allergy attributed to phenoxyethanol after topical contact with cosmetic products, medicines and metal-working

Table 4 Summary of studies related to the frequency of allergies attributed to phenoxyethanol[2,6,7,11] reported by the SCCS and the ANSM

Author, year	Country	Period of study	Number of patch-tested patients	Frequency of sensitization to phenoxyethanol (%)
Schnuch *et al.*, 1998 [32]	Germany, Switzerland and Austria	Between 1990 and 1994	6932	0.24
Bordel-Gómez *et al.*, 2010 [33]	Spain	Between 2000 and 2005	1092	0.2
Schnuch *et al.*, 2011[31]	Germany, Switzerland and Austria	Between 1996 and 2009	11 120	0.1

fluids.[35–42] Amongst these, three cases had contact urticaria and the remaining cases had contact dermatitis.[35,36,39] In all three cases of contact urticaria, the manifestations appeared minutes after application of the cosmetic products and no respiratory symptoms were reported. A serum sample from one of the patients was tested for immunoglobulin E (IgE) antibodies against phenoxyethanol, and the presence of specific IgE could not be confirmed.[35] According to the authors,[35] both an IgE-mediated mechanism and non-immunologic contact urticaria were possible causes. However, as phenoxyethanol is a hapten, protein-binding and elicitation of symptoms within a few minutes are unlikely, suggesting a non-immunologic pathogenesis. Contact urticaria[43] and contact dermatitis[44] were also reported in two cases after the use of phenoxyethanol-containing ultrasound gels. Open tests[43] and patch tests[44] on these subjects were positive for phenoxyethanol, suggesting that phenoxyethanol was the allergen in both cases.

Recent data from the scientific literature revealed that negative results for patch tests with phenoxyethanol had been obtained in 11 patients tested in Finland.[45] In addition, a review of contact allergens in natural hair dyes concluded that of all the cases of contact allergy to preservatives contained in these products, only very few cases were attributed to phenoxyethanol.[46]

Although phenoxyethanol is present in a large variety of rinse-off and leave-on cosmetic products,[7,8] allergy reactions – such as contact urticaria – are rare. Phenoxyethanol is one of the most well-tolerated preservatives used in cosmetic products, and it is not classified as a sensitizer by the ECHA.

Conclusion

Based on the currently available safety data, phenoxyethanol can be considered as safe when used as a preservative in cosmetic products at a concentration of up to 1%. Adverse systemic effects were observed in animal studies only at levels of exposure which were magnitudes higher than those that consumers would be exposed to when using cosmetic products containing phenoxyethanol. Despite its widespread use in cosmetic products, phenoxyethanol is only a rare sensitizer and it can be considered as one of the most well-tolerated preservatives used in cosmetic products.[11]

The SCCS concluded in 2016 that phenoxyethanol is safe for all consumers – including children of all ages – when used as a preservative in cosmetic products at a maximum concentration of 1%.[3] The only restriction given by the French ANSM is not to use phenoxyethanol as a preservative in cosmetic products intended for application to the nappy area (including wipes) of infants and children aged under 3 years.[30]

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