

# An epidemic of allergic contact dermatitis caused by a new allergen, caprylhydroxamic acid, in moisturizers

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## Summary

**Background.** In 2016, dermatologists in Finland suspected contact allergy in several patients using moisturizers under the trade name Apobase<sup>®</sup>. Following a formulation change, Phenostat<sup>™</sup>, which is a mixture of phenoxyethanol, caprylhydroxamic acid, and methylpropanediol, was used as a preservative in Apobase<sup>®</sup> moisturizers in Finland.

**Objectives.** To confirm the suspected contact allergy to Apobase<sup>®</sup> cream, oily cream, and/or lotion, and to identify the specific contact allergen and define its optimal patch test concentration.

**Methods.** Thirty-nine patients with suspected contact allergy to Apobase<sup>®</sup> creams or lotion were patch tested in four Finnish dermatological clinics. The patch tests included old and new Apobase<sup>®</sup> formulas and their preservative agents: phenoxyethanol, methylpropanediol, and dilution series of Phenostat<sup>™</sup> and caprylhydroxamic acid or its potassium salt.

**Results.** The patch tests showed positive reactions to the new Apobase<sup>®</sup> formulas, Phenostat<sup>™</sup>, and caprylhydroxamic acid or its potassium salt, but not to the old Apobase<sup>®</sup> formulas, methylpropanediol, or phenoxyethanol.

**Conclusions.** We found a new contact allergen, caprylhydroxyamic acid, which caused an epidemic of allergic contact dermatitis in patients using moisturizers containing this preservative. Whether the sensitizing capacity of caprylhydroxamic acid depends on the other chemicals used in Apobase<sup>®</sup> moisturizers needs further investigation.

**Key words:** caprylhydroxamic acid; caprylohydroxamic acid; capryloylhydroxamic acid; CAS no. 7377-03-9; CHA; contact allergy; moisturizer; N-hydroxy-caprylohydroxamic acid; N-hydroxy-octanamide; Oct HA; octanohydroxamic acid; octanoylhydroxamic acid; Phenostat<sup>™</sup>; Taselin.

Unscented moisturizers are widely recommended by Finnish dermatologists for the management of patients

with atopic eczema and other dry skin conditions. They contain substances intended to prevent dryness of the skin (urea, ceramides, humectants, and essential fatty acids) and excipients (e.g. emulsifiers, antioxidants, and preservatives).

Parabens have been used as preservatives in topical medications, moisturizers, cosmetics and food for decades. The incidence of contact allergy to these is very low (1). However, in the past 15 years, parabens have been under investigation for their possible oestrogenic effects, and for their possible role in the development

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of malignancies and infertility through this putative endocrine disruption. This has led the European Community to ban or restrict the use of some parabens. Although not all of them have been shown to influence the endocrine system, cosmetic companies have widely replaced all parabens with other preservatives. However, the substitution of parabens with new, less well known preservatives may lead to new cases of contact allergy (2, 3).

Apobase® moisturizers are widely used in Finland. At the beginning of 2014, the parabens in Apobase® oily cream, cream and lotion were replaced with a new preservative called Phenostat™, which is a mixture of phenoxyethanol (PE), caprylhydroxamic acid (CHA), and methylpropanediol (MPD). Both Phenostat™ and CHA are widely used in different cosmetic products, such as make-up, moisturizers, and shampoos, in many countries.

At the beginning of 2016, several Finnish dermatologists mutually reported suspected cases of allergic contact dermatitis after the use of Apobase® moisturizers. Some cases were severe enough to require hospitalization. Consequently, in February 2016 the creams were recalled from the Finnish market. The new preservative mixture, Phenostat™, was suspected early on to be the cause of the skin reactions, as it was the only new component in the new formulas of the moisturizers.

## Materials and Methods

The symptoms of patients with suspected contact allergy caused by Apobase® moisturizers appeared as acute, itchy, often sharply demarcated erythematous eczema of the exposed areas. Some patients were hospitalized because of widespread severe eczema or severe localized eczema of the face, hands, or legs. Eczema symptoms improved after discontinuation of the use of the suspected products. To determine the reason for the suspected allergic contact dermatitis, a total of 39 patients (age 22–78 years; mean age 57 years; 79% females) were examined in the dermatological clinics of Helsinki University Hospital, Kuopio University Hospital, Oulu University Hospital, and the Allergy Centre at Tampere University Hospital. Initially, most of the patients had used the Apobase® moisturizers for atopic dermatitis (11 patients), other types of eczema (8 patients), or dry skin (6 patients). Other reasons were, in 2 cases each, psoriasis, rosacea, and venous ulcer surrounding skin, and, in 1 case each, Hailey–Hailey disease, prurigo nodularis, skin transplantation, and hand cream for healthy skin. The reason was not recorded for 4 subjects.

Patch testing was performed according to the guidelines of the ESCD (4). The occlusion time was 2 days.

Readings were performed when the patches (Finn Chambers® on Scanpor® tape, diameter 8 mm; Smart Practice, Phoenix, AZ, USA) were removed, and on day (D) 4 or D5.

Patients were tested with the following Apobase® products 'as is': new formulas of Apobase® oily cream, cream and lotion (Actavis Group, Hafnarfirdi, Iceland) from different batches, old formulas of Apobase® oily cream and cream containing parabens instead of Phenostat™ from different batches, Apobase® oily cream and cream containing only PE as preservative, and Apobase® oily cream without any preservatives provided by the manufacturer. The patient's own Apobase® moisturizer was tested whenever available.

According to the manufacturer, the concentration of Phenostat™ in the new Apobase® moisturizers was 0.75%. According to the safety data sheet, Phenostat™ (Inolex Chemical Company, Philadelphia, PA, USA) contains 65–75% PE, 10–20% CHA, 5–10% MPD, and 5–10% aq. The patch test substance for PE 1.0% pet. was purchased from Chemotechnique Diagnostics (Vellinge, Sweden). For in-house dilution series, CHA was purchased from Chemos (Regenstauf, Germany). Owing to a delay in the availability of CHA, a potassium salt of CHA with similar chemical properties was selected for the first tests. The potassium salt of CHA and MPD were purchased from Sigma-Aldrich Finland (Helsinki, Finland). Both CHA and Phenostat™ were prepared with pet. as vehicle. To exclude other relevant contact allergies, the baseline series, a preservatives series and a skin treatment series were tested simultaneously if they had not been tested before. Twenty eczema patients without prior use of Apobase® moisturizers for the last 2 years served as controls, and were tested with the dilution series of Phenostat™ and the potassium salt of CHA. Also, 13 healthy volunteers were tested with the Apobase® formulas, the dilution series of Phenostat™, CHA, the potassium salt of CHA, and MPD.

## Results

The patch tests showed positive reactions to the new Apobase® formulas, Phenostat™, CHA, or the potassium salt of CHA, but not to the old Apobase® formulas, MPD, or PE. The patch test reactivities to CHA and to its potassium salt were similar in intensity with all concentrations. The patch test results on D4/D5 readings are summarized in Tables 1 and 2. Altogether, 25 different batches of the new Apobase® formulas were tested, and there were no marked differences in patch test reactivity. Patch tests in all control subjects gave negative results.

**Table 1.** Patch test results for dilution series of caprylhydroxamic acid (CHA) or its potassium salt, and Phenostat™, all tested in pet.

|            | CHA and its potassium salt |       |       |       |        |       |         |        | Phenostat™ |       |       |       |
|------------|----------------------------|-------|-------|-------|--------|-------|---------|--------|------------|-------|-------|-------|
|            | 3.2%                       | 1.00% | 0.32% | 0.10% | 0.032% | 0.01% | 0.0032% | 0.001% | 1.50%      | 0.50% | 0.15% | 0.05% |
| 3+         | 9                          | 10    | 4     | 1     | 0      | 0     | 0       | 0      | 5          | 2     | 0     | 0     |
| 2+         | 6                          | 21    | 15    | 6     | 3      | 0     | 0       | 0      | 10         | 6     | 3     | 2     |
| 1+         | 0                          | 7     | 17    | 18    | 14     | 1     | 0       | 0      | 16         | 10    | 8     | 7     |
| ?+         | 1                          | 1     | 2     | 10    | 6      | 3     | 1       | 0      | 4          | 10    | 8     | 0     |
| Negative   | 0                          | 0     | 1     | 4     | 16     | 8     | 6       | 7      | 3          | 10    | 18    | 30    |
| IR         | 0                          | 0     | 0     | 0     | 0      | 0     | 0       | 0      | 1          | 1     | 2     | 0     |
| No. tested | 16                         | 39    | 39    | 39    | 39     | 12    | 7       | 7      | 39         | 39    | 39    | 39    |

IR, irritant reaction; ?+, doubtful reaction.

The patch test reactivity was similar in intensity between CHA (21 subjects) and its potassium salt (18 subjects).

**Table 2.** Patch tests results for the Apobase® formulas

|            | Old preparations |       | New preparations |       |        | New with PE only |       | Preservative    |
|------------|------------------|-------|------------------|-------|--------|------------------|-------|-----------------|
|            | Oily cream       | Cream | Oily cream       | Cream | Lotion | Oily cream       | Cream | Free oily cream |
| 3+         | 0                | 0     | 7                | 6     | 4      | 0                | 0     | 0               |
| 2+         | 0                | 0     | 11               | 13    | 10     | 0                | 0     | 0               |
| 1+         | 1*               | 1*    | 15               | 13    | 12     | 0                | 0     | 0               |
| ?+         | 0                | 0     | 1                | 2     | 2      | 1*               | 1*    | 1*              |
| Negative   | 29               | 11    | 2                | 0     | 1      | 11               | 11    | 32              |
| IR         | 0                | 0     | 0                | 0     | 0      | 0                | 0     | 0               |
| No. tested | 30               | 12    | 36               | 34    | 29     | 12               | 12    | 33              |

IR, irritant reaction; ?+, doubtful reaction; PE, phenoxyethanol.

\*A patient with a simultaneous contact allergy to cetearyl alcohol, which is also found in the new formulas of Apobase® oily cream, cream, and lotion.

## Discussion

Contact allergy caused by ingredients in cosmetic products is well known and is mainly caused by fragrances and preservatives (5). In the EU and the United States, ingredients of cosmetics are strictly regulated, and the safety of preservatives used must be evaluated by expert committees. A total of 57 different preservatives are currently allowed in cosmetic products in the EU (6). However, only a few of these dominate the market: parabens, formaldehyde releasers, methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI), and MI. Many of the other preservatives are not as efficient, and require a low pH in order to be active. New preservatives that would be efficient and safe have been difficult to produce. Since the beginning of the 1990s, only a few new preservatives have been approved in the EU. Among these was methyldibromo glutaronitrile, which quite quickly caused an epidemic of contact allergy, and is now banned in cosmetics. MI also caused an epidemic of contact allergy after being approved for cosmetic use in the EU in 2005 (2, 3). Parabens were used widely as preservatives in cosmetics until EU restrictions were imposed because of suspected endocrine disturbances. This has led to extensive replacement of parabens in cosmetic

products with other preservatives. In 2014, parabens in Apobase® moisturizers were replaced by Phenostat™. Phenostat™ is efficient at neutral pH, and it also has antifungal properties. It has been used in cosmetic products at concentrations between 0.8% and 1.2%. In Apobase® moisturizers, the concentration was 0.75%, corresponding to 0.075–0.15% of CHA. Contact allergy to PE has been reported (7, 8), but there are no previous reports of contact allergy to CHA or MPD. Therefore, commercial patch test substances are not available for CHA and MPD.

CHA (octanamide; CAS no. 7377-03-9, C<sub>8</sub>H<sub>17</sub>NO<sub>2</sub>) has not previously been reported as a contact allergen (9). However, it is quite widely used in cosmetic products in many countries. Patented in 2012, it is not classified as an actual preservative but as a chelating agent. An impaired skin barrier function may increase the risk of contact sensitization to CHA, as most of our patients had pre-existing dermatitis. In some of our patients, the Apobase® creams themselves caused stronger allergic patch test reactions than Phenostat™ or CHA. Thus, it is possible that the other ingredients in Apobase® moisturizers, for example emulsifiers such as Cetareth-20, and solvents such as PE and MPD, may weaken the skin barrier and promote the absorption of CHA. The patch test concentrations of CHA producing positive allergic reactions were considerably

higher than the use concentrations in the products tested.

It appeared that the Phenostat™-containing formulas were produced during 2014–2016. Since summer 2016, Phenostat™ has been omitted from all Apobase® formulations marketed in Finland. Whether or not it is safe to use CHA in other cosmetic products with different compositions and different concentrations needs careful evaluation. For patch testing, a test concentration of 1.0% would seem to be appropriate, as this did not yield

false-negative reactions in our patients. We conclude that we have identified a novel contact allergen – the preservative CHA – causing an epidemic of allergic contact dermatitis in Finland.

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