

Lyrall: A Fragrance Allergen

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Fragrances are a common cause of contact dermatitis and account for a large percentage of reactions to cosmetic products. Novel fragrance compounds that may not be detected by the common fragrance screening agents (including balsam of Peru and fragrance mix) are continually being produced. Lyrall is one of those allergens found in many cosmetic and household products. This review will discuss the recent literature and the significance of this allergen to allergic contact dermatitis.

FRAGRANCES are a common cause of allergic contact dermatitis (ACD) and the most common cause of ACD from cosmetic products. Fragrances accounted for 23.2% of positive reactions in the recent North American Contact Dermatitis Group study, in which balsam of Peru was second to nickel as the most common allergen.¹ De Groot reported a 4.2% rate of cosmetic product allergy among 1,781 patch-tested patients; fragrance allergy accounted for 45.1% of the abnormal reactions.²

Unfortunately, discovering a specific fragrance allergen that causes ACD is difficult. Many cosmetic products may contain hundreds of different components that are not disclosed, owing to trade secrets and industrial policies. This may change in Europe, where within the next year, cosmetic products will be required to have a label indicating the common chemical names of their fragrances, making it easier for patients to avoid allergens.

The Research Institute for Fragrance Materials is responsible for testing new fragrances and determining sensitization profiles and other potential side effects. These data, along with clinical studies by the International Fragrance Research Association (IFRA), are used to establish guidelines for the use of various fragrance components as well as to establish limits on fragrance use to subsensitization thresholds. The two screening agents most commonly used to diagnose ACD from fragrances are balsam of Peru and fragrance mix.

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Balsam of Peru, a natural substance from fir trees, contains various allergens or fragrance components, including benzyl acetate, cinnamic alcohol, cinnamic aldehyde, eugenol, and isoeugenol. Balsam of Peru alone will detect 50% of fragrance allergies.³ The fragrance mix developed by Larsen contains eight allergens, each at 1%: oak moss absolute, cinnamic aldehyde, cinnamic alcohol, alpha-amyl cinnamic alcohol, geraniol, hydroxycitronellal, isoeugenol, and eugenol.⁴ This mix and balsam of Peru will detect over 90% of allergic cases. The addition of ylang ylang, sandalwood, and narcissus will bring the detection rate closer to 100%.³ These mixtures may also have the potential to detect allergies to other fragrances whose structural similarities may result in cross-reactions.

These statistics rely on the assumption that the cosmetic industry is static, which is not the case. Novel fragrance molecules are continually researched and produced for use in perfumes, soaps, and household products. Therefore, although balsam of Peru and the fragrance mix are good screening agents, they are by no means perfect. It is likely that patients will develop reactions to new fragrance allergens that are not yet known and that these allergens may not cross-react with balsam of Peru or fragrance mix. The sensitivity of these screening mixtures will subsequently diminish. As mentioned, the discovery of new fragrance allergens is difficult partly owing to nondisclosure by the cosmetic industry although many companies will release the components of a product for patch testing. This forces a fragrance-allergic patient to use a fragrance-free product or one found by trial and error through repeat open application tests (ROATs). This situation has already been observed with the fragrance molecule 3-cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methyl pentyl), known as Lyrall (International Flavors & Fragrances, Inc., New York, NY).

Lyrall is an aldehyde and bears an odor similar to that of lily. The manufacturer-recommended uses of this agent include use in antiperspirants, alcoholic lotions, deodorant sticks, fabric softeners, surface cleaners, shampoos, and

soaps. In 1989, Fenn published a list of the 25 most common fragrance materials in 400 fragrance products, including fine fragrances, household products such as fabric softeners, and soaps.⁵ Lyrall was found to be present in 46% of fine fragrances. Using mass spectroscopy and gas chromatography, Rastogi and colleagues analyzed the components of 73 deodorants that were on the European market.⁶ Lyrall was present in 59% of vapo-sprays (median concentration, 0.0387 g/mL), 77% of aerosol sprays (median concentration, 0.0210 g/mL), and 27% of roll-on products (median concentration, 0.0582 g/mL). One may assume from these data that Lyrall is in widespread use in many cosmetic and personal-use products, creating the potential for sensitization and ACD. Several case reports and large European studies have validated that assumption.

One of the earliest cases of sensitivity to Lyrall was reported in 1984 by Benke and Larsen.⁷ The aim of their study was to determine safety levels of fragrance allergens in shampoos and to study dose-response relationships in patients who had been previously sensitized to geraniol, hydroxycitronellal, and Lyrall. One patient in that study was a woman who was sensitized to both hydroxycitronellal and Lyrall at patch-test thresholds of 0.025% and 0.25%, respectively. Over a period of 6 years (1981 to 1986), De Groot studied 1,781 patients with contact dermatitis, 75 (4.2%) of whom had a cosmetic allergy²; a patient from that series was sensitized to Lyrall from a deodorant cream. In another series (of 119 patients with cosmetic allergies, over a period of 17 months from 1986 to 1987) studied by De Groot, Lyrall was found to be the causative agent in one patient who had a positive patch-test reaction to Lyrall at a 2% concentration in petrolatum (pet).⁸

Several reports have described cases of ACD from Lyrall in patients who have had negative reactions to the standard screening agents. Handley and Burrows reported a patient who reacted to Lyrall and whose deodorants contained the fragrance.⁹ The patient had negative patch-test reactions to the European Standard series (Trolab, Reinbek, Germany) and to the cosmetic and fragrance series (Chemotechnique Diagnostics, Malmö, Sweden). The patient had reactions to various concentrations of Lyrall (0.075–0.25% pet) as well as to 6.5% diisopropylene glycol. Given the negative reactions to the screening substances, the authors stressed the importance of testing individual fragrances and updating the screening series. Another case of ACD from Lyrall in an underarm deodorant was reported in a woman who had developed a dermatitis of her axillae lasting 5 months.¹⁰ The result of an ROAT with the deodorant was positive, but the patient

had a negative patch-test reaction to the European Standard series. Gimenez-Arnau and colleagues reported on a 50-year-old woman who had developed a dermatitis involving the neck, postauricular areas, and chest.¹¹ She had negative patch-test reactions to the fragrance mix as well as to the cosmetic and fragrances series (Trolab). She had a positive result to her eau de toilette on a use test. The authors patch-tested the patient with fragrance components supplied by the manufacturer as well as with fractions separated by chromatography and identified by mass spectroscopy. The patient was found to have positive reactions to benzophenone-2, α -hexyl cinnamic aldehyde, α -damascone, and Lyrall (2% pet). These case reports highlight the fact that patients sensitized to Lyrall may have negative reactions to the common screening agents.

Several large European studies on cosmetic and fragrance allergies have confirmed the sensitizing potential of Lyrall and its role in contact dermatitis from fragrances. A multicenter trial conducted by the European Environmental and Contact Dermatitis Research Group looked at reactions to the fragrance mix and to 48 other allergens derived from Fenn's publication on 1,323 patients at various centers.¹² A total of three patients reacted to Lyrall (5% pet) at the Barcelona test center. One patient was a woman with hand eczema who had no previous history of cosmetic or fragrance allergy. The second patient had a positive history of allergic reactions to sunscreens and perfumes, and the third had a positive ROAT reaction to a massage lotion. The first two patients had a positive reaction to the fragrance mix. In this series, patients reacted to only 7 of the 48 new allergens, and Lyrall was found to be the only one that was clinically relevant.

Another European multicenter trial, involving 1,855 patients, focused on 14 new fragrance allergens.¹³ All patients were patch-tested with the fragrance mix as well. A clinical history of fragrance allergy (ie, certain, probable, questionable, or none) was obtained. A positive reaction to fragrance mix (FM) was had by 11.3% of patients. The second most frequent reaction (2.7%) was to Lyrall (5% pet). In 24 cases, patients had positive reactions to both FM and Lyrall whereas 21 patients showed reactions solely to Lyrall. Of those who had a "certain" clinical history, 53.2% reacted to FM and another 7.2% reacted to Lyrall only. Of the patients who reacted to Lyrall, 80% had a history of fragrance intolerance, compared to only 58.6% of FM-positive patients ($p < .01$). Further history was then obtained from four patients who had a positive reaction to Lyrall and a negative reaction to FM. Lyrall was found in the products that were the suspected causes of their allergies; these products included eaux de toilette, perfumes,

aftershaves, hand lotions, and deodorants. On the basis of this study, the authors concluded that Lyrar (5% pet) should be included when testing patients for contact dermatitis.

A German study involving 3,245 patients was performed to establish patch-testing parameters for Lyrar as well as to look at the concomitant rate of FM positivity in patients sensitized to Lyrar.¹⁴ Lyrar was used at the 5% concentration in petrolatum. Positive reactions were found in 1.9% of patients. Irritant reactions were uncommon (0.1% of patients). A total of 3,185 patients were patch-tested with both Lyrar and FM. Positive reactions to both allergens were found in 40 patients, which accounted for only 67.8% of the patients who reacted to Lyrar. As a result of this study, Lyrar was added to the investigators' standard series. A similar rate of positive reactions was observed in a study of 766 consecutive patients in the United Kingdom.¹⁵ Patients were patch-tested with FM, balsam of Peru 25%, and Lyrar 5%. A 2% rate of positive reactions to Lyrar was observed, and 1.3% of the patients had reactions to both FM and Lyrar.

Recent evidence indicates that in addition to its role in patients with cosmetic and fragrance intolerance, Lyrar sensitivity affects patients with hand eczema. Heydorn and colleagues studied a group of 14 fragrance allergens found in products to which hands would be exposed.¹⁶ Of 658 consecutive patients, 10.2% had a positive reaction to one or more of the allergens. Lyrar (5% pet) was the third most common fragrance allergen that caused positive reactions; citral (2% pet) and hydroxycitronellal (5% pet) were the first and second most common, respectively. It is unclear what role this association between fragrance allergy and hand eczema has in initiating or propagating disease. A subsequent provocation study by Heydorn and colleagues found no association between exposure to a fragrance allergen (including Lyrar) and the development of hand eczema.¹⁷

Numerous case reports, case series, and large patch-test studies have provided evidence that there is a considerable prevalence of Lyrar sensitivity in the population, especially among patients with a fragrance or cosmetic allergy. The majority of studies have used the 5%-in-petrolatum formulation for patch testing, and this appears to be adequate for detecting a positive reaction while giving a limited number of irritant reactions. Owing to the substantial evidence that has accumulated concerning Lyrar sensitivity, IFRA has (within the past year) passed a standard that limits the concentration of Lyrar to 1.5% in skin contact and household cleaning products.¹⁸ This standard may not be enough, as was suggested by the re-

cent study by Johansen and colleagues.¹⁹ They studied the dose-response relationship of Lyrar contact allergy at various doses. Using patch tests as well as ROATs, they concluded that the sensitization level was below the level found in products and advised by the IFRA standard. They recommended a level of exposure of 0.02 to 0.03%. It is clear that as long as Lyrar is used in personal care and cosmetic products, it will contribute to a percentage of patients with fragrance-related ACD. Standard fragrance screening tests should be updated on a regular basis to keep up with the cosmetics industry. A large patch-test study establishing the prevalence of Lyrar sensitivity in the North American population is needed.

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