

## Ethylene oxide allergy may have been confirmed by patch testing to a similar epoxy compound

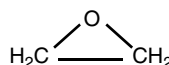
Dear Sir,

In the November issue of *Contact Dermatitis* Caroli et al (1) presented an interesting case of delayed-type hypersensitivity dermatitis to ethylene oxide (EtO), which had been used to sterilize her surgical gown. In this report, they mention that suspected delayed-type hypersensitivity reactions to EtO are difficult to test for, as no standardized patch test procedures for volatile substances such as EtO can be used. EtO is an epoxy compound, which was not mentioned in the case report, and this information may well have been of assistance in identifying the cause by traditional patch testing.

We draw the authors' attention to a report from our unit, which described a case of allergic contact dermatitis from epoxy propane in an electron microscopy technician (2). Epoxy propane is similar to EtO, in that it is also an epoxy compound but with one extra methyl group (Fig. 1) and is also used in sterilization of medical equipment. In this case, the patient was patch tested and had positive reactions to both epoxy propane (1% pet.) and epichlorohydrin (1% pet.), compounds that differ by only one chlorine atom. If their patient with presumed EtO allergy were to be tested with epichlorohydrin or epoxy propane, then they may well have shown a positive cross reaction, adding further weight to the diagnosis.

Epoxyethane

Ethylene oxide



Epoxypropane

Propylene oxide

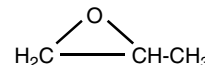


Fig. 1. The chemical structures of epoxyethane and epoxypropane illustrating how they differ by only one methyl group.

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## Cross-reactions in patch testing with ketoprofen, fragrance mix and cinnamic derivatives

Dear Sir,

We read with great interest the recent report by Matthieu et al. (1) on their experience in photo-testing patients with suspected contact dermatitis to ketoprofen (KP). The authors found a high frequency (69%) of contact allergy to fragrance mix. They discussed the already suggested hypothesis (2) that the presence of an aldehyde function in KP and cinnamic aldehyde (Cald)

(component of fragrance mix) may explain this cross-sensitivity. As there is no mechanistic nor structural evidence that cinnamic derivatives and KP can activate the same T lymphocytes subpopulation, the term cross-sensitivity is probably not adequate and requires further investigations. But for practical reasons, we will still use it in the following discussion. There is no true aldehyde function on KP molecule, but the oxygen group

close to the benzene ring resembles that found in Cald when it is folded into itself by carbonic double link. However, the authors did not test the different components of fragrance mix and their data could not support this. Cross-sensitization between KP and fragrance mix has been already reported by Pigatto et al. (2). Among 123 patients with allergic reactions to topical arylpropionic anti-inflammatory drugs, they observed 26 contact and 25 photocontact sensitivity to KP cases, and 39 patients (32%) demonstrated positive reaction to fragrance mix as compared to the total prevalence of positivity to fragrance mix (12%) in the outpatient clinic data (2401 cases). When tested with components of fragrance mix, 33 patients out of 39 reacted to Cald. However, no data for reaction to cinnamic alcohol (Calc) were given. The authors concluded that reactions to KP and fragrance mix were not due to chance. They suggested that an aldehyde group near a benzene ring could induce sensitization and cross-reactions between KP and fragrance mix. More recently, Frosch et al. (3) observed that 8.3% out of 1069 patients were positive to fragrance mix. Among them, 11% were positive to Cald.

In a previous study in 18 patients with contact photallergy to KP (4), we also found a high frequency of contact allergy to fragrance mix (83%). 8 positive patients were then tested with the different components of fragrance mix, including Calc and Cald (unpublished data). All patients demonstrated positive reaction with Calc and only 5 patients reacted to Cald. We do not have any clear explanation for the low reactivity to Cald observed in our study as compared to those found by Pigatto et al. (2) and Frosch et al. (3). Both Calc and Cald have been reported to cause allergic contact dermatitis in humans, with Cald a more potent skin sensitizer than Calc. However, in man, Calc is almost as frequent a cause of allergic contact dermatitis as is Cald (5). In addition, unexplained interindividual differences and cross-reactivities/cosensitization to these compounds in the clinic have been observed. Cutaneous sensitization to Cald may be dependent not only upon skin absorption kinetics but also upon the effectiveness of toxification/detoxification by cutaneous enzymes, which may demonstrate interindividual variations (6–8). Furthermore, the weak sensitization potential of Calc and the limited cutaneous conversion of Calc to Cald may be overcome by a higher degree of exposure to Calc. Indeed, Calc is a component of cinnamon spice, which is widely used in the food and fragrance industry. Our results thus do not support the role of the

aldehyde function in cross-reaction between KP and fragrance mix. In contrast, we postulate that Calc may be an independent antigen that does not necessarily require transformation into Cald to be a sensitizer. The mechanisms involved in this strong association between positive patch test to cinnamic derivatives, in particular Calc and KP are still unknown. Besides the immunological pathway of cross-sensitization, an enzymatic susceptibility for either toxification or detoxification of molecules may also be involved. However, we believe that the mechanism may involve the high reactivity induced by the association of a benzene ring with an oxygen group (4). Indeed, several molecules, including KP, Calc, Cald, benzophenone-3, fenofibrate, tiaprofenic acid and several unexpected and non-relevant allergens (4), share this chemical combination and are involved in cross-association. There are few available clinical data to confirm this demonstration, which to be true, requires that all patients with positive patch test to fragrance mix and cinnamic derivatives should also react to KP. However, such an investigation (photopatch test to KP in patients with positive patch test to cinnamic derivatives) as the retest method (KP on previously positive patch test to cinnamic derivatives and cinnamic derivatives on previously positive patch test to KP<sup>+</sup> irradiation with ultraviolet radiation) is restricted for ethical reasons.

In conclusion, on the basis of strong correlation between sensitization to cinnamic derivatives and KP, we suggested that cutaneous reactivity to cinnamic derivatives may represent a risk factor of KP sensitization. Furthermore, exposure to the sun may facilitate the direct transformation making sensitization and cross-sensitization occur more rapidly (2). For this reason, we recommend to test the patients positive to fragrance mix with the different components, in particular the cinnamic derivatives, and then to inform patients positive to cinnamic derivatives of the risk of sensitization to KP.

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