

The Evolving Landscape of Contact Dermatitis Diagnosis: A Critical Appraisal of Recent Regulatory Constraints

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SUMMARY

The current limited availability of patch tests for diagnosing Allergic Contact Dermatitis (ACD) and occupational or non-professional diseases, in accordance with AIFA regulations, has significantly affected the diagnostic approach for patients and affected workers. The issue is even more severe for haptens of occupational origin. In occupational medicine, the patch test is crucial for establishing the causal link between the skin disease and the patient's work activities. Accurate diagnosis is essential for occupational physicians both to determine the need for a job change and to assess workers' compensation. Due to limited diagnostics and regulatory restrictions, it remains impossible to diagnose occupational ACD. In this context, occupational doctors will focus on primary prevention by avoiding risk products and replacing them with non-sensitizing or non-cross-reactive alternatives. This paper addresses the challenges posed by the new AIFA (Italian Medicines Agency) diagnostic restrictions and explores potential solutions and future perspectives.

1. INTRODUCTION

Allergic contact dermatitis (ACD) is characterized by skin inflammatory processes that account for about 60% of cutaneous eczemas [1], caused by contact with various environmental allergens, aside from occupational ones [2]. Specifically, Occupational Allergic Contact Dermatitis (OACD) is estimated to affect between 6.7% and 10.6% of cases [3], although this data might be underestimated [2]. OACD is responsible for approximately one-third of all occupational diseases in industrialized countries [4]. A wide range of occupations are at risk for skin

disease, including bakers, cooks, hairdressers, beauticians, butchers, and other personal service workers [5]. OACD is a well-known Type IV hypersensitivity reaction that occurs in workers with repeated skin exposure to sensitizing haptens. The epicutaneous test (patch test) is an in vivo test and the gold standard for diagnosing OACD, confirming the causal relationship between work and the disease [6]. In the past, we used well-established clinical protocols to diagnose suspected OACD, employing standardized epicutaneous tests combined with occupational history and job analysis. The collaboration between occupational physicians and allergists/dermatologists

was straightforward because occupational doctors could request predefined epicutaneous test series from allergists during routine health surveillance. Today, this process is more challenging since these professional series are no longer available on the market. This paper discusses current challenges and the best approaches for diagnosing OACD, starting with the European Guideline on haptens and their Italian transcription [7, 8].

2. METHODS

The current regulatory classification of haptens for patch tests as medicinal products dates back to Directive 89/343/EEC, which extended the same obligations to these products as for all medicinal products regarding production, marketing authorization, and clinical use (Autorizzazione Immissione Commercio – AIC). In Italy, the process of regulating allergenic medicines began with the Ministerial Decree Healthcare of December 13, 1991, and experienced a long period of inactivity. Recently, it was resumed with AIFA (Italian Medicines Agency) DG Resolution n. 2130/2017, which established the criteria for completing the process and the possible issuance of the AIC for allergens on the market by law (*ope legis*): owners of allergen products used for diagnosis (i.e., haptens for patch tests) are required to submit an updated dossier for each hapten. To ensure patients' right to health, it was also necessary to publish a list of haptens temporarily authorized for marketing, attached to AIFA DG Resolution n. 98/2022, which is revised and updated whenever there are production changes or significant literature updates. In conclusion, the allergenic medicines currently on the market in Italy are three types: medicines with regular marketing authorization (AIC), medicines authorized for marketing by law (*ope legis*), and medicines marketed as specific products for individual patients (Named Patient Products – NPP). The products marketed *ope legis* (pursuant to the Health Ministerial Decree of December 13, 1991) are legally equivalent to products with an AIC. Products marketed as NPP are medicinal products prepared industrially upon written and unsolicited requests from a doctor, who commits to using the products on a specific patient under their

direct and personal responsibility. Patch test haptens cannot be classified as NPP because they are produced through a standardized process for use in a plurality of patients and not nominally intended for a single person.

3. RESULTS

The final process for AIC is currently underway; it involves the regulatory and technical-scientific evaluation of the dossiers filed for the admitted products with the purpose of issuing the AIC. Until this process is completed, the medicines admitted for evaluation will remain on the market as *ope legis* [9, 11]. Therefore, the conclusion of the first phase and the start of the next phase revealed many critical issues in the sector, creating a situation of unmet clinical need. In particular, regarding patch tests, the Italian Society of Dermatology and Sexually Transmitted Diseases (SIDeMaST) reported serious difficulties in diagnosing ACD or OACD, and in implementing suitable secondary prevention measures, resulting in increased direct costs (therapy for patients) and indirect costs (absence from work) [10, 11, 12]. To identify the best solutions to meet the needs of professionals and patients, and to develop guidelines aligned with the latest scientific standards and regulatory requirements, AIFA Technical Table was established to detect clinical test haptens through AIFA DG Determination n° 134/2022 (updated by AIFA DG Determination n° 447/2022). In occupational medicine, the patch test is essential for establishing the causal link between skin disease and the patient's work activity. Accurate diagnosis of OACD is vital for occupational physicians when deciding on job changes. The lack of recognition of the occupational nature of contact dermatitis prevents worker compensation from Italian Working Compensation Authority (INAIL) and contributes to underestimating the number of reported occupational diseases whose incidence in Italy is already low. Currently, most occupational haptens are not represented by commercially available haptens. In these cases, occupational doctors must use products from commercial or natural sources and resort to the extemporaneous preparation of patch tests. To ensure standardized procedures, a quality assurance

document for these preparations should be developed, updating the information provided by the Official Italian Pharmacopoeia for preparing extemporaneous medicines in pharmacies and radiopharmaceuticals in nuclear medicine. This document is being drafted by experts from the Technical Table and the Secretariat for the Official Pharmacopoeia.

4. DISCUSSION

The limited availability of patch tests for diagnosing ACD and occupational or non-professional diseases, according to AIFA regulations, has significantly impacted how patients and workers are diagnosed. In an unpublished study conducted in 2023 at our center, involving 437 patients, we observed a 44.5% rate of sensitizations compared to 52.1% reported in the literature [13, 14]; this difference may be due to a larger panel of haptens used in other countries where regulatory restrictions were not enforced. Among 14 workers with suspected OACD, 25.6% of sensitizations were identified using haptens without AIC. These cases could be missed with new diagnostic restrictions. Due to the limited supply of AIC tests, the near-future outlook in Italy is not promising. Occupational physicians, allergists, and dermatologists should increase their use of patch tests with products in use, similar to past practices where doctors prepared “at-home” epicutaneous tests. According to recent regulatory proposals, a quality assurance document (currently in progress) should be required, unlike the improvised preparations of the past. Currently, only a few authorized occupational allergology/dermatology centers can ensure standardized preparation procedures. Such an approach requires time and is complex because it demands technical knowledge and supplied materials. Additionally, it’s challenging to compile a comprehensive list of chemicals in specific workplaces or review safety data sheets, which are often incomplete due to missing sensitizing compounds. Haptens may also be listed under various names, adding to the complexity. A specialized occupational allergist/dermatologist’s expertise, including toxicological knowledge and awareness of industrial production cycles, is essential. Beyond identifying products, allergens, and critical manufacturing phases, the regulatory

framework for AIC and related legislation should facilitate case-specific extemporaneous patch testing through more nuanced analysis. Without these developments, limited diagnostics and regulatory restrictions may prevent accurate diagnosis of OACD. In this context, occupational physicians should focus on primary prevention by avoiding hazardous products that could be replaced with non-sensitizing, non-cross-reactive alternatives. If technological or environmental modifications are unfeasible, educational efforts, reduced exposure (such as shift work), and preventive measures (secondary prevention) should be adopted. For example, wearing gloves that are regularly changed and possibly combined with cotton underneath can protect not only hands but also part of the arms. Barrier creams may also be effective depending on the specific task and substances involved, but it is important to note that manual work involving hand rubbing can remove the cream, potentially giving workers a false sense of security.

5. CONCLUSION

In conclusion, new perspectives are emerging that require more complex analysis. Allergists and dermatologists need to collaborate with occupational doctors to identify new diagnostic tools and empirical approaches in light of stricter regulations. The key is always gaining more knowledge of the processes and identifying critical points. Therapies and health monitoring after implementing preventive measures can be successful, but strong support from specialists is now necessary. New approaches and tailored diagnoses are needed; understanding the problems and solutions from the perspective of expanding diagnosis remains the ultimate goal, which is closely tied to the available haptens [15].

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