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Development of a Methodology for Assessing Primary Dermal Irritation, Cumulative Irritation, and Skin Sensitization of Nail Products

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1. Introduction

Adverse effects from cosmetic and personal care products are relatively rare, considering the wide user base and ingredient variety. Nonetheless, to ensure consumer safety and regulatory compliance, companies routinely perform pre-market clinical evaluations of safety and efficacy.

The potential for irritation depends on several factors, such as ingredient concentration, exposure time, application site, skin condition, and cumulative effects [1]. Even correctly applied products may trigger reactions like contact dermatitis, urticaria, or pigmentary alterations [2,3].

Contact dermatitis, including irritant and allergic subtypes, remains a major concern in cosmetic safety [4,5]. While irritant reactions typically occur soon after exposure, allergic responses are delayed and immunologically mediated (type IV hypersensitivity) [4,8].

Patch testing is a widely accepted method for evaluating skin compatibility, including primary and cumulative irritation, sensitization, phototoxicity, and photoallergy [9,10]. Nail polishes are of particular interest due to their composition (e.g., formaldehyde, toluene, mica), which may penetrate the nail plate and trigger cutaneous responses [14].

This study proposes a clinical methodology to evaluate the primary and cumulative dermal irritation and sensitization potential of nail products through controlled application in healthy volunteers.

2. Participants

2.1.Inclusion, exclusion and discontinuation Criteria:

65 healthy male and female participants, aged 18 to 70 years (Fitzpatrick phototypes I–IV), with intact hands and nails, and without inflammatory dermatoses or tattoos at the application site, were included. Participants had to understand the procedures, agree to the study requirements, and sign the informed consent form. Volunteers were excluded if they were pregnant, lactating, using corticosteroids, antihistamines or anti-inflammatories, or had any dermatological condition (generalized or in the test area), active dermatoses, history of atopy or allergy to study materials, dermographism, immunodeficiencies, or conditions aggravated by UV exposure. Additional exclusions included recent aesthetic treatments, recent vaccinations, frequent sun exposure or tanning, participation in water sports, recent participation in other studies, and any condition that, in the investigator’s opinion, could compromise the study. Participants could be removed due to adverse events, pregnancy, protocol deviations, use of interfering medications, non-adherence (e.g., missing key visits), withdrawal of consent, or conditions compromising their continued participation. All discontinuations were documented, and adverse events were monitored until resolution or stabilization.

3. Materials and Methods

2.1. Application method | Sample preparation

The application of the investigational product nail polish was performed without dilution, directly on the nail region of the research participants.

3.1.1. Application site

The product was applied to the fingernails, while the thumbs of both hands served as untreated control areas. Applications and evaluations were distributed between the right and left hands of each participant.

Table1. Distribution of regions for application and evaluation of the investigational product

EVALUATION	Application site	Control
Primary Dermal Irritability	Right hand / index finger	Right hand / Thumb
Accumulated Dermal Irritability	Right hand / Middle finger	
Dermal Sensitization	Right hand / Ring finger	

3.1.2. Steps for distribution

For product application, a trained professional delegated by the investigator ensured that the participant was seated comfortably with hands resting on a table. The nail area was cleansed with ethyl ether, followed by full-length application of the investigational product on the nails.

3.3. Methodological description

3.3.1. Primary Dermal Irritability

All research participants received application of the investigational product in the nail region of the index finger of the right hand to assess primary dermal irritability. The region used as a control was the thumb of the right hand where no product was applied.

The investigational product was removed by the researchers after 48 hours of contact with the skin. The area was cleaned with cotton and sterile saline solution 0.9% (NaCl 0.9%) and 30 minutes after cleaning, the reading was performed and the results recorded according to the recommended reading scale. After another 48 hours, that is, 96 hours of application of the investigational product, the research participants returned for a last reading following the same criteria as before for the notes of the reactions.

3.3.2. Accumulated Dermal Irritability – Induction Phase

To assess accumulated dermal irritability, the investigational product was applied to the nail region of the right middle finger of all participants, while the right thumb served as the untreated control. Applications occurred three times per week on alternate days (Monday, Wednesday, and Friday) over three consecutive weeks, totaling nine applications (Table 02). This phase ran in parallel with the primary dermal irritability phase, but in distinct anatomical regions.

Table 02: Schedule of applications and readings - accumulated dermal irritability (induction)

1ST WEEK	**MONDAY**	**TUESDAY**	**WEDNESDAY**	**THURSDAY**	**FRIDAY**
	VISIT 01	REST	**VISIT 02**	REST	**VISIT 03**
	APPLICATION		REMOVAL, READING AND REAPPLICATION		REMOVAL, READING AND REAPPLICATION
2ND WEEK	**VISIT 04**	REST	**VISIT 05**	REST	**VISIT 06**
	REMOVAL, READING AND REAPPLICATION		REMOVAL, READING AND REAPPLICATION		REMOVAL, READING AND REAPPLICATION
3RD WEEK	**VISIT 07**	REST	**VISIT 08**	REST	**VISIT 09**
	REMOVAL, READING AND REAPPLICATION		REMOVAL, READING AND REAPPLICATION		REMOVAL, READING AND REAPPLICATION
4TH WEEK	**VISIT 10**	REST	REST	REST	REST

	REMOVAL, READING				

3.3.3. Dermal Sensitization – Challenge Phase

Following the nine applications and readings of the accumulated dermal irritability phase, a 10-day rest period was observed with no product application. After this interval, participants entered the challenge phase. The investigational product was applied to the nail region of the right ring finger—a site not previously exposed. After 48 hours, the product was removed by the research team, the area was cleansed with 0.9% sterile saline, and readings were taken 30 minutes later using the standard evaluation scale. A final reading was performed 24 hours later (72 hours post-application), following the same criteria.

3.3.1. Data collection procedures and data analysis procedures

The scale used to read reactions is the one recommended by the International Contact Dermatitis Research Group (IRCDG)[15]. The skin irritation index was calculated based on the scores assigned to adverse reactions as shown in **Table 03** and **Table 04**.

Table 03: Evaluation parameters for reading reactions.

REACTIONS	**RESULTS**	**SCORE**
No reaction	negative (-)	0
Doubtful reaction, mild erythema without definition borders	doubtful (+/-)	0,5
Clear erythema – Presence of homogeneous erythema, edema, possible papules and traces of vesicles.	positive (+)	1
Presence of erythema and edema, papules and medium-sized vesicles that possibly extravasate the area of application.	positive (++)	2
Presence of erythema and edema, appearance of papules and vesicles of considerable size, and in some cases, blistering.	positive (+++)	3

Table 04: Score attributed to each nail		
A) Onychoschizia	**B) Onychorrhexis**	**C) Roughness of the nail plate**
0 = no lamellar desquamation	0 = no signs of longitudinal fissure	0 = imperceptible longitudinal ridges and grooves
1 = mild: lamellar desquamation that does not affect the entire free edge of the nail	1 = mild: one longitudinal crack	1 = mild: some flattened elevations and longitudinal ridges
2 = moderate: lamellar desquamation that affects the entire free edge of the nail plate	2 = moderate: at least one deep longitudinal cleft	2 = moderate: some prominent elevations and longitudinal ridges
3 = severe: total involvement of the free edge and up to one third of the nail plate	3 = severe: multiple superficial and deep longitudinal fissures	3 = severe: more than 70% of the nail plate with prominent elevations and deep grooves

The evaluation results obtained at the different evaluation times were calculated to obtain the Individual **Skin Irritation Index** (IdiI). This value corresponds to the sum of all individual scores obtained for each reaction observed at all reading times.

The **Mean Skin Irritation Index** (MdiI) was calculated according to the following formula:

$$\boldsymbol{MdiI} = \frac{\sum (\boldsymbol{IdiI})}{\boldsymbol{Number\ of\ research\ participants}}$$

The irritation index obtained allowed classifying the product according to the following scale:

Table 05: classification of skin irritation potential	
MdiI	**RESULTS**
MdiI = 0,0	Non-irritating – Very good skin compatibility
MdiI < 0,2	Non-irritating – Good skin compatibility
0,2< MdiI <0,5	Slightly irritating – Regular Skin Compatibility
0,5< MdiI <1	Moderately irritating - Bad Skin Compatibility
> MdiI 1	Irritant - Very Bad Skin Compatibility

4. Results and discussions

No adverse cutaneous reactions were reported among the 65 participants across all phases of the study. The Mean Dermal Irritation Index (Mdil) was 0.00, indicating that the investigational nail product did not elicit any measurable irritation or sensitization.

Throughout the primary and cumulative dermal irritation phases, no signs of erythema, edema, papules, vesicles, desquamation, fissures, or nail surface alterations were observed. Similarly, during the sensitization challenge phase, no delayed hypersensitivity reactions occurred, and all participants remained within normal baseline parameters.

These consistent findings across different application phases demonstrate the product's excellent skin compatibility and support its classification as non-irritating and non-sensitizing. The robust design, including repeated applications and a standardized assessment scale (IRCDG), reinforces the reliability of the methodology.

5. Conclusion

The clinical methodology developed in this study proved to be effective and reliable for evaluating the skin compatibility of nail products. The investigational formulation showed no signs of irritation or sensitization across all study phases, resulting in a dermal irritation index of 0.00.

These results confirm the product's excellent safety profile for topical use on the nail region and contribute to the validation of dermatological testing protocols tailored for nail cosmetics. Furthermore, this approach supports both regulatory compliance and the formulation of products that meet consumer expectations for safety and tolerability.

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