

Can exposure limitations for well-known contact allergens be simplified? An analysis of dose–response patch test data

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Summary

Background. Allergic contact dermatitis is triggered by chemicals in the environment. Primary prevention is aimed at minimizing the risk of induction, whereas secondary and tertiary prevention are aimed at reducing elicitation.

Objectives. To identify the elicitation doses that will elicit an allergic reaction in 10% of allergic individuals under patch test conditions (ED₁₀ patch test) for different allergens, and to compare the results with those for different allergens and with animal data indicating sensitizing potency from the literature.

Materials and methods. The literature was searched for patch test elicitation studies that fulfilled six selected criteria. The elicitation doses were calculated, and fitted dose–response curves were drawn.

Results. Sixteen studies with eight different allergens—methylchloroisothiazolinone/methylisothiazolinone, formaldehyde, nickel, cobalt, chromium, isoeugenol, hydroxyisohexyl 3-cyclohexene carboxaldehyde, and methyldibromo glutaronitrile—were selected. The median ED₁₀ value was 0.835 µg/cm². The ED₁₀ patch test values were all within a factor of 7 from the lowest to the highest value, leaving out three outliers. No obvious patterns between the sensitization and elicitation doses for the allergens were found.

Conclusions. We found a rather small variation in the ED₁₀ patch test between the allergens, and no clear relationship between induction potency and elicitation threshold of a range of allergens. This knowledge may stimulate thoughts on introducing a generic approach for limitations in exposure to well-known allergens.

Key words: allergy prevention; dose–response; elicitation; exposure limitation; patch test.

Contact allergy and allergic contact dermatitis are triggered by chemicals in the environment, and approximately 20% of the general population in the western world is sensitized. Primary prevention is aimed at minimizing the risk of induction, whereas secondary

and tertiary prevention are aimed at reducing elicitation among those already sensitized (1). For primary prevention, a quantitative risk assessment model is used by the cosmetics industry (2). The quantitative risk assessment is often based on results from the local lymph node assay (LLNA), in which chemicals are tested in mice in order to define the sensitization potential. A threshold also exists below which only low levels of elicitation are expected in humans. This dose of allergen can be identified by experimental dose–response studies performed on allergic individuals. The relationship between the sensitization potency and the elicitation potency has not been determined. Even though it is expected that the

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dose needed to sensitize will probably be higher than the dose needed to elicit an allergic reaction (3, 4), it is not a given that an allergen with low sensitization potency will also require a high dose to elicit an allergic reaction in already sensitized individuals. Based on the experience of the nickel regulation, it has been shown that the dose that will elicit a reaction in 10% of allergic individuals will not only protect the already sensitized population, but will also decrease the incidence of allergy (5–7). The scope of this study was to identify the elicitation doses that will elicit an allergic reaction in 10% of allergic individuals under patch test conditions (ED₁₀ patch test) for different allergens, using published patch test dose–response studies, and compare the results. The focus was on patch test data, as data from repeated open application tests (ROATs) are available for only a limited number of allergens. The elicitation capacity was then compared with the sensitization potency for the different allergens.

Materials and Methods

Patch test elicitation levels from dose–response studies

The literature was searched for patch test elicitation studies that fulfilled the following criteria: (i) water or alcohol-based vehicle; (ii) Finn Chambers® method; (iii) at least four patch test dilutions; (iv) at least 10 participants; (v) it should be possible to calculate the applied $\mu\text{g}/\text{cm}^2$; and (vi) there should be data enough presented in the publication to allow calculation of the dose–response relationships. The search was carried out using Pubmed-Medline (last accessed May 2010) and the following search terms: patch test dilution series, elicitation, and patch test. The literature was manually searched for additional publications. Sixteen studies, in 15 publications, using either methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) (8), formaldehyde (9), nickel (10–14), cobalt (14), chromium (15), isoeugenol (16, 17), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (18–20), or methyldibromo glutaronitrile (MDBGN) (21, 22), were identified as fulfilling all of the selected criteria.

Statistics

Each study was analysed with a standard logistic regression analysis. The dose–response relationship in the patch test was estimated. The logistic dose–response model has been used previously to describe the dose–response relationship in contact allergy (23–25). The elicitation dose in the patch test that would elicit a reaction in 50%, 25%, 10%, 5% and 1% of allergic

individuals, the ED_{xx}, was calculated, and a fitted dose–response curve was drawn. The 95% confidence interval for ED₁₀ was calculated by using Fieller's method.

The dose metric used in this article is μg allergen/ cm^2 (26–29).

Comparison of the difference between ED₁₀ values and EC₃ values

In the LLNA, the allergen (25 μl) is applied to the ear of mice (on 1 cm^2), and lymphocyte proliferation in the local lymph nodes is measured. The sensitizing potency of a chemical is described by the concentration of chemical needed to produce a three-fold increase in the proliferation of the lymph node cells, the EC₃ value (4, 30). According to this value, test chemicals can be classified as skin sensitizers, and the potency can be determined (31, 32).

EC₃ values were identified in the literature for the same substances as used to obtain the patch test data (4, 33–37). If the EC₃ value was identified as a percentage, then the dose per area was calculated from the following equation, according to Griem et al. (4):

$$\begin{aligned} (\text{EC}_3\% \times 25 \mu\text{l}) \times 1000 \mu\text{g}/\mu\text{l}/1 \text{ cm}^2 \\ = \text{EC}_3 \text{ in } \mu\text{g allergen}/\text{cm}^2 \end{aligned} \quad (1)$$

Results

The dose–response curves for all selected studies are shown in Fig. 1. The concentration needed to elicit a patch test reaction in 10% of allergic individuals for each allergen, with 95% confidence intervals, is shown in Table 1, and the same result is shown in Fig. 2. The median ED₁₀ value was 0.835 $\mu\text{g}/\text{cm}^2$ (range 0.025–20.1 $\mu\text{g}/\text{cm}^2$), giving a span of a factor of 1000. There were three clear outliers: nickel 1999 (13), MDBGN 2004 (22), and formaldehyde (9). Leaving these studies out meant that the ED₁₀ patch test values were all within 0.23–1.58, with a factor of 7 from the lowest to the highest ED₁₀ value.

For MCI/MI, the EC₃ value as a percentage was 0.0049% (37), which corresponds to an area dose of 1.225 μg (MCI/MI)/ cm^2 ; for formaldehyde it was 0.54%, which corresponds to an area dose of 135 μg formaldehyde/ cm^2 (4); for nickel it was 2.5% (36), which equals 140 μg Ni/ cm^2 (3); for cobalt it was 297 μg cobalt/ cm^2 (4); for chromium it was 10 μg chromium/ cm^2 (33); for isoeugenol it was 550 μg isoeugenol/ cm^2 (4); for HICC it was 4275 μg HICC/ cm^2 (35); and for MDBGN it was 1.3% (34), which equals a dose of 325 μg MDBGN/ cm^2 (4). Table 2 shows the difference between the EC₃ values and the ED₁₀ patch test

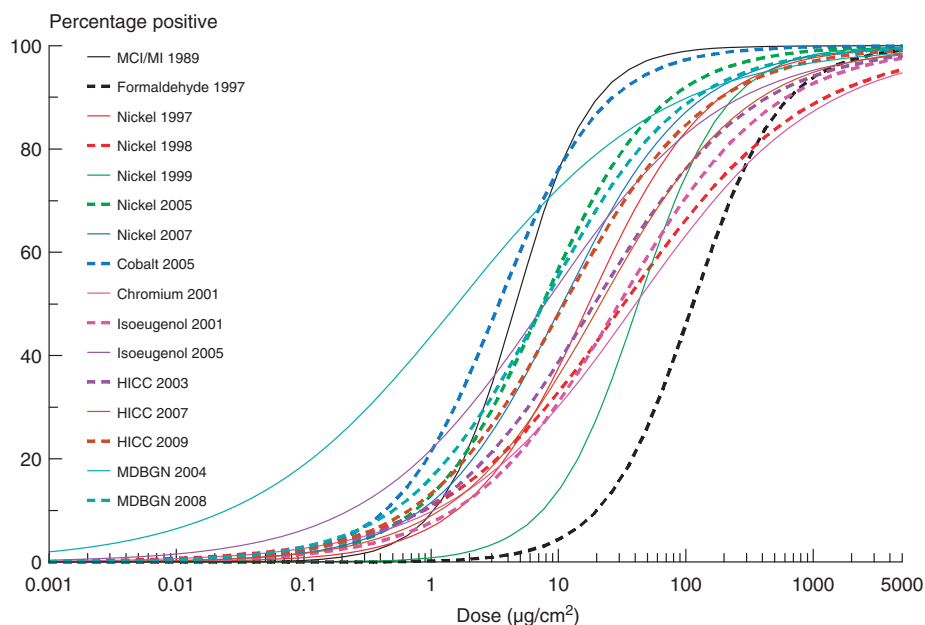


Fig. 1. Logistic dose-response curve for 16 patch test elicitation dose-response studies with methylchloroisothiazolinone/methyl isothiazolinone (MCI/MI) (8), formaldehyde (9), nickel (10–14), cobalt (14), chromium (15), isoeugenol (16, 17), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (18–20), and methyldibromo glutaronitrile (MDBGN) (21, 22).

Table 1. ED₁₀ patch test values from each of the 16 selected studies, with 95% confidence intervals, with the allergens methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (8), formaldehyde (9), nickel (10–14), cobalt (14), chromium (15), isoeugenol (16, 17), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (18–20), and methyldibromo glutaronitrile (MDBGN) (21, 22)

Study	No. of patients	ED ₁₀ (µg/cm ²)	95% Confidence interval
MCI/MI	12	1.05	0.17–2.27
Formaldehyde	20	20.1	4.09–43.9
Nickel 1997	24	1.58	0.32–4.04
Nickel 1998	19	0.8	0.078–2.59
Nickel 1999	26	7.49	2.42–14.5
Nickel 2005	13	0.74	0.066–2.38
Nickel 2007	20	0.82	0.13–2.37
Cobalt 2005	11	0.44	0.033–1.3
Chromium	17	1.04	0.0033–5.55
Isoeugenol 2001	24	1.48	0.22–4.74
Isoeugenol 2005	13	0.23	0.0073–1.32
HICC 2003	18	0.85	0.062–3.26
HICC 2007	14	1.17	0.043–5.05
HICC 2009	17	0.66	0.052–2.35
MDBGN 2004	19	0.025	0.00021–0.19
MDBGN 2008	18	0.50	0.052–1.69

for the different allergens, which varies from 1.2 to 4803, meaning that there is no obvious pattern between the sensitization dose and elicitation dose for the allergens.

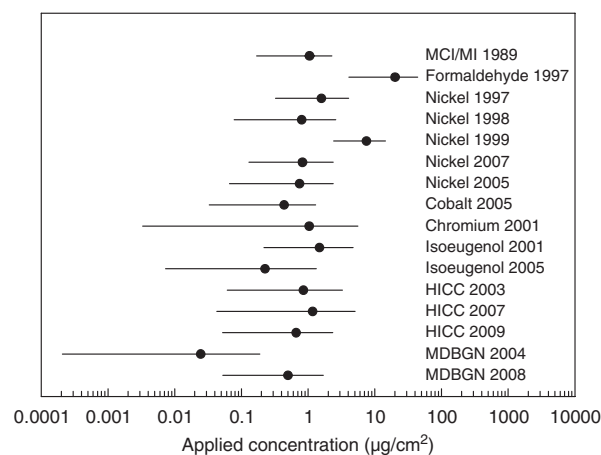


Fig. 2. ED₁₀ values from each of the 16 selected studies, with 95% confidence intervals, with the allergens methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (8), formaldehyde (9), nickel (10–14), cobalt (14), chromium (15), isoeugenol (16, 17), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (18–20), and methyldibromo glutaronitrile (MDBGN) (21, 22).

Discussion

Analysis of the ED₁₀ patch test for the 16 patch test studies showed that the ED₁₀ patch test differed with a factor of 1000 from the lowest to the highest ED₁₀. However, this relatively large difference was attributable to three

Table 2. EC₃ values for the allergens chromium (33), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (37), nickel (4), methyldibromo glutaronitrile (MDBGN), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), isoeugenol (4), formaldehyde (9), and cobalt (4), the concentration of allergen that will elicit a patch test reaction in 10% of allergic individuals (ED₁₀ patch test), and the relationship between the EC₃ and the ED₁₀ patch test (EC₃/ED₁₀ patch test) for each allergen

	EC ₃	ED ₁₀ patch test	Relationship between EC ₃ and ED ₁₀ patch test
MCI/MI	1.225	1.05	1.2
Formaldehyde	135	20.1	6.7
Nickel	140	1.58	141.4 (Mean ED ₁₀ patch test is used, outlier excluded)
		0.82	
		7.49	
		0.74	
		0.82	
Cobalt	297	0.44	675
Chromium	10	1.04	9.6
Isoeugenol	550	1.48	640 (Mean ED ₁₀ patch test is used)
		0.23	
HICC	4275	0.85	4803 (Mean ED ₁₀ patch test is used)
		1.17	
		0.66	
MDBGN	325	0.025	1250 (Mean ED ₁₀ patch test is used)
		0.5	

The EC₃ values are from studies in which different vehicles were used, so some variation in the values may be accounted for by technical details. All values are in µg allergen/cm².

studies (nickel 1999, MDBGN 2004, and formaldehyde). Some variations in the patch test procedure are to be expected; in particular, the reading method varies between studies, so this may account for some of the variation. The nickel study (13) is clearly an outlier, as four other studies exist that give different, but similar, results. In the MDBGN study (22), 6 persons were excluded because they did not react to the retesting, so the least sensitive persons were not represented, which might explain the low ED₁₀ value. In the formaldehyde (9) study, only patch test reactions giving a 1+ reaction and above were reported, which might explain the high ED₁₀ value. If these three studies were excluded, the span between studies in elicitation threshold would be a factor of 7 only. This is a relatively small variation, considering that the analysis was based on studies with different allergens performed over a period of 20 years. In a previous analysis of only nickel dose-response data, the variation within the studies was a factor of 10 (38).

It is generally accepted that the sensitization potency of allergens can be ranked into different potency groups (31, 32, 39). We show here that the ED₁₀ shows relatively

small variations between the allergens; thus, a general relationship between the sensitization potency and the elicitation capacity of an allergen cannot be expected. The result might be different if we had studied the least sensitive part of the sensitized population. This would be of scientific interest, but less relevant in terms of preventive measures, as the most sensitive part of the population also has the highest risk of allergic contact dermatitis. An explanation of this relatively small variation in ED₁₀ could be that when individuals are already sensitized, then the specific memory towards the allergen is already generated, so the dose needed to stimulate the immune system might be similar for different allergens. Sensitization studies with a potent allergen, dinitrochlorobenzene (DNCB), have shown that a high induction dose of allergen leads to highly sensitized individuals, in whom the dose of allergen needed to elicit will be low (3). It may be that those individuals identified by the ED₁₀ have been induced by such a high dose of allergen. However, recent studies have shown that repeated low-dose exposure has at least the same induction capacity as one single high dose (40, 41).

A range of factors will influence the elicitation dose under real-life circumstances, such as product composition, for example other allergens (42, 43), region of application (44, 45), number of applications (10, 18, 21), occlusion (18, 20), and exposure duration (16). An equation for conversion between patch test thresholds and ROAT thresholds is available (46), and the relationship between the patch test dose-response relationship and the ROAT dose-response relationship is expected to be approximately 0.03 for non-volatile compounds, so, upon repeated open exposure to allergens, the threshold is lower than in the patch test.

In conclusion, we found a rather small variation in the elicitation doses between the allergens, for the most sensitive part of the allergic population, and no clear relationship between induction potency and elicitation threshold for a range of allergens. This means that persons already sensitized will not be protected by exposure limitations based on sensitization thresholds, for example derived from animal assays. It therefore seems that elicitation doses for the most sensitive part of the population are fairly similar across different allergens. This knowledge may stimulate thoughts on introducing a generic approach for limitations in exposure to allergens that already have caused significant problems of allergic contact dermatitis for consumers or in the workplace.

This would also simplify the process of primary, secondary and tertiary prevention.

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