

Thresholds of elicitation depend on induction conditions. Could low level exposure induce sub-clinical allergic states that are only elicited under the severe conditions of clinical diagnosis?

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Abstract

While numerous studies have examined dose/response relationships occurring in the experimental induction of contact allergic dermatitis, fewer have examined the effects of varying the doses of both induction and challenge. Recently published studies have however done this and they all show the same remarkable observation: the threshold of elicitation decreases as the doses used to induce the allergy increase. This has important implications. One is that it may be more complicated to determine clear threshold doses below which allergic responses are not seen. It is also proposed that normal exposure to weak allergens such as some fragrance materials may induce “sub-clinical” allergic states which will not be elicited under these same exposure conditions but which may become apparent under the more severe conditions of clinical diagnosis. This may explain why the prevalence of Patch test reactions to some fragrance materials is apparently increasing in the absence of any clearly documented “epidemic” of consumer complaints. © 2004 Elsevier Ltd. All rights reserved.

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1. Introduction

Most toxicological effects follow a dose–response relationship and have a threshold dose below which no significant effects are seen. This dose is generally an intrinsic property of the chemical substance and relates to the way it acts on the organism relative to the organism’s ability to defend itself in one way or another against this substance’s effect. Cell-mediated (Type IV) contact allergy is no exception (e.g. Marzulli and Maibach, 1974; Basketter et al., 1997; Boukhman and Maibach, 2002; Roggeband et al., 2001). There are experimentally observable threshold doses below which the allergic state is not induced and also, once subjects

have been sensitized, there are also threshold doses below which the allergic state is not clinically elicited.

However, unlike most other toxicological thresholds that seem to be intrinsic properties of the toxic agent, there is increasing evidence to show that this *elicitation threshold* depends on factors that are additional to the intrinsic allergenic potency of the substance. Indeed, it would seem that the severity of the induction regime (i.e. the severity of the conditions under which allergy has been acquired) has an important influence over the threshold of elicitation.

2. Published evidence

The first clear evidence for this effect was probably provided by Chan et al. (1983) who demonstrated that the challenge dose concentrations necessary to elicit reactions in any given proportion of animals to the

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chloromethylisothiazolinone/methylisothiazolinone biocide in a Buehler Guinea Pig test, were inversely proportional to the concentrations used to experimentally sensitize them in the first place. A similar trend was seen in the testing of Tinuvin P in a modified Guinea Pig Maximization test (Yamano et al., 1993). In studies on human subjects, Friedmann and Moss (1985) demonstrated that the induction dose determines not only the proportion of subjects sensitized but also the intensity of the allergic response at challenge. In studies on three groups of volunteers who were experimentally sensitized by exposure to three doses of dinitrochlorobenzene, the increase in skin-fold thickness at challenge to three increasing doses gave three parallel dose response curves. When all three groups were challenged to the same three doses, the curve for subjects sensitized to $62.5 \mu\text{g}/\text{cm}^2$ was lower in terms of skin-fold thickness, than that for the subjects sensitized by induction to $500 \mu\text{g}/\text{cm}^2$ that in turn was lower than (and parallel to) that for those sensitized to $1000 \mu\text{g}/\text{cm}^2$.

Nakamura et al. (1999) were probably the first to show a clear numerical relationship between the induction dose and the observed threshold of elicitation. Although this study was primarily aimed at comparing the Guinea Pig Maximization test, the Adjuvant and Patch test and the Buehler test, it provides valuable data on this relationship involving threshold doses. The results (Appendix A) of these three tests on four substances show uniformly that as the induction dose increases, the subsequent threshold of elicitation decreases.

van Och et al. (2001) also performed similar studies on three chemicals using the Guinea Pig Maximization test (Appendix B). Here too the same trend was seen in each case.

Scott et al. (2002) have carried out studies on mice on two substances. Challenge was made on the flanks of the animals and despite the moderate degree of biological variation one would expect in this type of study, the threshold of elicitation (measured as the challenge dose which produced significant increase in flank-fold thickness) also showed the same dependence on the induction concentration. The results were presented graphically in this paper and hence it is not possible to reproduce them numerically in the appendices.

One of the earliest studies in this area (Jayjock and Lewis, 1992) was performed on the chloromethylisothiazolinone/methylisothiazolinone biocide. Although criticized for the low number of animals used (Basketter et al., 1997), these Buehler test results (Appendix C) reinforce the other studies reviewed above.

Other studies using a modified Guinea Pig Maximization test have also shown the same trend. Most notably these were the studies carried out on PTBS (*p-t*-butylphenylsalicylate) (Yamano et al., 1995) (Appendix D), on TPN (2,4,5,6-tetrachloroisophthalonitrile) and BIT

(1,2-benzisothiazolin-3-one) (Noda et al., 1998) (Appendix E) and on IPBC (3-iodo-2-propynylbutylcarbamate) and CPIP (*p*-chlorophenyl-3-iodopropargylformyl) (Shimizu et al., 2000) (Appendix F).

3. Conclusions

Separate studies (most aimed at studying other effects) reveal that the threshold for elicitation is not a constant property of an allergen. Remarkably, this effect is seen across species in Guinea pigs, mice and humans in a number of different allergens. Although each of these studies may be criticized individually because of the small numbers of test subjects and limited number of data points, when taken together they make an imposing case in support for the hypothesis that elicitation thresholds vary according to the severity of the induction regime. This has important implications. One is that it may be difficult to determine clear threshold doses that will not elicit allergic responses. This is especially true when attempts to determine these doses are based on experimental studies using a fixed induction regime or on clinical studies taking a sample of patients who have been sensitized under unknown circumstances.

This hypothesis is an opinion and meant to stimulate thought and experiments to either refute or support.

4. Further hypotheses with regard to fragrance ingredients

For laudable reasons, dermatologists have been using exposure conditions in patch testing that are far more severe than the exposure conditions that were thought to have caused the allergy from which the patient is suffering. This approach has been rewarded. Even when false positive reactions due to irritancy, excited skin, etc. are excluded, more positive reactions are obtained than if more “realistic” patch testing conditions had been used.

The relative severity of patch testing can be seen by comparing doses. For instance, an ingredient used at 1% in the product-type that produces the highest on-skin level of fragrance: a perfume spray would give rise to a dermal loading of $26 \mu\text{g}/\text{cm}^2$ (Gerberick et al., 2001). Yet the use of diagnostic Patch tests with 1% of the same ingredient in 19 mm Hill Top Chambers® will deliver a skin loading of $1770 \mu\text{g}/\text{cm}^2$ (Robinson et al., 2000), a 68-fold increase. The use of 2×2 cm Webril® patches, 8 mm Finn Chambers® and a Professional Products® 1.9×1.9 cm patch would result in 38-fold, 11-fold and 21-fold increases, respectively (Robinson et al., 2000). To this we should add the (dose-enhancing) potentiating effects of occlusion (numerous publications

including Kraus et al., 1990; Calvin and Menné, 1993; Ale and Maibach, 1995; Funk and Maibach, 1994; Zhai and Maibach, 2001) and the exceptionally long duration of the 48 h exposure compared to normal exposure (McFadden et al., 1998). Increasing use of use-tests with more realistic concentrations over the coming years may give greater insight into diagnosis.

Several articles (e.g. Boukhman and Maibach, 2002) have mentioned the possibility that there may be a good deal of *sub-clinical* allergy which will never manifest itself under normal exposure conditions and hence is a truly benign, non-disease state.

As we have seen, there would seem to be convincing proof that the threshold of elicitation depends on the severity of the induction conditions. If these conditions are not severe, the elicitation threshold may be so high that the allergy will only manifest itself under quite severe conditions.

If, after all, exposure to the weak allergens used in fragrances in cosmetics and other consumer products, constitutes a rather non-severe induction regime, then we can expect elicitation thresholds to be high. Under normally encountered conditions of exposure to these products, these thresholds may in fact be too high to produce allergic reactions in most consumers. Yet these thresholds are maybe not high enough to prevent reactions occurring under the more severe conditions used by dermatologists.

We do not wish to overemphasize; too minimal data exists to permit this data to be more than a hypothesis with many possible limitations.

This would explain the dramatically increasing prevalence figures from the clinics in the absence of any apparent “epidemic” of consumer complaints. This could also explain other observations such as why fewer patients reacted to the Fragrance Mix at 8% than at 16% (Santucci et al., 1987; Frosch et al., 1995) and why dermatologists frequently obtain positive Patch test reactions to multiple “allergens” that would seem to have played no causative role in the patient’s allergy. In other cases, it would seem unlikely that all fragrance allergens which give positive reactions (sometimes well over 10 different fragrance materials are positive, see for instance Meynadier et al., 1986) have played a role in the etiology of the patient’s condition.

Some recent publications have presented evidence that some fragrance allergens can have very low elicitation thresholds in some individuals. In serial dilution Patch tests the lowest observed elicitation doses were 0.009 ppm ($\approx 0.003 \mu\text{g}/\text{cm}^2$) for chloratranol (Johansen et al., 2003b), below 29 ppm ($\approx 0.9 \mu\text{g}/\text{cm}^2$) for hydroxyisohexyl 3-cyclohexene carboxaldehyde (Johansen et al., 2003b), 1.2 ppm ($\approx 0.03 \mu\text{g}/\text{cm}^2$) for hydroxycitronellal (Svedman et al., 2003), 20 ppm ($\approx 0.58 \mu\text{g}/\text{cm}^2$) for cinnamic aldehyde (Johansen et al., 1996a,b) and 5 ppm ($\approx 0.030 \mu\text{g}/\text{cm}^2$) for isoeugenol (Johansen et al.,

1996b). The same studies have shown that a large proportion of the same patients have also reacted to low doses in Repeated Open Application Tests (ROATs). Although it is not known to what extent the elicitation thresholds in these patients were lowered by the combination of sequential patch and open applications (the rarity of reactions during the first days of ROAT testing is an empirical testimony to this “boosting” effect described by Friedmann (1990)), the above hypothesis is not intended to be a generalization. If anything, the studies on sensitized patients cited above, have clearly demonstrated the widely ranging degrees of sensitivity that can be seen in patients. The causative allergens to which patients have become highly sensitized through environmental or consumer product exposures, will continue to be detected by appropriate clinical patch testing. The question raised here is whether this patch testing is not also detecting allergens to which patients have acquired only a low level of sensitivity.

In the case of chloratranol, one sensitizer of oak moss, 12/13 subjects developed a positive ROAT at 5 ppm in less than one week (Johansen et al., 2003a,b). A standard validated analytical method for quantifying this substance has not been found. First indications are that the level of chloratranol can vary significantly in different oakmoss extracts. Similar results were found with hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall) (Johansen et al., 2003a,b; Svedman et al., 2003). In this study 11/18 developed a positive ROAT within two weeks at a concentration of 0.5% which is far below the recommended IFRA limit of 1.5% and what was found in commercial products. Note that this data refers to use testing, i.e. elicitation, and not induction, as no data exists for the latter.

As a final point, the apparent increase in the incidence of positive Patch test reactions to fragrance materials, although far from being epidemiologically significant (Naldi, 2002), should not be ignored even if many of these reactions may in fact reflect allergic conditions that are only manifested during diagnostic patch testing. Such increases could still indicate potentially dangerous trends and merit risk management procedures aimed at restricting exposure. The benefits of restrictive procedures can be directly seen in trends in the incidence of positive Patch tests (Wesley and Maibach, 2003) and in particular in fragrances, the decreases in the incidence of reactions to some materials restricted by the International Fragrance Association have showed significant decreases over time, while other fragrance materials have not (Buckley et al., 2000).

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Appendix A. Nakamura et al. (1999)*A.1. DNCB (2,4-dinitrochlorobenzene)**A.1.1. Guinea Pig Maximization test*

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1	200	200
10	40	8
100	>40	8

A.1.2. Adjuvant and Patch test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
5	200	200
50	200	40
500	40	<8
5000	40	<8

A.1.3. Buehler test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
10	1000	–
100	200	–
1000	200	200
10,000	40	40

*A.2. Maleic anhydride**A.2.1. Guinea Pig Maximization test*

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1	10,000	–
10	<10,000	–
1000	<10,000	

A.2.2. Adjuvant and Patch test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
100	>100,000	–
1000	10,000	<10,000
10,000	<10,000	<10,000

A.2.3. Buehler test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
10,000	>100,000	–
100,000	>100,000	>100,000
500,000	10,000	10,000

*A.3. Hexylcinnamic aldehyde**A.3.1. Guinea Pig Maximization test*

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1000	>100,000	>100,000
10,000	<10,000	<1000

A.3.2. Adjuvant and Patch test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1000	>100,000	>100,000
10,000	10,000	10,000
100,000	10,000	1000
1,000,000	<10,000	<1000

A.3.3. Buehler test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
500,000	>100,000	10,000
1,000,000	<100,000	10,000

*A.4. DDSA (2-dodecen-1-yl succinic anhydride)**A.4.1. Guinea Pig Maximization test*

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
No. NOELs found		
10	10,000	–
100	1000	–

A.4.2. Buehler test

Dermal induction dose	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1000	10,000	–
10,000	10,000	1000
100,000	10,000	100

A.4.3. Adjuvant and Patch test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1	>10,000	23
10	10,000	–
100	1000	–

A.4.4. Buehler test

Dermal induction dose (ppm)	Challenge threshold dose (ppm)	Rechallenge threshold dose (ppm)
1000	10,000	–
10,000	1000	1000
100,000	1000	100

Appendix B. van Och et al. (2001)**B.1. DEA (diethylamine)**

Intradermal induction (%)	Topical induction (%)	Threshold at challenge (48 h) (%)
0.01	0.3	10
0.03	1	10
0.1	3	<3

B.2. TMTD (tetramethyl thiuram disulfide)

Intradermal induction (%)	Topical induction (%)	Threshold at challenge (48 h) (%)
0.01	1	10
0.03	3	3
0.1	10	<3

B.3. ZDMC (zinc dimethyl dithiocarbamate)

Intradermal induction (%)	Topical induction (%)	Threshold at challenge (48 h) (%)
0.01	1	<3
0.03	3	<3
0.1	10	10

Appendix C. Jayjock and Lewis (1992)

Induction concentration (ppm)	Threshold at challenge (ppm)	Dose producing reactions in less than 10% animals (ppm)
25–28	750	>2000
50	100	200–300
100	<100	100
275	<100	100
450–500	100	100
700–800	<100	200–300
900–1000	100	100
2000	20–25	20–25

Appendix D. Yamano et al. (1995)

PTBPS (*p*-*t*-butylphenylsalicylate) (modified Guinea Pig Maximization test)

Intradermal induction (%)	Topical induction (%)	Threshold at challenge (48 h) (%)
0.005	25	5
0.05	25	0.5
0.5	25	0.005
5.0	25	0.005

Appendix E. Noda et al. (1998)

E.1. TPN (2,4,5,6-tetrachloroisophthalonitrile) (modified Guinea Pig Maximization test)

Intradermal induction (ppm)	Topical induction (%)	Threshold at challenge (48 h) (ppm)
0.005	5	0.5
0.05	5	0.5
0.5	5	0.05
5.0	5	0.05
50	5	0.05

E.2. BIT (1,2-benzisothiazolin-3-one) (modified Guinea Pig Maximization test)

Intradermal induction (%)	Topical induction (%)	Threshold at challenge (48 h) (%)
0.005	25	0.005
0.05	25	0.05
5.0	25	0.0005

Appendix F. Shimizu et al. (2000)

F.1. IPBC (3-iodo-2-propynyl butylcarbamate) (modified Guinea Pig maximization test)

Intradermal induction (ppm)	Topical induction (%)	Threshold at challenge (48 h) (ppm)
0.5	25	>500
5	25	100
50	25	50
500	25	50

F.2. CPIP (p-chlorophenyl-3-iodopropargylformyl) (modified Guinea Pig Maximization test)

Intradermal induction (ppm)	Topical induction (%)	Threshold at challenge (48 h) (ppm)
0.5	25	100
5	25	5
50	25	5
500	25	5

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