ENZYMES:

Lack of Skin Sensitisation Potential

Introduction

European legislation requires that substances are evaluated so that (toxicological) hazards associated with them can be identified and suitable warnings provided via labeling to the users of these substances. It is recognised that enzymes are potential respiratory allergens and should be classified, in the context of the Dangerous Substances directive (92/32/EEC), as such and designated R42 "may cause sensitisation by inhalation'. However it has also been suggested that enzymes might need to have an accompanying hazard classification related to a potential to cause skin sensitisation (allergic contact dermatitis) designated by the use of R43 "May cause sensitisation by skin contact".

Since the 1930's, enzymes have been marketed and a wealth of experience is available. This involves animal tests, human predictive tests, clinical studies and employee and consumer monitoring. Most of the published literature refers to respiratory allergy. The purpose of this document is to review the evidence for the skin sensitisation potential of enzymes, including both published and unpublished data to assess whether such a hazard exists.

I) Scientific Background on Skin Sensitisation

Skin sensitisation, referred to as allergic contact dermatitis (ACD) in a clinical setting, is a cell mediated type IV delayed hypersensitivity. The cellular mechanisms involved have been reviewed recently (Scheper and von Blomberg, 1992, Kimber,1994).

To behave as a skin sensitiser, a substance must first penetrate the stratum corneum, partition into the epidermis and there react with proteins probably on the surface of the Langerhans cells, to form a hapten-carrier conjugate. This conjugate must then be processed and expressed in the context of MHC class II as it is then presented to T lymphocytes by the Langerhan cells in the draining lymph nodes. If recognised as foreign, it will give rise to a characteristic delayed allergic response which is dependent on TH1 lymphocytes. To fulfill these requirements, a substance will be of low molecular weight (normally < 400 D) and must be capable of reacting directly or indirectly with (cell surface) protein and produce a new antigenic determinant.

A single contact with a substance is not sufficient to cause ACD. First contact may initiate the immune response; more commonly multiple contacts are required for a significant immune response to develop. Only then will further contact with the substance give rise to the skin sensitisation reaction characteristic of ACD.

The clinical condition of ACD is not uncommon, with the major causes being metals, especially nickel, and the poison ivy/oak family (pentadecyl catechols). A very wide range of substances have been reported to cause ACD, including rubber chemicals, dyes, cosmetics, plant extracts, drugs, preservatives, plastics and resin monomer and industrial and pharmaceutical chemicals and intermediates (Cronin, 1980; Fisher, 1986; Rycroft et al, 1992). This is the phenomenon covered under R43.

However, there are other types of dermatitis in man, the most important being (non-immune) irritant contact dermatitis (ICD). In both occupational and nonoccupational settings, ICD is more prevalent than ACD (Frosch, 1992; Rycroft, 1992). This phenomenon is not covered by

R43. More details on ICD can be found in a new book devoted to this syndrome (Elsner and Maibach, 1995).

A much less common cause of dermatitis has been described as protein contact dermatitis, a type of contact urticaria (Hjorth and Roed-Petersen, 1976). Contact urticaria is a condition that is characterized by the appearance of swollen, red cutaneous elevation. Occasionally, this angioedema may occur in the dermis and subcutaneous tissue. The majority of contact urticaria is of non-immunologic origin, but a small proportion is Type I hypersensitivity mediated by IgE antibody. The disease and its epidemiology have recently been reviewed by Schafer and Ring (1993). This condition was recognised largely in the occupational context of food preparation and has a substantial skin irritation component (Cronin, 1987). Common causes are (shell) fish and vegetables. The constant wet work and exposure to surfactants can permit skin penetration of food proteins. In this case, protein may give rise to IgE mediated urticarial responses, typically having a time course of 30 minutes to 2 hours (Lahti, 1992). Although the potential to cause immunologic contact urticaria is not recognised as a basis for R43 classification, it is reviewed in more detail later in this document because of its relevance to proteins and thus to enzymes.

II) Enzymes

Animal Testing

To assess, in an animal model, the potential for a protein to cause skin sensitisation presents a difficult problem. Clearly, any foreign protein has the ability to cause an immune response, largely the formation of a specific antibody Thus, to assess potential to cause a T-cell mediated effect, it is vital to ensure the model is not biased towards B-cell responses. No animal model has been developed or validated for assessing proteins as contact skin sensitisers. This is also the conclusion of the US Environmental Protection Agency (US EPA subdivision M). In our experience all foreign proteins can be made to generate skin reactions in suitably treated animals, including in the OECD/EU recognised guinea pig maximization test and the Buehler test (unpublished data). The predominance of the antibody response in the guinea pig makes it impossible to discern to what extent, if any, a T cell mediated Type IV hypersensitivity reaction takes place. Consequently it is necessary to rely heavily on risk assessment and human experience.

Human Predictive Tests

The methods commonly used for assessing delayed contact skin sensitisation in humans (see Appendix 1 for details) have been :

1. Human Maximization test (Kligman, 1966).
2. Modified Draize test (Marzulli & Maibach, 1977).
3. Human Repeat Insult Patch Test (Stotts, 1980).

There have been a number of studies involving subtilisin protease (CAS No. 901401-1), alpha-amylase (CAS No. 9000-90-2) and cellulases (CAS No. 9012-54-8).
Specifically, a mix of subtilisin and amylase failed to cause skin sensitisation in modified Draize tests in three out of four studies involving 239 subjects. In a fourth study involving 138 subjects, no evidence of skin sensitisation was found in all volunteers which were appropriately followed-up. However, one volunteer who reacted at first challenge was not available for re-challenge to confirm whether their response was also irritant like the others. Eight studies have been performed with subtilisin, all of which on either challenge or on re-challenge were concluded to give no evidence of skin sensitisation. These studies

involved 249 subjects. Studies with alpha-amylase alone involving 183 volunteers and the one study with cellulase involving 25 volunteers did not give evidence of skin sensitisation. All results are given in Appendix 2. Overall these studies demonstrate that enzymes are not contact skin sensitisers.

This conclusion is supported by evidence from studies performed with detergents containing enzymes (Bannan et al, 1991; Griffith et al, 1969 and Rodriguez et al,1994), all of these studies showed that the presence of enzymes in the detergents did not result in contact skin sensitisation.

Clinical and general human experience Evidence

Most of the clinical evidence has been generated on proteases, amylases and cellulases as these have been widely marketed over many years (see Human Experience section).

a) Proteases

Whilst there is no doubt that some proteases (e.g. Subtilisin) can cause occupational dermatitis, clinical evaluation has demonstrated that this is of irritant, not allergic origin (Newhouse et al, 1970; Zachariae et al, 1972; McMurrain, 1970; Smith et al, 1989).

There are many instances of positive skin prick tests to proteases (Pepys et al, 1973; Pepys, 1992). However, it must be remembered that this test is purely a means to identify specific antibodies in the context of Type I hypersensitivity (e.g. respiratory sensitisation). It is not an indication of delayed contact skin sensitisation (Type IV hypersensitivity).

b) Amylases

In the food industry occupational dermatitis is common, especially hand eczema. This is normally cumulative irritant dermatitis. The important ,factors contributing to this are wet work and regular exposure to cleaning agents (Rycroft, 1992). This dermatitis is further complicated by exposure to food constituents from e.g. fish, shellfish and vegetables. When such irritant dermatitis severely compromises the skin barrier, proteins from the food can penetrate the skin giving rise to an antibody mediated response (Type I hypersensitivity). This problem has been recognised as the protein contact dermatitis syndrome referred to earlier (Hjorth and Roed-Petersen, 1986).

On two occasions (3 patients), amylases have been associated with allergic contact dermatitis (Schirmer et al, 1987; Morren et al, 1993) however no causal relationship was demonstrated. Given that neither of these reports provides substantive evidence of skin sensitisation and that amylases have been used very widely for several decades, these enzymes should not be considered skin sensitisers.

c) Cellulase

There is only one case reported in the literature where a hand eczema has been connected with a positive allergic patch test (Tarvainen et al, 1991) This subject also exhibited symptoms of IgE mediated allergy, was skin prick test positive and atopic. It is interesting to note that the mild hand eczema did not resolve when the subject was absent from work, suggesting factors other than cellulase might have played a role. Given that cellulases have been widely handled over many years, one reported case is not sufficient for cellulases to be considered skin sensitisers.

Human Experience with enzymes

Particularly in the early years of protease manufacture, exposure of worker to enzymes was relatively uncontrolled and this resulted in a significant incidence of dermatitis. A large group of such individuals were examined and patch tested with enzyme. None showed an allergic patch test response and it was concluded that all the occupational dermatitis was due to primary irritation (Zachariae et al, 1973). To date, we are not aware of a single case of allergic contact dermatitis in the enzyme producing industries.

In the detergent industry, the main focus has been on respiratory allergy, a risk which is now firmly under control. The monitoring procedures associated with this demonstrate that workers may be exposed, but that there has never been any report of skin sensitisation due to enzyme exposure from Occupational Health Departments (unpublished data, Henkel, Procter & Gamble, Unilever). This covers a period of 25 years with tens of thousands individuals exposed. This experience is in agreement with the conclusions of Goethe et al, 1972, who investigated medical problems in the detergent industry and the National Research Counci report published in 1971 which investigated both workers in the detergent industry and consumers, and found no cause of concern of contact skin sensitisation due to enzymes.

Enzymes have been widely used in many industries with varying degrees of skin exposure (first reported use in 1913 - Griffith et al, 1969). These industries include starch processing, brewing, distilling, baking, animal feed, sewage treatment, textile, pharmaceutical, paper, detergent, cheese manufacture, leather treatment, cosmetics and food and drink processing. The absence of any significant incidence of occupational allergic contact dermatitis to enzymes in these industries leads inevitably to the conclusion that enzymes are not contact skin sensitisers.

The most widely documented consumer exposure to enzymes is through the use of fabric washing detergents. Over a 25 year period, billions of consumers have had skin exposure to enzymes through handwashing of fabrics. Whilst the exposure levels are lower than in most occupational settings, skin exposure may be widespread, prolonged and repeated. There is no evidence that this exposure to enzymes gives rise to skin sensitisation. Furthermore, in a detailed investigation of 255 individuals with possible adverse reactions to washing powders containing enzymes, there were no positive patch test reactions to enzymes (White et al, 1985). This reconfirms the conclusions published in the National Research Council, Washington report in 1971.

Protein Contact Dermatitis

The existence of protein contact dermatitis as an entity was first realised in 1976 by Hjorth and Roed-Petersen (1976). They demonstrated that skin contact with protein, in an occupational setting, could give rise to an allergic dermatitis. The major problem was food proteins. The susceptible group was atopic individuals working in the food industry who had existing hand eczema. This initial description was quickly followed by others who recognized the potential skin problems associated with the penetration of damaged skin by foreign protein (Nutter, 1979, Forstrom, 1980, Janssens et al., 1995). In essence the syndrome being described is that of contact urticaria, probably of immunological origin (antibody mediated), superimposed upon a pre-existing irritant dermatitis, usually hand eczema. The importance of this syndrome, notable in the catering industry, has been reviewed (Rycroft, 1994). However, it is not clear whether repeated intact skin contact with a foreign protein will lead to the formation of specific IgE (homocytotropic) antibody. What is clear is that

immunologic contact urticaria may occasionally occur after skin exposure to the foreign protein in a sensitised individual.

Often, occupational exposure to foreign proteins (e.g. food industry, latex) can occur via several routes: respiratory, mucosal, skin. Induction of sensitisation can occur by any of these routes, however the role of dermal contact in this process is not very clear. What is clear is that immunologic contact urticaria can occur in a sensitised individual after skin exposure to the foreign protein. Therefore, it is important to realise that the route of exposure which induces specific IgE formation need not be the same as that by which clinical responses are elicited. In the case of enzymes, the most likely route of primary sensitisation is via the respiratory tract.

The most recent expression of protein allergy, including contact dermatitis, which is " hitting the headlines" is latex hypersensitivity. This subject has received much attention and has been reviewed recently (Hamann, 1993). In brief, the trace levels of protein(s) in natural rubber extracts have been clearly implicated as the cause of an increasing incidence of latex hypersensitivity. This is expressed as an increase in immediate, delayed and anaphylactic reactions to contact with latex. In these cases, mucosal and intraoperative procedures present the highest risk levels, whilst atopy and hand eczema are important predisposing factors for latex protein sensitisation. At particular risk are health care personnel and others whose occupation requires frequent and prolonged wearing of latex gloves. Again, exposure to latex proteins can occur via multiple routes e.g. the wearing of surgical gloves involves not only skin contact but also the generation of inhalable latex protein/dust. Thus it is not clear whether skin contact is responsible for the induction of sensitisation to latex protein. However it is evident from the literature that elicitation of contact urticaria can occur after skin contact with latex protein.

What are the key conclusions? Firstly foreign protein represents an immunological challenge to which the human immune system will respond, via antibody formation. Secondly, it is not clear from the clinical literature or from investigative literature, what role skin contact may play, if any, in the induction of sensitisation to foreign proteins. If skin contact caused sensitisation then the phenomenon should results in the R43 classification. We do consider that once sensitised, skin contact with protein allergen can elicit urticaria in some individuals, notably those with damaged skin. These responses may be in the form of a transient urticaria, but for certain individuals they can also contribute to more persistent dermatitis, especially that associated with the hands. In the light of the above considerations, it is important to be aware that this potential risk can also be associated with enzymes. However this is no different from the potential risk which could be associated with any foreign protein. It is our experience that the use of enzymes both in the workplace and by consumers has not led to a significant incidence of immunologic contact urticaria. The limited clinical case reports discussed above demonstrate that under sufficiently adverse conditions the problem can arise, although this seems to be only elicitation of responses in individuals sensitized by the pulmonary route. In view of this the appropriate risk management is that which will be dictated by the R42 classification.

III) Conclusions

After review of all the available evidence we conclude that enzymes should not be classified as skin sensitisers in the context of the Dangerous Substances directive and thus the use of R43 would not be justified. This conclusion is based on the following considerations:

1 The results of predictive testing in man demonstrate that enzymes do not have a significant skin sensitisation potential for man.

2. In a clinical setting, enzymes have only very rarely been suggested as a possible cause of allergic contact dermatitis. Even in these few cases a causal relationship has never been proven. More commonly clinical studies have demonstrated that enzymes are not a cause of ACD.

3. ACD has never been reported where there has been extensive occupational enzyme exposure in the detergent enzyme industries which, in the past, has led to respiratory sensitisation and/or irritant dermatitis.

4. Over a 25 year period, billions of consumers have had skin exposure to enzymes but there is no evidence that this exposure has given rise to skin sensitisation.

5. Whilst immunological contact urticaria (ICU) is not involved within the R43 skin sensitisation classification, enzymes like all other foreign proteins may cause this response. However ICU to enzymes will be controlled by minimising primary sensitisation by the inhalation route via the classification as R42.

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Appendix 1

Human Maximization test

This test was described in detail by Kligman (1966) as a rigorous and sensitive predictive assay for the identification of sensitization potential of chemicals. Further commentary was made on the technique some 9 years later (Kligman and Epstein, 1975). A group of 25 subjects is subjected to repeated 48 hours occlusive patch treatment with as high a concentration of a test chemical as possible on five occasions over a two week period. If the substance is not sufficiently irritating, the irritancy is enhanced by prior treatment of the site for 24 hours with sodium lauryl sulphate before each 48 hour patch. The extent of sensitization in the panel is assessed by 48 hours occluded patch challenge one week after completion of the 5 induction treatments on a slightly irritated skin site using the maximum non-irritant concentration of the test substance. The challenge sites are scored at 48 hours and 96 hours post application. The original publication (Kligman, 1966) which reports details of test results on about 90 chemicals of widely varying. sensitisation potential amply demonstrates the sensitivity of the protocol. In essence, this procedure can provide a stringent assessment of intrinsic sensitisation hazard and its relative potency. However, its practical application is limited by ethical considerations.

Repeated Insult Patch Tests (Human Repeat Insult Patch Test and Modified Draize)

In the HRIPT, generally 80-120 test subjects are employed (Stotts, 1980). The induction phase includes nine 24 hour patches at a single site with a 24 hour rest between patches (48 hours on weekends). In contrast the modified Draize protocol (Marzulli and Maibach, 1977) requires nine 48 hour patchers at a single site with no rest period between patches (72 hours on weekends). The concentration of material tested is determined by integrating the following factors: prior sensitisation test results, the assessment of skin irritation in repeated application patch studies in humans, the desire to exaggerate the exposure relative to anticipated normal use/misuse exposure (if irritancy considerations permit) and prior experience. It is often preferred that a material be tested at the highest minimally irritating concentration as determined in a human irritation screen. After induction, there is then a 14-17 day rest, followed by a 24 hour challenge patch for the HRIPT and 48 hour patch for the Modified Draize. In general, skin reactions are scored during induction (just prior to patch reapplication) and 24 and 72 hours after challenge patch removal, although scores from 48 hours, 96 hours, and even longer intervals after challenge may be included. Contact sensitisation reactions are generally characterized by erythema along with various dermal sequelae (e.g. edema, papules, vesicles, and bullae). A characteristic sensitisation response that occurs and persists during challenge is considered indicative of sensitisation and should be confirmed by appropriate re-challenge. The persistence of any challenge reaction, the delayed scoring, and the re-challenge procedure maximize the sensitivity and reliability of the test procedure.

Appendix 2

Human Studies performed by NOVO-Nordisk with Subtilisin CAS No. 9014-01-1

Study	Participants No.	Test Method	Conclusions	Date of Study
Human Maximization Test (Kligman, 1966)	25	Induction – 0.25% Challenge – 0.25%	Test sample (0.25%) did not elicit or induce allergic contact dermatitis.	1977
Human Maximization Test (Kligman, 1966)	25	Induction – 0.25% Challenge – 0.25%	Test sample (0.25%) did not elicit or induce allergic contact dermatitis.	1977
Human Maximization Test (Kligman, 1966)	25	0.3g material (concentration unknown)	Test sample (0.3g) did not induce or elicit allergic contact dermatitis.	1978
Human Maximization Test (Kligman, 1966)	24	Induction – Enzyme liquid at 0.1, 0.2, 0.3, 0.5, 1.0, 1.5 and 2.0% Challenge – Enzyme liquid at 0.3 and 0.5%. Enzyme concentrate at 0.07%	The test sample under protocol conditions did not elicit or induce allergic contact dermatitis. One volunteer was followed up with a re-challenge which was negative.	1981
Human Maximization Test (Kligman, 1966)	34	Induction – 0.25% Challenge – 0.01, 0.025, 0.1 and 0.25%	The test samples under protocol conditions did not elicit or induce allergic contact dermatitis. Two volunteers were followed up with re-challenge patch tests which were negative.	1982

Appendix 2

Study	Participants No.	Test Method	Conclusions	Date of Study
Human Repeat Patch Test (Kligman, 1966)	53	Enzyme alone Induction – 0.1% Challenge – 0.01, 0.02, 0.04 and 0.1% Enzyme in detergent Induction – 0.04% Challenge – 0.04, 0.08, 0.16 and 0.4%	The test samples under the protocol conditions did not elicit or induce allergic contact dermatitis.	1979
Human Repeat Patch Test (Kligman, 1966)	41	Induction – 0.4% reduced to 0.3% following some irritation. Challenge – 0.04, 0.08, 0.16 and 0.32%	The test sample under the protocol conditions did note elicit or induce allergic contact dermatitis. One subject was followed up with a rechallenge patch test which was negative.	1980
Human Repeat Patch Test (Kligman, 1966)	22	Induction – Enzyme liquid at 0.1, 0.2, 0.3, 0.5 and 1.0% Challenge - Enzyme liquid at 0.3 and 0.1%. Enzyme concentrate at 0.036%	The test sample under the protocol conditions does not elicit or induce allergic contact dermatitis. One subject was followed up with a re-challenge patch test which was negative.	1981

Appendix 2

Human Studies -performed by Genencor International with a mix of Subtilisin CAS No. 9014-01-1 and Alpha-amylase CAS No 9000-90-2

Study	Participants No.	Test Method	Conclusions	Date of Study
Human Modified Draize Test (Marzulli & Maibach, 1977)	42	Induction – 7.5% reduced to 2.5% because of irritation Challenge – 1.0%	Test sample (2.25%) did not elicit or induce allergic contact dermatitis.	1989
Human Modified Draize Test (Marzulli & Maibach, 1977)	153	Induction – 2.5% Challenge – 1.0%	Test sample (2.25%) did not elicit or induce allergic contact dermatitis. Three subjects were followed up on rechallenge and a further two had a subsequent rechallenge and were found to be negative.	1989
Human Modified Draize Test (Marzulli & Maibach, 1977)	44	Induction – 7.5% reduced to 2.5% because of irritation Challenge – 1.0%	Test sample (2.25%) did not induce or elicit allergic contact dermatitis. Five subjects were re-challenged and found to be negative.	1989
Human Modified Draize Test (Marzulli & Maibach, 1977)	138	Induction – 2.5% Challenge – 1.0%	The test sample under protocol conditions did not elicit or induce allergic contact dermatitis in all volunteers who were followed up. One volunteer was not rechallenged.	1989

Appendix 2

Human Studies performed by NOVO-Nordisk with Alpha-amylase CAS No 9000-90-2

Study	Participants No.	Test Method	Conclusions	Date of Study
Human Maximization Test (Kligman, 1966)	25	No information on concentration was available	Test sample (0.25%) did not elicit or induce allergic contact dermatitis.	1978
Human Maximization Test (Kligman, 1966)	25	Induction – 0.25% Challenge – 0.25%	Test sample (0.25%) did not elicit or induce allergic contact dermatitis.	1978
Human Repeat Insult Patch Tests (Stotts, 1980)	81	Induction – 1.0, 2.5, 5.0 and 10.0% (10% concn. after six patches was reduced to 0.5%) Challenge – 1.0%	Test sample (0.3g) did not induce or elicit allergic contact dermatitis.	1983

Human Studies performed by NOVO-Nordisk with Cellulase CAS No 9012-54-8

Study	Participants No.	Test Method	Conclusion	Date of Study
Human Maximization Test (Kligman, 1966)	25	No information supplied on concentration tested	Test sample (0.25%) did not elicit or induce allergic contact dermatitis.	1978

GLOSSARY OF TERMS

ALLERGEN:
An antigen responsible for inducing allergic reactions.

ALLERGIC CONTACT DERMATITIS (ACD):
A cell mediated immunological response to chemicals with a molecular weight generally less than 1000 that contact and penetrate the skin

ALLERGY:
An adverse reaction mediated by an immune response usually due to an exogenous substance.

ANAPHYLAXIS:
An immediate hypersensitivity reaction, sometimes fatal, occurring in sensitized individuals following re-exposure to an allergen, which results in vasodilation and constriction of smooth muscle, including that of the bronchi.

ANGIOEDEMA:
Swelling of the blood vessels

ANTIBODY:
A protein of the immunoglobulin class produced by plasma cells in response to an antigen which has the ability to combine specifically with the antigen that induces its formation.

ATOPIC:
Having a genetic predisposition to develop Type I hypersensitivity.

B LYMPHOCYTE (B-CELL):
Lymphocytes which express membrane immunoglobulins and are the precursors of antibody forming plasma cells.

CELL-MEDIATED IMMUNITY:
An immune response mediated by antigen specific lymphocytes.

ENZYME:
A protein with catalytic activity.

EPIDERMIS:
The outer layer of the skin which constantly regenerates the stratum corneum.

HAPTEN:
A chemical capable of binding with antibody when associated with a carrier protein but which on its own is unable to stimulate an immune response.

HAPTEN CARRIER:
A protein which a hapten must be associated with in order to induce an immune response.

HAZARD:
A toxic effect, in this context a sensitizing effect occurring as a consequence of exposure.

HOMOCYTOTROPIC ANTIBODIES:

Antibodies which bind to cells in animals of same or similar species in which they were produced.

IMMUNOGLOBULIN E (IgE):
The major anaphylactic antibody in man and mice.

IRRITANT CONTACT DERMATITIS:
Non-immunological inflammatory reaction in skin resulting in eczema.

LANGERHAN CELLS:
The antigen presenting cell of skin.

MHC:
Major Histocompatibilty Complex

SENSITIZATION :
An immune status resulting from an immune response to antigen which may result in a clinical hypersensitivity reaction, following a subsequent exposure to the same antigen.

SKIN PRICK TEST:
A direct skin test to detect IgE antibody.

STRATUM CORNEUM:
The outer layer of the skin.

T LYMPHOCYTE (T-CELL):
A thymus-derived lymphocyte which participates in a variety of cellmediated immune reactions.

TH I LYMPHOCYTES:
The subset of T lymphocytes responsible for Type IV delayed hypersensitivity

TYPE I HYPERSENSITIVITY:
A type I hypersensitivity reaction results from the interaction between antigen and antibody (normally IgE) bound through specific receptors to the surface of mast cells or basophils. The interaction between antigen and antibody on the cell surface results in an immediate release of pharmacological mediators (e.g. histamine) which may induce clinical symptoms (e.g. hayfever, urticaria, etc.).

URTICARIA:
A weal and flare reaction in skin which is normally transient