

Enzymes, detergents and skin: facts and fantasies

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Summary

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In their raw state, enzymes of bacterial/fungal origin cause allergic reactions in the lung. Proteolytic enzymes also cause irritation to skin, eyes and the respiratory tract. For 40 years, encapsulated enzymes have been used worldwide in detergent products, especially laundry formulations, and have increasing importance due to biodegradability and functionality at low temperatures, offering environmental benefits. Uniquely to the U.K., for years it has been suggested that the inclusion of enzymes in such products leads to adverse skin reactions, including erythema, pruritus and exacerbation of eczema. In this review, we look at the facts, asking whether there is evidence that the hazards identified for enzymes translate into any risk for consumer health. By considering the actual exposures in consumer use and exaggerated product usage, it is concluded that the irritating and allergenic hazards of enzyme raw materials do not translate into a risk of skin reactions, either irritant or allergic. Investigations of numerous individuals with skin complaints attributed to laundry products demonstrate convincingly that enzymes were not responsible. Indeed, enzyme-containing laundry products have an extensive history of safe use. Thus, the supposed adverse effects of enzymes on skin seem to be a consequence of a mythology. The important practical lesson is that when primary or secondary care practitioners are presented with a skin complaint, it should not be dismissed as a result of using an enzyme-containing laundry product as the diagnosis will certainly lie elsewhere. Education for healthcare professionals could usefully be enhanced to take this on board.

Processes for the cleaning of clothes (laundry) have been with mankind for millennia, but the use of soaps and detergents represents only a relatively recent step. 'Sunlight' soap (a surfactant made by alkaline saponification of long-chain fats), usually recognized as one of the first to be subject to large-scale production and marketing, was first manufactured in the 1880s, and heralded the new way to wash laundry, first in the U.K. and then over the next decades, in many countries in the world.¹ True soaps were then superseded by synthetic detergents (a range of types of surfactant often made from petrochemicals) during the mid-decades of the 20th century. However, the next big step change in cleaning came in the second half of that century with the introduction of proteolytic enzymes into laundry detergent products. Once the large-scale manufacture of enzymes which were stable in alkaline wash solutions and which were also resistant to the combination of relatively high temperature, the presence of oxidation systems and surfactants had been developed, this permitted

the removal of a variety of stubborn stains at increasingly low temperatures.² In the most recent decades, other enzymes classes have been incorporated, notably amylases and lipases, which further enhanced cleaning ability.³

The manufacturers of these enzyme-containing laundry detergents contend that their products are safe for the consumer; indeed, they should not place them on the market if this were not the case. However, it has long been recognized that the enzymes used in these products have the potential to produce respiratory allergy during manufacture, thus requiring very strict exposure control for the workforce.⁴⁻⁶ Additionally, proteolytic enzymes, the type most commonly used, have also been known to produce skin irritation, again occupationally.⁶ This is consistent with the observation of skin reactions to enzymes in other occupational settings, although some of these skin reactions may be urticarial as well as irritant.⁷ In the early period of marketing, some respiratory reactions were very occasionally seen in consumers.⁸ Particularly in the U.K.,

this background awareness of questions about allergy and irritation has translated into concern among some consumers and consumer groups that enzyme-containing detergents may be related to a variety of consumer skin complaints.⁹ Anecdotally at least, a similar view appears to be held by a variety of healthcare professionals. The purpose of this review is to investigate whether there is any truth behind these concerns. Are they factually based, or are they just fantasy?

Irritation

It has long been recognized that a combination of wet work and detergent/surfactant exposure can lead in many individuals to skin irritation, most often expressed as hand eczema.^{10–12} In this section, the evidence that normal consumer use of enzyme-based laundry detergents can lead to skin irritation is considered. Special attention is paid to whether there may be susceptible subpopulations who might be predisposed to the development of this effect.

As with all toxicological effects, clinical skin irritation arises from a combination of the hazardous properties of materials and exposure, in this case, skin exposure. The surfactants in laundry products are known to have the intrinsic ability to cause skin irritation. This can occur as a consequence of repeated exposures to the diluted solutions used during normal laundry procedure and can be simulated in suitable exposure studies.^{13,14} It is the authors' view that nowadays consumers do not normally experience this problem as they are aware of the risk and tend to avoid repeated/prolonged contact together with rinsing hands after any exposure. Typically, manufacturers provide guidance in this respect on their packaging.

In an early and comprehensive study, 739 subjects took part in several double-blind cross-over tests involving a range of main wash and presoak detergent formulations, with and without proteolytic enzymes.¹⁴ In their patch tests, detergent formulations containing enzymes or enzyme concentrates applied under occlusion were more irritating to the skin than nonenzymatic controls. However, this type of exposure is grossly exaggerated compared with normal consumer contact and has been shown to lead to irrelevant results.¹⁵ With the tests employing exaggerated use conditions, there was no significant increase in skin irritation in any of the hand or arm immersion assays that could be attributed to the presence of enzyme.¹⁵ To confirm that the increased irritancy of the enzyme-containing formulations seen in patch tests would not result in any adverse effects during normal use, further tests were conducted. Products were used normally in a total of 5943 subjects and the hands examined by a dermatologist. No differences were observed between the enzyme and control treatments. In the second (involving 360 infants), babies' nappies were washed in the test and experimental products and the nappies worn. There was no difference in the incidence or severity of nappy rash between groups of infants wearing nappies laundered in the products with or without enzymes.¹⁴

The direct effects of wash solutions under reasonably foreseeable use conditions were evaluated by Bolam and colleagues.¹⁶ Consumers were asked to use a laundry detergent containing a proteolytic enzyme or an enzyme-free product for 2-week periods for dishwashing and general household cleaning as well as for hand-washing fabrics, in order to simulate extended consumer use, including uses not intended by the product manufacturer. The results of this work showed that the addition of proteolytic enzymes did not enhance irritancy. As other classes of enzyme are of lesser intrinsic irritant hazard potential, then clearly they would also not induce skin irritation reactions in practice.

In a rigorous series of investigations in Germany reported in a pair of publications, the effects of enzyme-containing detergents on the skin were examined.^{17,18} Undertaking studies not only of normal but also of irritated, acid or alkali damaged or tape-stripped skin, several days of skin contact with enzyme dilutions were without effect (in total, 912 tests were completed). As mentioned in the introduction to this review, the authors concluded that any effects caused by laundry detergents could not be due to the (proteolytic) enzyme content. In a second phase of the work, enzyme-containing and enzyme-free formulations were employed in a study design which intended to produce visible skin irritation; the formulation with enzyme behaved in the same manner as the enzyme-free formulation, confirming that the enzyme at the product use concentration was not making a detectable contribution to the skin irritation potential for the formulation.¹⁸

There are also several published reports on the lack of irritant effects of enzyme residues on fabrics.^{19,20} These studies employed 2-day patch tests of fabrics containing detergent residues and a variety of exaggerated exposure tests. In all the studies, no evidence that residues in the fabrics caused irritancy was obtained. Similar results were obtained by Rodriguez and colleagues who used a variety of European detergents under European washing conditions.²¹

More recently than the above studies, but still completed a decade ago, was the excellent work undertaken by a Danish group.²² These workers completed a placebo-controlled blinded study of some months' duration, concluding that 'it is unlikely that consumers with "normal skin" will experience any skin discomfort when enzyme-enriched detergents are used'. This conclusion was reached on the basis of a study using 25 patients with atopic dermatitis, individuals commonly considered to be much more likely to experience adverse skin effects,²³ but who in fact showed no greater reaction to the enzyme-containing products than to those without enzymes.

Ultimately, the balance of all the evidence, much of which is reviewed above, is that enzymes in laundry detergents are not a cause of skin irritation in practice.

Allergy

As is the case with irritation, enzymes have long been recognized as a potential cause of type I allergy of the respiratory

tract.^{6,7} Within the European Union, enzymes are labelled as potential respiratory sensitizers.²⁴ Where there has been sufficient exposure, individuals have developed allergic asthma, a situation which did occur to a considerable extent occupationally in the early years of use of enzymes,^{4–6} but which is now very largely under control.^{25–27} However, it is still the case that even though enzyme workers may be free of clinical symptoms, a minority still does become sensitized.^{26,27} The question to be addressed here is whether there is any risk that any reasonably foreseeable consumer use of enzyme-based products might present any risk of allergy, either for the lungs or for the skin.

Both the induction and the elicitation of allergy require an appropriate degree of exposure, with each of these components of the allergic mechanism being subject to a threshold, i.e. below a certain level of exposure there is no response. Evidence from occupational exposure suggests that the threshold for the induction of allergic reactions to enzymes may be lower than that for elicitation, as a proportion of workers is sensitized, but appears generally to be symptom free.^{27,28} Where exposure control is not sufficient, however, then symptoms do occur.^{25,28} The occupational exposure limits applied to enzymes that relate to proper controls represent the strictest airborne exposure limits for any material as far as we are aware; typically the limits used are 60 ng m⁻³ or less.²⁹ However, it seems reasonable to expect that in an uncontrolled consumer environment, then to be safe, exposure levels should be well below these occupational exposure limits, and such does appear to be the case.³⁰ Industry guidelines on consumer risk assessment for enzymes indicate that a 10-fold lowering of the occupational limit should be appropriate.^{29,31,32} The primary point of control which enables such strict limits to be achieved is encapsulation of the enzyme (surrounding the enzyme with a robust inert barrier), so that material cannot become airborne and is unlikely to deliver any significant skin contact.

Industry information indicates that the probable consumer exposure to enzymes is actually much lower than even one-tenth of the occupational limits.^{29–32} Ultimately, though, the demonstration of the effectiveness of controlling enzyme exposure arises not from estimations/measurements of the exposure, but rather from a determination of whether the immune system of exposed individuals has responded by the development of IgE antibodies which would mediate the allergic reaction. The seminal publication on this aspect came from the work of Pepys *et al.*³³ In this study, 2500 people attending a hospital for allergic investigation of respiratory disease were skin prick tested. Only two patients yielded weak evidence of a positive response to proteolytic enzyme and neither had any suggestion of clinical sensitivity. A similar proportion of individuals was found to have weak, but clinically irrelevant, skin test reactions as part of a screening for a large consumer test (unrelated to laundry products).³⁴ It is inevitable that when such random screenings are undertaken, then there will be a modest number of inexplicable 'false positives' as the sensitivity and specificity of such tests are established in

relation to the guided testing of clinical populations rather than the general population.

Since the original publication, further work has been conducted in other locations to try to confirm an absence of the induction of type I and/or type IV allergic reactivity. For example, a study of 2000 consumers in the Philippines, of whom one third were described as atopic, found no evidence of sensitization, despite a 6% prevalence of hand eczema.³⁵ This work was enhanced by later results from a long-term follow-up study which had the same outcome.³⁶ Quite recently (2002), an independent group of investigators representing the North American Contact Dermatitis Group reported on a substantial body of work which examined the question of allergic contact dermatitis to laundry products (i.e. not only to enzymes in such products). Their overall conclusion was that the frequency of allergy to such products was, at best, very low and in all probability presumed positive reactions tended to arise from misinterpretation of skin responses, i.e. they were false positives.³⁷

Ultimately, the most telling publication on potential adverse skin reactions to enzyme-based laundry detergents arose from a focused investigation of complainants. The launch of an enzyme-containing washing powder was quickly followed by numerous complaints from domestic users suggesting it was responsible for an adverse skin reaction. Eighty of 255 individuals living in London (U.K.) postal districts who complained to the manufacturer agreed to be investigated by patch and prick testing, and to a use test involving the double-blind wearing of vests washed with the product. The results showed that the enzyme-containing washing powder was not responsible for any dermatological problem, either irritant or allergic in nature.³⁸

Such observations as those described above are consistent with what we know of the (patho)physiology of skin allergy. Substances must penetrate the outer skin barrier to reach the viable epidermis and do so in a sufficient quantity and in an appropriate antigenic form in order to activate the immune system in such a manner as to lead to the development of allergic reactivity. By virtue of their size, enzymes are unlikely to penetrate the skin to any great degree;³⁹ the encapsulation of enzyme in the laundry product means that actual skin exposure will be extremely low. Thus, the only occasions when there is likely to be some degree of exposure is either to the wash solution (when the enzyme encapsulate has dissolved) and/or from any enzyme residues on fabrics. As shown by the studies already mentioned earlier, contact with wash solutions does not lead either to irritation or to allergy; residues on fabrics are also trivially low and do not give rise to any skin effects.^{19–22,38}

On occasions, enzyme-containing laundry products may be misused. Sekkat and colleagues investigated such a situation. In a retrospective study of mechanics in Egypt who had used enzyme-containing laundry granules for personal cleansing (including showering) over at least a 12-month period, no sensitization to enzymes was detected.⁴⁰

As with skin irritation, the overwhelming direction of all the evidence leads to the conclusion that enzymes in laundry

detergents are not a cause of skin allergy. This outcome has been confirmed by the prospective studies which have been outlined above.

Urticaria

As enzymes are capable of triggering the formation of IgE antibodies, then as with other proteins (e.g. natural rubber latex proteins), skin contact with them could, in theory at least, give rise to the potential risk of immunological contact urticaria.⁴¹ Consequently, this aspect of enzyme safety must be considered in relation to consumer exposures. Contact urticaria presents clinically as an immediate erythematous and oedematous skin reaction, arising within minutes of skin contact, peaking in 10–20 min and usually subsiding after about 1 h. In our experience, consumers do not report this type of response to enzyme-containing laundry powders and such reactions are not recorded in the literature as far as we are aware. Consistent with this absence of any clinical evidence for its occurrence in consumers is the general absence of reports of such an effect in sensitized workers. The original observations of enzymes as respiratory allergens described the situation where many (even a majority) of the workforce had antigen-specific IgE and a minority had respiratory symptoms.^{4–6,42} A number of workers also experienced skin irritation due to the proteolytic nature of the enzyme and the relatively high exposure concentration. However, even in this situation, no immediate urticarial skin type reactions were reported. In a very recent review of over 30 years' experience in the enzyme manufacturing industry with more than 1200 occupationally exposed individuals, of those sensitized only about 1% showed urticaria symptoms.⁴³ As the exposure doses are so much lower in consumers, where the enzyme has been encapsulated, and/or where it has been very substantially diluted in wash solutions, then it becomes unsurprising that skin contact urticaria to detergent enzymes seems not to occur.

From first principles, enzymes may have the potential to cause urticaria, but there is no evidence, both occupationally and in consumers, that this actually occurs in practice.

Conclusions

Enzymes were incorporated into fabric washing products to assist in stain removal, but have attained an increasing importance due to their biodegradability and because they can function at low washing temperatures, thus offering environmental benefits. These matters appear to contrast, at least in the minds of some, with perceived risks to human health, notably concerning adverse skin effects such as allergy and irritation. Despite the very clear recognition of the potential risks associated with occupational exposure, an authoritative German review concluded over 20 years ago that 'biodegradants in particular present no increased risk of skin damage for the user'.⁴⁴ The weight of evidence is now convincing that consumer use of enzyme-containing laundry detergent

products does not pose any greater risk of skin irritation than that of their 'nonbiological' variants, that the potential for respiratory allergy has been successfully controlled by limiting exposure and that there is no evidence for enzymes leading to contact dermatitis (allergic or irritant) or immunological urticaria from their use. The consequence of this is that healthcare professionals should, in our view, avoid explaining rashes, on adults, children or infants, as due to use of enzyme-containing laundry products. Rather, they should seek more carefully for the true causation of an eczema in order to come to a correct diagnosis.

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