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Review

Defining occupational and consumer exposure limits for enzyme protein respiratory allergens under REACH

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ABSTRACT

A wide range of substances have been recognized as sensitizing, either to the skin and/or to the respiratory tract. Many of these are useful materials, so to ensure that they can be used safely it is necessary to characterize the hazards and establish appropriate exposure limits. Under new EU legislation (REACH), there is a requirement to define a derived no effect level (DNEL). Where a DNEL cannot be established, e.g. for sensitizing substances, then a derived minimal effect level (DMEL) is recommended. For the bacterial and fungal enzymes which are well recognized respiratory sensitizers and have widespread use industrially as well as in a range of consumer products, a DMEL can be established by thorough retrospective review of occupational and consumer experience. In particular, setting the validated employee medical surveillance data against exposure records generated over an extended period of time is vital in informing the occupational DMEL. This experience shows that a long established limit of 60 ng/m^3 for pure enzyme protein has been a successful starting point for the definition of occupational health limits for sensitization in the detergent industry. Application to this of adjustment factors has limited sensitization induction, avoided any meaningful risk of the elicitation of symptoms with known enzymes and provided an appropriate level of security for new enzymes whose potency has not been fully characterized. For example, in the detergent industry, this has led to general use of occupational exposure limits 3–10 times lower than the 60 ng/m^3 starting point. In contrast, consumer exposure limits vary because the types of exposure themselves cover a wide range. The highest levels shown to be safe in use, 15 ng/m^3, are associated with laundry trigger sprays, but very much lower levels (e.g. 0.01 ng/m^3) are commonly associated with other types of safe exposure. Consumer limits typically will lie between these values and depend on the actual exposure associated with product use.

Contents

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1. Introduction

The potential for enzyme proteins to give rise to respiratory allergy has been recognized for several decades, since the time of the introduction of these materials into fabric washing products. The subject and its history has been extensively reviewed elsewhere, such that details do not need to be extensively repeated here (Flindt, 1969; Pepys et al., 1969; Zachariae et al., 1981; Juniper et al., 1977; Schweigert et al., 2000). The salient points are that initially, the risk of the generation of respiratory allergy was not fully appreciated when bacterial proteolytic enzyme was first introduced in the 1960s, such that after period of about a year, an occupational problem began to appear. It transpired that a substantial proportion of the exposed workforce had developed specific immunoglobulin E (IgE) antibodies against the enzyme, i.e. sensitization had been induced. Furthermore, of this group a fair proportion also displayed symptoms of respiratory allergy, including asthma, i.e. elicitation had occurred. These aspects, exposure, the lag phase, induction and then elicitation, are key characteristics of allergy. Once the problem had been identified, then substantial steps were taken over the next few years to reduce the level of occupational exposure until evidence of respiratory allergy could be shown to be absent (Schweigert et al., 2000; Sarlo and Kirchner, 2002; Sarlo, 2003). In essence, this is the situation that still pertains to this day.

Whilst the occupational situation was the most acute and widely reported, and since the risk was not fully appreciated initially, consumer exposure to the proteolytic enzyme being incorporated into the fabric washing product was not sufficiently well controlled. As would be expected, the consumer exposure was much lower than that experienced occupationally, but nevertheless, a number of reports of adverse effects were published in the early 1970s (Belin et al., 1970; Bernstein, 1972; Zetterstrom and Wide, 1974). The efforts to limit occupational exposure were also relevant to consumer exposure insofar as they involved encapsulation of the enzyme which dramatically limited the level of dustiness of the raw material. Consequently, since that time, as far as we are aware, there have been no further reports of adverse effects in consumers, whereas there has been some clear demonstration of the absence of adverse effects (US SDA, 2005; Basketter et al., 2008).

In the present review, we have examined this historical experience from the perspective of the establishment of safe limits for occupational and consumer exposure in order to make recommendations for generically applicable levels which can be used for both existing and new bacterial and fungal enzyme proteins. Furthermore, it is suggested that this knowledge and the limits recommended should also be suitable for application to other enzymes (including engineered enzyme proteins) unless there is additional information which would suggest that a different limit would be appropriate. However, it is also important to appreciate that the DMEL values proposed represent a starting point for the definition of a safe exposure level, since these will always depend on the characteristics of occupational and/or consumer exposure associated with a particular use scenario.

2. Induction versus elicitation

In toxicology, the expression of any adverse effect requires that there is exposure. However, for allergy, the situation is a little more complex and occurs in two distinct phases. Allergy requires that the immune system is first exposed in a manner that enables it to recognize the allergen (in this case enzyme protein) so that it can proceed to develop a specific response (in this case, the production of enzyme specific IgE). This is termed induction. The exposure characteristics necessary for this to occur are not fully appreciated (Thorne et al., 1986; Hillebrand et al., 1987; Jones, 2008). Once the induction process is complete, an individual has become "sensitized" and further exposure to a sufficient dose can give rise to the second phase, the elicitation of clinical allergy symptoms.

There is no doubt that there exists a (complex) relationship between exposure level, exposure duration, exposure interval, (i.e. frequency) and of course individual susceptibility for induction and for elicitation. Questions arise also about the relative importance of peak exposures versus more chronic low level exposure. None of these aspects have been well characterized, either by in vivo experimentation or by interrogation of occupational health data, not least since these would represent very substantial challenges in their own right. The limited information that is available has been reviewed very recently (Jones, 2008; Basketter et al., submitted for publication). Despite the limitations, what is quite certain though is that ultimately, it has been the reduction in airborne exposure which resolved the occupational and consumer problems of approximately 35 years ago.

The induction of the sensitized state can be detected in a number of ways. Most commonly, the presence of (enzyme specific) IgE antibody is assessed either by a skin prick test or by radioallergosorbent test applied to a blood sample (Wide et al., 1967; Pepys, 1972). It is not appropriate to review the details of these and other diagnostic tests here. What is important is that these tests, with a considerable degree of accuracy, demonstrate the presence or absence of IgE sensitization. What they do not do is to indicate anything about whether the elicitation of allergy has occurred. The existence of the clinical symptoms of allergy requires that a sensitized individual has a sufficient degree of exposure to produce the classic signs of respiratory allergy, these being rhinitis, conjunctivitis, bronchoconstriction and asthma (Bernstein, 2007; Chan-Yeung and Malo, 1999). Note that the sensitized state is required for elicitation, but does not mean that clinical symptoms are inevitable.

3. Thresholds

Given the above, it is evident that for allergy there are two general thresholds that can be derived, one related to the induction of the sensitized state and another for the elicitation of clinical symptoms. This of course raises a number of questions, not least which of these thresholds is the most important, relevant, practical and so forth. Before that though, it is worthwhile to consider some background information on our current understanding of the science in this area. In allergy, it is commonly stated that once sensitized, an individual will react to much lower levels of exposure (Chan-Yeung and Malo, 1999). Teleologically, this seems self evident in that the induction process involves a dramatic expansion of the number of cells producing IgE antibody to allergen. Experimentally, such an apparent increase in sensitivity is what has been seen when guinea pigs have been sensitized experimentally (Thorne et al., 1986; Hillebrand et al., 1987; Magnusson and Kligman, 1970; Buehler, 1985) or when humans have been deliberately sensitized (Friedmann, 2007), accepting of course that some of these studies were with a different form of allergy. However, when it comes to