Moving beyond hazard identification towards hazard characterisation

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Sensitisers, hazard, potency and regulations

Health warning
This is a cartoon version of how these matters relate.

Sensitisers, hazard, potency and regulations

True non-sensitising chemicals
Hazard characterisation

This has two elements:

1. Is my sensitising substance a potential respiratory allergen?

2. If yes, what is its relative potency?
Chemicals and sensitisation

**Skin**
- Positive in guinea pig skin testing
- Positive in the LLNA and/or
- Positive in DPRA/Keratinosens/h-CLAT
- Preferentially activates Th1 pathways

**Respiratory**
- Positive in guinea pig skin testing
- Positive in the LLNA and/or
- Positive in DPRA/Keratinosens/h-CLAT
- Preferentially activates Th2 pathways
Do in vitro skin sensitisation tests inform?

<table>
<thead>
<tr>
<th>Resp. allergen</th>
<th>Number in LLNA/GPMT</th>
<th>In Vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid anhydrides</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Platinum salts</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Reactive dyes</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Glutaraldehyde etc</td>
<td>8</td>
<td>+</td>
</tr>
</tbody>
</table>
Regulatory tests aim to identify skin sensitisers.

Of these, a small minority also appear to be respiratory sensitisers.

Generally all foreign proteins will produce a response in *in vivo* models of respiratory allergy, but what about chemicals?
CHEMICAL RESPIRATORY ALLERGY ASSESSMENT

New chemical
Positive in skin sensitisation
eg. structure/in vitro/LLNA

Think! Adopt benchmark

Is exposure well below adopted benchmark?

No
Th2
Stop

Yes
Cytokine fingerprint

Th1
Market

2%
+ -

98%

No issue
RESPIRATORY ALLERGY - 2

- There is no way to estimate potency, but...
- ...are there situations where we know occupational respiratory allergens are inhaled as these could form benchmarks?

- Isocyanates: 0.02 mg/m$^3$ (8h MEL) and 0.07 mg/m$^3$ (15 min STEL); NIOSH/ACGIH limit for HDI is 0.035 mg/m$^3$ (10 min STEL)
- Acid anhydrides 0.04 mg/m$^3$ (8h MEL)
- Platinum salts 0.002 mg/m$^3$ (8h MEL)
- Enzymes 60 ng/m$^3$ (effectively an 8h limit)
If a new exposure is below an appropriate example of these benchmarks (level and time) then could it be considered as safe?

Experience from the factory situation indicates that these benchmark levels can be protective, but there are still cases of asthma; whether these are always due to excursions above the limit is unclear.

This therefore indicates a need to be cautious when these benchmarks are used.

Not least, it implies that generally a “margin of error” should be considered a requirement.
BENCHMARK EXAMPLE - 1

- New sensitising ingredient X in a shampoo at 1%

- Assume 10 ml shampoo used (= 100 mg of X)

- Measurements in the breathing zone during simulated use (either with X or with a fluorescein marker) gave an airborne concentration of approximately 0.2 µg/m³ (0.0002 mg/m³)
Exposure to X at 0.2 µg/m³ compares favourably to the STEL for the potent chemical respiratory sensitiser (isocyanate) where the STEL is 70 µg/m³.

The margin of error is 350.

I conclude that this level of exposure is so far below the benchmark standard that even if the substance was an isocyanate that use should be acceptable.
REMEMBER...

None of this shows that the sensitiser being assessed is a respiratory sensitiser, just that if it was then its use would still be safe in a shampoo at a level of 1%!
Chemicals and sensitisation

Skin
- Positive in guinea pig skin testing
- Positive in the LLNA and/or
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Respiratory
- Positive in guinea pig skin testing
- Positive in the LLNA and/or
- Positive in DPRA/Keratinosens/h-CLAT
- Preferentially activates Th2 pathways

…which suggests that cytokine profiling is likely to be a good route to distinguish the true respiratory sensitisers…
CYTKOKINE FINGERPRINTING : COMPOUND X

**IFN-γ**

- **DNCB**: 1 ng/ml
- **X**: 1 ng/ml
- **TMA**: 2 ng/ml

**IL-12**

- **DNCB**: 7.5 ng/ml
- **X**: 5 ng/ml
- **TMA**: 10 ng/ml

**IL-5**

- **DNCB**: 150 ng/ml
- **X**: 100 ng/ml
- **TMA**: 50 ng/ml

**IL-10**

- **DNCB**: 2 ng/ml
- **X**: 1.5 ng/ml
- **TMA**: 1 ng/ml

**IL-13**

- **DNCB**: 5 ng/ml
- **X**: 3 ng/ml
- **TMA**: 2 ng/ml
Compound X is a respiratory allergen – what next?

- Do LLNA EC3 values correspond with respiratory sensitisation potency?
  - No
- Does the extent of cytokine production correlate to potency?
  - No
- Why?
  - There is no mechanistic basis to suggest they should
  - There is no clinically based potency categorisation
- Set occupational exposure limits based on a worst case view and/or do an exposure based risk assessment using worst case benchmarks and safety margins
- Monitor to confirm the success of the risk assessment/management action
Protein respiratory allergy – first thoughts

- In the absence of accepted predictive tests, perhaps it is simplest to regard all novel/foreign proteins as potential respiratory allergenic hazards.

- The subsequent possibility of calibration for relative potency may be limited:
  - ...in a similar manner to what has been done for food protein allergens?
  - ...but using what set of protein aeroallergens of known potency to calibrate the assay?

- Conversely, using a benchmark risk management approach could prove to be very conservative.
LET'S LOOK AT ENZYMES, HISTORY AND CONSIDER THE EVIDENCE FOR WORKERS
**THE LESSONS OF HISTORY**

<table>
<thead>
<tr>
<th>THAT WAS THEN</th>
<th>THE OUTCOME?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ENZYMES WERE INTRODUCED INTO FABRIC WASHING POWDERS ALMOST 50 YEARS AGO</td>
<td>• NEARLY THREE-QUARTERS DEVELOPED ALLERGY</td>
</tr>
<tr>
<td>• TOXICOLOGISTS WERE UNAWARE OF THE RISK</td>
<td>• ALMOST HALF OF THOSE SUFFERED ASTHMA</td>
</tr>
<tr>
<td>• FINELY POWDERED ENZYMES WERE USED</td>
<td>• NOT EVERYONE RECOVERED FULLY</td>
</tr>
<tr>
<td>• AIRBORNE DUST WAS UNCONTROLLED</td>
<td>• A MAJOR PR PROBLEM AROSE</td>
</tr>
<tr>
<td>• WORKERS WERE NOT SCREENED FOR LUNG DISEASE</td>
<td>• ENZYMES WERE VERY NEARLY LOST FROM THIS BUSINESS AREA</td>
</tr>
</tbody>
</table>
WHAT WAS THE RESPONSE?

• LOWER THE INHALATION EXPOSURE LEVEL (ACGIH 60ng/m³)
• CONFIRM THAT EXPOSURE IS BELOW THE LIMIT BY DAILY AIR MONITORING
• CHECK THE WORKFORCE ANNUALLY FOR THE DEVELOPMENT OF SPECIFIC IgE
• MONITOR WORKFORCE PULMONARY FUNCTION

Publicise guidelines for good practice
Enzyme dust exposure and attack rate of asthma
Enzymes in cleaning products: An overview of toxicological properties and risk assessment/management

David Basketter, Nina Berg, Case Brodkorb, Mark Fielden, Sheila Kilkwood, Carolina Klöss, Sophie Mathews, Carlos Rodrigues

ABSTRACT
Enzymes are attracting interest in industry as a way of increasing efficiency and reducing environmental impact. However, there are concerns about the potential for adverse health effects, particularly in the case of food enzymes. This review provides an overview of the current state of research on enzymes in cleaning products, including their properties, potential risks, and regulatory frameworks. It highlights the importance of understanding the toxicological properties of enzymes to ensure safe use in consumer products.

1. Introduction
It has long been recognized that enzymes, such as those produced industrially by bacterial and fungal fermentation, have the potential to cause serious allergic reactions in individuals exposed frequently or for sufficient time to high enzyme concentrations. Thrall (1958), Poppe (1961), Zocher (1961), and Pitcher (1962) noted that the risk of anaphylactic reactions from exposure to airborne enzymes is more pronounced in food processing environments, where enzymes are used to improve the quality and safety of food products. However, exposure to enzymes has been associated with various health effects, including respiratory symptoms, dermatitis, and allergic reactions. Understanding the toxicological properties of enzymes is crucial to ensure safe use in cleaning products. This review provides an overview of the current state of research on enzymes in cleaning products, including their properties, potential risks, and regulatory frameworks.

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Managing the Risk of Occupational Allergy in the Enzyme Detergent Industry

David A. Basketter,1,2 Francia H. Kruzewski,2 Sophie Mathieu,3 Donald Bruce Kirchner,4 Anthony Panepinto,5 Mark Fieldsend,5 Volker Siegert,6 Fiona Barnes,7 Robert Bookstaff,7 Merete Simonsen,8 and Beth Concoby4

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2American Coating Institute, Washington, DC
3AISE, Brussels, Belgium
4Procter & Gamble Company, Cincinnati, Ohio
5Unilever, Brussels, United Kingdom
6Henkel KGaA & Co. KGaA, Düsseldorf, Germany
7Robert Mifrid Ltd., Manchester, United Kingdom
8Novozymes A/S, Bagsværd, Denmark
9DuPont, Palo Alto, California

Enzyme proteins have potential to cause occupational allergic sensitisation. Consequently, as a series of enzymes in formulated products, detergents manufactured have implemented a number of control measures to ensure that the hazard does not translate into health effects in the workforce. To that end, trade associations have developed best practice guidelines which emphasize occupational hygiene and medical monitoring as part of an effective risk management strategy. The need for business to recognize the utility of this guidance is reinforced by experts where facilities which have failed to follow good industrial hygiene practices have proven to be incidents of occupational allergy. In this article, an overview is provided of how the industry guidelines are actually implemented in practice and what experience is to be derived therefrom. Both medical surveillance and an monitoring practices associated with the implementation of industry guidelines at approximately 100 manufacturing facilities are examined. The data show that in using the approaches described for the limitation of exposure, for the protection of good occupational hygiene and for the active monitoring of health, the respiratory, allergic risk associated with enzyme proteins can be successfully managed. This therefore represents an approach that could be recommended to other industries contemplating working with enzymes.

Keywords: consumer products, detergents, enzymes, IgE allergy, industrial hygiene, occupational allergy, occupational hygiene, risk assessment

INTRODUCTION

It has been known for several decades that enzymes, such as those of bacterial, plant, and fungal origin, have the potential to cause occupational respiratory allergy, even asthma, depending on exposure levels and conditions.1,2 As a direct consequence, it is necessary to control occupational exposure to enzymes so that the risk is appropriately controlled. Additionally, it is necessary to monitor the working environment and the workforce to ensure that exposure control is being adhered to, and that impacts on employee health are minimized. In the United States and Europe this has led trade associations to issue best practice guidelines, based on the accumulated experience of the detergent industry, which detail how to handle enzymes safely in the factory situation.30 Key elements of these guidelines are presented in Table I. Independent commentators in this area have also appeared. For example, the American Conference of Governmental and Industrial Hygienists (ACGIH) has addressed the general topic of the safety of enzymes, with particular focus on the endpoint of respiratory sensitization.4,5 The United Kingdom (UK) and the Netherlands have also addressed the issues.13,14 Evidence has been presented showing that adherence to best practices can deliver a safe working environment.5,6 Evidence of this negative work to improve adequate operating standards can result in occupational health problems.8,9 Although the precise boundary between what is best practice and what is inadequate is rarely well defined, as will vary across different industrial situations, ingredients, and specific detergent formulations. It has therefore been

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WHAT ELSE DID INDUSTRY DO?

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Review

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

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3Unilever, Rijssen, Netherlands
4Robert Mifrid Ltd., Manchester, United Kingdom

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 THAT TO BE USED THEY ARE 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 ENVIRONMENTAL SUBSTANCES, THEN A DERIVED MINIMAL EFFECT LEVEL (DME) IS RECOMMENDED. FOR THE MATERIALS AND Fungal enzymes which are well recognized respiratory sensitizers and have widespread use industrially as well as in a range of consumer products, a DNEL can be established through thorough retrospective review of occupational and consumer experience. In particular, plotting the validated employee medical surveillance data against exposure records generated over an extended period of time is vital in informing the occupational DNEL. This experience showed that a long established limit of 60 ng/ml for pure enzyme protein has been a successful starting point for the definition of occupational health limits for sensitization in the detergent industry. Application of this mix 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 in general use of occupational exposure limits 3–10 times lower than the 60 ng/ml starting point. In contrast, consumer exposure limits vary because the types of enzymes themselves cover a wide range, which are allowed to be used in home use. At least 30 enzymes are associated with laundry trigger spray, and very much lower levels (e.g. 0.01 mg/ml) are commonly used with other types of safe exposure. Consumer limits typically will be between these values and depend on the actual exposure associated with product use.

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Managing the Risk of Occupational Allergy in the Enzyme Detergent Industry

INTRODUCTION

It has been known for several decades that enzymes, such as those of bacterial, plant, and fungal origin, have the potential to cause occupational respiratory allergy, even asthma, depending on exposure levels and conditions.1,2 As a direct consequence, it is necessary to control occupational exposure to enzymes so that the risk is appropriately controlled. Additionally, it is necessary to monitor the working environment and the workforce to ensure that exposure control is being adhered to, and that impacts on employee health are minimized. In the United States and Europe this has led trade associations to issue best practice guidelines, based on the accumulated experience of the detergent industry, which detail how to handle enzymes safely in the factory situation.30 Key elements of these guidelines are presented in Table I. Independent commentators in this area have also appeared. For example, the American Conference of Governmental and Industrial Hygienists (ACGIH) has addressed the general topic of the safety of enzymes, with particular focus on the endpoint of respiratory sensitization.4,5 The United Kingdom (UK) and the Netherlands have also addressed the issues.13,14 Evidence has been presented showing that adherence to best practices can deliver a safe working environment.5,6 Evidence of this negative work to improve adequate operating standards can result in occupational health problems.8,9 Although the precise boundary between what is best practice and what is inadequate is rarely well defined, as will vary across different industrial situations, ingredients, and specific detergent formulations. It has therefore been
AN EXAMPLE OF SUCCESS

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of factories</th>
<th>No. of workers</th>
<th>Uptake(^2) (%)</th>
<th>Incidence(^2) (%)</th>
<th>Prevalence(^3) (%)</th>
<th>Symptoms(^4) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>107</td>
<td>22100</td>
<td>96.0</td>
<td>0.99</td>
<td>8.6</td>
<td>0.11</td>
</tr>
<tr>
<td>2007</td>
<td>109</td>
<td>23668</td>
<td>95.6</td>
<td>0.76</td>
<td>8.1</td>
<td>0.08</td>
</tr>
<tr>
<td>2008</td>
<td>114</td>
<td>23976</td>
<td>94.4</td>
<td>1.04</td>
<td>7.8</td>
<td>0.26</td>
</tr>
<tr>
<td>2009</td>
<td>106</td>
<td>22686</td>
<td>97.0</td>
<td>0.82</td>
<td>7.3</td>
<td>0.05</td>
</tr>
<tr>
<td>2010</td>
<td>106</td>
<td>24773</td>
<td>94.9</td>
<td>0.97</td>
<td>8.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

\(^1\)The percentage of the workforce that participate in the surveillance programs.
\(^2\)The percentage of new cases of sensitization during the calendar year.
\(^3\)The prevalence of sensitization in the exposed workforce.
\(^4\)Evidence of rhinitis, conjunctivitis, impaired lung function, asthma, not clearly linked to a non-occupational causation.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of factories</th>
<th>No. of readings</th>
<th>No. above action standard</th>
<th>Incidence(^1) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>82</td>
<td>288318</td>
<td>1592</td>
<td>0.55</td>
</tr>
<tr>
<td>2007</td>
<td>83</td>
<td>276193</td>
<td>1344</td>
<td>0.49</td>
</tr>
<tr>
<td>2008</td>
<td>89</td>
<td>267147</td>
<td>2546</td>
<td>0.95</td>
</tr>
<tr>
<td>2009</td>
<td>90</td>
<td>306986</td>
<td>2400</td>
<td>0.78</td>
</tr>
<tr>
<td>2010</td>
<td>95</td>
<td>344853</td>
<td>1715</td>
<td>0.50</td>
</tr>
<tr>
<td>Mean</td>
<td>88</td>
<td>296681</td>
<td>1919</td>
<td>0.65</td>
</tr>
</tbody>
</table>

\(^1\)Proportion of readings above the action standard (i.e. 60ng/m\(^3\) or lower; typical occupational action standards for enzymes are 6–15 ng/m\(^3\)).
Detailed guidance and examples of risk assessments are provided in a range of documents, including:


**American Conference of Governmental and Industrial Hygienists**: Enzymes in the Workplace: Strategies for Minimising Health Effect. September (2004).

**UK Health and Safety Executive**: OELs and the effective control of exposure to substances hazardous to health in the UK (Version 3). October (2001).

DETERGENT ENZYMES ARE POTENT ALLERGENS

- With uncontrolled airborne exposure, two-thirds become seropositive and one-third had occupational asthma.
- Control of air exposure to below 60ng/m³ still leads to almost 10% rate of IgE induction; symptoms are rare.
- It is only incessant vigilance that avoids a major health problem.
- The strongest allergens have the capacity to cause a substantial health problem in a significant number of individuals despite relatively low exposure.
- Even without an ability to do potency ranking, surely these type of enzymes have demonstrated this at the clinical level.
DIISOCYANATES ARE POTENT RESPIRATORY ALLERGENS

• ACCORDING TO SOME, THE LEADING CAUSE OF ASTHMA

• OCCUPATIONAL ASTHMA PREVALENCE OF UP TO 5%-10%

• …DESPITE AN EXPOSURE LIMIT OF 20ug/m³

• …AND DECADES OF AWARENESS

• THE STRONGEST ALLERGENS HAVE THE CAPACITY TO CAUSE A SUBSTANTIAL HEALTH PROBLEM IN A SIGNIFICANT NUMBER OF INDIVIDUALS DESPITE RELATIVELY LOW EXPOSURE

• EVEN WHEN EXPOSURE IS CONTROLLED TO A LOW LEVEL, ASTHMA OCCURS TO A CONSIDERABLE EXTENT
WHAT LEVEL OF HEALTH ALERT DO WE NEED IN ORDER TO ACCEPT THAT ACTION IS APPROPRIATE?

WHERE THAT ACTION IS NOT SUFFICIENT, MIGHT NOT REGULATORY ENFORCEMENT CONTAIN SOME PUNITIVE ELEMENT?
Assessing the potency of respiratory allergens: Uncertainties and challenges
David A. Backett1,*, Ian Kimber2
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2Institute of Biomedical Sciences, University of Manchester, Manchester M13 9PL, UK

ABSTRACT

In this review and methodology, we have collected 32 instances of each respiratory allergen. Therefore, we present an assessment of respiratory immunostimulatory potential of allergens with significant challenges and uncertainties. Furthermore, we have provided the data for a known potent respiratory allergen, and we have assessed the regulatory framework of classification and labelling of chemicals. Among other things, we consider the potential for respiratory allergens to induce chronic respiratory diseases.

1. Introduction

It is well established that certain chemicals and preservatives have the potential to cause allergic sensitization of the respiratory tract that leads to late-onset respiratory allergies and asthma. These substances are often used in the production of labelling and labelling of chemicals. Therefore, we present an assessment of respiratory immunostimulatory potential of allergens with significant challenges and uncertainties.

For respiratory immunostimulatory potential of allergens, we provide an analysis of the literature and relevant published resources.

2. Classification criteria for substances

2.1 Respiratory allergens

2.1.1 General criteria

For the purpose of this review, we have classified respiratory allergens into three categories: A, B, and C. Where data are available, and when required by a competent authority, a refined method is provided in the classification paragraph following the allocation of respiratory allergens.

3. Conclusions

4. Acknowledgements

5. References

18:

Keywords: respiratory allergens, respiratory immunostimulatory potential, classification, labelling, regulatory framework.

Footnotes:

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1Available online 12 November 2011

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Making progress on hazard characterisation requires a comparison to human clinical data, with access to a sufficient amount of such information placed in the context of exposure. This remains the most critical, but currently unavailable, need.

I must respectfully submit that in the absence of the above, no observations on the relative potency of respiratory allergens can possess any defensible scientific/regulatory basis.
Questions are welcome, but will only delay lunch!