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INVITED REVIEW

Rapid lateral flow tests in a Hazard Analysis of Critical Control Points-based approach for allergen monitoring

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Abstract

Allergen management in food companies is now becoming increasingly important. Under Article 5 of the European Commission Hygiene Code 852/2004, food companies are required to introduce, carry out and maintain regular hygiene controls based on Hazard Analysis of Critical Control Points principles. The Codex Alimentarius contains a general description of the Hazard Analysis of Critical Control Points principles. Thus, Hazard Analysis of Critical Control Points is defined as a system, which is designed to identify the health risks from food and to implement preventive measures for their control. With sensitive people, even slight traces of allergens can trigger an allergic reaction, which may result in anaphylactic shock in the severest cases, and this can be lethal if untreated. To ensure food safety for consumer protection, the products must be correctly labelled and cross-contamination by contaminated raw materials, in production processes, during storage or transportation must be prevented. R-Biopharm supports food companies when optimizing the allergen management system by offering rapid allergen tests for analysing processes. Food manufacturers should use fast and reliable processes to check for allergen contamination in food production. The increased importance of these detection methods is indicated by the current debate and the fact that some of these methods have been officially validated and approved.

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Introduction

What is Allergy? An *allergy* results in a reaction of the immune system to a normally harmless substance, like food proteins, pollen, mould spores, etc. Allergic reactions can manifest as dermal, gastrointestinal, respiratory or circulatory reactions of the human body or result in an anaphylaxis.

Codex Alimentarius Commission (CAC) determined in 1993 a list of food or food products whose presence should always be declared in the list of ingredients on a food label, because of their potential to induce an allergic reaction. The list includes cereals containing gluten (i.e. wheat, rye, barley, oats, spelt, or their hybridized strains and products of these), crustaceans and products of these, egg and egg products, fish and fish products, peanuts, soybeans, milk and milk products, tree nuts and nut products, sulphites at concentrations of 10 mg kg^{-1} or higher.

Different countries determined their own list of food allergens, depending on a variety of factors.

Current EU *legislation* recognizes 12 foods known to potentially produce severe adverse reactions across the EU (directive 2000/13/EG, 2003/89/EG, 2005/26/EG, 2005/63/EG, 2006/142/EG and 2007/68/EG). These 12 allergenic

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foods specified in the legislation were determined by the European Food Safety Authority Scientific Panel on Dietary Products, Nutrition and Allergens. They present the greatest risk and therefore should be considered in the risk assessment process. In addition to the eight allergens, Codex Alimentarius stated that celery, mustard, sesame seeds and lupine must be declared as allergens. Other allergenic foods might be added in the future, dependent on the prevalence of adverse reactions in sensitive consumers and their inherent potency to trigger severe reactions.

In the United States eight allergens were determined by the US Food and Drug Administration in the Food Allergen Labeling and Consumer Protection Act of 2004.

Ten allergens were determined in the Australia and New Zealand Food Standard Code (the Code) in 2002. The Food Industry Guide to Allergen Management and Labeling, prepared by the Australian Food and Grocery Council with support from the New Zealand Grocery Marketers Association, was released with the purpose of assisting the food industry in meeting the requirements of the Code.

Health Canada establishes food standards, policies, regulations and guidelines. Health Canada defines a food allergen as 'any protein from any of the following foods or any modified protein, including any protein fraction that is derived from the following foods: almonds, brazil nut, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts, peanuts, sesame seeds, wheat, triticale, eggs, milk, soybeans, crustaceans, fish, shellfish'.

The Hong Kong list of priority allergens is identical to that proposed by the CAC in its recommendation.

In Japan the Ministry of Health, Labour and Welfare of the Government of Japan instituted its labelling programme for foods containing allergens, based on provisions of the Food Sanitation Law in April 2001. Firstly five food items were designated as allergens, which have to be labelled and for another 19 food items labelling was recommended.

South Africa adopted the CAC's recommendations about labelling of allergenic ingredients. Regulation 46–50 under the Foodstuffs, Cosmetics and Disinfectants Act of 1972 (Staatskoerant, 2007) define food allergens and specify their labelling conditions.

In Japan, 10 p.p.m. is used as the *threshold* for all allergens, but no other countries have set official thresholds, except for sulphur dioxide ($10\,mg\,kg^{-1}$). A scientific based allergen-inducing dose under which no allergic symptoms occur could not be defined. The minimum triggering level varies for different patients and shows a correlation to the constitution of allergic persons. Only for gluten the threshold $20\,mg\,kg^{-1}$ is defined for 2012 in the European legislation EG No. 41/2009. Products containing $< 20\,mg\,kg^{-1}$ gluten can be labelled with 'gluten free'.

A standardized protocol for clinical experiments that allows determination of the threshold dose is needed in the future (Taylor *et al.*, 2002, 2009a).

Comparable detection methods are needed to determine thresholds or action levels. Thus *harmonization* of allergen detection methods like enzyme-linked immunosorbent assay (ELISA), lateral flow device (LFD), polymerase chain reaction (PCR) in different food matrices is aspired to (Lineback *et al.*, 2008). For that purpose the dialog between public authority, science, consumer and industry is encouraged.

Diaz-Amigo & Pöpping (2010) discusses the possibilities and limitations of existing allergen detection technologies [ELISA, mass spectrometry (MS), PCR] for threshold or action level finding to enable correct allergen labelling. At the moment thresholds are unofficially used by most enforcement agencies and food-producing companies.

Food allergies are increasing in *prevalence*. Approximately 6–8% of children under 3 years and 3–4% of adults have at least one food allergy (Grundy *et al.*, 2002; Sicherer *et al.*, 2003, 2004). Many infants outgrow their allergy.

Trace amounts of food proteins can cause an allergic reaction. But the lowest dose able to provoke a reaction has not been calculated. The sensitivity differs between individuals and depends on the type of the food. Avoidance of the food is the only protection of allergic consumers to prevent adverse reactions.

The food industry has to take awareness of food allergies to protect consumers from severe reactions. Consumer's lives are at risk from eating formulated foods. The allergenic food often contains allergens as hidden ingredients resulting from cross-contamination. Awareness, education and communication can improve the quality of life of food-allergic consumers.

The food industry has to be aware on different levels to reduce the risk of allergic contamination of food. Risk can occur during research and development, engineering and system design, in raw materials, during production scheduling, labelling and packaging, rework, cleaning and because of human errors.

In Australia 50% of product *recalls* were caused by food allergens between May 2004 and April 2005 (Allergen Bureau). The main components that caused recalls were milk (30%), peanut (17%), egg (17%) and gluten (17%).

In the United States approximately 17% of product recalls were caused by food allergens between 1999 and 2009 with its maximum in 2002 (USDA-FSIS).

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Allergen management in food companies contains an allergen control plan for consumer protection

Allergen management in food companies is essential. Consumers depend on food companies to provide safe products. An *allergen control plan* helps food producers to make food products safe. The most important point is to prevent allergic ingredients from finding their way into products for which they are not intended. The food company uses the allergen control plan as written documentation regarding storage, handling, processing, packaging and identification of allergenic food ingredients.

Training manuals, policies and procedures, certification and plant communication can prevent risk. An *allergen management policy* should include identifying and minimizing of allergen hazards in the plant. Therefore training and education for the staff, suppliers, contractors and vendors is necessary. Labelling and precautionary statements should be defined. The summary of regulations and laws and how to avoid cross-contamination should be included in training.

Different interacting key areas of the food company are important parts of the allergen management system. The allergen management involves people, cleaning and packaging procedures but also new product development and reformulation procedures, manufacturing premises, equipment and processes and also the raw materials and supply chain has to be verified under the allergen management procedure.

Hygiene control and allergen monitoring via the Hazard Analysis of Critical Control Points (HACCP) concept following the allergen control plan protects consumers health

Hidden allergens cause the highest risk for allergic consumers and they mostly come from *cross-contaminations* in plant. Reasons for cross-contamination could be, e.g. cross-contact before and after receipt, poor storage, contaminated shared equipment, airborne dust, improper incorporation of re-work material, incomplete or incorrect packaging and other reasons.

Avoiding contamination of food with potential allergens is the most effective way to protect sensitive consumers from adverse reactions. One important point of the allergen management is the *HACCP* concept. HACCP concepts are mandatory in food producing firms and are the best approach to control the risks in food products.

The HACCP concept requires monitoring harmful residues in food. Several interpretations have now been derived from the original HACCP concept of 1973 via Codex Alimentarius and European legislation Article 5 VO (EG) No. 852/2004 which contains a general description of the HACCP principles. Thus, HACCP is defined as a system, which is designed to identify the health risks from food and to implement preventive measures for their control. Health risks due to contaminated food must be detected and prevented in time (Taylor & Hefle, 2005).

An effective HACCP system contains two components, the prerequisite programme and the HACCP Plan.

The *prerequisite programme* is designed to ensure a suitable and safe environment for food manufacturing that does not present sources of contamination. It serves to control hazards in the facility environment and personnel. The sanitation programme must include procedures that are specific for the equipment that is used within the plant. The prerequisite programme is implemented before the HACCP plan because it controls a large number of general hazards that then do not need to be controlled in an HACCP plan.

The *HACCP plan* is developed to determine hazards significant to food safety. Control measures are put into place to prevent, reduce or eliminate these hazards. The control measures are monitored for effectiveness. If a hazard is not adequately controlled, actions are taken to correct the failure. The HACCP plan controls hazards in the manufacturing process and ingredients.

For HACCP plans, *seven HACCP principles* were standardized by the CAC as follows:

1. Conduct a hazard analysis.
2. Determine the Critical Control Points.
3. Establish critical limits.
4. Establish monitoring procedures.
5. Establish corrective actions.
6. Establish verification procedures.
7. Establish record-keeping and documentation procedures.

The HACCP programme involves evaluating the whole 'lifecycle' of the product. The plant has to test *three different areas* of food production to fulfil the HACCP plan. The critical points where allergens can be introduced into products during manufacture should be identified. Testing for allergens has to be done in raw materials, during the production process and with finished products. Incoming goods, vehicles, containers should be checked. The cleaning efficiency should be verified. Cross-contaminations

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in shared equipment have to be prevented and detected. Checking for spillages and verification of correct labelling is also necessary to prevent risks. If checking of raw material gave a positive result for allergens the material has to be rejected or designate to other products. The cleaning efficiency has to be verified during the production process. If finished products were tested positive confirm the result, redirect, rework or re-label product. The worst case is stopping sales, recall and destruction of products. To prevent this time-consuming recall procedure keep the production process clean and test for cross-contamination.

Allergen labelling is an important point of the allergen control plan

For an effective allergen control plan as part of the allergen management in the food industry, along with the HACCP, the concept the *allergen labelling* is another important point. Allergens must be declared when present as an ingredient or an ingredient of a compound ingredient or a food additive or component of a food additive or a processing aid or component of a processing aid. The label should provide information that is useful to consumers. The labelling could be near or in the ingredient list and in common English language. Detailed information which allows recognition of the allergen should be used. Pre-packaged food has to be labelled for allergens as ingredients after European legislation 2003/89/EG. These regulations do not address contaminations which may result from pollute residues during the production process. Furthermore unpackaged food or loose fare, e.g. in restaurants has not to be labelled.

'May contain' *precautionary labelling* should be avoided. Food producers should make the safety decision and do not leave it to the consumer to guess. Products with precautionary allergen labelling should be avoided by allergic consumers, even if no traces of the allergen were present. Only traces of allergens can trigger an allergic reaction in patients, but methods are available to sensitively and reliably detect potential contaminants in food products and the food-producing environment.

The precautionary labelling should not be used as a replacement for poor GMPs or when there is no risk of cross-contamination. But 'May contain' precautionary labelling should be used when necessary. When cross-contamination is unavoidable, then precautionary labelling should be used to warn allergic consumer.

Cross-contamination should be prevented or eliminated by improving cleaning or changing production methods.

Immunochemical methods for allergen detection in food

Food allergens are reliably detectable with immunochemical methods

For allergen analysis effective extraction and sensitive measuring methods for raw or processed food must be available. Currently different technologies are offered. In addition to the immunological detection methods ELISA and LFD, also PCR and chromatography/mass spectrometry (LC/MS) are used.

MS and PCR are used by official laboratories and research units because of the high cost of implementation and education and training of personnel. If applied correctly it can be a tool for confirmation.

ELISAs for allergen detection allow high sample throughput, with quantitative results and an optimal sensitivity. ELISAs are used by commercial and official laboratories, research units and central industrial labs. The technology requires some low-cost instrumentation for sample preparation and measurement and thus it is suitable for places with middle to high sample volumes.

Of the different methods mentioned for allergen detection, lateral flow tests are the only true on site tests, and thus have the broadest potential application sites, like industrial laboratories, food and beverage producers, ingredient suppliers, inspection services, canteens, convenience stores, etc. Actually, these tests play their role at any site, where food, ingredients, beverages are produced, stored, transported or prepared.

The increased importance of these detection methods is indicated by the fact that some of these methods have been officially validated and approved.

Immunochemical test methods have recently become established due to the ease of preparation and their increased efficiency. Immunochemical methods of determination are based on the reaction of the analyte with an antibody. Since the biochemical reaction is specific, determinations can also be carried out in complex matrices.

ELISA – immunological detection methods for the quantification of allergens in food

Immunological methods like ELISA are often used for food analysis because of their simplicity of handling and potential for automated use. The quantifiable antibody-antigen reaction takes place in microtitre plates.

For example an ELISA for gluten analysis detects highly sensitive coeliac toxic cereals and gives negative results for non-toxic grains like soy, rice or millet. The method was

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published on the basis of the monoclonal R5 antibody (Osman *et al.*, 2001). The antibody detects the pentapeptide QQPFP (glutamin–glutamin–prolin–phenylalanin–prolin) and related proteins. The epitope appears repeatedly in prolamines of wheat, barley and rye varieties. After heat treatment the QQPFP epitope remains relatively unmodified because of its short linear structure and therefore can be quantitatively detected in processed food. For different kinds of processing, different test formats are available.

ELISAs have many advantages but some could function unreliably with special processed food under certain circumstances. Heat processing is able to influence the antibody binding on epitopes in an ELISA. Processing can lower the solubility of proteins. Small lipophilic residue proteins are hardly detectable, due to issues of low solubility/extractability.

ELISA has been traditionally used to detect food allergens. But like all other allergen detection methods it will suffer from recovery issues, if insufficient sampling was done before analysis. Effort should be focused on sampling plans and extraction protocols to receive reliable results.

Incurred samples, which closely mimic real life samples are very helpful for validation of allergen detection methods, and can be used to calibrate ELISAs results and increase reliability in future (Taylor *et al.*, 2009b).

LFD – rapid and reliable hygiene controls using immunochemical lateral flow test for allergen management

Sensitive, specific, easy handling and rapid tests are needed to monitor the efficiency of the allergen sanitation procedure. Lateral flow tests are qualitative immunochemical methods for the rapid and specific detection of analytes by means of test strips. Lateral flow tests can be used for allergen screening and hygiene controls in food companies because they run quick and are sensitive. LFDs can handle small volumes of multiple sample types. They are suitable for use in field that enable onsite analysis during food production.

While the lateral flow tests are qualitative only, confirmation of positive findings can be done with ELISA or a complete set of PCR tests.

The lateral flow technology uses chromatographic test strips and is based on the rapid flow of liquids through a membrane. Antibodies are fixed on different places of the strip to bind antigens and give coloured results in the form of test and control lines on the strip.

A conjugation pad at the beginning and an absorption pad at the end of the strip are responsible for the developing flow. Competitive and non-competitive formats are available for LFD. Antibodies used for LFDs are usually labelled with latex or nanogold particles which are visible to the naked eye but also fluorescent label are used.

First LFDs were used to monitor pregnancy and drug abuse. New applications like testing for food allergens have also increased.

Allergen residues can be detected with LFD in surface samples (e.g. industrial plants for food preparation) or rinsing waters (CIP), food end products and raw materials.

Different companies developed LFDs to detect, for example *egg* residues that are specific for the whole egg protein or only for ovalbumin or ovomucoid. The different available egg LFDs show limits of detection between 0.5 and 1 p.p.m. ($mg\,kg^{-1}$) egg protein.

For the screening of *nut* residues LFDs were developed for routine use. These tests are available embedded in a plastic material casing or without such casing. Different extraction methods with or without heating procedures are recommended. But all available LFDs offer comparable sensitivity to ELISAs (Röder *et al.*, 2009). Most nut LFDs show detection limits between 0.1 and 10 p.p.m. nut commodity.

Milk LFDs on the marked show detection limits about 15 or 1 p.p.m. milk protein depending on the provider. Some tests need special equipment for sample preparation others do not.

All *bioavid LFDs* distributed by R-Biopharm AG show low detection limits (see Table 1). The lowest detectable concentration of the homogenized diluted analyte (analytical sensitivity) lies between 1 and 5 p.p.m. analyte commodities. Swabbing experiments show that 10 µg of an allergen embedded in matrix in a dried spot can be detected. Besides bakery goods, ice cream and cookies, further matrices are validated in an ongoing process.

To determine the analytical sensitivity, the analyte of interest (e.g. Almond) was prepared according to the kit instructions by grinding 50 g with 4 g salt and 450 mL water in a household mixer for 5 min. With the aqueous phase, six further dilutions from 1:100 to 1:10–7 were made by consecutively adding 0.1 mL of sample extract to 0.9 mL saline (0.9% NaCl in water). Then following the procedure in the corresponding instructions for use, running buffer was added into eight reaction vials. The first reaction vial served as negative control and received saline as sample. The remaining seven vials received the diluted sample extract. The assay was performed and evaluated according to the instructions.

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Table 1 The validation data of bioavid test kits show analytical sensitivities between 1 and 5 p.p.m. (mg kg^{-1} commodity) and sensitivities from surfaces of mostly 10 μg analyte

Product	Analytical sensitivity (buffer) (p.p.m.)	Sensitivity from dry surface (Melamine and stainless steel)	Cross-reactivity
Lateral flow coconut	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	10% peanut (roasted and steamed)
Lateral flow almond	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	100% apricot seed, 0.001% Brazil nut
Lateral flow Brazil nut	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	None
Lateral flow mustard	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	None
Lateral flow hazelnut	5	Butter cookies, ice cream (vanilla, chocolate): 10 μg	0.01 % pumpkin seed, 0.1 % walnut
Lateral flow Macadamia nut	1	Ice cream (vanilla): 10 μg	None
Lateral flow peanut	5	Butter cookies, ice cream (vanilla, chocolate): 10 μg	None
Lateral flow egg	1	Cooked/fried egg: 3 μg Fresh/sprayed egg: 1 μg	Chicken
Lateral flow sesame	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	None
Lateral flow cashew kernel	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	10% Brazil nut, 1% hazelnut, 0.01%, peanut (roasted or steamed), 1% walnut
Lateral flow pistachio	1	Butter cookies, ice cream (vanilla, chocolate): 10 μg	0.1% Brazil nut, 4% cashew, 0.1% hazelnut, 0.1% pumpkin seed, 0.8% walnut
Lateral flow milk	1	Milk, ice cream: 10 μg Milk powder: 0.2 μg	None

The negative control must be negative, otherwise all results were invalid. The highest dilution with a positive result is defined as 'analytical sensitivity' of this test and expressed in p.p.m.

Solid analytes (e.g. cookies) were extracted with saline and diluted to 1 mg mL^{-1}. Liquid matrices were spiked directly. Zero matrices were spiked with the analyte to the 10-fold and 100-fold concentration of the analytical sensitivity. Cooked or baked products were heated again at 160 °C for 30 min in a convection oven. Solid matrices were suspended 1 in 10 in water.

To determine the sensitivity from dry surface, each spike level was dispensed at 0.1 mL on a stainless steel plate and on a melamine plate and dried over night at room temperature. One Reaction Vial was used for each spike level and one for the negative control (with saline as sample).

The assay was performed and evaluated according to the instructions.

The negative control test must be negative, otherwise all results were invalid. The lowest amount of antigen dried on a plate and recovered was defined as 'sensitivity of the swab method' of this test and expressed in μg mL^{-1}. If results were negative, the assay was repeated with higher concentrations of spike solution. The dilution factor of the solid samples was considered in the calculation.

The tests are quick to carry out, taking approximately 15 min without requirement of any laboratory equipment.

The three different sample preparation procedures in general are very simple. Food products are mixed with water and salt in a household mixer for 5 min. The aqueous phase from the supernatant is applied into the test. Rinse water (CIP) is directly applied into the assay. With a Swabbing kit, that contains buffer, tubes, swabs and pipettes, taking a swab from a surface is done in 2 min. The extract from the surface is applied directly into the assay.

The extracted sample is pipetted into a reaction vial, which contains the specific antibodies ready for use. If the sample contains the antigen in question, an antigen–antibody complex is formed in the reaction vial. This is then detected on the test strips. The qualitative evaluation is

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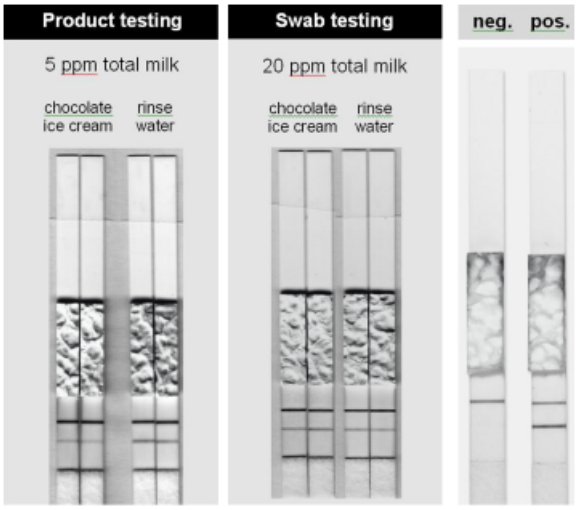

Figure 1 The results from bioavid lateral flow test strips can be read out visually. One line indicates a valid negative result and two lines indicate a valid positive result (see legend right). The example for product testing (left) shows two lines for 5 p.p.m. ($\mu g\,mL^{-1}$) milk in chocolate ice cream and rinse water. The other example (right) shows two lines for 20 p.p.m. milk after swabbing of a surface. In both cases low concentrations of total milk are reliably detectable.

carried out visually (see Figure 1). The presence of two coloured lines on the test strip, the control line and the test line, indicates a positive result whereas the presence of one coloured line indicates a negative result.

The bioavid milk test detects 5 p.p.m. ($mg\,kg^{-1}$) of defatted skimmed milk powder which equates to approximately 1.8 p.p.m. ($mg\,kg^{-1}$) milk protein.

Conclusions

Allergen management is becoming increasingly important in food companies. Analytical laboratories have to choose an appropriate detection method for allergens in food. Their problem is that today no official validated standards and reference materials are available. Therefore no comparable statements to choose the most appropriate tests can be stated. Mostly the detection methods which show the most reliable results for the requested detection limit or which were successfully validated a particular laboratory are chosen. The detection method must be practicable fast, reliable and cost-efficient.

Health risks due to contaminated food must be detected and prevented in time. However, it is possible to carry out hygiene controls by means of immunochemical tests like ELISA and LFD.

ELISAs can be used to quantify allergen contents in food. With lateral flow rapid tests it is possible to qualify food allergen residues rapidly and reliably even while the production process is underway. The sensitivity of specific lateral flow tests is comparable to that of commercial ELISAs. The use of lateral flow allergen tests is an important part of allergen control and HACCP systems during food production.

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