

Where are we in risk assessment of food allergens?

The regulatory view

Assessing the risk of exposure to chemicals is done every day worldwide. This assessment includes hazard identification, dose (concentration)-response (effect) assessment, exposure assessment and risk characterization. The present paper discusses the possibilities and limitations of using these procedures when assessing the risk of food allergens. It is concluded that hazard identification is not a problem. The medical literature is full of descriptions of cases of food allergy where the offending food or even allergen is identified. More knowledge on the relationship between dose and response of different allergens in different patient populations is needed. Exposure assessment is possible but may not be easy. Determining the distribution of contamination with an allergen may be crucial. To do risk characterization, and as a consequence to be able to manage risk, knowledge of a threshold for effect is needed and the possibility of using a safety factor. If we do not manage to establish thresholds for elicitation of allergic response in food allergy, risk assessment and management will be very difficult. It will be difficult to avoid labeling like “May contain peanuts” used with and without reason. In the long run, unjustified warnings will not help the allergic consumer but will create more confusion than guidance.

Charlotte Madsen

Danish Veterinary and Food Administration, Søborg,
Denmark

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Charlotte Madsen, Danish Veterinary and Food
Administration
19, Mørkhøj Bygade
DK-2860 Søborg
Denmark

Risk assessment – general principles

When assessing the risk of exposure to a chemical, the following elements are included:

- hazard identification
- dose (concentration)-response (effect) assessment
- exposure assessment
- risk characterization

Hazard identification includes description of the toxic effects of the chemical as such. What are the possible adverse effects that may be caused by the chemical?

In dose-response assessment the dose that elicits a toxic response is considered, including the shape of the dose-response curve. Ideally, data from animal studies includes information of a no observable adverse effect level (NOAEL).

In exposure assessment the total exposure is estimated using information on level and duration of exposure from direct and indirect sources.

Risk characterization involves the qualitative estimation of whether or not adverse effects are likely to occur in human populations exposed to the substance. This is achieved by comparing the hazards of the substance and their relationship to dose, with the exposure patterns and exposure levels for each relevant human population (1).

For most toxic effects it is assumed that there is a threshold dose below which no adverse effects occur. If an NOAEL from animal studies is available it is possible to compare it with the exposure level of the population of concern. The NOAEL/exposure ratio is also called the margin of safety (MOS). The MOS is the ratio between the dose not giving an adverse effect in an animal study and the dose derived from the actual human exposure. The larger the MOS, the safer. Normally, a MOS > 100 does not give rise to concern.

In chemicals where the exposure is regulated, e.g. food additives, the NOAEL is used to calculate an acceptable daily intake (ADI). The NOAEL is normally divided by 100 to give the ADI. The ADI is used to determine the acceptable use of a chemical.

There is no threshold for skin sensitizers as it is currently not possible to identify an elicitation dose below which adverse effects are unlikely to occur in people already sensitized to the substance.

Genotoxic carcinogens are also considered to have no threshold below which the substance is harmless. A mathematical approach is being used to answer questions like: how much aflatoxin (a genotoxic carcinogen) is acceptable in corn? (a question that has to be answered because zero is not an option). By using the available dose-response data from animal carcinogenicity studies or epidemiological data it is possible to

calculate the relationship between dose and cancer risk. An acceptable risk is often considered to be the risk of one case of cancer in one million individuals exposed during their entire life.

After risk has been assessed it is time to decide what measures, if any, should be taken, i.e. risk management. In the case of aflatoxin in corn and other cereals a maximum residue level of 4 µg/kg has been set.

Risk assessment – food allergens

When estimating the ability of a chemical or of pathogenic bacteria to cause illness (hazard identification) it is reasonable to assume that there is a potential hazard to all humans. The susceptibility may vary, but given the dose is high enough, all individuals are at risk. When working with hazard identification and risk assessment of foods that may cause allergic reactions it is evident that for the majority of the population there is no hazard and as a consequence of this, the risk, even at extreme doses, is zero.

With the ubiquitous classical food allergens it is almost impossible to perform allergy risk assessment on sensitization. There are several reasons for this.

It is not possible to establish dose, time of exposure or frequency.

Little is known about the circumstances necessary to sensitize (age, dose, frequency of exposure, route of exposure, GI-tract infection, etc.).

The protein causing the risk of eliciting a response may not be the same as the protein sensitizing, e.g. cross-reaction between birch pollen and apple.

There are some exceptions to the above. There are cases where newborn children have been sensitized to cow's milk during the first day of life; here the dose, age and frequency is known. In UK, mothers of high risk infants are advised not to eat peanuts during pregnancy and lactation, to breastfeed their babies for 4–6 months and not to feed their babies peanuts until they are at least 3 years of age (2). This advice (risk management procedures) is given on the basis of risk assessment on sensitization to peanuts during early life. Here the UK authorities have chosen to perform a risk assessment and to suggest how risk can be managed even though all necessary information is not available.

For new proteins with unknown allergenic properties, e.g. from genetically modified food, different approaches has been suggested to predict potential sensitizing capacity despite our limited knowledge of the sensitization process.

Hazard identification

A description of a case of food allergy where the offending food has been identified and properly linked to symptoms is hazard identification. Often the entire

foodstuff is identified as the cause of allergy. Sometimes, immunoblots illustrate that certain proteins are responsible for the specific IgE reaction.

Hazard identification in allergy is unique because the hazard only exists for individuals sensitized to the allergen or to cross-reacting allergens.

Dose (concentration)-response (effect) assessment

For the individual patient the dose that elicits an allergic response may vary over time. In the clinic the primary goal is to establish which foods elicit a response and less emphasis is put on establishing the precise dose.

The study on peanut allergy by Hourihane et al. (3) is probably the only study designed specifically to address the dose-response relationship in food allergy. Here, 14 peanut allergic adult subjects were challenged orally with increasing doses of peanut flour. The no effect level/ lowest effect levels provoking subjective reactions were 50 and 100 µg, respectively. The no effect level/ lowest effect level provoking objective reactions (symptoms were supported by observable signs such as urticaria or lip swelling) was 1 and 2 mg, respectively. It is apparent that choosing either subjective or objective symptoms as the relevant response will change the result by a factor of 20.

Exposure assessment

A food allergen is not dangerous where it is apparent and can be avoided. It is the unexpected and unavoidable exposure that is dangerous.

It is possible to measure unwanted allergens during the manufacturing process. Does the milk chocolate contain hazelnuts and how much? It may also be possible to do calculations. If peanut cookies are reused in the production of chocolate cookies, how much peanut protein will the chocolate cookies contain? It is important to consider whether the allergen will be evenly distributed.

For the food allergic the relevant exposure will be the amount of allergen in one serving.

Risk characterization

If the results from the Hourihane study are used in the same way as results from toxicity studies of a chemical, safety factors are used. A no effect level established in an animal study will normally be divided by 10 to account for interspecies differences (mouse to man) and another 10 to account for intraspecies differences (age, sex, strain). A no effect level from a study in humans will generally only be divided by 10 to account for intraspecies differences. For subjective/objective reactions this will give an acceptable intake of 5 µg/100 µg peanut protein.

Discussion

Is it possible to use classical risk assessment procedures when dealing with food allergy?

Hazard identification is not a problem. The medical literature is full of descriptions of cases of food allergy.

Dose-response assessment is a problem. The peanut dose-response data are unique, and even these may only be valid for adults. It would be useful to know if levels found in this study can be translated to other allergens. Is 100 µg allergen the level at which concern should begin? Dose-response data with other food allergens is needed as well as dose-response data in children. Järvinen et al. (4) studied cow's milk challenge through human breast milk in cow's milk allergic children. Data from the study points toward a β-lactoglobulin eliciting dose around 5–10 µg. Dose-response is not the remit of this paper, but with few extra analyses, valuable dose-response data could have been obtained.

Exposure assessment is possible but may not be easy. Analyses of proteins in a matrix may be difficult. Determining the distribution of contamination with an allergen may be crucial.

To carry out risk characterization and, as a consequence, to be able to manage risk, knowledge of a threshold for effect is needed. The Hourihane study finds a dose below which there is no effect. From here the discussion on safety factors or margins of safety can begin, as well as discussions on what

constitutes an acceptable risk. More knowledge on thresholds of food allergy is needed before one can determine whether it is acceptable to use a fixed safety factor, and the size of this factor.

If we cannot establish thresholds for elicitation of allergic response in food allergy, risk assessment and management will be very difficult. This would mean that even an extreme low dose, and with ELISA it is possible to measure nanograms of allergen, is not safe.

If everything is dangerous and we cannot give guidance to manufacturers on what level of contamination is acceptable, it will be difficult to avoid labeling like "may contain peanuts" used with and without reason. In the long run, unjustified warnings will not help the allergic consumer but will create more confusion than guidance.

In conclusion it is possible to use the elements from chemical risk assessment in food allergy risk assessment, but more knowledge on the relationship between dose and response of different allergens in different patient populations is needed.

Acknowledgment

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