More than any other consumer product range, food represents an emotional issue with a strong cultural dimension. In a Eurobarometer survey of 2002, 89% of the Europeans interviewed considered food safety to be very important; interestingly 80% considered animal welfare to be very important in the same survey. Food also has an enormous economic impact on society, with the European food and drink industry boasting a turnover of about 600 billion € (i.e. 15% of the manufacturing output of Europe) and 2.6 million employees (Holland and Pope, 2004). This still excludes the agricultural sector, which produces 220 billion € of products and provides 7.5 million people with jobs. In an often quoted speech made in 1962, John F. Kennedy declared consumer safety a fundamental right. Due to globalisation (roughly 50% of our food is nowadays imported) and condensation of the industry, in particular of food retailers, to a rather small number in recent years, an asymmetry of information with respect to the safety and control of food products has developed which requires international attention.

Consideration 1: The general public is not aware of the extent of animal experimentation carried out for food products

According to the official statistics (European Commission, 2007), food related issues appear to consume only a small number of experimental animals: About the same number of animals are used for the testing of food additives for humans as for cosmetics, i.e. 0.4-0.5% of all experimental animals in toxicology, which represents 10% of all experimental animal use. This small percentage arises not from the limited testing of food additives but from the small number of new food additives developed and the requirement to test only the new additives, not the products. Hence animal use to test the safety of animal feed additives is already 10-times higher (3.3%), largely because for several types of animal feed additives (such as grow factors) all products containing these additives should be tested. The testing of plant protection products (PPP, i.e. fungicides, herbicides, insecticides etc.) makes up 9.5% of all toxicological animal use, which is just about the same percentage of animals as that used to test industrial chemicals (9.4%). This is a remarkably high number, since only about 8 new PPPs enter the market each year. However, since PPPs are intended to be biologically active (and destructive) the testing requirements are the most stringent and require substantial animal use for each PPP. Furthermore, of the 353 thousand tons of PPP sold in Europe per year (Eurostat. Food, 2006), a substantial percentage (estimates range from 20 to 40%) is likely to be replaced in the coming years by better products (with less impact on the environment or a lower chance of inducing antimicrobial resistance in the exposed pests) and as a result of the expected revision of pesticide thresholds and a hazard-based restriction of use. It is thus likely that animal use in this field will increase in the next years in order to enable the marketing of substitutes.

While animal use for experimental purposes is covered by European statistics, some testing for the safety of products and for diagnostic purposes is not. One example is the testing of botulinum toxin: This issue was addressed in an IC-CVAM/NICEATM/ECVAM Scientific Workshop on Alternative Methods to Refine, Reduce, and Replace the Mouse LD\textsubscript{50} Assay For Botulinum Toxin Testing (November 13-14, 2006, Silver Spring, MD: http://iccvam.niehs.nih.gov/docs/biologics-docs/BoNTwkshprept.pdf): Though it is hardly relevant in the EU as a potential food poison, 17 test laboratories carry out botulinum toxin determinations in the US alone (Susan Maslanka (Centers for Disease Control and Prevention, USA), http://iccvam.niehs.nih.gov/methods/biologics/botdocs/biolowkshp/wkshp_pres.htm), and they use 48 mice per sample (Shashi Sharma (U.S. Food and Drug Administration, CFSAN), same website). Although no numbers are known, this might be an indication of some animal use associated with severe suffering.

A further example is the assessment of marine biotoxins that are absorbed by shellfish. These occasionally prove lethal for humans (Anderson et al., 1993), but more often result in nausea and diarrhoea. The regular controls are still to a large extent performed using a mouse assay despite available (non-validated) alternatives (Hess et al., 2006). No animal use numbers are available, but some experts in this field estimate the number of mice used to be between 350 and 700 thousand per year. The ECVAM workshop was one of the most effective of its kind: It led to proposed changes of animal use associated with severe suffering.

Food for Thought … on Food Safety Testing

Thomas Hartung\textsuperscript{1} and Herman Koëter\textsuperscript{2}

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has subsequently adopted two opinions on particular groups of marine biotoxins and recommended in both opinions that the evidence available at this moment suggests that liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) based methods have the greatest potential to replace the mammalian assays (EFSA, 2007a; EFSA, 2008a). As a result of these activities one may expect that animal testing for marine biotoxins will strongly decrease in the coming years.

The area of food allergy is receiving increasing attention. About 200 food allergens are known (although the “big 8” are responsible for 90% of clinical cases). There is increasing interest in possible allergenicity, for example of genetically modified organisms (GMO). Food and products have already been withdrawn from the market because of such concerns (Houghton et al., 2008). Animal models exist (Houbena et al., 1997; McClain and Bannon, 2006) also in larger animals (Helm et al., 2003) but have not made it to routine tests among others because of their limited predictability for humans. Currently this issue is being addressed by a working group of the EFSA GMO Panel. Food allergies are already difficult to diagnose in humans: The allergen often only forms during digestion (thus the raw product often induces no skin reaction), and the symptoms are delayed. With the differences in the digestive system of rodent laboratory animals and also known differences of individual strains (being in-bred and by far not reflecting the variability of human immune reactions), no animal model is likely to reflect a human population risk for food allergy. Approaches which may work in the future include proteomics and metabolomics of in vitro models rather than animal tests.

Consideration 2: The rigorous scientific approach to assure food safety can be a role model for other areas

Food safety problems are as old as mankind: One of the first recorded cases occurred in AD 944 when about 40,000 people died in Southern France due to ergotism, the long-term ergot poisoning resulting from the ingestion of the alkaloids produced by the Claviceps purpurea fungus, which infects rye and other cereals (Knowles et al., 2007). The need for food safety regulation is likewise very old, e.g. the British Impure

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Likely associated deaths in EU per year</th>
<th>Estimated animal use for research and testing 2008</th>
<th>Trend for animal numbers</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbial contamination</td>
<td>10,000 – 100,000</td>
<td>10,000 – 100,000</td>
<td>←→</td>
<td>Only academic research</td>
</tr>
<tr>
<td>Marine biotoxins</td>
<td>100-1,000</td>
<td>300,000 – 700,000</td>
<td>↓↓</td>
<td>Alternatives available and under validation</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>10-100</td>
<td>1,000 – 10,000</td>
<td>↓↓</td>
<td>Alternatives available</td>
</tr>
<tr>
<td>Food allergy</td>
<td>Low</td>
<td>1,000 – 10,000</td>
<td>↑↑</td>
<td>No sufficient model available</td>
</tr>
<tr>
<td>Chemical contaminants</td>
<td>Low</td>
<td>1,000 – 10,000</td>
<td>←→</td>
<td>Academic research</td>
</tr>
<tr>
<td>Food additives toxicity</td>
<td>Low</td>
<td>1,000 – 10,000</td>
<td>←→</td>
<td>Few new products</td>
</tr>
<tr>
<td>GMO</td>
<td>none</td>
<td>1,000 – 10,000</td>
<td>↑</td>
<td>Increasing testing requirements</td>
</tr>
<tr>
<td>Positive health effects</td>
<td>n.a.</td>
<td>10,000 – 100,000</td>
<td>↑↑</td>
<td>So far mostly academic research</td>
</tr>
<tr>
<td>Low nutritional value</td>
<td>1,000,000 – 10,000,000</td>
<td>10,000 – 100,000</td>
<td>↑</td>
<td>Academic research</td>
</tr>
<tr>
<td>Plant protection products</td>
<td>Low</td>
<td>150,000 – 200,000</td>
<td>↑</td>
<td>New legislation prompts substitutes</td>
</tr>
</tbody>
</table>
Act dates back to 1226 and the German “Reinheitsgebot” for beer to 1516. Most European countries introduced more extensive regulations between 1860 and 1890 (Ansell and Vogel, 2006). European legislation started in 1962 with a Directive on food colourants. Today food worth about 430 billion € is traded between European member states (Holland and Pope, 2004) and, due to the principle of mutual recognition, lawfully produced products from one member state are marketable in all.

But there is also a downside to good food risk management: It has been called “the paradox of progress” (Houghton et al., 2008) and relates to the perception of risks: increasingly lower detection levels of food contaminants, stricter standards, quality controls and monitoring procedures inevitably lead to an increasing number of food safety alerts. These, in turn, may easily result in a higher perception of risk in the consumer and, consequently, in a loss of consumer confidence. It is not unimaginable that a loss of confidence would trigger more testing.

An example of progress in risk assessment originating from the food area is the concept of a threshold of toxicological concern (TTC) (Munro et al., 2008). Its possible role in the evolution of toxicology has been discussed previously (Hartung and Leist, 2008; Köetter, 2008). The idea is remarkably simple: Very low amounts – very low risk, very low amounts and noncritical structural features – negligible risk. From a large database of substances, a general threshold of regulation (TOR) of 1.5 μg/day was developed by the FDA for packaging migrants (i.e. contaminants which pass from the package material into the food), regardless of possible structural alerts. In Europe, this approach was further developed to differentiate between three chemical classes by setting separate thresholds of toxicological concern (TTC) of 1,800, 540 and 90 μg/day, respectively (Kroes et al., 2005). This is used internationally for flavouring substances, but the approach is currently being considered for other areas of chemical assessment, such as packaging materials and food contaminants. Especially for cosmetic ingredients but also for pesticide risk assessment, this offers opportunities to meet the legislative challenge of phasing out animal experimentation (Hartung, 2008, Köetter 2008).

Similarly, the food area was the first to adopt elements from evidence-based medicine for risk assessment (McCullum et al., 2005), as is currently being pursued for toxicology (Hoffmann and Hartung, 2006; http://www.ebtox.org).

Whereas the safety testing of food and feed ingredients is not different from any other area of chemical assessment, whole and novel food safety testing in animals is quite limited, because normally the typical high-dose approach cannot be applied, because the maximum tolerated doses are typically limited to 5-10% of the diet to avoid nutritional imbalance. Given the normally low toxicity of whole foods, such low doses would make it impossible to establish dose-response curves and, hence, to characterise the hazard profile. Therefore, whole foods are normally assessed by comparing their molecular characterisation to that of already accepted foods and by focussing the testing on those components which are different. Furthermore, close surveillance of consumers following controlled exposure is possible. Thus, at least in principle, control is possible after marketing of novel foods.

As a consequence of various food scandals a very rigorous, science-based regulation emerged with the European General Food Law (regulation 178/2002) of 2002. It formed the basis for creating the independent European Food Safety Authority (EFSA). According to paragraph 6 of the regulation, risk assessments have to be based on scientific evidence and must be independent, objective and transparent. The following paragraph introduces the precautionary approach principle. Furthermore, a rapid alert system for food and feed safety problems has been created. Thus, the law does not only foresee a rigorous risk assessment, but also acknowledges that risks will remain (e.g. through adulterated food, contaminations, etc.) and that post-market surveillance of products is important. Other areas could benefit from such an approach, but as discussed earlier in this series of articles, there is a tendency to close the books after a risk assessment is completed and to ignore the fact that intentional or unintentional human interventions may alter the assessed risks on which the risk management was based.

**Consideration 3:** Future food safety testing has to go beyond testing of ingredients and microbiological and chemical contamination testing

Consumers are aware of food safety (Fig. 1) as something which can affect them personally (42% according to Eurobarometer 2006): 63% are worried about pesticide residues, 62% about viral contamination like avian influenza, 62% about antibiotics and hormones in meat, 62% about hygiene outside home, 59% about contaminants like mercury and dioxins, 58% about GMO, 57% about food additives, 53% about BSE and 49% about chemical substances formed during the cooking process. Considerably less importance is given to the far more threatening health risks, i.e. putting on weight (48%), food allergies (43%) and, in particular, poorhygienic handling of foods at home (32%). Experts consider consumers to be inadequately aware of these significant health risks (Houghton et al., 2008), which are in their importance roughly just reverse to the ranking given above. Microbiological risks from poor hygiene are much more serious than those related to food contamination early on in the food production chain, which costs hardly any lives (Knowles et al., 2007). According to Danish data (Lobstein, 2002) on the frequency of food-born diseases, there are about 12,000 cases of Campylobacter infection per million inhabitants; Campylobacter is associated with 24 deaths per 10,000 culture-confirmed cases (http://www.emedicine.com/PED/topic2697.htm), i.e. up to 14,400 deaths in Europe. For Salmonella he reports approximately 20,000 cases per million inhabitants (Mead et al., 1999 estimated 5,000 for the USA), with a lethality of 0.04%, i.e. about 4,000 deaths in Europe. Notably, the number of reported cases (750 per
Infectious pathogens, e.g. Salmonella, Campylobacter, Hepatitis
Toxins, e.g. botulinum, marine biotoxins, mycotoxins, aflatoxin
Lack of essential nutrients
Unhealthy nutrients and calorie overload
Food additives, ca. 3,000 substances
Plant protection products, ca. 1,000 substances
Contaminants, e.g. dioxins, heavy metals, acrylamide
Food allergens

Source of picture: animated fast-food superheroes of "Aquas Teens Hunger Force" from Cartoon Network

Fig. 1: Food safety concerns

Consideration 4: Animal testing must not be abused to create non-tariff barriers or delay marketing of products

The risk approach for GMOs adopted by EFSA is based on a case-by-case assessment depending on the crop, the introduced traits, the intended use and the receiving environment. It is a tiered approach whereby the available information determines the requirements for further steps in the risk assessment. The assessment of GMOs, as for whole and novel foods, is based on a comparative principle, whereby the food being assessed is compared with its traditional equivalent that has an accepted level of safety, often based on a history of safe use. If needed,
tailor-made studies are requested because the hazard characterisation of novel foods, including GMOs, requires special considerations for their safety. As an example, the need for a 90-day animal feeding trial depends on the evidence already available and additional data needed to assess the safety of the GMO. In practice, however, certain EU countries with a history of consumer aversion against any GMO tend to require more studies (in particular long term animal studies) for reasons unrelated to a scientific need or uncertainty in the hazard characterisation. This practice, often used as a strategy to delay approval for import or cultivation, has already resulted in unnecessary animal testing and is likely to trigger many more animal studies as a barrier to delay or avoid marketing, rather than for risk assessment purposes.

Consideration 5: The food area is predestined for private-public partnerships complementing limited regulatory involvement

The food area has undergone a remarkable concentration in recent years. While the 10 biggest retailers in Europe covered less than 20% of the market in 1989, this rose to more than 45% in 2002 (Ansell and Vogel, 2006). Today, five major retailers account for 80% of all food shopping in France and four retailers for 80% in Germany (Caraher and Coveney, 2004). In some cases, large retailing chains have installed quality assurance schemes that go beyond the legal requirements. This is part of a broad strategy to promote consumer trust, minimise liability and achieve competitive advantage (Houghton et al., 2008). Global coalitions of food producing industry and retailers have formed to set food standards, such as Eurepgap/Globalgap (http://www.globalgap.org) and the Global Food Safety Initiative “GFSI” (http://www.ciesnet.com/2-wewed/2.2-programmes/2.2.foodsafety.gfsi.asp). In addition, the food-producing industry has established scientific institutions to address food technology and safety issues jointly with academia and government experts. The International Life Sciences Institute (ILSI) with branches in North America, Europe and Asia is an example of such an excellent cooperation. The food industry is also active in the European Technology Platforms (ETP), partly financed by the European Commission (DG Research, Framework Programme 7), in particular in the Programme Food for Life (http://etp.ciaa.be/asp/home/welcome.asp).

All these initiatives might be leading toward a new type of public/private partnership, where legislation defines minimum standards but jointly higher voluntary standards are developed and promoted. Such a model would be considerably more flexible to incorporate new approaches.

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Gesetze zur Regulierung der Nahrungsmittelsicherheit begleiten uns schon viele Jahrhunderte. Die heutige, gute Überwachung und die sensitiven Tests führen häufig zu Problemmeldungen, welche aber das Vertrauen der Verbraucher erschüttern statt zu stärken. Die Nahrungsmittelsicherheit übernahm in vielen Fällen eine Vorreiterfunktion, von der andere Bereiche der Sicherheitsprüfung profitieren könnten: Sie führte die „thresholds of no concern (TOC)“ ein und übernahm früh Elemen-

