Memorial Lecture Tihomil Beritić

FOOD TOXICOLOGY - FROM FORENSIC TO POLICY TOOL: AN EVOLUTION FROM REACTIVE TO PROACTIVE ACTION*

Marcel HOFMAN

SCIBB, Brussels, Belgium

Received in June 2004

Since the nineteenth century, food toxicology has evolved in several ways. The analytical power of the food toxicologist has been increased. The concept of adulterated food was modified significantly. Most commodities are now processed and addition of numerous non-nutrient additives is legalised. Other "alien" compounds get introduced in the food chain from background contamination or during processing and distribution. This makes the task of the food toxicologist more complex. From forensic science food toxicology developed to a policy aid.

KEY WORDS: *background contamination, bovine spongiform encephalopathy, dioxin, food additives, food adulteration, genetically modified organisms, manufactured food, mercurial compounds, mercury, polychlorinated biphenyls, pre-packaging, public perception, risk assessment*

NINETEENTH CENTURY UK

Food toxicology lifted off as a scientific discipline with the publication of "A Treatise on Adulterations of Food and Culinary Poisons: Exhibiting the Fraudulent Sophistications of Bread, Beer, Wine, Spirits, Spirituous Liquors, Tea, Coffee, Cream, Confectionery, Vinegar, Mustard, Pepper, Cheese, Olive Oil, Pickles, and Other Articles Employed in Domestic Economy, and Methods of Detecting Them" by Frederick Accum in 1820 (1).

Back then, food supply was different in many ways from what we have now. Most food products on the market were native commodities. Addition of foreign substances or removal of any intrinsic component was considered "tampering", and "adulterated food" was suspect enough to call the toxicologist in.

Manufactured food items were almost inexistent and food distribution was rather local, spanning little more than a few miles from the production site to the consumer's table.

Yet the food safety situation was far from rosy. With food products offered to the customer in bulk, common crooks, be it on the retail or wholesale level, had an easy job of going for a quick buck. Food fraud was a widespread evil and more often than not food adulterants were toxic, with such examples as the addition of alum to inferior meal to bake nice white bread or the use of copper sulphate to colour depleted tealeaves, again nicely green.

Most compounds a food toxicologist was confronted with were classical chemicals with a well-established dose-effect relationship, which did not migrate through the food chain.

If the practices of perpetrators were crude, the panoply of the nineteenth century toxicologist was not very sophisticated too. The food toxicologist mainly focused on forensic chemistry, detecting the presence of abnormal substances in food, ascertaining their eventual toxic nature and providing proof so that the offenders could be convicted.

* Presented at the 3rd Croatian Congress of Toxicology, Plitvice, Croatia, 26-29 May 2004

Chemical analysis often lacked sensitivity and speed. Microscopic and sensorial examination remained for long the most efficient tools. The development of tools to detect intentional food fraud brought about food legislation in the nineteenth century. *Hassal*, a British scientist, was the first to publish methods of detecting the presence of chicory in coffee (2). A parliamentary committee in 1855 was formed and following this, the UK Adulteration of Food and Drink Act was enacted in 1860, but not until 1872 did it come into force (3). The US followed with the Pure Food and Drugs Act in 1906 (4).

TWENTIETH CENTURY FOOD MANUFACTURING

Except for canned food, factory pre-packed food did not exist before 1894 (5) when John Harvey Kellogg first used "brightly coloured cardboard boxes" for "easy to prepare" foods. This mundane event had a profound impact on the food distribution scene. From then on, food manufacture, pre-packaging, branding and global distribution developed hand in hand.

TRENDS IN MODERN FOOD MANUFACTURE

Manufactured food

Most food on the supermarket shelves is manufactured, or at least processed. A lion's share of products is pre-packed and branded. At first, pre-packaging had a positive effect on food safety as it significantly reduced the probability of tampering in distribution. However, not all effects were positive. Marketing has made it difficult for customers to recognise the product's own look and feel. Furthermore, while the farm gate price of all food decreases, processing, marketing and distribution costs take an ever-increasing part in the food's sale price. Packaging alone for goods offered in the UK supermarkets accounts for one sixth of the consumer's budget. An almost equal portion of the budget goes to automotive transport of the goods (6, 7).

FOOD UNDER CHALLENGE

Background contamination

The development of food technology coincided with general industrialisation and the ever-increasing footprint of the human race on the ecosystem. There is a widespread background contamination with toxic compounds even in what may seem pristine environment at first sight. More often than not these are the result of old sores, that is of activities which used to be tolerated if not authorized. Toxicology can do little more than determine maximal tolerable doses or issue a straightforward "not to eat" notification for certain commodities or the produce harvested from certain habitats (8, 9). The final stage of the classical forensic research, the provision of proof to bring the offenders to justice, is left out.

Cultural evolution

Contemporary market food safety concerns are much complex than in Frederick Accum's days. Food adulteration has become more sophisticated and even acquired legitimacy. Operations that either add alien compounds to food or remove intrinsic ingredients from it are no longer perceived as "adulteration" if these actions find justification either in technological necessity or customers' desire.

The advertising power of the food industry is shaping up consumers' perception of food; its lobbying is directed to influence regulatory authorities and even steer scientific research.

Food additives go the full range from texture-, colour-, flavour-, taste- enhancers to added substances with real or presumed nutritional qualities (10). Dietetics has made room for a market of "light" products, made either by removing fat or adding water. Substitutes for fats or carbohydrates either not metabolized or with negligible caloric value have been developed and marketed.

Food from the fields, stables and even forests or seas is challenged by chemicals, which are not only accidental contaminants from industrial activity, but also products used to protect crops or abate pests and parasites. Other chemicals may be introduced in food processing, from post harvest protection to packaging.

Food, as any other product, is now distributed globally, and often travels a long distance between the producer and consumer, making it much more difficult to trace back an accident to the cause. Added substances can be metabolized and their degradation products can be very different in nature and action than the parent substance. The dose-effect relations of the adulterants can be far from linear. Migration and concentration through the food chain play an important role.

In today's technological context, short-term toxicological tests are not sufficient to forward a weighted advice. Simple presence of a toxic ingredient is no longer a sufficient reason to ban consumption of a product.

INCREASED ANALYTICAL CAPABILITY

The meaning of "presence" of a compound has changed. Instrumental analysis has overtaken the classical gravimetrical and volumetric technologies. We measure almost anything in everything and our analytical capacity is often more limited by the background contamination in our reagents and standards than by the sensitivity of our methods.

Even though the days when a judge could tell the expert "show me the poison you recovered or at least the mirror it made on your instrument's wall" are bygone, the discussion about the significance of analytical data has heated more than ever.

RISK-BASED FOOD TOXICOLOGY

The meaning "Natural unadulterated food" is now quite different from what it meant in Accum's time for several reasons: our analytical capabilities have been extended up to the point where we can trace almost anything in everything; background contamination has become much more widespread; and cultural stance about food adulteration has noticeably changed.

Under these circumstances, basing a "go" or a "no-go" decision on the "presence" of a toxic compound in food or feed to decide if it is safe or not, is impossible. More than ever before, the discussion is about the significance of the amount detected. This discussion is about risk. Once we start to discuss the safety of food in the light of the risk of bodily harm from background contamination, the next natural step is to accept treatment of food additives which increase that risk.

Food toxicology has become more and more technology directed. The toxicologist is to be involved in the risk assessment, risk control and risk management from the very early development of any food-related process.

SOCIAL DIMENSIONS OF FOOD TOXICOLOGY

Regulatory and industry

Risk assessment in food toxicology is complex. Toxicologists are involved both on the side of regulatory bodies and on the side of industry. On the regulatory side, the reference plane can vary a lot. Policymaking is a subjective business and often subject to direct political influence. Pure food safety risk assessment would be limited to such questions as what is the impact on consumer health, both short and long-term, and what are the options for a smooth roll-back if any adverse effect shows up. A political goal very near to that is the acceptance of risk to combat malnutrition.

We go more and more to social balancing of risk when we consider: the need to accept risk not to hamper free enterprise; the impact of new introductions on the equilibrium in the food supply chain (this has to do with economic as well as with social turmoil); the risks incurred by the ecosystem beyond direct impact on the human habitat.

For every plane and even for the whole regulatory action there will be a pre-emptive debate about the justification of regulatory action. The outcome of the debate completely depends on the moral and political vision of the society supported by the population of the territory the regulation is intended for.

When considering risk related to development, two very different issues are tackled:

- The objective risk of negative properties of the final product. There is some incentive to screen only for anything that is above the threshold that would trigger regulatory action impeding the introduction of the product.
- The subjective risk of non-acceptance by the consumer. Consumer acceptance is related to sensorial properties of the product such as taste, colour, odour, the "looks and feel", but also to psychological influence. Even unfortunate naming of a process step can spark distrust and kill an otherwise perfectly acceptable product. The best known example is the term "genetic manipulation" which seemed perfectly inoffensive to the scientists who used to call lots of lab operations "manipulation". However, they overlooked the negative connotation of the term in the behavioural field.

Most final decisions are political in nature, be it on the regulatory side because it is the government's role to serve strategic goals of the population by whom they are mandated, be it on the industries side because of management's obligation to foster corporate benefit through selection of appropriate product strategies.

Public perception and expert's view

When discussing risk we should not forget that in a democratic system the ultimate judge is the consumer. Scientists tend to look into risk as an objective parameter that can be quantified. In the scientific approach, often a number of simplifications are implied. Allergy experts tend to reduce risk for allergy reactions to those compounds that cause the formation of specific IgE immunoglobulins, which accounts for only a minor part of the conditions laymen experience as allergy. Experts evaluate risk in terms of narrowly defined adverse events and try to define a statistical incidence rate for these.

General public, however, has a more subjective view of the risk. Research conducted in the past 20 years has firmly established that public assessments of risk from modern technologies and activities is different from expert assessment (11). General public considers broader factors such as control, catastrophic potential, fear (possible delayed and/or disturbing effects), level of knowledge, equity, clarity of benefits, trust, effects on future generations, and effects on children.

While experts attribute these differences to intuitive biases, economic interests and cultural values, a model consumer is convinced that expert views are too narrow and that experts are not immune to economic interests. The fact is that there is no possibility to measure potential risk for a number of threats. Scientific reasoning in risk assessment is based on model experiments or even on paradigms and it too has a strong cultural bias.

Much of what guides political decisions is based on what is in the head of those for which we cater, be it as citizens or customers. How they react will largely depend on their reminiscences of past crises and alarms.

CASES IN THE PUBLIC EYE

From time to time food intoxication takes a dramatic turn. It makes the headlines of daily papers and television prime time. From the scientific point of view, such events are important because a rigorous study of their causes and effects offers the possibility to validate our models and projections.

Food toxins largely covered by the media are dioxin (12, 13), polychlorinated biphenyls (14-16), and mercury and mercury compounds (17, 18). Food-related poisoning with these three groups is only the tip of the iceberg; they are all notorious occupational hazards and ecotoxic agents.

A threat of a novel type are prions, not organisms and yet "infective". Bovine Spongiform Encephalopathy (BSE) (19) is definitely not a lesser threat than dioxin, PCB or mercury. And as for mercury, the threat in nature only required a little push by humans to develop from laboratory curiosity to a calamity. And if we widen the scope of food toxicology to food safety, an issue receives even greater public scrutiny than BSE - genetic modified organisms or GMOs (20-22). Any of the former four cases can teach us how to handle the last one.

DIOXIN

Even when a substance is manufactured "for contained use only", accidents will happen; a deliberate release in war, and one minor and one major industrial accident were prominent demonstrations of the dioxin threat.

The evil combination is the one of high chemical stability and liposolubility which results in long half-life in any organism, concentration through the food chain and a lasting reservoir in the ecosystem.

The 1953 Ludwigshafen accident (23) taught us not to jump to optimist conclusions; twenty years after it was concluded that the damage was limited to minor temporary lesions, the real damage, increased cancer incidence became apparent.

There are two things to keep in mind about dioxin: the long lag time between exposure and effect and the absence of any technology for a rollback, where we can only hope for the development of a GMO-based bioremediation.

PCB

Polychlorinated biphenyls were developed to respond to a real need, the one for a cooling fluid to make mass transportation of electrical energy safe. In contained use in transformers and capacitors they offered tremendous advantages over mineral oil.

Yet from the very beginning of their use, they were, due to accompanying dioxins, recognized as an occupational hazard. Nevertheless, they were gradually used for all kinds of uses and released in the environment. One use that can only be characterised as tempting fate was its use as heat-transfer medium in the food oil industry. Intoxications due to this practice occurred at the end of the 1960s and 1970s in Japan and Taiwan (24-27).

In the aftermath of these accidents, mainly because of the awareness of a build-up of PCBs in the ecosystem and to the media coverage on dioxin, PCBs were completely banned in the 1970s. Whereas the ban of PCB in open-ended applications or in vicinity of food oil is not subject to argument, the decommissioning of electrical equipment containing PCBs was counterproductive and actually increased the worldwide burden of PCBs on the ecosystem (28, 29).

To conclude, mankind has sinned three times: it allowed widespread use of a potentially dangerous substance; neglected early warning signs; and yielded to the media pressure to ban PCB without planning ahead.

MERCURY

Mercury illustrates the cyclic character of human awareness of toxicity. Under heavy suspicion, even as an occupational hazard, at the end of the 19th century, the use of mercury compounds rose in the first half of the 20th century, not only in industry and agriculture, but also in general, for example in household paints of the "latex" type (30), subjecting the whole population to continuous exposure. Here we also experienced a swing back going for a complete ban around the 1970s.

Banning mercury proved even harder than banning dioxin or PCBs. As this is an element, "destroying" it is not a real option. The speciation of mercury is such that the element cycles over a number of forms. However, none of these forms is a permanent sink that would block mercury permanently.

Central to this discussion are the chloralkali plants. The amount of mercury used in these plants makes the lion's share of the mercury reservoir we can control. Even on the basis of ecotoxicology, the phasing-out of amalgam-based chloralkali activities is not justified. Except for Sweden that has opted for permanent safe storage of decommissioned mercury, all other countries go for a valorisation approach, in an arrangement that the mining of pure mercury in Spain is reduced by the amount of reclaimed mercury (31). In practice, this means that the mercury price remains low and that the reclaimed mercury goes almost in its entirety to open-ended application in artisanal mining in Brazil (32) and so increases the global burden of mercury in the ecosystem.

There is a discussion whether the huge increase in mercury in the Amazon basin is caused by mining activities alone (33). Another cause could be the liberation of mercury stored in the humin fraction of soil due to deforestation.

To conclude, the mankind has not learned much from past lessons. The ecosystem has a long memory. Contaminants are often multi-sourced. Old sores can make for new treats. Body burden of a contaminant can be treacherous. Where clearance studies for mercury point to elimination between 10 and 70 days, mercury remains present in the brain 20 years after exposure (34, 35).

BSE

Bovine Spongiform Encephalopathy and the related variant Creutzfeld-Jacob Disease (vCJD) may be the most dramatic phenomena to which the food chain has been subjected in the recent years (36).

It is easy to incriminate by hindsight, but the lack of foresight often borders with criminal behaviour. Given what was known about Kuru and Scrapie and in the light of *Stanley Prusiner*'s work on prions published in 1982 (37), it now looks more than foolish that the carcasses of animals affected by scrapie epizootic were converted into feed in the UK, nor was it clever to respond to increasing energy prices by lowering the rendering temperatures (38). There was of course a widespread belief in a "species barrier" (39) that would prevent prions of one species to infect other species. And there was the conviction that any infective material left could be diluted far below the minimum infective doses.

However, we have learned since that "species barrier" offers little protection (40) and the discussion is still ongoing about how low the dilution should be.

The BSE case has taught us that even under low challenging doses phenomena with low probability will happen when the incidence rate is high enough and exposure time is long enough. All pay for errors made by a few.

Some optimistic voices are heard now because the number of cases of vCJD is levelling off in the UK. We hope of course that vCJD will not claim the predicted number of victims, only the history of Kuru, cases occurring as long as twenty year after the last case of cannibalism that was at the origin of the epidemic, should prevent us from being too optimistic, too fast. (41, 42).

In addition, BSE had a tremendously economic price; high protein material that earlier was recycled is now to be burned. At the limit BSE adds to the dioxin burden, as incineration, unless well controlled, is one of the most important sources of dioxin.

GMO

Genetic modified organisms are for some the panacea for all human sores, from malnutrition in the South to the replacement of all herbicides, insecticides and fungicides in the industrialized agriculture of the West by natural means. For others this new technology is just the ultimate brew from the devil's kitchen. As usual, there where strong convictions clash, the truth is in the middle. If there is harm, it is not in the technology, but either in the aims to which technology is put or in certain operational details.

The use of antibiotic resistance to make for easy segregation between wanted and unwanted plantlets can be questionable, but that is not essential for GMO technology. Breeding for resistance to a "total herbicide" can be questionable; it is questionable for sure when different operators start breeding for resistance each to their own brand of "total herbicide" and when than the resultant cultivars start crossbreeding (43).

The introduction of a systemic insecticide, what remains present in the product "as consumed" is questionable independently if it is introduced by chemical application or genetic modification.

Much of what former food intoxication crises have taught us is not to proceed with GMO otherwise than with utmost care. On the other hand, "old sores" of dioxin, PCB, mercury and even BSE have left us with a legacy for which only GMO technology might bring solace (44-47).

CONCLUSION

Combined, the "cases in the public eye" teach us that the biological clock ticks much slower than classic toxicology would hope for, think about Ludwigshafen, think about Kuru.

Combined, these cases have confirmed the old truth, that if you spread the feathers of a bird in the wind, it is almost impossible to reclaim them. Before authorizing anyone to take risks of that size, the least we can do is to ensure a smooth rollback if things turn sour. The most effective way of containment is to prevent self-propagation of modified organisms.

The minimum is to place financial liability where it belongs: with those who reap profit from the introduction of the hazard.

The BSE case has taught us that events of low probability will happen when the number of challenges is high over a sufficiently long time. What can go wrong will go wrong.

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Sažetak

TOKSIKOLOGIJA HRANE - OD SUDSKE MEDICINE DO POLITIKE STRUKE: RAZVOJ OD REAKTIVNE DO POTICAJNE METODE DJELOVANJA

Od 19. stoljeća do današnjih dana toksikologija hrane razvijala se u nekoliko pravaca. Osobe koje raspolažu znanjima o analitičkim postupcima za određivanje toksičnih sastojaka u hrani dobivaju veliko značenje, čime je znatno umanjena mogućnost dodavanja nepoželjnih i nedeklariranih sastojaka u hranu. Većina artikala proizvodi se posebnim procesiranjem uz dodavanje brojnih ne-nutritivnih dodataka, koji imaju dozvolu uporabe. Mnogi "strani" spojevi ušli su u hranidbene lance iz onečišćenog okoliša ili pak za vrijeme prerade i distribucije. Nova saznanja dovode do znatno veće odgovornosti toksikologa pri određivanju zdravstvene ispravnosti hrane. Toksikologija hrane obuhvaća područje od sudske medicine do novih zakonskih propisa.

KLJUČNE RIJEČI: *dioksini, dodaci hrani, genetički izmijenjeni organizmi, goveđa spongiformna encefalopatija, industrijski proizvedena hrana, krivotvorenje hrane, onečišćenje okoliša, poliklorirani bifenili, prihvaćanje javnosti, procjena rizika, spojevi sa živom, živa*

REQUESTS FOR REPRINTS:

Marcel Hofman
SCIBB
Hondsbergen 2, B-3080 Tervuren, Belgium
E-mail: *marcel.hofman@skynet.be*