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Review

Bio-markers: traceability in food safety issues*

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Research and practice are focusing on development, validation and harmonization of technologies and methodologies to ensure complete traceability process throughout the food chain. The main goals are: scale-up, implementation and validation of methods in whole food chains, assurance of authenticity, validity of labelling and application of HACCP (hazard analysis and critical control point) to the entire food chain. The current review is to sum the scientific and technological basis for ensuring complete traceability. Tracing and tracking (traceability) of foods are complex processes due to the (bio)markers, technical solutions and different circumstances in different technologies which produces various foods (processed, semi-processed, or raw). Since the food is produced for human or animal consumption we need suitable markers to be stable and traceable all along the production chain. Specific biomarkers can have a function in technology and in nutrition. Such approach would make this development faster and more comprehensive and would make possible that food effect could be monitored with same set of biomarkers in consumer. This would help to develop and implement food safety standards that would be based on real physiological function of particular food component.

Keywords: biomarkers

In 2002 approx. 20 000 new food items entered the food market taking into account that in an average market shop we can select among 25 000 food products we can estimate the complexity on the process (Lang & Heasman, 2004). For food safety reasons, among other commercial reasons, we need to trace items from farm to the fork, which implies complex solutions that are not always practical and cheap. However, traceability of foods has emerged over the past century as a way to produce and market foodstuffs (Raspor, 2001). In particular this was connected to a specific origin/region. This includes bread, dry meat like sausages and ham, cheese, oils and wine and many other specific products with clear origin. For example, geographical or regional indicators have to define the varieties of products that can be delivered to consumers in food stores at a large distance from the actual production area. Certain regions, like Champagne or Cognac in France, depend on identity preservation schemes and batch traceability, as products are traded and sold to consumers.

In the past years, computer technology has made tracing and tracking of items possible in many new and innovative ways (Podgornik *et al*., 1994). The development of biological identification technologies and DNA testing enables straightforward traceability of individual farm animals. Today there are sophisticated meat traceability software systems that enable producers to track a meat product all the way from the animal's birth to the supermarket display case and every step along the way.

Bar-coded ear-tags or electronic identifiers for tracking make it possible to keep information about each individual animal or group of animals like poultry or even farmed fish. With information gathered and stored automatically in computer databases, we can retrieve and access the identifying number as well as the name and location of the farm.

On this basis food products can be identified
— by origin of food products and ingredients,
— by processing and production methods,
— by relevant distribution and location of the food product after each delivery.

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Traceability, as we have seen, is not a novel concept, but it should be seen as a necessity for food safety, as it can help to preserve the identity of unique quality traits and thus facilitate innovation in the food sector.

TRACEABILITY

The International Organization for Standardization defines traceability as the: "ability to trace the history, application or location of an entity by means of recorded identifications".

An integrated production chain control system should be able to identify and document with accuracy materials and actions applied in food processing (Table1).

Table 1. What should be traced in food chain

1.	ALL materials and ingredients used
2.	Production processes
3.	Personnel involved
4.	Final products

Traceability systems have a broader scope and aim to document the history of a product along the entire production chain from primary raw materials to the final consumable product. The scope of these systems is not limited to the ability to detect and trace batches of high-risk products, but to support quality assurance processes for products. Quality is defined as "the totality of characteristics of an entity that bears its ability to satisfy stated and implied needs". Therefore, in the field of food safety, traceability can be defined as the ability to document all relevant elements — movements, processes, controls — needed to define a product's life history. In this sense, traceability becomes the principal tool to both ensure the effective responsibility of food manufacturers, farmers and food operators in relation to the final product quality (Raspor, 2002) and to assess and manage risks effectively (Table 2).

Table 2. Tracing and tracking goals

1.	Increasing product safety
2.	Identifying the source of possible contamination
3.	Facilitating the product recall procedure.
4.	Controlling public health risks derived from product consumption

Traceability can be used to certify food quality and origin as well as safety relative to a known standard (Raspor, 2003). Traceability refers to an unbroken chain of measurements relating an instrument's item to a known standard.

However, requirements for traceability are driven by practitioners or by scientists. Each definition differs in emphasis and delimits scope. No single one covers all concerns but it is useful to elucidate broadness of the issue and problems around.

Purpose-driven (defined in terms of what it should do): "...the ability to adhere to the business position, project scope and key requirements that have been signed off". Solution-driven (defined in terms of how it should do it): "...the ability of tracing from one entity to another based on given semantic relations". Information-driven (emphasising traceable information): "...the ability to link between functions, data, requirements and any text in the statement of requirements that refers to them". Direction-driven (emphasising traceability direction): "...the ability to follow a specific item at input of a phase of the software lifecycle to a specific item at the output of that phase"(Gotel & Finkelstein, 2004).

Food is defined by *FAO/WHO Codex Alimentarius Commission* (http://www.codexalimentarius.net/) as a substance, whether processed, semi-processed, or raw, which is intended for human consumption and any substance that has been used in the manufacture, preparation, or treatment of food, but does not include cosmetics, tobacco, or substances used only as drugs. In this respect EU food law is very broad: "Food means any substance or product intended to be, or expected to be, ingested by humans." (http: //europa.eu.int/comm/dgs/health_consumer/library/press/press82_en.html).

Regarding European legislation we shall be able to trace our food from farm to the fork and track it back from plate to its source. This has to be in practice not later than January 2005. We are consequently forced to do this as well as possible to protect producer and consumer.

The food source identification system would allow knowing where the food has been and where it is going as it travels from ports, factories or distributors on the globe. The development of the system is one of several provisions mandated by the Food Law in Europe or by Bioterrorism Act in US. In the event of a food borne illness or criminal food contamination it would be possible to quickly trace the source.

Developing and evaluating new foods and new nutrition practices is based on the capability of tracing food and its components in the meal. Current practices are forcing us to develop new and compatible systems in less time and at lower cost, which would be of enormous potential benefit for modern food industry, food market and also for consumers health. Primary identifiers of food items using bio-logical markers can be defined as anatomic, physiologic, biochemical, or molecular parameters which ensure complete traceability throughout the food chain.

(BIO)MARKERS DEFINITION

The idea of using exposure biomarkers is that they could provide, in some cases, a more accurate

method for assessing exposure and, ultimately, risk (Schulte & Waters, 1999). While the use of biomarkers can reduce mis-classification, it is also possible that measurement error in a particular biomarker may confuse the situation (White, 1997; Saracci, 1997). However, with good laboratory practice this problem can be reduced to minimum.

The validity of biomarkers is the ultimate driving force for their applicability (Raspor, 2004). Validity is a complex characteristic that describes the extent to which a biomarker reflects a designated event in a system. Generally, these events are exposure, effects of exposure, disease and susceptibility. Validity has a meaning according to discipline as well. To the laboratory scientist, validity often refers to the nature of the biomarker and the characteristic of the assay for the biomarker. Thus, the sensitivity of the assay to detect a signal at a given concentration, and the ability of the signal to be specific for a particular event are indications of validity to the laboratory scientist. In addition, the scientist wants to know what factors might influence an assay. The epidemiologist relies on the laboratory definition of validity as the cornerstone of population studies, reliability of the assay under field conditions and the frequency of the marker varying in different population subgroups defined by age, race, gender, preexisting illness, diet and various behavioural factors. A biomarker is ready for the full spectrum of uses only when the validity at the laboratory and population level has been established. Most biomarkers have not reached that level of validation. A broad effort is underway, but the products of this activity are not yet available. Additional confusion is generated if we compare definitions of biomarkers:

— any biological response to an environmental chemical at the individual level demonstrating a departure from "normal" status (Walker, 1997);

— a biochemical, physiological or histological change or aberration in an organism that can be used to estimate either *exposure* to chemicals or resultant *effects* (Hugget *et al.*, 1992);

— a change in a biological response that can be related to an exposure to, or toxic effect of an environmental chemical or chemicals (Peakall, 1999);

— functional measures of exposure to environmental stresses, which are usually expressed at the suborganismal level of biological organization (Adams, 2002).

If we go to medicine and pharma there are many definitions like "A pharmacological or physiological measurement which is used to predict a toxic event in an animal" or "A specific biochemical in the body, which has a particular molecular feature that makes it useful for measuring the progress of disease or the effects of treatment" (http://www.hyperdictionary.com/medical/biomarkers).

This finally brings our attention to two terms biomarker and bioindicator, which are often mixed and not well distinguished. Bioindicator means biological response at higher levels of organization (populations, communities, ecosystems) (Walker, 1997). It is understand as anthropogenically induced variation in biochemical, physiological, or ecological components or processes, structures, or functions that has been either statistically correlated or causally linked to biological effects at organism, population, community, or ecosystem levels (Adams, 2002). Basically we are looking for biomarkers which have a selection of characteristics important in tracking/tracing procedures (Table 3).

Table 3. Characteristics of biomarkers

Characteristics	Biomarker
Type of response	Biochemical, cellular, tissue, organ
Sensitivity to stress inductors	High
Response variability	High
Specificity to stress inductors	Moderately high
Linkage to higher-level effects	Marker specific
Time scale of response	Short
Ecological relevance	Low

For the purpose of food tracing we can select markers from the pool on the basis of three characteristics: exposure, effect and susceptibility**.** Biomarkers of exposure indicate that exposure to a chemical has occurred, but do not provide knowledge of adverse effects at the organism level. Biomarkers of effect measure responses indicate that both exposure and adverse effects have occurred. Biomarkers of susceptibility measure responses are used to assess an organism's inherent or acquired limitation to cope with a chemical exposure.

Generally we need biomarkers to chase and trace quality and safety of foodstuffs during their production or consumption and we have to select such biomarkers which can be used in may different places and different circumstances along the food chain. Controlling the safety of foods one should respect safe production and distribution with ensuring recipe design (hurdles), packaging, heating regime, fast cooling, chilled storage regime, GMP/HACCP practises and shelf life evaluation.

Simply we have to respect all safety principles which are specified as requirements for awareness of the possible risks associated with the handling of hazardous materials, knowledge of mechanisms by which exposures may occur, use of safeguards and techniques that reduce the potential for exposure and vigilance against compromise and error.

As it is known there are many possibilities to compromise safety along the food chain: in each

step food farming, food processing, food preservation, food storage and distribution, food consumption. We have to chase and trace the food to ensure its authenticity, safety, quality and quantity.

For food tracing and tracking we need primary and secondary identifiers. Food items can be traced using bio(logical) markers, i.e.: (chemical, physical, physiological, morphological) characteristic which has a stable signal that can be traced in complex environment and food matrices.

Biomarker is a specific (bio)chemical with a particular molecular feature that makes it useful for measuring (Zolg & Langen, 2004). Generally we need biomarkers to chase and trace quality and safety of foodstuffs during their production or consumption. All this has to be respected when we approach selection of potential biomarker, which can be suitable for application. Currently we respect the following criteria which help us to make proper decision (Table 4).

Table 4. Criteria for evaluating biomarkers

1.	General indicators
2.	Absolute and relative sensitivity
3.	Biological specificity
4.	Chemical specificity
5.	Clarity of interpretation
6.	Time to express/attain endpoint
7.	Persistence or permanence of the response
8.	Inherent variability
9.	Linkage to higher-level effects
10.	Applicability to field conditions
11.	Method considerations
12.	Equipment and instruments considerations
13.	Validation
14.	Utility

On this basis we can search and isolate appropriate marker from the groups of biomarkers which are listed in Table 5. Grouping them on the basis of criteria in Table 4 one can see that we have many potential markers but just a few applied in practice.

Table 5. Currently used types of biomarkers

1.	Anatomical (reproductive, morphological, histopathological)
2.	Physiological (trascriptome, proteome, metabolome)
3.	Immunological
4.	Biochemical (enzymes, metabolic products)
5.	Genome (genetic/DNA alterations)
6.	Chemical
7.	Man-made/engineered (xenobiotics, residua, microflora)

We have to respect the possibilities with different techniques and methods available (Table 6). Additionally it is important to consider how we can extend particular method/analytical instrument in the complex food matrices and finally if databases are available for data mining and comparison.

Table 6. Currently available methods with suitable analytical instruments to measure biomarkers

1.	DNA techniques
2.	Enzyme techniques
3.	Imuno techniques
4.	Near infra-red absorption technology
5.	NMR spectroscopy in food authentication
6.	Isotope ratio mass spectrometry (IRMS)
7.	Spectrophotometric techniques
8.	Gas chromatography
9.	High pressure liquid chromatography (HPLC)

Validated biomarkers are useful in reducing uncertainty in food and also other biological assessments. Successful use of biomarker data implies an understanding of the mechanisms. The incorporation of mechanistic data is certainly important for further development of the systems in food traceability. Evaluation of particular markers in the food chain would be considerably more extensive than is permitted with this publication. This allows us just to list the possibility for tracing GMO foods (Cunningham & Meghen, 2001; Jerman *et al.*, 2004).

The most common way to trace GMO foods is to deal with point DNA alterations in the genome, assuming that we know where and what was changed (Ahmed, 2002). We have a few possibilities: direct measurement of DNA structural damage/alteration, direct or indirect measurement of DNA repair, and measurement of mutations in the genome of exposed organism. Currently we use predominantly genetic/DNA alterations as is shown in Table 7.

Table 7. DNA alterations can be traced

1.	DNA adducts
2.	DNA strand breakage
3.	DNA methylation
4.	Unscheduled DNA synthesis
5.	Cytogenetic effects
6.	Nuclear or chromosomal DNA content
7.	Oncogene activation
8.	Mutation rates

Validation and successful use of biomarkers require a high degree of analytical accuracy (Norton *et al.*, 2001) and knowledge of what they mean in terms of food composition and its status. Recent developments in information technology, molecular biology and instrumentation have provided new tools for the use of many biomarkers potentially useful in food tracing. The specificity and sensitivity of many biomarkers will be improved by the introduction of new analytical methodologies, e.g., speciation of metal ions by inductively coupled plasma mass spectrometry (ICP-MS) and mass-spectrometric techniques to detect metabolites and adducts (Diemer *et al.*, 2002). Application of new detection methods, i.e., primed *in situ* labelling (PRINS) and fluorescence *in situ* hybridization (FISH) will extend the observation

from the chromosome level to specific genes relevant for the tracing process (Hiroyasu *et al.,* 2002; Sharpless *et al.,* 2004). Imaging technologies such as magnetic resonance or positron emission tomography (PET) (de Graaf *et al.,* 2004) and single photon emission computerized tomography (SPECT) (Blankenberg, 2004) are particularly interesting for studies, as these methods are non-invasive and can measure changes at the molecular scale.

High output technologies, such as DNA microarray (Service, 2004), can be used to trace genes in GMO foods (Vazquez *et al.,* 2004).

The explosion of polymorphism data requires an extension of the bioinformatics approaches towards suitable databases (Temnykh *et al.,* 2001).

Biomarker application in food tracing is entering daily practise, for this reason we should respect the following issues (Table 8).

Table 8. The range of possibility for biomarkers improvement

1.	Biomarkers measurement should be easy and relatively inexpensive, permitting quantification in food items
2.	Biomarker should respond in a dose or time-dependent manner to allow correlations and comparisons
3.	Biomarkers should be sensitive at relevant concentrations
4.	Variability due to experimental setting (environmental and other factors) should be understood and acceptable
5.	Biomarkers should be suitable for post-market surveillance to confirm the validity of original and surrogate food items

Analysing these statements, we will see that many issues are still open and questionable. Constant changes in development, largely driven by mechanistic research and analytical identification (Looney, 2002) of chemical residues does not allow good transparency over method and comparison of results. This situation is additionally complicated since we know that data available in databases are under strong pressure of electronic aging and do not represent the state of the art. Nevertheless the number of permanent markers (standards) is limited and proper/standardised application protocols are still rare.

Ultimately, the critical issue in discussing biomarkers is to answer the question like "valid for what purpose?" Validation is a measure of degree, not an absolute determination (Ponce *et al.,* 1998). Any compendium of validation status will need revision and updating, as new biomarkers are developed or as information about current biomarkers is enhanced. There is a need for critical thinking about when to use a biomarker in an epidemiological study instead of some more traditional measure of exposure or disease. Some of these criteria have been suggested (WHO, 2001). Too often temptation exists to use sensitive laboratory techniques to measure something, merely because it can be measured rather than because it provides better and more useful information. This temptation should be resisted. Similarly in food tracing and tracking the criteria for utilizing biological markers includes whether they add to the quality and credibility and whether they reduce uncertainty. Thus biomarkers that provide insight about mechanisms, support biological plausibility, or assist in refining risk estimates will be most useful. Scientists, government regulators, and industry have all recognized the potential of biomarkers. But to enrol them in real application, we should work together and proceed step by step.

CONCLUSIONS

In order to have the maximum output from biomarkers, improvements are needed with respect to design and optimization of the applied protocols. It is not to be ignored whether we deal with production or processing of food or with efficacy at realistic intake levels which needs to be established with humans. By using suitable biomarkers we shall be able to measure them directly. The human body is able to deal with (bio)chemical entities irrespective of their origin, and the pharmaceutical terms "absorption, distribution, metabolism and excretion" have relevance also in the case of biomarkers. However, this is at present neither an established science nor common practice in food technology and nutrition research and practice.

As we can see much of the work has been done on the information and technical side of tracing and tracking. Biomarkers are slowly stepping into food science and technology with high potential to add value for producers and consumers alike.

One particular issue, which is entering our domain from the point of view of consumers and producers, is shelf life, through the dimension of freshness. This specific and complex issue will be more and more important, since it is connected to the aging process. And aging is a process that can affect almost all the systems in the organisms. Scientists are looking for a more complete understanding of the aging mechanisms, to elucidate questions about the biological processes that account for an inevitable decline in vitality speaking about organisms, and in freshness, when discussing about food. In other words, is aging a single process or are there separate processes going on in different systems? Among other problems, this is the one which can be deeply touched and resolved for the benefit of the consumer. Based on this, we can see biomarkers much more as a tool in this episode of further research and development in the food arena.

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