The need for an "integrated safety assessment" of GMOs, linking food safety and environmental considerations

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Running title: Integrated safety assessment

Keywords: GMO, GM food, LMO, food safety, environmental safety, CODEX, Cartagena Protocol on Biosafety, integrated safety assessment

Summary:

Evidence for substantial environmental influences on health and food safety comes from work with environmental health indicators which show that agro-environmental practices have direct and indirect effects on human health, concluding that "the quality of the environment influences the quality and safety of foods". In the field of GMOs, Codex principles have been established for the assessment of GM food safety and the Cartagena Protocol on Biosafety outlines international principles for an environmental assessment of living modified organisms. Both concepts also contain starting points for an assessment of health/food safety effects of GMOs in cases where the environment is involved in the chain of events which could lead to hazards.
The environment can act as a route of unintentional entry of GMOs into the food supply, such as in the case of gene flow via pollen or seeds from GM crops. But the environment can also be involved in changes of GMO-induced agricultural practices with relevance for health/food safety. Examples for this include potential regional changes of pesticide uses and pesticide poisoning with Bt- tolerant crops, or influences on immune responses via cross reactivity. Clearly, modern methods of biotechnology in breeding are involved in the reasons behind the rapid reduction of local varieties in agro-diversity, which constitute an identified hazard for food safety and food security. The health/food safety assessment of GM foods in cases where the environment is involved needs to be informed by data coming from environmental assessment. Such data might be especially important for hazard identification and exposure assessment. International organisations working in these areas will very likely be needed, in order to initiate and enable cooperation between those institutions responsible for the different assessments, as well as for exchange and analysis of information. An integrated assessment might help to focus and save capacities in highly technical areas such as molecular characterisation or profiling, which are often necessary for both assessments. In the area of establishing international standards for traded foods, such as for the newly created Standards in Trade and Development Facility (STDF), an integrated assessment might help in the consideration of important environmental aspects involved in health and food safety. Furthermore, an established integrated view on GMOs may create greater consumer confidence in the technology.

Introduction:

Experience based on conventional methods of food production shows that agriculture often affects health, food safety and the environment where these aspects interact (Millennium Ecosystem Assessment, 2005; Fehr R, 1999). Work on environmental health indicators suggests (WHO, 2002) that various agricultural practices have direct and indirect effects on human health and development. Hazards can take many forms, wholly natural in origin or derived from human activities and interventions. Potential environmental health hazards of releases of GMOs in the environment have also been discussed in a report by WHO/ANPA, where health effects have been analysed "as an integrating index of ecological and social sustainability" (WHO, 2000).

As regards the interaction of the environment with conventional food production, the summing up suggested that "the quality of the environment influences the quality and safety of foods and an unhealthful environment can render food unwholesome" (Fennema, 1990). A review on risk management frameworks for human health and environmental risks (Jardine et al, 2003) has also focused on guidelines for assessing human health risks from environmental hazards and stresses" the role and relationship between risk assessment and risk management" as well as the principle of "consulting with the community to identify their concerns ".

The aim of this paper is to discuss how products of modern methods of biotechnology, especially GMOs, can indirectly affect human health and food safety through their intended or unintended presence in the environment, from agro-ecosystems to natural ecosystems. Based on this discussion the paper argues for a better integration of environmental and food safety assessments that inform policy and regulatory decisions. The presence in the environment can involve an introduction of the GMO or parts of the GMO via the environment, for example by gene flow or by contamination or by effects of the GMO on or in the environment, eventually including changes in agricultural practices. Evidence from conventional methods of food production suggest that this interaction between the environment and health and food safety is quite common. Therefore, food safety assessment needs to be informed by findings from an environmental risk assessment. The general need for an integrated assessment of effects of GMO has already been stressed before (WHO, 2005).

Molecular basis for possible risk of GMO:

When GMO are developed, some of the existing characteristics of the organisms can be altered unintentionally, affecting the expression of constitutive components. The transgene DNA could integrate into or adjacent to plant genes and perturb their expression either by decreasing or increasing their expression. The transgene could be expressed in an unanticipated manner through actions from promoters in adjacent plant genes or via interactions of plant gene open reading frames (ORFs) with promotor elements in the plant transgene. Transgene rearrangements during integration can create spurious ORFs and spurious ORFs could allow the transgene to produce unintended gene products. Recombination due to repeated sequences in the transgene could result in intralocus instability or may lead to ectopic recombination. (Andow et al., 2004). Furthermore, effects of gene-silencing can interfere with the desired gene expression (Kumpatla et al, 1997; Meza et al, 2002).

A FAO/WHO expert consultation (2003) acknowledged that introduction of a transgene into a recipient organism is not yet a precisely controlled process, and can result in a variety of outcomes regarding integration, expression and stability of the transgene in the host. Many of the unintended effects discussed as potential consequences of the introduction of transgenes into organisms have also been seen in foods already derived from organisms developed by conventional breeding methods or methods like the introduction of unspecific mutagenesis by irradiation or chemicals or tissue cultures (Kuiper et al, 2001; Konig et al, 2004).

Development of risk assessment concepts for GMOs:

The development of risk assessment concepts has reflected progress in the understanding of possible unintended effects of biotechnological methods in breeding. Early regulations for GMO did not differentiate between environmental and product specific risks assessments, whereas most modern concepts differentiate between a general environmental assessment often including monitoring concepts and assessments for specific products, such as pharmaceuticals, foods and feeds, seeds or chemicals (European Commission, 2004; Health Canada; Chassy,2002; Haslberger, 2000). Specific risk assessment procedures were developed for these products. This specification led to diversification for assessment; however, experiences drawn from a growing body of risk assessment processes often indicate similar underlying problems. In particular, the need for a molecular characterisation and assessment of potential unintended molecular effects was identified as the basis for assessment in all fields (Andow et al., 2004; FAO/WHO, 2003).

The concept that a comparison of a final product with one having an acceptable standard of safety provides an important element of safety assessments of GMOs used to be a commonly used basis for the development of both food safety and environmental risk assessment (WHO, 1991). This concept was elaborated by FAO, WHO and OECD in the early 1990s and referred to as substantial equivalence for the assessment of GM foods. But in 2000 a FAO/WHO consultation acknowledged that this concept had attracted criticism because of the perception that it was the end-point of a safety assessment rather than the starting point (FAO/WHO 2000; Canadian Royal Society, 2001; Millstone et al.,1999; Schenkelaars, 2002). The consultation concluded that a consideration of compositional changes is not the sole basis for determination of safety and that safety can only be determined when the results of all aspects under comparison, and not merely comparisons of key constituents, are integrated. More recently the concept has evolved to a Comparative Safety Assessment for GMO foods (Kok et al., 2003) where a comparison of the GMO with its conventional counterapart is a starting point (Kearns and Mayers, 1999). By 2003, both international systems covering GMO, GM food safety (Codex) and environmental safety(CPB) became effective, both systems being based on the concept of a case by case approach. More recently the need for a comprehensive molecular characterisation of each transformation event, including the analysis of integrated constructs and the flanking region, as well as the need to address potential unintended effects, was appreciated for food safety and environmental assessments (FAO/WHO, 2003) and this idea was also enforced by general recommendations of a US-FIFRA expert panel (FIFRA-SAP, 2004).

Codex principles for the risk assessment of GM foods:

The Codex Alimentarius Commission adopted the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology, and the Draft Guidelines for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants and Microorganisms (Codex work on GM foods). The principles for the safety assessment dictate a case by case pre-market assessment on the basis of a comparative safety assessment (CSA). The CSA is basically a two-tiered approach. The initial step is comprised of a thorough comparison with the closely related conventional food organism counterpart in order to identify any differences that may have safety implications for the consumer. This comparison includes both phenotypic characteristics as well as compositional analysis. The second step comprises the toxicological and nutritional evaluation of the identified differences between the food derived from the GMO and its comparator. Hazard identification and characterization are typically the first steps in any risk assessment and an extensive molecular characterisation of the inserted genetic material construct is required. The safety of the gene product must be assessed on a case-by-case basis. Following the phase of hazard identification, characterization and food intake assessment, an integrated toxicological evaluation will combine all the information with relation to the food safety of the GMO-derived food. For the identification of potentially occurring unintended effects, profiling methods have been proposed and different possibilities for profiling methods have been characterized (Kuiper et al., 2003). In addition to investigating health risks directly associated with food production, the broadening of the Codex risk assessment to include indirect effects now encompasses effects of novel food on the environment that may have an indirect impact on human health (Haslberger, 2003)

The Environmental safety assessment of GMOs

A case by case assessment considering any organisms derived from a transformation event, as well as different receiving environments, is broadly recognised as the best framework for assessing environmental risks of GMOs. Internationally the concept of familiarity was developed also in the concept of environmental safety of transgenic plants. The concept facilitates risk/safety assessments, because to be familiar means having enough information to be able to make a judgement of safety or risk (NAS, 2002; Conner et al., 2003). Familiarity can also be used to indicate appropriate management practices, including evaluating whether standard agricultural practices are adequate or other management practices are needed to manage the risk (OECD, 1993). As familiarity depends also on knowledge of the environment and its interaction with introduced organisms, the risk/safety assessment in one region may not be applicable in another. Currently the Cartagena Protocol on Biosafety (CPB, 2005) to the Convention on Biological Diversity is the only international regulatory instrument which deals specifically with the potentially adverse effects of GMOs on “the conservation and the sustainable use of biological diversity”, an important amenity of the environment, taking also into account effects on human health. The CPB covers transboundary movements of any genetically modified foods that meet its official definition of living modified organisms (LMOs). Article 11 of the CPB asks for a risk assessment where annex III of the Protocol specifies general principles and steps for environmental risk assessment of LMOs and focuses especially on identification of any novel genotypic and phenotypic characteristics that may have adverse effects on biological diversity in the potential receiving environment. Annex III recommends that the risk assessment should also take into account risks to human health and evaluate the likelihood of these adverse effects. Information on the receiving environment includes data on location, geographical, climatic and ecological characteristics, including relevant information on biological diversity and centres of origin of the likely potential receiving environment. As the focus of the CPB is biodiversity, in line with the scope of the Convention itself, its consideration of human health safety is limited, since it concentrates on situations in which an LMO itself may end up in the food supply, such as might happen via trade of crop seeds (Miraglia et al, 2004). Pharmaceuticals are explicitly excluded.

Recent work on the implementation of the CPB recommends analysis of effects of GMOs on species in the environment before an assessment of effects on the biodiversity for the assessment of non target environmental risks. This is mainly because of better access to species assessment and methodological limitations of an analysis of effects to diversity (Andow et al., 2004).

Starting points for assessing effects of GMOs on food safety mediated through the environment

Both the Codex principles for food safety and the risk assessment provisions of the CPB provide opportunities to consider more explicitly interactions between food safety and environmental safety. The broadening of the Codex Risk assessment to include indirect effects provides for an assessment of effects on the environment that may have an indirect impact on human health (Haslberger, 2003).

In the explanatory guide to the CPB (CPB, explanatory guide) indirect effects on the environment are described as effects on human health or the environment occurring through a causal chain of events, through mechanisms such as interactions with other organisms, transfer of genetic material, or changes in use or management. Observations of indirect effects are likely to be delayed. Given examples include impacts which can arise from changed agricultural practices associated with the management of a genetically modified (GM) crop rather than from the genetically modified crop itself. The explanatory guide suggests that questions related to human health effects were intended to be covered by the Protocol only if the human health aspect is linked to biological diversity. Such a link exists if the health effect is consequent to exposure in situ; for instance, if a farmer were to develop an allergenic reaction to pollen from genetically modified plants. It also exists if the health effect resulted from effects on biological diversity (secondary effect). Direct effects on human health (e.g. caused by consumption of GM food) would, however, not be covered by the Protocol.

Examples for potential effects of GM food production on health/food safety through the introduction of GMO via the environment

GMOs can affect human health and food safety via an introduction of GMO to the environment, such as by gene flow, by contamination or dispersal of transgenic pollen or seeds as well as via potential effects or changes in the agro-environment. Although scientific evaluation has achieved considerable progress in the assessment of mechanisms underlying the flow of recombinant sequences to unintended areas, considerable differences in the conclusions on consequences for health, food- and environmental safety still became obvious e.g. in the arguments under the WTO debate on suspected trade barriers for GMOs (EC.,2005. WTO dispute settlement).

Gene flow and human dispersal affecting the food chain: When GMOs enter the human food supply this introduction could involve unintended events such as gene flow or dispersal of GMP pollen or seeds as well as escapes of organisms. In these cases, environmental risk assessment results would likely be valuable for food safety assessment. This would not be necessary e.g. when only ways of the product processing or distribution are responsible for unintended contamination of commodities. Modern research shows that genes conventionally flow between related species: wild type, domesticated and lines bred for agricultural uses. The likelihood of GMO entering and persisting in the environment will vary depending on characteristics of the GMO, the system in which they are farmed or produced and the receiving environments (Ellstrand, 2001; Snow, 2002; Eastham et al., 2002,). The appearance of Star Link corn, not approved for food use, in numerous maize food products in the US (Taylor et al., 2002) has demonstrated that gene flow can become a major pathway for unintended movement of GMO ingredients into the food chain. Although this case did not result in any observed human health problems it reinforces the need to assess any potential environmental spread that can pose unintended impacts on human health and safety.

Furthermore, the development of GM plants for the expression of pharmaceuticals has become a topic of intense discussion of food safety relevant consequences, including environmental aspects (Peterson et al., 2004; PewAgbiotech Vol 12). The production of about 800 different available pharmaceutical active proteins resulted in limited production capacities and the need for efficient means of therapeutic protein production (Wilke, 1999, Fischer et al, 2004,). Permanent modification of the plant genome or of the chloroplast DNA would offer the advantage of stable, ongoing protein production with repeated planting alone. However, the pharmaceutical production in plants can create a potential for the flow of pharmaceutical materials into the human food chain, especially when food crops are used. This could occur as a result of inadvertent cross-contamination of foodstuffs, GM plants and through spontaneous growth of genetically engineered plants where they are not desired, or by virtue of pollen flow with some plants (e.g. corn). Despite prior toxicological assessment of the protein products, health effects could include local effects on the gastro-intestinal tract or the possibility of immunological effects, as seen in the context of oral vaccines. Consultations including international organisations evaluated hazards and possible measures for protection (Mascia et al., 2004). But improved knowledge about mechanisms and regional specific consequences of gene flow of the different plants under consideration for pharmaceutical production will be needed for final conclusions. Some experts do not yet see the possibility of containment measures providing a sufficient level of safety and discourage the use of food related plants for production of pharmaceuticals, while others support further development of methods for containment, control and identity preservation of pharma crops (Pew Agbiotech, Vol 12). While confinement of GMOs needs to be seen specifically for each organism a recent study of the NRC recommends the use of multiple containment systems, better testing and the use of non food organism for the production of pharmaceuticals and chemicals (Snow et al, 2002; Kirk et al., NRC ,2004). Reliable confinement systems might be even more important as experiences shows that markers used for monitoring of the parental plants can disappear with continuous breeding (Remacle and van der Ede, 2005, p. comm.).

The presence of transgenes and other alleles in Mexican traditional varieties, deriving obviously mainly from various US transgenic maize, by way of unintended uses or exchange of seeds including transgenic cultivars (CEC, 2004) illustrates the general threats of gene flow. For example, it is not known if transgenes from cultivars which are banned in the US, but can still be found in low levels in grain systems, are present in Mexican varieties (Biotech-info.net, BT corn gene flow). The final report (CEC, 2004) of a consortium of scientists on the Mexican experiences concludes that the transgenes in the lines have the potential of persisting indefinitely but transgenes may increase if these traits are given a reproductive advantage. The report underlines that agricultural practices have important effects on the genetic diversity of the Mexican local lines, e.g. if economic pressure associated with modern agriculture and trade characteristics cause small farmers to abandon use of native varieties.

The scientific assessment of a horizontal transfer from recombinant genes of GMOs to bacteria in the environment or in the human gut at present points to the conclusion that a transfer of especially antibiotic resistance genes from genetically modified plants to bacteria via mechanisms of transformation and homologous or illegitimate recombination is unlikely, but not impossible (FAO/WHO, 2003). Based on most recent findings in different bacterial species a "homology facilitated illegitimate recombination" can increase the frequency of a basically illegitimate incorporation of genes when heterologous DNA of up to 2.9 kb is flanked by a short sequence homologous to the integration site. (de Vries et al., 2002;

Prudhomme et al., 2002). Mechanisms underlying bacterial competence have been found to be critical for the uptake of DNA by different bacteria where these mechanisms are also dependent on ecosystem characteristics (Averhoff et al., 2003). The transfer of genes from modified bacteria, e.g. in foods or developed for agricultural purposes to bacteria in the environment or the gut needs to consider especially mechanisms of conjugation. Evidence is gathering that intestinal bacteria not only exchange resistance genes among themselves but might also interact with bacteria that are passing through the colon, causing these bacteria to acquire and transmit antibiotic resistance genes (Salyers et al, 2003).

In both scenarios, in the transfer from genetically modified plants as well as from genetically modified bacteria the risk assessment for food safety needs important information from the environmental assessment such as details of the receiving environment. For both, food safety and the environmental risk assessment similar basic molecular assessments of the constructs are necessary.

Potential effects of GMO food production on human health and the environment via effects on the agro-environment

Effects on uses of pesticides: Whereas in the assessment of effects from an unintended introduction of GMO via the environment the chain of events is often evident, any assessment of effects from changes in the agro-environment often leads to calculated complex scenarios. This can be seen in the discussion of effects of resistances in GM crops. A main aim for the production of GM plants is the development of improved resistance against pests. Since the development of BT-crops the discussions about possible benefits of BT crops for the environment and for human health or a desirable preference of alternative, more ecological informed methods such as Integrated Pest Management have reached no final conclusion and may need a more local specific assessment (GMO guideline project, 2005). One example where a presumably beneficial outcome was reported as a result of agro-environmental changes through the use of a GMO will be used to illustrate the need for an integrated health/food- and environmental risk assessment. For some areas of China where high level of pest- pressure, pesticide uses and pesticide poisoning of farmers and children were a general background (Lu et al., 2002) the use of BT cotton was reported to decrease overall pesticide uses and to implement the use of pesticides which may have fewer toxic characteristics for the environment and human health compared to products used before . This resulted in decreases of pesticide poisoning of farmers and children living in these areas (Hossain et al, 2004) and would be of relevance for a health/food safety relevant assessment. Evidence from other studies shows locally very different effects (Frisvold et al.,2003) and may point to the need of a generally more regional assessment. Also in the very comprehensive investigation of the UK farm scale trial which tested effects of herbicide resistant crops on biodiversity (Andow, 2003) different effects on diversity were found to be dependent on GM crop specificity and site of analysis. These results suggested that the differences are not due to changes in the crop induced by the genetic modification but obviously much more because the GM crops give farmers new options for weed control where they use different herbicides and apply them differently. The regiment of different herbicides affects human health /food safety by different patterns of toxicity and residues as well as the environment by often drastic changes of availability of weeds and seeds for wildlife (Biotech-Info.Net, weed shift worries). This evidence indicates the need to assess consequences from changes in agricultural practices in an integrated health/foods safety and environmental assessment.

Agricultural practice and immune responses. The assessment of GM food safety includes the assessment of potentially toxic properties, especially effects on immune responses such as allergenicity. Potential toxic effects could affect agricultural workers or the public. The principles for an assessment of a potential allergenicity include the comparisons of epitopes of newly expressed proteins in GM foods from sources without a history of food safety with known food allergens. (FAO/WHO, 2001). The predictability of currently used bioinformatic methods are the subject of controversial discussions (Bindslev-Jensen et al, 2003; Jank et al., 2003; Stadler et al., 2003). Experiences from conventional methods of food production, furthermore, suggest that changes of immune responses within certain groups of consumers could also be mediated by changes in the food production methods: Pollen-allergic patients frequently present allergic symptoms after ingestion of several kinds of plant-derived foods presumably by crossreactive structures. Allergenic structures that sensitize pollen-allergic patients are also present in grass and weed pollen (Vieths et al.,2002). Effects of grasses and weeds on allergenicity, including sensitization, and possibly also induction of tolerance, are well known. For example rice plants contribute a huge pollen load in agricultural fields during flowering which results in a seasonal trigger of hay fever and respiratory allergy in field workers and people living in the vicinity (Chen et al, 2004; Yabuhara et al, 2004). On the other hand farmers who have grown up on farms present a lower prevalence of atopy (Portengen et al, 2002) . Agricultural changes such as weed shifts induced by conventional agronomic methods, known to be a still insufficiently explored consequence of herbicide resistant crops (Biotech-Info.net, weed shift worries) could result in changes of the amount of potential allergens. This could affect both improvements and hazards for humans. As such investigations need profound epidemiological analysis there are few experiences available from conventional agriculture and certainly no analysis for effects of GM crops. However, also here experiences indicate that a better understanding of agro-environmental changes is an important element for the health/foods safety assessment of GM foods.

Consequences from a reduced agro-diversity: Constituents of many pathogens for crops, such as mycotoxins are important hazards for food safety. A good understanding of regional and seasonal environmental conditions is known to be important in order to assess and prevent hazards of mycotoxins derived from infections e.g.with Fusarium. The knowledge of environmental influences on resistances induced in GMOs under development against such infections with pathogens will be of importance for an integrated health/foods safety assessment. A more indirect effect of biotechnology affects breeding. Breeding aims to develop resistances to pathogens to ensure yields and increased food safety, but methods used for breeding interfere with the diversity of organisms, which have relevance for further breeding. The dominant business strategy of agricultural biotechnology companies has been to focus research and development expenditures on genetic improvement of a limited number of elite lines and then sell the line to as much of the global market as possible in order to return considerable investments. This endangers the propagation of traditional local races and knowledge. The majority of locally adapted land races e.g. will not be propagated further. There is growing scientific and public concern about consequences from the rapid decline observed for agro diversity e.g. in the number of landraces since the implementation of modern biotechnological breeding strategies (Zhu et al., 2002, Falcon et al., 2003; Petschow, 2004). A decreased availability of local breeding resources enabling e.g. the development of lines with new resistances against pathogens might therefore need to be seen as indirect hazards for food safety.

Implementation of an integrated health/food and environmental assessment and establishment of safety

The discussed examples for effects of GM food production show that integrating an ecological risk assessment and a health/food safety assessment should strengthen the assessment of safety and potential benefits of GM foods. Ways for the best possible organisation of an integrated assessment need to be detailed. In most cases information from a preceding environmental risk assessment should be considered in the appropriate parts of the GM food safety assessment, such as in the hazard characterisation or in the calculation of the exposure. But not only should the assessment integrate health/food safety and the environment. The planning of post market safety management also needs to consider these interactions. The integrated health/ food and environmental GM assessment should therefore preferably be implemented within a system, which establishes safety, combining risk assessment, management and risk communication. An attractive possibility would be the use of a system, which tries to establish safety from the beginning of a development. Based on analysis of the long history of efforts to improve safety within different established industries, the Safety First Initiative has adopted experiences in safety assurance from various industries for GM food production where these principles, applied early in the design process, can benefit multiple stakeholders concerned with environmental safety, food safety and the security of their investments: The approach aims to establish safety from the beginning of a development by establishing the minimum tolerable safety level by comparing the severity of possible harm (impact) against the likelihood of the previously agreed-upon maximum acceptable harm. One reaches agreement on the "maximum acceptable harm" through a multi stakeholder deliberative process, informed by case –specific scientific analysis (Kapuscinski et al., 2003). Applications of GMOs which may be beyond the border of acceptable minimal safety are discouraged.

The use of an integrated health/food safety and environmental assessment where appropriate, as well as a proactive approach to establish safety, would certainly have several advantages. It may help to structure and improve communication between experts engaged in the different risk assessments. It may bring together data and experiences from both sides which may stimulate improved cooperation in developments of safer GMOs and of more effective safety assessment and management methods, which would benefit both sides. Especially important fields for such cooperation are certainly advances in the assessment of unintended molecular changes using modern molecular profiling methods or the analysis of different environmental factors using advances in genomics and proteomics. A conclusive integrated assessment may help in capacity building for molecular characterisation and profiling methods especially in developing countries. Last but not least, an integrated assessment in combination with a modern proactive safety approach might also help to provide a better integration of the needs and participation of stakeholders from the areas of foods and environmental safety in the discussion of common objectives for developments and establish increased confidence in the conclusions of the assessment. These advantages of an integrated health/food safety and environmental risk assessment would presumably outweigh some increased organisational needs for the integration.

Discussion

In the present paper we argue for the need and the benefits of integrating food safety and environmental safety assessments of GMOs where the possible chain of events suggests that environmental factors may affect human health and food safety. We acknowledge that also products of other methods of biotechnologies can show effects which are usually discussed with regard to GM organisms or GM foods, such as unintended effects and could benefit from the proposed improvements. The scope of the definitions for modern methods of biotechnology or GMOs is still diverging in many national regulations, such as in the field of vaccines where integration or expression of constructs determines possible inclusion under GMO relevant regulations (Norwegian Biotech Advisory Board). In this field in particular a good integrative evaluation of environmental and health effects would be desirable scientifically (Pharmacos).

Any understanding of the chain of events between the environment and food safety might become more important in the future as our understanding of local, regional and ecological processes improve. Accelerating work in organismal and environmental genomics and proteomics might change our understanding of these interactions. Analyses of constituents of GM crops have already shown a more profound influence of regional factors, such as heat, compared to effects from the genetic modification (Novak et al., 2000). An analysis of the need for a regional approach to assess consequences of modern methods of food production on food safety and the environment is described in a forthcoming publication.
The use of integrated assessments would also improve mutual understanding and knowledge sharing among experts working in different areas. Whereas important elements of the food safety and the environmental safety assessments address similar elements and problems the largely separate work in the different fields has hindered a common understanding of important issues. This can be seen in a central point of both types of risk assessments, the case-by-case-principle. In the food safety assessment this addresses often addresses the understanding that each product deriving from a single transformation event, or a stacking of events, needs to be analyzed independently. In the environmental risk assessment, in addition to this, the case-by-case-principle also dictates a case-by-case assessment of different possible receiving environments because unique conditions of a particular ecosystem may affect the safety of GMO entering different environments. The need of consideration of characteristics of receiving regions may not be so evident for the safety assessment of many foods although exposure assessment and nutritional assessments often need to consider local or regional conditions.

In general, a better consideration of individual and local conditions may become more important as increased knowledge from human genome research "has opened the door for an improved analysis of effects of diets and other environmental factors on individuals". Technological advances make it feasible to envisage that in the future personalized drug treatment and dietary advice and possibly tailored food products can be used for promoting optimal health on an individual basis, in relation to genotype and lifestyle"(Desiere, 2004). The risk of disease is often associated with genetic polymorphisms, but the effect is dependent on dietary intake and nutritional status.

An integration of health and environmental assessment of modern methods of food production might also be an important objective in the establishment of standards for traded food in cooperation with the objectives of the CPB. Here "the use of international standards for traded food, focusing on food safety, but in the future also most likely on environmental issues, will have the potential to improve not only internationally traded food but also local food, and thereby the health of local consumers" (FAO/WHO, 2004). The cooperation between international agencies to focus development in these areas is exemplified by the creation of the STDF (STDF, Standards in Trade and Development Facility) a joint effort between WHO, FAO, World Trade Organization, World Animal Health Organization and World Bank.

Clearly the analysis of effects resulting from interactions among food production, environment and health requires information from specific assessments for food and environmental safety. This requires that national governments encourage integration of work among groups engaged in food safety and ecology. It demands specifically a cooperation of international to enable exchange and analysis of generated data and experience. It also needs capacity building in specific regions. Doubts regarding good cooperation or the possibility of an even competitive behavior of national and international concepts and organizations have been articulated recently (Giddings, 2004). But the realization of the common objectives and the considerable challenges to overcome methodological difficulties to achieve a sustainable development of food production which integrates appropriate ways of modern biotechnology in the adequate areas might help to guarantee an engaged cooperation.

Acknowledgement: The preparation of this paper at the Institute for Social, Economic and Ecological Sustainability (ISEES) of the University of Minnesota, USA, was supported by a Fulbright grant.

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