

ANNE INGEBORG MYHR and TERJE TRAAVIK

THE PRECAUTIONARY PRINCIPLE:  
SCIENTIFIC UNCERTAINTY AND OMITTED RESEARCH  
IN THE CONTEXT OF GMO USE AND RELEASE

(Accepted June 1, 2001)

**ABSTRACT.** Commercialization of genetically modified organisms (GMOs) have sparked profound controversies concerning adequate approaches to risk regulation. Scientific uncertainty and ambiguity, omitted research areas, and lack of basic knowledge crucial to risk assessments have become apparent. The objective of this article is to discuss the policy and practical implementation of the Precautionary Principle. A major conclusion is that the void in scientific understanding concerning risks posed by secondary effects and the complexity of cause-effect relations warrant further research. Initiatives to approach the acceptance or rejection of a number of risk-associated hypotheses is badly needed. Further, since scientific advice plays a key role in GMO regulations, scientists have a responsibility to address and communicate uncertainty to policy makers and the public. Hence, the acceptance of uncertainty is not only a scientific issue, but is related to public policy and involves an ethical dimension.

**KEY WORDS:** extended consent, GMO, Precautionary Principle, omitted research, scientific uncertainty, secondary effects

INTRODUCTION

Risk regulation of genetically modified organisms (GMOs) is at present subjected to heated scientific and public debate. Release of GMOs into the environment, and the use of food ingredients from GM sources, raise concerns about environmental and health impacts. Scientific information on environmental and health effects is limited, both from the industry and from public research institutions. No long-term studies to elaborate environmental and health effects of GMO use and release have been performed (Domingo, 2000; Wolfenbarger and Phifer, 2000). Scientific literature contains hypotheses and preliminary results indicating possible adverse effects. Such observed effects have lent increased credence to other possible, but unproven, processes and interactions. Particularly, questions related to secondary effects on non-target organisms and unwanted gene transfer have been discussed. Genes, and parts of genes, may be spread by cross-pollination of wild or cultivated relatives, and to other organisms



*Journal of Agricultural and Environmental Ethics* 15: 73–86, 2002.  
© 2002 Kluwer Academic Publishers. Printed in the Netherlands.

by horizontal gene transfer. Secondary effects may also arise from the expression products of the transgene(s), or the insertion(s) of transgene(s) may cause pleiotropic effects that divert the gene expression patterns of the recipient organisms, and have unexpected mutagenic effects.

The obvious lack of data and insufficient information calls for application of the Precautionary Principle (PP) in the decision making process. The PP emphasizes an awareness of scientific uncertainty about potential negative effects resulting from a phenomenon, product, or process (Freestone and Hey, 1996). There is no precise definition of the PP, and no version of it is concrete enough to provide a basis for its implementation. However, scientific uncertainty and prospects of irreversible damage are proposed as important elements.

In this paper, we give a short overview of risk issues related to GMO use and release. We express concern as more and more adverse ecological effects relevant to use and production of GMOs are reported. Hence, this paper presents hypotheses and preliminary evidence, and the predictability of effects is discussed. Present experience is connected to commercial and field releases of genetically modified plants (GMP). Ecological effects are exemplified by the potential environmental and health effects and health effects of herbicide-tolerant plant (GMHT) use and release.

Application of the PP in the decision process demands that the scientific uncertainty is made explicit. However, in a GMO context, there may be divergent opinions among scientists about the relevance of a problem, criteria for significant evidence of harm, and whether to take action to prevent harm (Myhr and Traavik, 1999). We address the importance of the scientist's responsibility, both with regard to clarification of uncertainty and with regard to communication of uncertainty to the public and policymakers. Furthermore, it is crucial to discuss normative baselines concerning predictability and acceptability of adverse effects, i.e., how much knowledge is necessary and sufficient?

## PRINCIPLES OF RISK ASSESSMENT

A risk analysis contains both risk identification (of possible undesired effects and the probability of their occurrence) and a risk assessment (which intends to quantify risks and evaluate the probabilities of possible outcomes on the basis of scientific data). Risk management concerns methods used to reduce the scientifically identified risk. Risk can be presented as a characteristic of a situation or action wherein two or more outcomes are possible, the particular outcome that will occur is unknown,

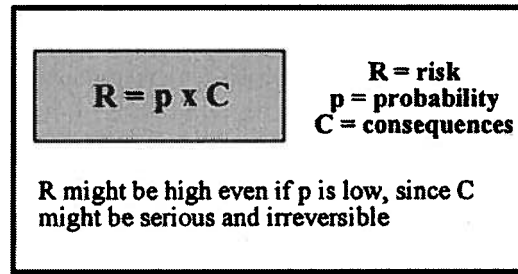


Figure 1. Risk.

and at least one of the possibilities is undesired (Covello and Merkhofer, 1993).

#### *The Precautionary Principle (PP)*

The PP emerged in European environmental policies in the late 1970s, and has become increasingly integrated into international treaties and national legislation as a foundation for environmental decision making (Freestone and Hey, 1996). Arguably, the Rio declaration is the most significant international acceptance of the PP. According to the Rio Declaration principle 15: "In order to protect the environment the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of scientific certainty shall not be used as a reason for postponing cost effective measures to prevent environmental degradation."

A recent communication by the European Commission emphasizes that the PP would play an increasing role in future European environmental and health policies (EU, 2000). The commentary does not have binding status, but is considered to provide guidance for future Commission decisions. Most importantly, the communication provides recommendations aimed at risk management, and the application of the PP is considered to be strictly political. As for the Rio Declaration, the commentary opens up space for cost-effective measures and discretionary judgment. A special version of the PP has been implemented in the appendix to the Convention on Biological Diversity, the Cartagena protocol on biosafety (CBD, 2000). A precautionary approach is considered as a guiding principle for transboundary movement of GMO, taking preventive measures in situations considered as "threat of significant reduction or loss of biological diversity."

A comparison between language in the Cartagena protocols and in the EU commentary reveals important similarities, since they both include a science-based risk assessment as the basis for a precautionary action.

#### *Threshold for PP Application*

Application of the PP entails a shift from a reactive practice that demands scientific prior to preventive actions. Regulatory regimes do not prescribe to what extent the PP should be involved, neither are "adverse effects" defined. Threshold terms include "threats of serious or irreversible damage" and words such as "harm." Clear guidelines are missing for evaluation of evidence to apply the principle (Foster et al., 2000). The precautionary measures to be applied in given situations might vary from restricted use, based on requirements to monitor impacts, or to label the product, or to delay action as by moratoria.

#### *The Difference between Sound Science and Precautionary Measures*

The relation of the PP to science-based risk assessment is causing considerable controversy. Particularly, the meaning of the principle, its scope, and its application raise debates. Advocating action without waiting for definitive science based answers has been interpreted by some as deviating from science (Holm and Harris, 1999). The disputes among scientists center on the issue of whether the PP should be involved when proofs of a cause-effect connection is lacking. According to the EU commentary, some scientific evidence about the nature of the adverse effect must be available before the PP is applied in environmental and health decision-making processes (EU, 2000). However, the difference between speculative theories and scientific evidence is problematic. The EU commentary adds that in situations where scientific uncertainty is disputed, a minor fraction of the scientific community may be heard if the scientists have a certain reputation and credibility (see 6.2 in EU, 2000).

Scientists developing new technology have acted as advisors for political authorities in connection with risk assessment and management of the very same technology. Earlier failure by expert-led health and environmental policies has created a mistrust of the use of mainstream scientific advice, and has raised questions whether scientific advice is independent and unbiased. New approaches to risk-associated questions may need to involve other sources, i.e., scientific judgments from other perspectives and practical knowledge (i.e., the public).

Many scientists have feared that initiatives to involve the PP in some instances may imply calling a halt to research. The opposite might, however, often be the case: acting on the basis of the PP might automati-

cally trigger research (Raffensperger et al., 1999). Hence, application of the PP may provide the best opportunity to narrow uncertainty about health and environmental cause and effects (Sternheimer, 1999).

#### GENETICALLY MODIFIED PLANTS (GMPs): RISK ISSUES

GMPs are at present being developed for a variety of purposes. Different generations are presented by the industry (RAFI, 2000). The first generation can be divided into three groups with regard to inserted transgenes: herbicide tolerance (74%), insect resistance (19%), and stacked genes (7%) (both herbicide tolerance and insect resistance) (James, 2000). Such GMPs are commercially available, and are developed to step up farming productivity, increase yield, and reduce costs for farmers. The second generation includes plants modified with the purpose of reducing processing energy, storage, and transport costs for food processors and food traders. Slow-ripening tomatoes belong to this generation, as well as plants with modified oils to meet specific requirements of processors. Applications with benefits for the consumers, the third generation, include anti-cancer vegetables, cholesterol reducing grains, plants with improved content of vitamins, and modified ornamental plants (as blue carnations and long-lasting flowers). The third generation also includes plant derived edible vaccines. They can be delivered at a lower cost for developing countries, as they will be easy to administrate, provide adequate and long-lasting protective immunity, and eliminate the need for refrigerated storage (Mor et al., 1998). Despite the immense potential benefits of these generations of GMPs, they are all inherently unpredictable due to lack of gene targeting. Hence, they may represent potential immediate and long-term environmental and health risks.

In order to modify an organism, a recombinant genetic vector needs to be constructed. The vector contains the gene(s) of interest (i.e., a herbicide tolerance gene), a control element (promoter/enhancer) to ensure gene expression, and a marker gene (i.e., providing resistance to antibiotic or cytotoxic substances). The integration site in the recipient chromosome is impossible to target with present methods, and whether multiple copies of the vector is inserted cannot be predetermined. After integration into cell chromosomes, the genetic modification may affect the gene expression and replication of the recipient cells. The cauliflower mosaic virus (35S CaMV) promoter is used as a control element in practically all GMPs commercialized or in field trials. The CaMV promoter may enhance or reduce expression of endogenous gene products. Formation of fusion proteins is possible, by read-through of the inserted DNA and plant DNA.

Mutagenesis may happen by random insertion into the genome, employing risk of activating silent genes. Different regulation of gene expression may disrupt the cell metabolism and alter biosynthetic pathways, hence causing serious changes in the functional properties of the organism (Doerfler et al., 1997). Potential secondary effects include changed levels of bioactive compounds in the organism, epigenetic silencing of genes, and altered levels of antinutrients as well as potential allergens and toxins (Inose and Murata, 1995; Lappé et al., 1999; Novak and Haslberger, 2000).

#### *Gene Transfer*

Data indicating gene flow from GMPs to natural, wild relatives, and feral population represents a real risk. Cases of cross-pollination have already been reported (Mikkelsen et al., 1996; Chèvre et al., 1997). Horizontal gene transfer to other organisms might happen between some species and across kingdoms (Nielsen et al., 1998). Horizontal gene transfer from transgenic plants to bacteria in the soil has been demonstrated under contained conditions (De Vries and Wackernagel, 1998). Special undefined ecological conditions and chemical pollutants (xenobiotics) may affect the frequency of horizontal gene transfer (Traavik, 1999). Although it has been clearly demonstrated that gene transfer may occur, no scientific consensus has been reached with regard to the significance it deserves in risk assessment.

In general, GMOs are designed to survive in the environment, they are able to migrate, mutate, and replicate. If the novel genes confer ecological advantage, they may be retained in the new organism and thereby creating widespread horizontal and also, possibly, vertical gene transfer (Myhr and Traavik, 1999). Hence, it is imperative to be aware of the irreversibility of ecological change that is inherent in the technology.

#### *Potential Ecological Effects of Herbicide-tolerant Plants (GMHTs)*

GMHTs promise decreased and changed use of herbicides. A number of first-generation GMPs are modified to tolerate glufosinat and glyphosat. Such transgenic plants hold promises for improved weed control and hence diminished use of chemicals and reduced soil erosion. It has, however, not been proven that glufosinat and glyphosat are environmentally inert. The increased application of these herbicides in commercial release causes a strong selection pressure towards the development of herbicide tolerant weeds. Herbicide tolerance genes might escape and be transferred into weedy relatives or other crops through cross-pollination. This has been reported for both oilseed rape and sugar beet (Mikkelsen et al., 1996; Chèvre et al., 1997). The use of DNA markers in GMPs can enhance

pollination of other plants. *Arabidopsis thaliana*, modified to tolerate the herbicide chlorsulphuron, developed higher ability to cross-pollinate than non-modified lines (Bergelson et al., 1998). In addition, wild type *A. thaliana* was more frequently fertilized by pollen from the transgenic plant than from non-modified plants, which in its turn also increased the probability of herbicide tolerance gene transfer. These findings have general relevance since the herbicide tolerance gene (*csr-1*) is now introduced into several plants as a selection marker for transformation. But so far, for most GMHTs, antibiotic resistance genes have been used as selection markers.

### THE LIMITATIONS OF RISK ASSESSMENT

In order to minimize health and environmental risk, pre-assessment of planned GMO release is demanded on a case by case basis. The purpose of the case-by-case practice is to treat every release as unique, since every GMO represents different genetic characteristics. Each applicant or notifier must obtain a prior consent from the authorities and has to perform deliberate release and field trials according to a step by step procedure, before the GMO may be commercialized. Risk management based on these principles is considered to be precautionary, since the use and production of GMO are regulated prior to documented harm, and it is required for any experimental or commercial release.

Extrapolation from one context to another, i.e., from laboratory research to small scale field trials and finally to commercial scale, raises many unanswered questions concerning the environmental fate of the GMO (Wolfenbarger and Phifer, 2000). Small scale use may provide valuable information related to, for instance, survival and persistence, competitive fitness, and some ecological implications of release. However, small scale trials are limited by size and management, and commercial release involves a higher number of GMOs to be released, as well as different and more complex ecosystems. Biological and ecological processes are complex and of a non-linear character. Ecological studies need to be carefully carried out over time, and at different sites, to reveal impact on relationships between species and ecosystem interactions. Inevitably, it is crucial to be aware that potential adverse effects may evolve slowly and through long chains of effects, which in most cases can not be reflected within small scale trials (Smith, 2000). Gene transfer of herbicide tolerance to weeds and crops is assumed to happen at low frequencies, but in the long run it might create resistant weeds and have impacts on ecosystems. Current practice is dependent on value-laden norms and judgments both with regard to evaluation of potential effects to be prevented

and standards of evidence (Levidow et al., 2000). In the case of GMPs, effects on surrounding agricultural and natural environment are too often excluded. Whether a more effective weed control, by use of GMHTs, causes declines in bird (Watkinson et al., 2000), invertebrate, and plant diversities needs to be properly investigated. How gene spread might effect conventional and organic agriculture as well as biodiversity in farmland and surrounding areas is unknown (Butler and Reichardt, 1999; Johnson and Hope, 2000). With the possibility of long term impacts, it is critical to determine whether the use of glufosinat and glyphosat have adverse effects on both the agricultural and natural environment. Development of alternative ways to deal with weeds, i.e., integrated pest control strategies, should be considered in order to lower pressure on ecosystems and biodiversity.

Market stage precaution, detection and monitoring of effects after the GMO has been introduced at a commercial level, intends to test claims about safety and benefits, as well as to avoid potential harm. Accordingly, the methods for detection and monitoring of effects become crucial, since they may influence whether important ecological considerations are overlooked or omitted. Encouragement of new monitoring and detection methods and tools are therefore vital for assessment and control of environmental and health impacts as well as collection of ecological knowledge of relevance to future releases.

#### ABSENCE OF PROOF IS NOT PROOF OF ABSENCE

It has been argued that there is not enough evidence to reject the hypothesis that GMO and GM food is safe. The fact is, however, that experiments designed to clarify potential adverse effects on health or the environment are nearly absent in peer-reviewed journals. Hence, scientists and regulators are more interested in avoiding false positives (type I-error), than false negatives (type II-error). Given the asymmetry in the consequences depending on the chosen hypothesis, application of the PP entails prevention of false negatives at the expense of some false positives. Consequently, if further research proves that there was no unintended adverse effects, the GMO is safe, the expense of safeguarding welfare might be some lost opportunities and economic profit.

For risk assessment of GM food, the concept of substantial equivalence has been used as a safety measure. Based on a chemical analysis, GM foods are compared with the non-GM counterpart. If a GMP is characterized as substantially equivalent to its traditionally bred counterpart, it is considered to represent similar risk and will then be approved for commercial use. Adequate assessment does, however, require a broader basis.



Evaluation based on biochemical and toxicological tests should be imperative (Millstone et al., 1999), but such comprehensive tests have not been applied to risk assessments so far. The reliance on the "substantially equivalent" has caused important research on possible risks of consuming GM food to be left on the shelf (i.e., immunology studies, feeding experiments, etc.).

Recent studies have strengthened the plausibility of adverse effects that were earlier considered insignificant, i.e., horizontal gene transfer, non-target effects, secondary effects on gene expression. The Ewen and Pusztai study has raised concern about the effects of lectin modification of plants (Ewen and Pusztai, 1999). They reported that feeding GM potatoes expressing the snowdrop bulb lectin (GNA) to rats, resulted in variable effects on different parts of the rat gastrointestinal tract. Another study that has been highly debated from a scientific point of view is the monarch butterfly study (Crawley, 1999). It was reported that monarch butterflies were susceptible to *Bacillus thuringiensis* (Bt) toxins expressed in Bt transgenic plants (Losey et al., 1999). The results were obtained in small scale laboratory, where the insects were fed on milkweed dusted with maize pollen at high levels in a non-choice test.

The snowdrop lectin and the monarch study has evoked a debate over the appropriate models and methods for testing secondary effects. Although the results were preliminary, they demonstrated that the present scientific uncertainty warrants further research. Furthermore, these studies have highlighted the risk of bias relying on hypotheses that dominate mainstream science, and hence the problem of omitted research (Garattini, 2000). Consequently, there is a need for independent research that is without prejudice and is unbiased by economic and professional interests. Experimental testing of carefully elaborated risk hypotheses may result in a solid basis for avoidance of potentially harmful GMOs. Such research may, however, also demonstrate ways to eliminate risks.

### COMMUNICATING UNCERTAINTY

Scientists ought to have a social and moral responsibility about the application of their work (Rotblat, 1999). This responsibility is with regard to research and technology development. In addition, scientists have a responsibility towards the environment and society. In this context, communication of uncertainty to the public and decision-makers becomes crucial. Particularly, if uncertain effects are not reported, the evidence required for the application of the PP in a particular case might not be known (Buhl-Mortensen and Welin, 1998). The decision-makers may

neither be aware of limitations to evaluation of scientific uncertainty nor possibilities for exclusion of important risk aspects (Lemons et al., 1997). More openness about both scientific evidence and uncertainty would make science more useful in risk regulation.

The bovine spongiform encephalopathy (BSE) epidemic has drawn attention to the inadequacies of conventional risk assessments and limitations of scientific advice. Contrary to conclusions from scientific advisers, the BSE prions passed a species barrier and initiated a new variant of Creutzfeld-Jacob Disease (v CJD) in humans. Although there was growing evidence supporting an etiological link, the British government failed to take the scientific uncertainty into account. To avoid such failures in the future, assumptions in risk assessment should be made clear and scientific uncertainty communicated (Aldhous, 2000). A quality assurance of information from scientific advisers is in this context essential. There is a need of means for incorporating information about uncertainty connected to estimates and evidence in the scientific advice (Funtowitz and Ravetz, 1993). Scientific uncertainties related to available GMOs may have been downplayed. The lesson from the BSE story should be that potential adverse effects should not be overlooked or underestimated, but communicated.

### TRUST AND PUBLIC INVOLVEMENT

In situations with uncertainty, risks estimated by experts often differ from the risks perceived by others, including the public (Thompson, 1997). In Europe, GMO use and production are met with growing skepticism among consumers (Gaskell et al., 1999). The industry has treated public concern as a problem based on ignorance and emotions. Although the public has gathered more knowledge and levels of conception have improved, the skeptical attitude has persisted (Nielsen, 1997). Hence, public concern may be due to public experience with earlier failures of scientific advice related to food security and ecosystem health. Such events have caused a distrust in the food industry, reduced the credibility of governmental agencies, and highlighted limitations of scientific advice.

Imposition of risk involves some sort of consent and opportunity of the public to take free and informed choices. Public information and participation are therefore required in matters with potential long-term effects, as with GMOs. Imperative for public participation is that scientific information and understanding are shared and transmitted openly and honestly. Einstein said, "We should be on our guard not to overestimate science and scientific methods when it is a question of human problems: and we should

not assume that experts are the only ones who have a right to express themselves on questions affecting the organization of society." This advice is still valid. However, mechanisms for balancing scientific advice with the involvement of other parties is needed. Extended peer-review might catalyze debates between the affected parties in meaningful ways, thereby integrating different viewpoints and enabling wider consideration of risk (Funtowiz and Ravetz, 1993).

A systematic way to measure public perception is consensus conferences. In 1995, 16 lay persons in Norway had the opportunity to confront experts and discuss whether genetically modified food was wanted in Norway. The lay panel concluded that at that time, there was no need for such food, and furthermore it emphasized the unclarified health and environmental aspects (NENT, 1996). Establishment of extended peer communities, also as a means of public involvement, represents important instruments during GMO decision processes for directing future GMO development.

Use and production of GM food products has evoked disputes about labeling. The consumers prefer to make their own informed choices, based on labeling of GM food or GM based products. At present, labeling raises questions about the reliability of detection methods that need to be further developed (Williams, 1998). Labeling is also a necessary basis for future epidemiological studies concerning GM food related diseases. Consequently, labeling is both an issue of consumer choice and of public health studies.

#### FUTURE OPTIONS

Regulation of GMO deals with a trans-scientific problem, i.e., the resolution of the problems is beyond the competence of the scientific system (Von Schomberg, 1998). A broader basis for decision is needed. Public perception and acceptance are dependent on trust and whether the products or processes benefit them as citizens and consumers. To take proper accounts of uncertainties and public concern, consideration of social, economic, and ethical impacts is needed. Hence, with the objective to capture benefits and to minimize the risk of adverse effects, application of the PP provides goals for future development and use of genetic engineering.

## ACKNOWLEDGEMENT

The research of one of the authors, Anne Ingeborg Myhr, was supported by the Norwegian Ethics Program, the Norwegian Research Council.

## REFERENCES

- Aldhous, P., "Inquiry Blames Missed Warnings for Scale of Britain's BSE Crisis," *Nature* 408 (2000), 3–5.
- Bergelson, J., C. P. Purrington, and G. Wichmann, "Promiscuity in Transgenic Plants," *Nature* 395 (1998), 25.
- Buhl-Mortensen, L. and S. Welin, "The Ethics of Doing Policy Relevant Science: The Precautionary Principle and the Significance of Non-significant Results," *Sci Eng Ethics* 4 (1998), 401–412.
- Butler, D. and T. Reichardt, "Long-term Effects of GM Crops Serves up Food for Thought," *Nature* 398 (1999), 652–656.
- CBD: Cartagena Protocol on Biosafety, Internet <http://www.biodiv.org/biosafe/protocol>, 2000.
- Chèvre A. M., F. Eber, A. Baranger, and M. Renard, "Gene Flow from Transgenic Crops," *Nature* 389 (1997), 924.
- Covello, V. T. and M. W. Merkhofer, *Risk Assessment Methods: Approaches for Assessing Health and Environmental Risks* (Plenum Press, New York, 1993), pp. 1–7.
- Crawley, M. J., "Bollworms, Genes and Ecologists," *Nature* 400 (1999), 501–502.
- De Vries J. and W. Wackernagel, "Detection of nptII (kanamycin resistance) Genes in Genomes of Transgenic Plants by Marker-rescue Transformation," *Mol Gen Genet* 257 (1998), 606–613.
- Doerfler W., R. Schubert, H. Heller, C. Kamner, K. Hilger-Eversheim, M. Knoblauch, and R. Remus, "Integration of Foreign DNA and its Consequences in Mammalian Systems," *TIBTECH* 15 (1997), 297–301.
- Domingo, J. L., "Health Risks of GM Foods: Many Opinions but Few Data," *Science* 288 (2000), 1748–1749.
- Ewen, S. W. and A. Pusztai, "Effects of Diets Containing Genetically Modified Potatoes Expressing *Galanthus nivalis* Lectin on Rat Small Intestine," *Lancet* 354 (1999), 1353–1354.
- EU: Commission of the European Communities COM, *Communication on the Precautionary Principle*. Brussels 02. February, Internet <http://europa.eu.int>, 2000.
- Foster, K. R., P. Vecchia, and M. H. Repacholi, "Science and the Precautionary Principle," *Science* 288 (2000), 979–981.
- Freestone, D. and E. Hey, "Origins and Development of the Precautionary Principle," in D. Freestone and E. Hey (eds.), *The Precautionary Principle and International Law* (Kluwer Law International, Netherlands, 1996), pp. 3–15.
- Funtowiz, S. O. and J. R. Ravetz, "Science for the Post Normal Age," *Futures* 25 (1993), 739–755.
- Garattini, S., "The Risk of Bias from Omitted Research," *BJM* 321 (2000), 845–846.
- Gaskell, G., M. W. Bauer, J. Durant, and N. C. Allum, "Worlds Apart? The Reception of Genetically Modified Foods in Europe and the U.S," *Science* 285 (1999), 384–387.

- Holm, S. and J. Harris, "Precautionary Principle Stifles Discovery," *Nature* 400 (1999), 398.
- Inose T. and K. Murata, "Enhanced Accumulation of Toxic Compound in Yeast Cells Having High Glycolytic Activity: A Case Study on the Safety of Genetically Engineered Yeast," *Int J Food Sci Technol* 30 (1995), 141–146.
- James, C., *Global Review of Commercialized Transgenic Crops: 2000*, ISAAA Briefs No. 21 (Ithaca, New York, Internet <http://www.isaaa.org>, 2000).
- Johnson, B. and A. Hope, "GM Crops and Equivocal Environmental Benefits," *Nature Biotech* 18 (2000), 242.
- Lappé M. A., E. B. Bailey, C. Childress, and K. D. R. Setchell, "Alterations in clinically important phytoestrogens in genetically modified, herbicide tolerant soybeans," *J Med Food* 1 (1999), 241–245.
- Lemons J., K. S. Shrader-Frechette, and C. Cranor, "The Precautionary Principle; Scientific Uncertainty and Type I and type II Errors," *Foundations of Science* 2 (1997), 207–236.
- Levidow L., S. Carr, and D. Wield, "Genetically Modified Crops in the European Union: Regulatory Conflicts as Precautionary Opportunities," *J Risk Res* 3 (2000), 189–208.
- Losey J. E., L. S. Rayor, and M. E. Carter, "Transgenic Pollen Harm Monarch Larvae," *Nature* 399 (1999), 214.
- Mikkelsen T. R., B. Andersen, and R. B. Jørgensen, "The Risk of Crop Transgene Spread," *Nature* 380 (1996), 31.
- Millstone E., E. Brunner, and S. Mayer, "Beyond 'Substantial Equivalence'," *Nature* 401 (1999), 525–526.
- Mor T. S., M. A. Gomez-Lim, and K. E. Palmer, "Perspective: Edible Vaccines – a Concept Coming of Age," *Trends Microbiol* 6 (1998), 449–453.
- Myhr A. I. and T. Traavik, "The Precautionary Principle Applied to Deliberate Release of Genetically Modified Organisms (GMOs)," *Microb Ecol Hlth Dis* 11 (1999), 65–74.
- NENT (The National Committees for Research Ethics), *Fast Salmon and Technoburger, Report from the Consensus Conference on Genetically Modified Food* (Oslo, Forskningsparken, Norway, 1996).
- Nielsen K. M., F. Gebbard, K. Smalla, K. M. Bones, and J. D. van Elsas, "Horizontal Gene Transfer from Transgenic Plants to Terrestrial Bacteria – a Rare Event?" *FEMS Microbiol Rev* 22 (1998), 79–103.
- Nielsen, T. H., "Behind the Color Code of 'No'," *Nature Biotech* 15 (1997), 320–321.
- Novak, W. K. and A. G. Haslberger, "Substantial Equivalence of Antinutrients and Inherent Plant Toxins in Genetically Modified Novel Foods," *Food Chem Tox* 38 (2000), 473–483.
- Raffensperger C., J. Tickner, T. Schettler, and A. Jordan, "... and Can Mean Saying 'Yes' to Innovation," *Nature* 401 (1999), 207–208.
- RAFI (Rural Advancement Foundation International), *Biotech's Generation 3. RAFI* (Communiqué 67/nov/dec, Winnipeg, Canada, Internet <http://www.rafi.org>, 2000).
- Rio Declaration on Environment and Development, Un.Doc/CoNF.151/5/Rev.1 (1992).
- Rotblat, Sir J., "A hippocratic Oath to Scientists," *Science* 286 (1999), 1475.
- Smith, J., "Nice Work – but Is It Science?" *Nature* 408 (2000), 293.
- Sternheimer, J., "How Ethical Principles Can Aid Research," *Nature* 402 (1999), 576.
- Thompson, P. B., *Food Biotechnology in Ethical Perspective*, Techniques and perspectives in Food Biotechnology 1 (Chapmann & Hall, London, 1997), pp. 216–240.
- Traavik, T., *An Orphan in Science: Environmental risks of Genetically Engineered Vaccines*, Research report for DN. No. 1999-6 (Directorate for Nature Management, Trondheim, Norway, 1999).

- Von Schomberg, R., *An Appraisal of the Working in Practice of Directive 90/220/EEC on the Deliberate Release of Genetically Modified Organisms* (Luxembourg: STOA, European Parliament. PE 166.953/Final/Rev, 1998).
- Watkinson, A. R., R. P. Freckleton, R. A. Robinson, and W. J. Sutherland, "Predictions of Biodiversity Response to Genetically Modified Herbicide-tolerant Crops," *Science* 289 (2000), 1554–1556.
- Williams, N., "Can Regulations Requiring Labeling of Genetically Modified Foods Work?" *Science* 281 (1998), 269.
- Wolfenbarger, L. L. and P. R. Phifer, "The Ecological Risks and Benefits of Genetically Engineered Plants," *Science* 290 (2000), 2088–2093.

*Department of Microbiology and Virology*  
*University of Tromsø and Norwegian*  
*Institute of Gene Ecology*  
*N-9037 Tromsø, Norway*  
*E-mail: annem@fagmed.uit.no*