Trend Analysis Biotechnology 2007

Options and Opportunities

Contents

SUMMARY 4

CHAPTER 1 INTRODUCTION, PLAN OF APPROACH 7

CHAPTER 2 APPROACH, METHOD OF ANALYSIS, AND JUSTIFICATION OF SELECTED TRENDS 9

CHAPTER 3 TRENDS, SOCIETAL OPPORTUNITIES AND DILEMMAS 15

3.1 ENVIRONMENT: BIOTECHNOLOGY OFFERS OPPORTUNITIES FOR THE ENVIRONMENT 15
3.2 ECONOMY: THE POTENTIAL OF THE DUTCH BIOTECHNOLOGY SECTOR IS INSUFFICIENTLY EXPLOITED 17
3.3 VACCINES: VACCINES AND THE RISE OF (SUB)TROPICAL INFECTIOUS DISEASES 20
3.4 LEGISLATION: TECHNOLOGICAL DEVELOPMENTS IN PLANT BIOTECHNOLOGY CALL FOR A RECONSIDERATION OF THE LEGISLATIVE AND REGULATIVE FRAMES 24
3.5 FOOD: IN THE YEARS AHEAD THE NUMBER OF GENETICALLY MODIFIED FOOD PRODUCTS ON THE STORE SHELVES WILL INCREASE 26
3.6 ANIMALS: PRODUCTS OF GENETICALLY MODIFIED ANIMALS END UP IN PHARMACIES 30
3.7 DIAGNOSTICS: STRONG INCREASE OF THE OPPORTUNITIES FOR GENETIC DIAGNOSTICS WHILE TREATMENT POSSIBILITIES ARE LAGGING 31
3.8 ETHNICITY: ETHNICITY AS A FACTOR IN SCIENTIFIC RESEARCH, GENETIC DIAGNOSTICS, AND GENETIC SCREENING 34

CHAPTER 4 TREND ANALYSIS 2004 37

CHAPTER 5 FINAL WORD, SOCIETAL OBJECTIONS AND GOVERNMENT POLICY 39

APPENDIX 1: ASSIGNMENT LETTER TREND ANALYSIS 41

APPENDIX 2: COMPOSITION PROJECT COMMISSION AND STEERING COMMITTEE 41

APPENDIX 2: COMPOSITION PROJECT COMMISSION AND STEERING COMMITTEE 42

APPENDIX 2: COMPOSITION PROJECT COMMISSION AND STEERING COMMITTEE 43

APPENDIX 3: LIST OF STAKEHOLDER RESPONSES 44

APPENDIX 4: TREND ANALYSIS BIOTECHNOLOGY 2004 47

Summary

Today biotechnology is having a growing impact on social and economic developments on a worldwide scale. To exploit its many opportunities maximally and make the proper choices regarding its various interrelated dilemmas, the Dutch government should be alert and adequate in its adopted policy approach. This trend analysis report focuses on eight ongoing trends that deserve particular attention from politicians and policymakers. In addressing these trends, three recurring and interconnected elements stand out: the pressure of globalization on national policy space, issues associated with public-private collaboration, and regulation that no longer ties in with global technological developments.

Environment: Biotechnology offers opportunities for the environment

Industrial biotechnology facilitates the realization of cleaner and sustainable production methods as well as the replacement of fossil resources by renewable ones. Industrial biotechnology can only live up to its promise, however, in a government-directed enhancement of the collaboration between government, industry, and social and scientific institutions.

Economy: The potential of the Dutch biotechnology sector is insufficiently exploited

The Netherlands has a strong position in the life sciences, an above-average number of biotech start-ups, and an above-average number of biotechnological patent applications. Still, the economic potential of the Dutch biotechnology sector is under-used. The Dutch government has to decide whether it will maintain its current policy, reduce restrictive legislation and regulation, and/or support larger investments through subsidies and fiscal measures in ways similar to those of governments in neighboring countries.

Vaccines: Vaccines and the rise of infectious diseases

In recent years there has been a strong rise of, often (sub)tropical, infectious diseases (‘emerging and re-emerging diseases’) in both humans and animals. In many cases treatment of these diseases is possible only to a limited extent. In addition, resistance to antibiotics in pathogenic bacteria is evolving into an increasingly larger problem. Vaccines are needed to avert their further spread and protect humans and animals. Modern biotechnological techniques enlarge the opportunities for the development and production of vaccines, yet for companies the development costs are high while they have no certainty about any returns. The Dutch government faces the issue of whether it should wait for businesses to start developing the appropriate vaccines on time, whether it should itself take the initiative to have vaccines produced, or whether it should put forward an European initiative.

Legislation: Technological developments in plant biotechnology call for a reconsideration of the legislative and regulative frames

The Dutch and EU GMO regulation considers an organism or product to be genetically modified if during the production process genetic modification is applied. In plant biotechnology, however, genetic modification can be applied as an intermediate step without the final product, the plant, being genetically modified. Regulation falls short here. The GM product cannot be distinguished as such, cannot be monitored when imported, and can be sold

without being labeled as GMO. This puts pressure on the consumers' freedom of choice and thus the government's credibility. The government has to decide whether to take the increasing shortcomings of the EU-system for granted in this respect, to no longer consider unmodified final products as GMO, and/or to look for new ways to ensure the consumers' freedom of choice, for instance through process monitoring.

Food: In the years ahead the number of genetically modified food products on the store shelves will increase

Given the increase of both the acreage and the number of genetically modified crops, in the near future consumers will encounter more and more genetically modified foodstuffs, be it as labeled product or as inadvertent mixture. This will seldom involve actual safety risks for public health, but it does affect the consumers' freedom of choice. As the number of incidents pertaining to labeling goes up, the call for more effective control will increase as well. This entails huge investments, however, while no surveillance system can be perfect. The government will have to find a balance between public perception, regulation geared to safety, and measures aimed at ensuring freedom of choice.

Animals: Products of genetically modified animals end up in pharmacies

The approval of medicines is currently an EU-affair. Medicines produced by GM animals are allowed on the European market because they may be advantageous to patients. In the Netherlands, however, genetic modification of animals is only permitted under special conditions. Given this situation, medicines may become available in the Netherlands whose production is potentially not allowed in this country on ethical grounds. The Dutch government has three options: accept the situation as it is, pursue adjustment of the EU-regulation to Dutch legislation, or bar these medicines from entering the country by imposing import restrictions.

Diagnostics: Strong increase of the opportunities for genetic diagnostics while treatment possibilities are lagging

More and better molecular-biological detection methods are becoming available for congenital and non-congenital disorders, which will allow for ever earlier and more frequent detection of these diseases, while treatment is not possible (yet). In the Netherlands treatability carries much weight in population screenings, but this principle is challenged by the increasing availability of tests. In addition, more and more dubious self-tests are offered, notably via the internet. The government faces the dilemma of how to deal not only with the call for more diagnostic tests with the costs involved. This puts pressure on genetic diagnostics and its careful embedding.

Ethnicity: Ethnicity as a factor in scientific research, genetic diagnostics and genetic screening

Genetic predisposition for certain diseases varies among ethnic groups. Moreover, the effectiveness of treating diseases with the help of medicines is affected by the patient's genetic background. In Europe, however, ethnicity is a charged issue, especially in relation to genetics. As a rule, one does not register the ethnic background of patients and subjects in medical trails in the Netherlands. The absence of these data is an impediment to genetic

diagnostics, screening, and scientific research. The government has to decide whether registration of ethnicity should be allowed, and if so, for which purposes and under which conditions.

Chapter 1
Introduction, plan of approach

This trend analysis has been performed at the request, dated 21 June 2005, of the then state secretary of the Netherlands Ministry of Housing, Spatial Planning and the Environment (VROM), also on behalf of his colleagues from the Ministry of Agriculture, Nature and Food Quality (LNV) and the Ministry of Health, Welfare and Sport (VWS) (cf. Appendix 1). This request followed in the wake of the first Trend Analysis Biotechnology, presented to the Dutch government in July 2004. The state secretary of VROM specifically asked the Commission Genetic Modification (COGEM), the Commission Biotechnology in Animals (CBD), and the Dutch Health Council to do a trend analysis of the developments in biotechnology that should contain the following elements:

- a sustained analysis of national and international biotechnological trends, with particular attention for trends that transcend the subfields of biotechnology;
- attention for shifts in the experience of relevant values in society;
- attention for the social risks and opportunities of biotechnology, in particular with respect to aspects of public health, the environment, agriculture, industry, and the economy. It was also asked to emphasize the extent to which specific developments may contribute to solving major social concerns at the national level, without thereby losing sight of the global context.

In the summer of 2005 the three organizations involved set up a steering committee in charge of organizing the performance of this trend analysis. This committee consisted of the chairpersons and secretaries of the three organizations involved and the chairperson of the joint project commission, led by the chair of COGEM (Appendix 2). The steering committee formulated a plan of approach, set up a joint project commission, initiated the process of realizing the trend analysis, and monitored its progress.

The project commission's formal assignment was to write the trend analysis at hand. The project commission was composed of members from the three organizing bodies (see Appendix 2). The commission's members were appointed on the basis of their expertise, with Prof. Dr. N.J. Leschot acting as commission chair. In early 2006, prior to the actual writing of this trend analysis, the various stakeholders in biotechnological developments in the Netherlands were given the opportunity to send in a list of trends or topics that in their view deserved attention. Furthermore, during a workshop a draft version of the trend analysis was presented to a broad group of stakeholders to be commented upon. A report on this workshop meeting can be found in Appendix 1 of the background study that is part of this trend analysis. The various points and concerns raised by these stakeholders were taken into account in drafting the final version of this trend analysis.

The authors of this trend analysis would like to indicate that the various stakeholders, who were granted the opportunity to name topics and comment on a draft version, had no say whatsoever in which topics were eventually addressed in this trend analysis, nor did they have specific input as to their actual treatment in the final version.

Chapter 2
Approach, method of analysis, and justification of selected trends

Biotechnology covers a broad field and the influence of modern biotechnology on both society and the economy is substantial. Biotechnological applications have made inroads in all sectors of society, including industrial and agricultural production and medical science. The new biotechnology also comes with specific social opportunities, such as cleaner and sustainable industrial production, improved chances of detecting diseases or genetic disorders, and the development of new pharmaceuticals. Some of the new applications, however, also trigger ethical dilemmas or provoke social concerns and fears. Examples include genetic modification in agriculture, the use of embryos in stem cell research, and specific health effects of new techniques for diagnosing genetic disorders.

The scientific developments in the field of biotechnology advance rapidly, X-omics[a] research serving as the main driver. As a result of our growing knowledge about genes, their regulation, and the organization of the genome of various organisms, new applications have come within reach, including new concerns and dilemmas as well. Research in the X-omics sciences is only in its infancy, it seems, and in the years ahead this work is bound to be further developed and expanded.

The newly gained scientific insights have already caused a blurring of the boundaries between the various sectors involved. Increasingly, specific developments are no longer subsumed under a single denominator such as agriculture, medicine, or industry. For example pharmaceuticals can be produced with genetically modified crops or living animals.

What is more, also the boundaries between scientific disciplines are disappearing. ICT has gained a steady foothold in biotechnology. Bioinformatics has become an essential and indispensable tool for analyzing and understanding the data flows of the genomics sciences. Some scientists believe that the next step is so-called ‘systems biology’, or model-based description of biological systems and the ability to predict interferences and adaptations in biological systems. Other scientists work on the convergence of biology and physics into one field of research, bionanotechnology. These developments give rise to a much wider scientific domain than merely biotechnology, genomics, or genetic modification as distinct practices.

The ongoing globalization also extends to science. It is increasingly harder for both the Netherlands and Europe as a whole to shield themselves from technological developments viewed as undesirable. Aside from the traditional scientific superpowers, Europe and the United States, new countries, especially in Asia, have become active players in biotechnology. Outside Europe, however, quite different considerations regarding biotechnological applications are put forward. The acreage of genetically modified crops continues to grow unabatedly outside of Europe, genetic modification of animals is hardly contested in many Asian countries, while (obscure) self-tests for diseases and genetic disorders are offered on the internet unregulated. All this has implications for the Netherlands. Whether we like it or not, these global developments put pressure on our national policy space.

[a] The term ‘X-omics research’ is used here as an umbrella term for such closely interrelated technologies as genomics, proteomics, and metabolomics.

Given the size of the biotechnology field, the rapid scientific developments, the countless trends to be identified, and the many questions triggered by the various technological developments, it is no simple matter to outline all the opportunities and dilemmas associated with biotechnology. There is, in addition, the risk that a mere summing-up of all trends, dilemmas, and opportunities will cause one to lose sight of the overall picture, while also the policy urgency of some trends is underexposed.

This is why in this trend analysis it was decided to zoom in on a limited number of trends that according to the authors deserve special attention from politicians and policymakers. Many of these trends are in fact closely intertwined because they are all guided by the new technological possibilities while also being influenced by developments abroad and changing levels of public acceptance.

Aside from the trends discussed in this trend analysis, the accompanying background study provides a *tour d'horizon* of major developments in biotechnology. Policymakers address some of the topics and trends mentioned in this background study already. Other issues will be raised in a subsequent trend analysis, when their plausibility increases.

Definition of biotechnology

It is hardly easy to determine which developments or applications should be subsumed under biotechnology and which should not. Because biotechnology is used to refer specifically to modern biotechnology in this trend analysis, a distinction should be made between modern and classic biotechnology. The latter comprises applications human beings may have employed for thousands of years already, such as the use of microorganisms to make cheese, beer, wine, or yogurt. The beginnings of molecular biology as foundational science for modern biotechnology, however, go back only to the middle of the twentieth century, when it was established that DNA is the carrier of genetic information.[1,2] Modern biotechnology itself emerged in the early 1970s, when genetic modification was first applied. Yet, biotechnology is more than just genetic modification. It also comprises applications such as marker-assisted breeding of plants and animals, stem cell research, cloning of animals, and modern diagnostic methods of forensic DNA research. In fact it is difficult to draw a strict line between what belongs to biotechnology and what does not. A clearly delineated scientific definition is absent. The OECD has formulated two, often referred to definitions of biotechnology.[3] The first definition seeks to give a description of biotechnology,[b] while the second one offers an extensive yet incomplete list of techniques and applications that fall under biotechnology.

This second trend analysis, including its related background studies, capitalizes on a pragmatic approach of biotechnological issues. It seeks to link up as closely as possible with how the media, policymakers, and the public at large, conceive biotechnology. Instead of pursuing a purely scientific interpretation of the term.

[b] *"Biotechnology is the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services."*

Criteria for selecting the spotlighted trends

The authors of this trend analysis realize that decisions on spotlighting trends are partly arbitrary and possibly influenced by the composition of the project commission in charge. In order to meet this concern as well as to arrive at a maximally objective and transparent selection procedure, the commission has formulated the following selection criteria:

- **Impact of a development:** The size and the intensity of the possible effects – positive as well as negative – on individuals or society. This applies, for instance, to the number of people involved, the financial impact (positive or negative) of the consequences, or the seriousness and size of effects. This criterion can be summarized as the following formula: Impact = intensity x size;
- **Policy/social relevancy:** Policy and political actions are possible and relevant in this field, whereby the Dutch Cabinet and Parliament serve as groups toward which this trend analysis is geared in particular[c];
- **Five-year timeframe:** The trend should be a current issue or require a policy or political action/decision within the next five years. This timeframe is partly tied to the fact that this trend analysis is performed every three years;
- **Verification:** It must be possible to establish the trend's topic scientifically or otherwise;
- **Newness:** The trend or topic has not been discussed yet in detail in recent reports from other Dutch organizations, unless the authors of this trend analysis disagree with the findings of these reports.

On account of these five criteria, several topics that have received much public attention are not spotlighted as a specific trend in this report. One example is stem cell research, which was addressed as a major trend in the 2004 trend analysis. This research has gained much attention in recent years and has also provoked great expectations as to its potential. In the near future stem cell research may perhaps enable regenerative cell therapy in many diseases, such as neurological disorders, but also heart diseases, diabetes, and rheumatism. Currently, stem cells capable of developing into various tissue types (pluripotent) can only be isolated from embryos. This has met with ethical concerns and objections. Stem cells can also be isolated from other tissue, but they are not capable of differentiating into any kind of tissue one prefers. In many countries it is prohibited to use human embryos for stem cell research. Before stem cell research will lead to clinically applicable results, much fundamental and clinical-experimental research is needed. It is likely, then, that the first applications will not be developed for years. Although right now stem cell treatments are offered, their scientific

[c] The following policy areas in which the Dutch Parliament can undertake action are distinguished:
- *Finances*. Does the trend identified lead to a desired increase or decrease of spending in specific fields?
- *Stimulating, slowing down or adjusting developments*. Can or should politics or policymakers take measures to stimulate the development, to adjust it into a specific direction, or to slow it down? (This involves the full array of measures available: financial measures in the form of subsidies or tax measures, measures to improve the entrepreneurial or research climate, and so on);
- *Ethical evaluation*. Does the development call for a guiding decision by Parliament, or should it reconsider an earlier decision?
- *Safety*. Should extra measures be taken to ensure safety, or is it in fact possible to do away with specific measures (legislation and regulation)?

basis and effectiveness are questionable, to put it mildly. Consequently, this topic does not meet the criterion of the five-year timeframe. The issue of whether embryos should be used does call for a political assessment, however. But on this matter much has already been published by various organizations, interest groups, and researchers, while several times the issue was debated in the political arena. Recently the new Dutch government coalition's agreement stipulated to prolong the moratorium on the specific generation and utilization of embryos for research in the Netherlands.[4] Based on these various factors, we have decided not to address stem cell research again in this new trend analysis.

Another novel development, the application of DNA testing in forensic detection techniques, is not included as a specific trend for similar reasons. Today, the options of DNA testing exceed merely the determination of whether particular DNA traces match with a suspect's DNA. Based on DNA traces it is possible today to make claims about the appearance of the potential perpetrator, such as his skin color. It is to be foreseen that in the near future much more far-reaching claims can be made. Although these new possibilities have triggered ethical and social concerns, it is an issue that has already been on the agenda of the Dutch Parliament. It was decided that based on DNA traces of unknown perpetrators only external personal features may be determined. Many other aspects associated with (large-scale) DNA testing have also been regulated by law.[5] In 2006 the Research and Documentation Center (WODC) issued an elaborate report that treats its technical possibilities and impossibilities, as well as its social and ethical concerns.[6]

Likewise, bionanotechnology has not been included as a prevailing trend. In recent years this branch of science has received much attention from the media and policymakers. Various organizations, including the Dutch Health Council[7] and COGEM,[8] have issued (advisory) reports on the implications of bionanotechnology. This scientific field holds great promise, yet within the next five years we do not anticipate major developments in the field of biotechnology or the life sciences that will lead to particular social or political dilemmas.

Science generally involves sustained efforts over lengthy periods of time. The media regularly announce new scientific breakthroughs that may lead to new treatments of diseases. Similarly, the emergence of new scientific fields, such as pharmacogenetics, synthetic biology, or 'systems biology', is often accompanied by claims, notably from the experts involved, about the spectacular new possibilities ahead. It should be noted, however, that usually many years pass between a first scientific discovery and an applicable product. Developing a pharmaceutical product into a commercial medicine lasts more than ten years, as is true of the development of a genetically modified crop. It takes many years before a new scientific field matures and its actual findings or applications become clear. The genomics era took off in 1991 with the Human Genome Project (HUGO), geared to unraveling the sequence of the humane genome. By 2007 the enormous impact of genomics sciences on the development of the life sciences and biotechnology is gradually becoming more evident.

Stakeholder consultation

As indicated, stakeholders in the professional field of biotechnology were given the opportunity at the start of the project commission's activities to send in a list of topics and trends. In its considerations the commission has taken into account the responses it received.

In late March 2007 the project commission has presented its preliminary findings to stakeholders in the format of a workshop. Based on a presentation and summary texts, eight trends were discussed. A report of the workshop meeting is added to the background study (as Appendix 1). The commission also received several written responses in relation to the workshop. An overview of all stakeholders who responded or participated in the workshop is provided at the end of this trend analysis report (cf. Appendix 3).

The responses from stakeholders during and after the workshop proved constructive and valuable input in the actual realization of this trend analysis. Their comments have led to the inclusion of additional and refined formulations in the text. Furthermore, during the workshop some ten topics were mentioned that in the view of one or more stakeholders should be included into this trend analysis. This involved the following topics (in at random order): 'free choice producers developing countries,' 'shifting regulation concerning GMOs leads to high costs for producer and others,' 'no guidelines but regulation,' 'personalized medicine,' large-scale scans of individuals possible within five years,' 'patenting of genetic material,' 'development of health claims about food,' 'the Netherlands is lagging in the area of using transgenic laboratory animals,' 'biobanks,' and 'stem cell research.'

The authors of this trend analysis subscribe to the importance of these topics, yet they feel that these trends do not (yet) represent a significance that warrants their inclusion in this report's limited number of prevailing trends. The reasons for not including stem cell research are discussed elsewhere in this trend analysis. The problem involving patenting genetic material is largely not biotechnology-specific and extensively treated in many reports. Similarly, developments surrounding health claims about food are not biotechnology-specific. In addition, European regulation on this topic has been enacted recently. Regarding 'genetic scans' and 'personalized medicine' it is doubtful whether these topics are realistic within the chosen five-year timeframe or whether they require policy adjustments. Regulation and its effects on innovation and society ('no guidelines but regulation' and 'differences in regulation in EU concerning GMOs lead to high costs') is a topic that is currently brought under the attention of both the government and the public along other ways already.[9] Biobanks are of preeminent significance for the further development of diagnostics and research, while there are also concerns involving privacy and such. However, because the KNAW recently issued a report on biobanks[10] and legislative initiatives have been taken, it was decided not to address this topic again in this report. Finally, the problem of genetically modified crops and developing countries was addressed in an advisory report recently issued by COGEM.[11]

Citizen consultation

In collaboration with the Ministry of VROM, a study was done of the views of Dutch citizens. This citizen consultation consisted of two parts: a qualitative study based on focus groups and a quantitative study in the form of a (web) survey. At the time of concluding this trend analysis, unfortunately the results of this citizen consultation were not yet available. Although the qualitative study was completed, verification of the focus groups' views in the form of a (web) survey was not yet performed. Given the limited size of focus groups and the risk that they do not provide a representative picture of the views of Dutch citizens, it was decided not to make use of the available preliminary results in this trend analysis. The outcome of the citizen consultation will be published together with Cabinet's response to this trend analysis.

Chapter 3
Trends, societal opportunities and dilemmas

In this chapter, eight trends are described that in the view of the authors of this trend analysis warrant discussion and deserve attention from the policy and political sectors. Biotechnology, like every science and its ensuing applications, is closely entwined with society at large and a host of developments within. The dilemmas and opportunities triggered by biotechnological developments are linked to general social concerns and developments. Recurring and interconnecting elements in the prevailing trends discussed below are influenced by globalization, the issue of public-private collaboration, and regulation that no longer ties in with actual developments. Each trend is described in terms of the specific dilemmas and opportunities involved. However, we offer no direct recommendations on how to deal with those dilemmas. It is up to politics to make decisions based on its discussion of these topics.

3.1 Environment: Biotechnology offers opportunities for the environment

Industrial biotechnology facilitates the realization of cleaner and sustainable production methods as well as the replacement of fossil resources by renewable ones. Industrial biotechnology can only live up to its promise, however, in a government-directed enhancement of the collaboration between government, industry, and social and scientific institutions.

The environmental problem is one of the great challenges of the twenty-first century. Questions that concern politicians, citizens, and scientists alike include, for instance, how CO_2 emissions can be reduced, how waste flows can be diminished, and how the spread of environmentally hazardous substances can be countered. The 2007 Dutch government coalition's agreement articulates as specific goals a nationwide energy saving of 2% per year, an increase of the share of sustainable energy to 20% by 2020, and a reduction of the emission of greenhouse gasses of 30% by 2020.[4] Industrial biotechnology[d] can play an important role to achieve this.

Biofuels

Both at home and abroad investments are done in the development of the so-called first generation biofuels. These fuels are made from edible plant parts, such as maize kernels and soy. First generation biofuels are already produced on a commercial level, but they have substantial disadvantages. In many calculations the CO_2 emission of the first generation biofuels is negative when compared to that of fossil fuels.[12] The amount of fuel needed for the production of first generation biofuels is in some cases even larger than the amount of fuel produced. Furthermore, the growing demand for biofuels leads to expansion of the acreage of oil palm and sugar cane plantations. These are partly realized in areas in tropical regions that

[d] In industrial biotechnology products are made with the help of (genetically modified) microorganisms of isolated enzymes. Enzymes are used to enable or speed up biological reactions. Microorganisms are deployed for the production of all sorts of substances such as vitamins, antibiotics, ethanol, enzymes, colorants, and aromatic substances. Today mainly sugars are used as basic material. It is expected that other renewable resources, such as biomass, will also be deployed more often in the future.

are still pristine; this leads to the fear of a further clearing of rainforests, which will have major consequences for biodiversity.[13] Finally first generation biofuels also come with other ethical and sociatal dilemmas, such as the recently raised price of maize for food products as a result of the increased demand for biofuels.[14] Recently, at the request of the Dutch government, specific criteria for sustainable biofuel development were formulated.[15]

The above mentioned objections have led to investments in second generation biofuel. The remainder and side flows from the agrifood sector are thereby deployed as resource, as in, for instance, the production of ethanol from potato peels, straw, and beet green. Wood chips, used paper, or special energy crops can be used as well. In the conversion of raw materials into biofuels, biotechnology is applied in the form of enzymes and production organisms that activate the conversions. Likewise, plants are genetically modified to allow for their easier deployment in the production of second generation biofuels.[16,17]

Second generation biofuels offer better chances for the environment than first generation biofuels because CO_2 reduction proves higher. Moreover, the remainders of food crops can be used, whereby the edible parts can serve as food supply. Non-food crops such as grasses can be exploited as well. Estimates on the timeframe in which one hopes to begin large-scale commercial production vary from five to ten years.[18,19,20]

Today, companies invest most in first generation biofuels while the share of second generation fuels is substantially lower.[21] Given the European[22] and American[23] plans to replace fossil fuels with biofuels in the short run and the interrelated tax breaks and subsidies, first generation biofuels have good returns on investments. Before large-scale production of second generation biofuels is possible, investments in (pre-competitive) research, among other things, are required.

Cleaner production methods

Industrial biotechnology has already produced environmental benefits, such as detergents that contain fewer phosphates and that are suitable for washing at lower temperatures through the adding of enzymes. Also, in the production of certain substances such as vitamin B_2 significant savings in the usage of energy, raw materials, and CO_2 emission have been realized through the deployment of genetically modified microorganisms.[24] It is expected that in 2010, ten percent of the fine chemicals, such as vitamins and artificial aromatics and flavors, are produced with the help of biotechnology.[25] Likewise, bulk chemicals such as plastics will increasingly be produced from renewable resources and based on biotechnology, even if here the share is likely to remain fairly small.[26] The success of this conversion will partly depend on the difference between sugar and oil prices. Companies will only invest if a product made with the help of biotechnology provides more economic benefits than one produced based on petrochemical production methods. Today industrial biotechnology is still largely dependent on sugar or food crops as raw material. In the light of the current high oil prices, many industrial biotechnology products increasingly compete with traditionally produced products. However, before the industry is really prepared to make a shift, there must be a stable price advantage of sugar over oil because otherwise the inevitably large investments will be too risky.

Focal points

- *Deployment of biotechnology offers opportunities in solving environmental problems. Before real breakthroughs can be achieved, large investments are required, for instance, to do pre-competitive research.*
- *Biofuels are often mentioned as possible solution for the environmental problem. However, first generation biofuels, in contrast to second generation biofuels, are hardly beneficial to the environment, if at all. Some calculations even show that the refining of one liter ethanol costs more energy than the same liter supplies through combustion in an automobile engine. Moreover, first generation biofuels come with specific ethical and social objections.*
- *Currently, however, it is still more interesting for businesses to invest in first generation fuels than in second generation fuels. The development of second generation fuels requires major and risky investments in research, which do not automatically result in easy returns.*
- *The degree to which chemical production processes can be replaced with cleaner biotechnological production processes is largely dependent on the interrelated pricing of raw materials, oil and sugar.*
- *The Netherlands has much of what is needed to attain a leading position in industrial biotechnology and the 'biobased economy.'[27] Dutch universities have long had a strong position in the fields of microbiology and process technology. But also Dutch knowledge institutions and businesses may contribute significantly to acquiring that position. The Netherlands has, moreover, various ports that can play a major role as mainport for biomass.[28] Only if government, business, and science will closely collaborate in the development of industrial biotechnology this country will be innovative and pioneering in this area.*
- *With the establishment of research programs such as "Kluyver Centre for Genomics of Industrial Fermentation" and "B-Basic" a first move has been made toward shaping this collaboration.[27] A decision has to be taken on whether continuation and further development of such initiatives is desirable.*

3.2 Economy: The potential of the Dutch biotechnology sector is insufficiently exploited

The Netherlands has a strong position in the life sciences, an above-average number of biotech start-ups, and an above-average number of biotechnological patent applications. Still, the economic potential of the Dutch biotechnology sector is under-used. The Dutch government has to decide whether it will maintain its current policy, reduce restrictive legislation and regulation, and/or support larger investments through subsidies and fiscal measures in ways similar to those of governments in neighboring countries.

The Netherlands has articulated the aspiration of wanting to belong to the leaders of the European knowledge economy by 2010.[29] Life sciences or biotechnology should play a key role. The Netherlands, after all, can build on an excellent basis. The Dutch universities and knowledge institutions belong to the best in Europe and the world. Recent study by the

NOWT shows that the numbers of scientific publications in the various subfields of biotechnology are way above global averages and belong to the highest in Europe.[30] The quality of scientific publications is above-average as well, based on the number of worldwide scientific citations per publication. Moreover, the patent position of the Netherlands in biotechnology can be qualified as average to good.[31]

Economic position new biotechnology companies

Comparison of the biotechnology sectors of various countries reveals, however, that the Netherlands is clearly lagging behind.[32] The specialized biotech companies in the Netherlands have on average few employees, a low output, and fail to attract venture capital[32,33]; at the same time, the number of companies is exceptionally high. Moreover, the contribution of the biotechnology sector to the gross domestic product (GDP) is lower than that in other countries.

It should be pointed out that data on the biotechnology sector are only available for companies that fully concentrate on biotechnology, the so-called 'dedicated' companies. They are seen as a major indicator of the strength of the biotechnology sector. No data are available on companies where biotechnology is only part of their activities, the so-called 'diversified' companies. These companies largely include the large established corporations such as Unilever, DSM, or processing companies. It is possible that in the Netherlands biotechnology is particularly strong in these 'diversified' companies and that the biotechnology sector is in better shape than the data on 'dedicated' companies suggest. However, the low R&D spending in the Netherlands seems to indicate this is not the case.[30,32]

The investments in the Dutch biotechnology sector are, in absolute terms, comparatively low, both in terms of government investments and private sector investments. That the country's R&D investments are falling behind is not a biotechnology-specific problem, however. The so-called R&D intensity in the Netherlands has strongly dropped over the last five years, which has caused the country to trail behind its neighboring countries and other competitors.[30] This decline is attributed in part to Dutch businesses' moving R&D activities to other countries.

In the case of the biotechnology sector, moreover, the limited availability of venture capital plays a role. The newly established small companies or start-ups have great trouble to keep on growing in the Netherlands. Venture capital is insufficiently available which has created a lack of funding. This cripples the development of start-ups in biotechnology in particular because the product development time is generally longer than in other sectors. In response to this situation, recently the BioGeneration Ventures Fund was set up with a capital of thirteen million euro. The financing of this fund has been realized through a combination of public and private means.[34] The fund is geared toward Dutch start-ups and young life sciences companies with the aim of bridging the current financing gap. But the available funds of thirteen million euro fall short by a wide margin, of course, when it comes to having more lasting effect.

The more limited availability of venture capital in the Netherlands and Europe in relation to the situation in the United States is hardly a new fact. In 2005 there was a strong hike in invested venture capital in European biotech companies.[35] Whether this rise will also become

visible in the Netherlands is uncertain. In countries such as Germany and France the government appears to have adopted a leading role by making available large sums as venture capital.[35]

In general, it seems, government in most countries invests more money in biotechnology and life sciences than in the Netherlands. Dutch public spending on biotechnology R&D is low compared to neighboring and other relevant countries.[32]

Biotechnology policy

In the past years the policy effort in the Netherlands has mainly been geared toward valorization of scientific knowledge, the stimulating of the entrepreneurial spirit at universities and knowledge institutions, and the establishment of new companies. Regarding this latter aspect, the Biopartner program has been very successful.[36] The target was to have seventy-five start-ups within four years, yet the actual number was exceeded by far.[37]

This seems to warrant characterizing the policy as successful. Moreover, the patent position and the many new start-ups also indicate that the entrepreneurial spirit at universities and knowledge institutions has gone up. Researchers show to be aware of the value of their results and protect them by patent applications. Universities and knowledge institutions promote, facilitate, and support the establishment of new companies in order to bring about the marketing of knowledge.

Even so the question can be put whether the Dutch government's policy in the past years, which was chiefly geared toward valorization by means of setting up new businesses by scientists and knowledge facilities, has been sufficiently effective. It is unclear whether most of these start-ups are viable at all. In this respect the lack of venture capital for further growth can be the ailment, but also a symptom. It is not impossible that these companies' (prospective) products prove less interesting than one initially thought or hoped.

Strikingly, biotechnology has made inroads into some business sectors, almost silently and largely unnoticed by the Dutch government. An example is the plant breeding industry. Companies in this sector transformed into biotechnology companies with the help of general fiscal stimulation measures such as the Promotion R&D Activities Act (Wet Bevordering Speur- en Ontwikkelingswerk, WBSO).

Aside from purely economic causes for a partly trailing biotech sector, other reasons may be pointed out. Lobby groups for biotech companies and research facilities denounce the many regulations and too restrictive legislation in the Netherlands and Europe.[38] The Dutch government has meanwhile decided to reduce the bureaucratic burden and simplify authorization procedures.

Already in the 2004 Trend Analysis Background Study it was observed that Flanders appeared to be doing better. By 2007 this is still true. Although the number of start-ups is low in Flanders, more foreign companies have branches there, while the biotech companies are larger, have more employees and sales, and are better at attracting investments. The success in Flanders is attributed to the Flanders Interuniversity Institute for Biotechnology (VIB). The approach of the VIB involved the selecting of a limited number of outstanding research groups, bringing them together in a single institute, and, importantly, leaving the valorization

of the knowledge generated to companies, rather than to scientists and knowledge institutions. This means that choices were made on actively supporting certain fields rather than others.[39]

Focal points

- *The economic situation of the Dutch biotechnology sector continues to trail that of other countries, despite its excellent starting position.*
- *The Dutch policy has been successful in raising the entrepreneurial spirit among scientists and knowledge institutions, but this has not (yet) led to a catching up with the other countries.*
- *The Dutch policy has led to a very high number of new start-ups, which as of yet do not seem to grow.*
- *In successful countries in this sector, such as the United States, Singapore, Belgium, France, and Germany, public and private investments are substantially higher than in the Netherlands.*
- *Too restrictive regulation may be an element, but a clear and well-founded comparison between the pressure of regulations in the Netherlands and other European countries is unavailable.*

3.3 Vaccines: Vaccines and the rise of (sub)tropical infectious diseases

In recent years there has been a strong rise of, often (sub)tropical, infectious diseases ('emerging and re-emerging diseases') in both humans and animals. In many cases treatment of these diseases is possible only to a limited extent. In addition, resistance to antibiotics in pathogenic bacteria is evolving into an increasingly larger problem. Vaccines are needed to avert their further spread and protect humans and animals. Modern biotechnological techniques enlarge the opportunities for the development and production of vaccines, yet for companies the development costs are high while they have no certainty about any returns. The Dutch government faces the issue of whether it should wait for businesses to start developing the appropriate vaccines on time, whether it should itself take the initiative to have vaccines produced, or whether it should put forward a European initiative.

Emerging diseases

Many (sub)tropical viruses have extended their range and today they are also found in regions with a moderate climate. Viral diseases can spread rapidly. The *West Nile virus* offers a case in point. Originally this virus only occurred in Africa. It is transmitted by mosquitoes and may infect human beings, animals, and birds. In the late 1990s this virus surfaced in New York and within four years it had spread across 70% of the United States. By 2006 it was found throughout United States.[40]

The spread of this kind of viruses is often closely linked up with increased dispersal of their transmitters, mainly mosquito species. Since the 1980s, Dengue (dandy fever) has been on the rise worldwide. The virus is transmitted by various species of mosquito, including *Aedes albopticus* and *A. aegypti*. Until into the 1970s, partly thanks to eradication programs, the latter occurred in the Americas only in a limited number of countries around the Caribbean, roughly the area from Suriname, Venezuela, the Caribbean islands to Florida in

the United States. Today this mosquito is found throughout South and Central America, except mountainous areas at higher elevations.[41] Dengue, absent until the 1980s, now occurs from Mexico way down into most of South America.

The spread of diseases and their transmitters involves an intricate range of social, technological, and ecological factors, such as increased globalization and global warming. It is unmistakable that the recent winters in Europe were milder,[42] which is why these viruses survive in more northerly regions. The recent outbreak and persistence of the Blue tongue virus in Belgium, Germany, and the Netherlands is an example of this.[43] Given the projected climate warming, the chances of having mild winters further increase. This means that in the near future Europe will be confronted with a variety of new diseases that previously only occurred in (sub)tropical regions. Treatment of viral diseases tends to be very difficult. The availability of vaccines may stop or prevent the further expansion of these diseases.

Many bacteria can cause diseases in human beings as well. Generally these diseases are fought effectively through administering antibiotics. The number of cases of antibiotics resistant bacteria is increasing, however.[44] Excessive administering of antibiotics to human beings and the application of antibiotics in livestock has caused bacteria to become resistant more often and more rapidly.[45] Many older antibiotics are no longer usable, and there are bacteria that are resistant to (nearly) all antibiotics. Antibiotics resistance is seen as one of the largest worldwide problems in health care.

In the absence of antibiotics, vaccines are an effective tool for preventing infections and the spread of diseases. In some cases vaccines can be deployed as curative tool as well.

Vaccines

Vaccination of human beings has occurred already since the early nineteenth century. In the Netherlands children are currently vaccinated against eleven diseases. This has led to the nationwide eradication of several diseases, such as diphtheria. Apart from the vaccines that are part of the current National Vaccination Programme, several vaccines against other diseases are available. Quite recently the Dutch Health Council issued an advice on the future of the National Vaccination Programme and which vaccines ought to be part of it.[46] In this trend analysis, therefore, this issue will not be further addressed.

Previously vaccines consisted of weakened or inactivated stems of a virus or bacteria. Vaccination leads to an immune response, which protects the vaccinated individual against later infections with wild-type pathogenesis. Biotechnology and the new DNA techniques have led to major changes.[47] Techniques such as ‘reverse genetics’ have led to identification of virulence factors (factors that determine the pathogenic level). Today genetically modified weakened viruses can be constructed from which the genes responsible for pathogenesis and virulence have been removed. The advantage is that one can work with fully characterized viruses and that the chance of reverse mutation to a more pathogenic virus is strongly reduced. It is also possible to use only one or some proteins of the pathogen as vaccine. This fully prevents problems of injecting a potentially strong pathogenic organism. The proteins involved can be produced in fermentors with the help of cells, GM bacteria, or yeasts.

Modern biotechnological techniques have also opened up the possibility of producing so-called DIVA vaccines (Differentiating Infected from Vaccinated Animals) for the vaccination of animals. Before, it was not possible to distinguish between animals vaccinated against a certain animal disease and infected animals. Both animals have the same antibodies in their blood. This implies that exports of meat and livestock are not possible because importing countries demand that animals are disease-free. This explains why vaccination against livestock diseases such foot-and-mouth is not allowed for economic reasons. By applying DIVA vaccines it is possible, however, to distinguish vaccinated animals from infected ones because the vaccine consists of specific proteins rather than the whole pathogen. The removal and killing of healthy animals in response to the outbreak of diseases such as foot-and-mouth or avian influenza meets with major sociatal objections. The availability of DIVA vaccines, which seems to eliminate one of the main arguments against immunization, puts pressure on the current practice.
Also, methods of vaccine production have changed. More often vaccines are produced in cell systems in large fermentors, the advantage being that large quantities of vaccine can be produced rapidly, as opposed to the traditional egg culture methods.

The new techniques and broadened options for vaccine development and production have led to substantially higher costs. This proved a threshold for pharmaceutical companies to invest in this industry, while the number of vaccine producers has dropped over the past years.[47]

Vaccines and 'emerging diseases'

The currently available vaccines are chiefly directed at diseases that occur in the Western world. There are also vaccines available against pathogens from developing countries for which it is fairly simple to produce a vaccine. Yet it proved hard to produce vaccines against a number of tropical diseases, such as Dengue or the West Nile virus. Vaccine production is a largely private affair. Large investments are required for partly risky scientific (biotechnological) research to develop vaccines against complex viruses and bacteria. For companies it is uncertain whether they can recover the costs of these investments if this will depend on the hardly substantial market of developing countries. This accounts for the fact that no vaccines are available yet against a number of now rapidly spreading diseases. Only when a disease surfaces outside the developing countries, the development and production of a vaccine is taken up.

That new viral diseases will crop up in Europe is certain.[48] It is harder to predict, however, when and where they will occur. The development and production of a vaccine against one such disease can last up to fifteen years and is accompanied with substantial costs, without prior certainty that the vaccine will ever be sold in Europe. Companies, therefore, are unlikely to take a proactive approach in this area.

Another issue is whether countries should view this concern as a national affair. Today vaccine production is mainly a commercial and national affair without there being much coordination among countries. But coordination and collaboration that relies on specific expertise available at institutes and facilities in the various European member states would potentially reduce both the cost and the development time of vaccine production. Moreover,

the various parties might share the costs involved. This requires active coordination at an European level.

New vaccines

Because of the new opportunities provided by biotechnology for the development and production of vaccines, several new applications have become available. Recently the new vaccine against cervical cancer was in the news. This involved questions such as: should both women and men be vaccinated and at what age, and should the vaccine be integrated in the National Vaccination Programme? The Dutch Health Council has announced to issue an advisory report on this in the short run. The vaccine is geared toward the *Human papilloma virus* and thus it does not differ, at least from a strictly scientific angle, from other vaccines.

The increased knowledge about the role of genes, proteins, and the new possibilities for producing vaccines also leads to entirely new opportunities. There are vaccines being developed that are not aimed against pathogens and that give rise to entirely new concerns. For example, experiments with a vaccine against prostate cancer which targets antigenes present on tumor cells.[49,50] This forces the immune system to attack and remove the cancer cells. Work is also being done on vaccines to help smokers quit their addiction. Preliminary results from small-scale phase I and II studies seem positive.[51] In 2007 one of these vaccines will be tested on six hundred subjects in the Netherlands.[52,53] This topic involves a number of concerns. For example, does it turn smoking into a disease with mainly physiological causes? And can it be demanded in some cases that a patient has himself vaccinated, such as when smoking forms an immediate and acute threat? And what is an immediate and acute threat, partly in light of the risk of lung cancer of both smokers and those exposed to passive smoking?

Focal points

- *Europe and the Netherlands will be confronted in the near future with the outbreak of partly new human and animal diseases whose treatment will be challenging if not impossible.*
- *These diseases partly originate in (sub)tropical regions and they spread rapidly on account of a complex of climatological, societal and ecological factors.*
- *Vaccines constitute an essential instrument to counter the spread of these diseases and protect the population. The development and production of a vaccine can by a lengthy affair. This is why vaccine development requires a timely approach.*
- *Biotechnology has enhanced the opportunities for developing and producing more effective vaccines.*
- *The development of technically difficult vaccines is expensive. Business will only manage to recover these costs when there is a substantial market. This is one of the reasons that no vaccines have been developed yet against a number of the major (sub)tropical diseases.*
- *It may be considered whether better coordination and collaboration within Europe between public and private parties allows for a more proactive approach of vaccine development.*

3.4 Legislation: Technological developments in plant biotechnology call for a reconsideration of the legislative and regulative frames

The Dutch and EU GMO regulation considers an organism or product to be genetically modified if during the production process genetic modification is applied. In plant biotechnology, however, genetic modification can be applied as an intermediate step without the final product, the plant, being genetically modified. Regulation falls short here. The product cannot be distinguished as such, cannot be monitored when imported, and can be sold without being labeled as GMO. This puts pressure on the consumers' freedom of choice and thus the government's credibility. The government has to decide whether to take the increasing shortcomings of the EU-system for granted in this respect, to no longer consider unmodified end products as GMO, and/or to look for new ways to ensure the consumers' freedom of choice, for instance through process monitoring.

In the European regulation it was chosen as a reference point that genetic modification comes with inherent risks and that all products in which genetic modification played a role in the production process should be subject to stringent safety standards. This has led to the so-called process approach. One should speak of a GMO if genetic modification is deployed in the production process. This is defined in European legislation and regulation. Directive 2001/18[54] defines a GMO as "*an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.*" As the directive stipulates "*Within the terms of this definition: (a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1.*"

This suggests on the one hand that a genetically modified organism (GMO) has to contain changed genetic material, but, on the other hand, that there is genetic modification if certain techniques are used. This leaves room for different interpretations. The definition of a GMO relies on a product approach (the final product is modified), while the definition based on techniques relies on a process approach (in the production process specific techniques are employed).

At the time of the legislation's formulation this constituted no problem, as application of the techniques listed resulted in an organism with changed genetic material. Today, however, because of the technology's advances it has become possible to use recombinant DNA techniques without it giving rise to an organism with changes in the genome.[55] This problem plays a role in particular in plant biotechnology or plant breeding.

An example of a technique in plant breeding whereby during the process genetic modification is used is 'reverse breeding'.[55,56] The aim of this technique is not to produce a modification in the plant, but to accelerate the breeding process by skipping specific steps, such as reverse crossings and selection steps. In an intermediate step in the 'production process' one of the parent plants is genetically modified. In the later breeding process, however, the transgene is removed by outcrossing and the ultimate plant contains no inserted sequences or other changes to the genome.

A second example of no longer suitable regulation is mutagenesis. Breeders select, among other things, on spontaneous mutations in the genome through which the plant or animal obtains altered features. Mutations can also be induced by means of radioactive radiation or chemical mutagentia. This form of mutagenesis falls explicitly outside the scope of the GMO regulation.[54] In the past mutagenesis was frequently applied in plant breeding, but it comes with a host of drawbacks. A large number of random mutations are inserted in the genome of which the effects are unknown. The breeder tries to select plants with what to him are favorable mutations and to get rid of the other mutations through reverse crossing. By linking mutagens to a small piece of DNA (oligonucleotide) a site-specific mutation can be fitted. The base sequence of the oligonucleotide is complementary to the DNA base sequence in the genome where the mutation is to be inserted. Thus the oligonucleotide binds on that specific site, after which the mutagens can do its work. Thus the number of random mutations in the genome is minimized.

Today it is also possible to insert specific mutations in the genome with the help of only an oligonucleotide. Thereby random mutations are almost completely prevented. Despite both methods being safer than 'classic' mutagenesis, while also bringing about the same results, in Europe, according to the Dutch government, they do fall under GMO regulation because a nucleic acid, the oligonucleotide, is used.

Considerations

First, regarding the application of new biotechnological techniques it is impossible in a number of cases for the government to monitor how the product is made. A 'reverse breeding product' cannot be distinguished from a wild-type plant. Products that result from site-specific mutagenesis cannot be distinctive from classic mutagenesis products or normal breeding products. If the developer does not indicate the product falls under GMO regulation, it is not identifiable as such.

Second, in regulation in countries such as the United States the product approach is used. In these countries a GMO is an organism in which foreign genetic material is inserted. The above-mentioned products will not be considered as a GMO in the United States and many other countries. When imported in the Netherlands or the European Union, however, these products would suddenly have to be labeled as a GMO. Chances this will actually occur are small. After all, in the producing country these are not registered as such, and they can neither be recognized as such nor controlled.

Focal points

- *The government faces the decision whether it will continue to rely on the process approach. If it does, this means it will put pressure on the labeling of GMOs. After all, in imports from other countries it cannot be checked if the production process involved application of genetic modification. This may cause non-labeled products to enter the market that according to Dutch regulation should be considered as GMOs. This may undermine not only the consumer's freedom of choice, but also the government's trustworthiness.*
- *If it is decided to employ the product approach, it will be one that better links up with major trade partners. The problem of controllability is better met as well.*

- *Some groups in Dutch society (such as the biological sector) favor a strict process approach and want to remain free of products whereby genetic modification has played any role.*[57]*In the choice for a product approach their current right to freedom of choice is restricted. In order to guarantee this freedom of choice, the adoption of a GMO-free quality mark seems the ultimate consequence. This calls for complete process control, which probably can only be executed by large companies. Also the burden of proof of the current labeling requirement is reversed, as is true of the associated cost of labeling, process control etc.*
- *The business sector meanwhile argues that the development and commercial application of these economically interesting techniques are frustrated because it is not clear whether the products fall under GMO regulation indeed. But abroad, such as in the United States and Canada, this lack of clarity is absent while developments seem to progress rapidly.*
- *The decision on either a product approach or maintaining the current process approach is no national affair. This issue is decided at the European level. The Netherlands, due to its large and active plant breeding sector, is taking the lead in this discussion. Most European countries still seem hardly aware of the technological developments within plant biotechnology and their social consequences. Given these consequences and the economic interests of the breeding sector it seems justified that the Dutch government both defines its position on this and initiates the discussion in Europe.*

3.5 Food: In the years ahead the number of genetically modified food products on the store shelves will increase

Given the increase of both the acreage and the number of genetically modified crops, in the near future consumers will encounter more and more genetically modified foodstuffs, be it as labeled product or as inadvertent mixture. This will seldom involve actual safety risks for public health, but it does affect the consumers' freedom of choice. As the number of incidents pertaining to labeling goes up, the call for more effective control will increase as well. This entails huge investments, however, while no surveillance system can be perfect. The government will have to find a balance between public perception, regulation geared to safety, and measures aimed at ensuring freedom of choice.

Increase GM crops acreage leads to inadvertent mixture

The acreage of GM crops continues to grow worldwide.[58] In addition, the number of GM crops will also go up, given the many ongoing field trails worldwide.[27] This will cause a growth of the number of GM products on the world market, which in turn increases chances of (inadvertent) mixture of a batch of food products with GM products.

In Europe there is an obligation to label GMOs.[59] The absence of a GMO label does not mean that the product cannot contain GMOs. If a GMO in Europe has been approved, a minor contamination to 0.9% with this GMO in non-GM batches is permitted; this means GM labelling is not required for the contaminated product. For non-approved GMOs the threshold value is zero. The threshold value of 0.9% offers producers the possibility to export GM-free products from regions where also GM cultivation occurs and where zero tolerances are

untenable. Such a threshold value thus allows minor mixture during processing. It is to be expected that in the future minimal mixture will occur ever more frequently because it is impossible to keep the production chain fully GMO-free. It should be added that it is a requirement for GMO authorization to supply a detection method. This allows for detection of mixtures with authorized GMOs. This does not apply to non-approved or unknown GMOs. Detection methods are unavailable, which makes it hard to uphold the zero tolerance.

In the past years, the European Union has been confronted several times with mixture of commercial batches with non-authorized GMOs. In 2005 it turned out that an approved GM maize line had become mixed with small quantities of the GM maize line used in research.[60] The mixture was sold between 2001 and 2004. In 2006 a producer reported to the authorities in the Unites States and Europe that a non-approved GM rice variant had become mixed with normal batches of rice.[61] After checks in European countries several shiploads proved to be contaminated. Late 2006 there were also reports of adventitious presence of GMOs in Chinese rice. Greenpeace and Friends of the Earth reported to have found GM rice in imported rice products from China, notably in Asian specialties stores in Great-Britain, France, and Germany. After these reports the European Commission took immediate measures, such as intensified surveillance and the refusal of contaminated batches. Based on these reports, one importer in the Netherlands removed rice vermicelli from the store shelves.[62] Although at the time of reporting it was not possible to provide full certainty, in these incidents with non-authorized GMOs it was established afterward that at no point the food and environmental safety was compromised.[63,60] In its inspections, the Dutch Food and Consumer Product Safety Authority (Voedsel en Waren Autoriteit, VWA) also regularly discovers mixtures of foodstuffs and feedstuffs with GMOs (2 to 5% above the threshold value of 0.9%) for which a validated detection method is available (in EU-authorized GMOs).[64]

These incidents involving GM maize and GM rice reveal several similarities. In these cases there was an adventious presence of experimental lines that also the producing country did not approve for commercial applications, while the reports are from the company itself, or an NGO. And only in later, targeted control, the government was able to establish the adventious presence.

The incidents call into question whether the EU policy can be held up in practice. After all, the monitoring of non-approved GMOs seems all but watertight, while the willingness of companies to report the possible adventious presence of GMOs, which are approved in the producing country, will probably be smaller.

The European Union is a large-scale importer of many agricultural products from all parts of the world. For governments it is impossible to monitor imports effectively. It is also a very costly affair: sampling a shipload of rice amounts to about € 25,000.[64] This is why monitoring is largely left to the market parties. Official guidelines or standards for testing of mixture are absent in part, notably regarding non-approved or unknown GMOs. The business sector currently spends millions on tests (as on sowing seed purity) which are not generally accepted and of which it is unclear whether they work. It is also an issue whether it is possible to develop standard tests or guidelines for the detection of unknown GMOs.

Increase of labeled GMOs

The number of GM products on Dutch store shelves dropped to about sixteen in recent years.[65] These are mainly products that contain GM soy, such as soy sauce or margarine. For the large foodstuffs corporations and large store chains it seems to have been no problem so far to put GM-free products on their shelves.

Some foreign producers (farming organizations, breeding associations) who in the past were very critical about the development of GM crops for fear of losing the European market, currently appear to be more positive about newly developed GM crops. The traits inserted in the past offered farmers too little advantage over the risk of losing markets. With the insertion of new traits this same consideration may well have another outcome. On account of a change of mind among producers the share of GM-free on the world market can decline while rates go up in respect to GM products.

In the past years the processing industry proved capable of finding alternatives for GM products. The supply of especially other kinds of oil and fats is large on the world market, and the food industry can switch to various vegetable oils and fats without needing to adjust the final product or production process. There were no large price differences. With the increasing demand for biofuels, the prices of vegetable oils and products go up. This makes it harder for the processing industry to switch to non-GM products against the same rates. Consequently, it is possible and not unlikely that the number of products containing GMO and labeled as such will increase on the store shelves.

Flavorings and aromatic substances and products derived from animals fed with GMOs

Increasingly the application of biotechnology finds its way into food ingredients, such as aromatic substances and flavorings. Consumers hardly have knowledge of this because food additives, vitamins and such produced by genetically modified micro-organisms do not need to have a GMO label. Meat, milk, eggs, and other products from animals fed with GM feed also fall outside the labelling obligation. The share of GM feed is expected to go up in the years ahead. Opponents of GM agriculture, such as Greenpeace, resist such lack of labelling obligation for milk and meat from animals fed by GM feed.[66] These products can in no way be distinguished from that of animals fed with conventional feed. The government would therefore be unable to monitor such labelling obligation, unless by monitoring and certifying the entire production chain.

Societal acceptance

Various studies have been conducted on the attitude of European and Dutch citizens and consumers regarding GM food and GM agriculture. Some of the results are at odds. The Eurobarometer study shows that support for GM food and agriculture in the Netherlands has dropped in the past years.[67] A recent survey by TNS NIPO, commissioned by commercial TV channel RTL4, reveals a more positive attitude regarding genetic modification of plants.[68] Both studies reveal a strong increase of the consumer's willingness to buy if the GM product is healthier. By the same token, a substantial number of Dutch consumers and citizens

continues to reject GM food, partly on fundamental grounds. This group rejects being exposed to GM products in any form. Results from surveys should be interpreted critically, however. The manner and sequence of questioning can have much influence on the results. Only a wider availability of GM products in the stores may generate more unambiguous information on societal and consumer acceptance.

Government

Based on legislation, strict approval standards, and the deployment of science, the government tries to create credibility and support for its policy regarding genetic modification.

The government monitors food safety through an extensive authorization system and strict approval standards. GM food products are allowed to enter the market only after extensive testing for food safety and other aspects. In the light of the elaborate approval standards it is hardly surprising that there are no indications that consumption of GM products has led to public health problems. In large parts of the world, GM food products are being consumed on a large-scale basis without adverse effects. Most scientists feel, then, that GM food is as safe as conventional food products. Still, a segment of the consumers in Europe perceive GM food products as unsafe.

Furthermore, the government tries to protect the consumer's freedom of choice by a labelling obligation for GM food products. Incidents with inadvertent mixture with GM products constitute a threat of that freedom of choice. So far there have been no health risks whatsoever. Still, there are citizens and consumers who view such incidents as a threat to food safety. These incidents, moreover, can strengthen the sense that the government's safety monitoring falls short. The labelling obligation thereby seems to have an opposite effect: if the government requires labelling of food containing GM components the product is likely to be harmful in some way. A similar yet non-related problem pertains with the reference of 'E-numbers' of food additives on food labels.

Focal points

- *In the years ahead it is to be expected that the number of labeled GM food products on the store shelves will increase.*
- *The number of cases of the adventious presence of GMOs will go up. Although most of these cases will not exceed the EU threshold value of 0.9 %, some will do so.*
- *It is impossible for the government to exercise effective control of imported batches on the presence of GMOs. What is more, surveillance of non-approved GMOs is technically difficult if not impossible because detection methods are absent. This implies that business itself is in charge of control efforts, which are very expensive without offering guarantees that the control methods are effective or offer protection against liability. Moreover, companies run the risk of damage to their image and loss of sales. Poor monitoring can undermine the labelling obligation and thus erode guarantees of freedom of choice.*
- *The government tries to guarantee the safety for human beings and the environment by strict regulation and authorization standards, while also creating credibility and support for its policy regarding genetic modification. Given the limited support for GM food and the public's distrust regarding the safety of GM food, this appears not to have succeeded.*

After all, the government allows GM food products on the market that a segment of society views as unsafe, while it also proves incapable of fully barring contaminations with non-approved GM food products from imports.

- *An increase of incidents with the adventious presence of GMOs can harm the confidence of the public and consumers in the government. These incidents are mainly a threat to consumer's freedom of choice and pose no risk to public health. The incidents can lead to a call for more and more stringent government control. More effective surveillance, however, requires huge investments, while it is impossible to have a waterproof control system in this context.*
- *The government faces the challenge to bridge the gap between societal acceptance and public perception on the one hand and actual safety risks and its options for ensuring safety on the other. Thereby the government will have to distinguish clearly between risks for humans and the environment, such as food safety, and ensuring the freedom of choice of consumers.*

3.6 Animals: Products of genetically modified animals end up in pharmacies

The approval of medicines is currently an EU-affair. Medicines produced by GM animals are allowed on the European market because they may be advantageous to patients. In the Netherlands, however, genetic modification of animals is only permitted under special conditions. Given this situation, medicines may become available in the Netherlands whose production is potentially not allowed in this country on ethical grounds. The Dutch government has three options: accept the situation as it is, pursue adjustment of the EU-regulation to Dutch legislation, or bar these medicines from entering the country by imposing import restrictions.

The Netherlands has adopted a 'no, unless' policy regarding genetic modification of animals. This implies that in the Netherlands animals can be genetically modified only if a. the interventions have no unacceptable consequences for the health and wellbeing of animals, and b. there are no ethical objections to the interventions.[69] These criteria constitute the starting point of an ethical assessment in the context of the extensive public authorization procedure, whereby it is also assessed whether there are no realistic alternative ways to achieve the same goals. This ethical assessment is done by the Committee for Animal Biotechnology (Commissie Biotechnologie bij Dieren, CBD). In practice this means that genetic modification of animals is not approved for sports, entertainment, food production and such, but that applications for medical-scientific research are acceptable. No other country in the world has such separate legislation. There are signs that this legislation has led to less application of genetic modification of animals in the Netherlands than elsewhere and that companies have moved their activities to other countries.

The production of raw materials for medicine through genetically modified animals is growing outside the Netherlands. These products will be offered on the European market for registration. If the European Commission approves them, the Netherlands will also have to approve them on its market. For authorization on the European market, attention is paid in particular to the effects and the side-effects of these products.

A good example of this development involves the introduction of ATryn on the European market and thus the Dutch one. On 2 August 2006 the European Commission authorized the placing on the market of ATryn. The antithrombin alfa (ATIII), produced by transgenic goats, is approved for application in patients with a congenital antithrombin deficiency. This disorder is inherited by one in 3000-5000 people. Treatment of antithrombin deficiency with ATIII is already taking place. So far the protein is derived from human blood conserves, with all its associated risks and drawbacks. The new preparation is produced by an American company and will be made available in Europe in 2007.

To justify the generation of transgenic production animals based on the Dutch criteria, the transgenic product ought to have clear advantages, such as in purity, health risks or sufficient availability. It is up to the CBD to assess this on a case by case basis.

Considerations

It is to be expected that in the years ahead several products that were developed in a similar way will be made available on the European market. A number of products is already in an advanced stage of development. This means that the Dutch government will increasingly be confronted with the situation outlined above, namely that (effects of) developments have to be accepted which based on national regulation would meet with objections or of which it is at least unclear whether they would be allowed to occur in the Netherlands.

Focal points

- *In society, there is a strong opposition against biotechnology in animals. However, there is also the factual reality that products of biotechnology in animals become increasingly available. The government faces the challenge of making these opposites subject to discussion and if possible reducing the existing tension.*
- *Ways to reduce this tension include:*
  1) *Refusing the products – medication – on the Dutch market. This policy would conflict with European regulation and might harm patients' interests disproportionately.*
  2) *Pursuing European harmonization. This can be done by adjusting the typically Dutch approach to the European regulation, which has the further advantage of generating a more attractive context for research in our country. On the other hand, genetic modification of animals will increase in the Netherlands. Another option is to try to integrate those elements from the Dutch approach in European regulation that are more broadly supported at the European level (assessment of the effects for animal health and wellbeing).*

3.7 Diagnostics: Strong increase of the opportunities for genetic diagnostics while treatment possibilities are lagging

More and better molecular-biological detection methods are becoming available for congenital and non-congenital disorders, which will allow for ever earlier and more frequent detection of these diseases, while treatment is not possible (yet). In the Netherlands treatability carries much weight in population screenings, but this principle

is challenged by the increasing availability of tests. In addition, more and more dubious self-tests are offered, notably via the internet. The government faces the dilemma of how to deal not only with the call for more diagnostic tests but also with the issue of who pays for them. This puts pressure on genetic diagnostics and its careful embedding.

Prenatal diagnostics and pre-implantation genetic diagnostics

Couples that want to have children but that also have an increased risk of getting a child with a monogenetic disorder, for instance because it runs in the family, may be referred for heredity counseling. The same applies to inherited chromosome disorders. If there proves to be a raised chance of the disorder among descendants, there are several options. One can decide against having children, or opt for a form of prenatal diagnostics or pre-implantation genetic diagnostics (PGD) if available for the disorder involved.[70] In prenatal diagnostics through chorion villus sampling (CVS) or amniocentesis this specific disorder is targeted, and then there are only two options: either it is excluded that the unborn child will be affected by the disorder or it is established that it will surely be affected. In this case the parents can opt for terminating the pregnancy. In PGD eventually only a non-affected embryo will be put back into the womb.

Molecular diagnostics in hereditary disorders that occur later in life

A growing group of clients who ask for advice will receive a referral for 'heredity counseling' in relation to a possibly raised chance of contracting a particular congenital disease themselves. This mainly applies to hereditary forms of breast/ovarian cancer as well as colon cancer. If indeed a congenital form of cancer is involved, the emphasis is on prevention. This entails difficult considerations of course, such as on preventive removal of mammary gland tissue. Furthermore, it applies to neurodegenerative diseases, such as Huntington's, for which no preventive options are available. In this case, the motivation for genetic testing lies strictly in the desire to know, so as to be able to take it into account in one's life plan.

Population screening

Another effort is geared toward stimulating the prevention of inherited disorders through screening.[71] Today every pregnant woman is informed about the options of prenatal screening for Down syndrome.[72] Only for women over 35 this screening is free of charge. If there is a raised chance of Down syndrome, invasive diagnostics can be performed by CVS or amniocentesis. Today prenatal determination of a chromosome disorder is also possible via molecular methods. It is possible to limit the diagnostics to Downs syndrome excluding other chromosome disorders. Its pros and cons are currently a topic of debate. In addition, all pregnant women are offered an extensive ultrasound test some twenty weeks into their pregnancy. In the case of deviations additional laboratory diagnostics is needed. This has to be done quickly because if serious disorders are found, parents may request the pregnancy to be terminated up to 24 weeks in the Netherlands.

Since early 2007 all newborns are tested for 17 disorders.[73,e] In selecting these 17 disorders the notion of 'treatability' was center-stage. Recently a discussion was started on whether infant screening should be extended to include several untreatable disorders in relation to the risks for a following pregnancy.[74,75]

New insights into the regulation of gene expression, transcription, and translation have also led to new ways of unraveling and predicting the molecular pathogenesis of various non-specific genetic disorders. For some forms of cancer there are tests available that may give insight into a patient's prognosis. This also allows for more targeted treatment.

Multifactorial disorders

The options for molecular diagnostics of the more often occurring multifactorial disorders (caused by interplay of various factors, both genetic and exogenous ones) are substantially more limited today. The molecular unraveling of this group of disorders is still in its infancy. It is assumed that these disorders involve a genetic sensitivity because of small variations (polymorphisms) in multiple genes. One thereby assumes an exogenous influence that would respond to the individual variation(s) in the DNA as well. People tend to have high expectations from testing options, partly thanks to the publicity around monogenetic disorders. Some internet businesses that offer (self) tests cater to this, but the quality and reliability of their tests is dubious. For patients and consumers it is not clear how reliable these tests are and how results should be interpreted.

The increased possibilities of genetic testing have resulted in great expectations among the public. The demand for genetic tests is expected to rise further. The possibilities of treating genetic disorders are still very limited, though. At the same time, a genetic diagnosis has almost always drastic consequences for relatives as well, which is why genetic testing is always embedded in hereditary advising via the Special Medical Interventions Act (Dutch: Wet op bijzondere medische verrichtingen).

Focal points

- *With the introduction of 'high-throughput' technologies the development of diagnostic testing occurs ever more rapidly.*
- *The gap between diagnostics and treatment is bound to increase for the time being.*
- *The demand for genetic testing keeps rising: this puts pressure on its careful embedding.*
- *Patients/consumers will increasingly use the internet to have a DNA test performed. For its proper interpretation, they will still call on the Dutch health care system.*
- *The basic assumption of treatability in neonatal screening will also be challenged.*

[e] Phenylketonuria (since 1974); congenital hypothyroidism (since 1981); adrenogenital syndrome (since 2000); and as of 1 January 2007: biotinidase deficiency; galactosemia; glutaric aciduria type I; HMG-CoA-lyase deficiency; holocarboxylase synthase deficiency; homocystinuria; isovaleric acidemia; long-chain hydroxyacyl-CoA dehydrogenase deficiency; maple syrup urine disease; MCAD deficiency; 3-methylcrotonyl-CoA carboxylase deficiency; sickle cell anemia; very-long-chain acyl-CoA dehydrogenase deficiency; and tyrosinemia type I (on 22 February 2007 it was decided to remove screening for this last disorder from the neonatal 'heel prick' for the time being because of too many fault-positive results. A new test is being developed).

3.8 Ethnicity: Ethnicity as a factor in scientific research, genetic diagnostics, and genetic screening

Genetic predisposition for certain diseases varies among ethnic groups. Moreover, the effectiveness of treating diseases with the help of medicines is affected by the patient's genetic background. In Europe, however, ethnicity is a charged issue, especially in relation to genetics. As a rule, one does not register the ethnic background of patients and subjects in medical trails in the Netherlands. The absence of these data is an impediment to genetic diagnostics, screening, and scientific research. The government has to decide whether registration of ethnicity should be allowed, and if so, for which purposes and under which conditions.

Scientific research

In the scientific research of multifactorial disorders the interrelationship between genetic predisposition and multifactorial disorders will only become clear if the ethnic background of patients and subjects in the control group is known. Today this is mostly not the case. In so-called association studies that are used in the research of multifactorial disorders, one tries to establish small changes (polymorphisms) in the DNA that are specifically associated with the chance of contracting a certain disorder. Increasingly it is found that the results of such studies in one ethnic group cannot be automatically translated to another ethnic group.

Diagnostic DNA testing

In diagnostic DNA testing ethnicity can play a role as well. The laboratory search for a mutation in the BRCA genes, which are associated with hereditary breast and ovarian cancer, still involves a very time-consuming process. One type of mutation is found more often in women with an Ashkenazi-Jewish background, and it differs from that found in women with another ethnic background. It would be effective to take this data into account in DNA diagnostics. But this requires that this ethnic background is known in the laboratory where the test is performed. Today this is not the case.

Large-scale screening

Also in large-scale screening a choice will have to be made whether ethnicity should or should not play a role and whether one should or should not do specific testing. An example of this is the recently extended 'heel prick' examination. All newborns in the Netherlands are now tested for sickle cell anemia. Although in the Netherlands this is a rare disease, it occurs mainly among people who live in or come from malaria-stricken regions, such as in Africa.

On the island of Cyprus, targeted genetic screening for forms of hereditary anemia (thalassemia) has led to the virtual disappearance of this serious group of disorders. In the Netherlands one has not yet dared to offer such testing in a systematic way to people only based on their ethnic background.

Against this backdrop the concern is raised whether it could be meaningful to start registering the ethnic background of patients and subjects in situations outlined above. But registration of data on ethnicity is still controversial for historical reasons as well as concerns about their possible abuse and/or discrimination.

Focal points

- *More insight into 'ethnic' predisposition can have advantages in the treatment of patients. Genetic background may determine how patients respond to medication and the raised risk for specific disorders.*
- *Also, in scientific study one can achieve results faster regarding genetic unraveling of common disorders if ethnicity is used as a variable. In setting up biobanks, ethnicity of patients and control groups (non-patients) is also relevant.*
- *Furthermore, in diagnostic testing and screening a choice will have to be made on whether ethnicity should play a role and whether one should target specific groups in testing.*
- *Registration of ethnicity can have benefits but is also contested. Some worry that the registration of ethnicity will not be restricted to the above mentioned medical purposes, but will also extend to other (social) terrains, which poses the risk that ethnicity will be tied to ethnic discrimination.*

Chapter 4
Trend analysis 2004

Trend analysis 2004

In 2004 the first trend analysis on biotechnology in the Netherlands was put together by the CBD, the Central Committee on Research involving Humane Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO), and the COGEM. The three commissions were asked to pay attention in particular to moral dilemmas that emanate from biotechnological developments. The 2004 trend analysis was set up differently than the current one. In 2004 some twenty trends were identified that might lead to public debate and that more or less offered a representative picture of the developments in biotechnology. Eight of these trends were singled out as being principal (see Appendix 4).

Several of the trends marked as most important in 2004 still prove current and are addressed again in this 2007 trend analysis. Other trends are not treated in this analysis because they have been surpassed by other developments and are thus no longer relevant or because they did not meet the 2007 selection criteria.

Two of the trends in 2004 involved the increased options of diagnosing genetic deviations and disorders, including the interrelated consequences for the individual and society. These trends return in this analysis, albeit in a changed form and with other accents. The concerns expressed in 2004 regarding the insurability in relation to the growing diagnostic options as regards inherited diseases have not (yet) materialized. But many in society are greatly concerned about this topic.

The influence of globalization on the policy design concerning biotechnology was a major theme in 2004 as well. Topics such as the (im)possibility to stop imports of GMOs are again on the agenda. In 2004 it was observed that in this context the co-existence of conventional and genetically modified agriculture in order to safeguard the freedom of choice of consumers and producers would grow more important. Meanwhile the various parties in the Netherlands agreed on a covenant on the co-existence, including the organic farmers and the seed industry.[76]

One of the other primary trends involved the ecological risks of the introduction of GMOs in the field to fight diseases or plagues or to protect local animal species. Over the past three years little has happened regarding this topic and plans for the introduction of such GMOs appear to have been mothballed, partly on account of the risks for the fauna in other parts of the world. This is why it was decided not to discuss it in this new trend analysis.

A trend that attracted attention in 2004 involved the destruction of field trails, the possible growing radicalism of activists and the pressure this put on the issue of governmental transparency (‘openbaarheid van bestuur’) and a policy of *not* disclosing actual field trail sites. In 2004 a reversal of public opinion in favor of gentech-agriculture seemed immanent, on account of which arguments from fanatic opponents would reverberate less strongly in public opinion, which could have provoked radicalization among those who want to be put in the right after all. By 2007 a clear turn in public opinion does not seem to have materialized. Various studies in this area partly conflict with each other, but they make clear that today there is no widespread acceptance.[67,68] Since the first experiments in 1986 field trails have been sabotaged in the Netherlands. In the early years groups claimed responsibility for

specific actions, but for several years this has not happened any longer. It must be observed that in the past twenty years not one activist was arrested for destroying field trails. Although personal attacks on scientists or farmers as occurred in England did not take place in the Netherlands, the issue of animal testing and biotechnology in animals does provoke more aggressive actions from activist groups. In 2005 VROM changed the rules regarding the location-indication of field trails. No longer are exact locations being published, but a four square kilometer indication to make it harder to destroy crops. Before the success of this new approach could be established, the Dutch Council of State judged that it is too large an area indication in relation to the field trial size. The importance of the transparency of governance seems to be given priority over the importance of countering destruction and preventing possible damage for the operator. Given the abovementioned developments, this trend is not discussed again.

Because of the afore mentioned reasons, the trend selected in 2004 involving stem cell research is not included in this current trend analysis.

Finally, the 2004 trend analysis discussed pharma crops and the potential interrelated risks. Pharma crops are geared toward the production of medication in plants. In the United States various field trails have already been conducted. The production of pharmaceuticals in genetically modified plants offers both economic and social benefits.[77] It may also be tied to social resistance and risks, however, especially when food crops are used. In the United States one conducts mainly experiments with crops such as genetically modified maize or rice because there is much experience in processing these products. Large food corporations fight experiments with pharma crops for fear of contamination of their products and the associated negative publicity. This has partly contributed to a delayed development of pharma crops. Producers and developers increasingly look for other possibilities such as non-food crops or the production of pharmaceuticals in plant cells in fermentors. In the light of these developments, it was decided not to discuss pharma crops as one of the selected trends in this 2007 trend analysis.

Chapter 5
Final word, societal objections and government policy

A trend-based analysis of scientific developments and the opportunities and dilemmas caused by these developments has its limitations. Both the opportunities and the dilemmas implied in technological innovations cannot be seen in isolation of the wider challenges and problems of society. It is not possible to treat these in an all-comprehensive manner. In composing this trend analysis it was purposefully decided to restrict analysis to the immediate effects of biotechnological developments. This also means that the developments are set alongside contemporary society and its current norms and values and the ways in which it is structured and functioning.

The development of science and its applications does not occur in a vacuum. Rather there is mutual influencing of science and society. Science practitioners, companies, and institutions are part of society. Technological innovations, then, not only raise social questions; they are simultaneously part of and answer to existing public concerns or dilemmas.

One of the stakeholders was right to observe that biotechnology may render the production of aromatic substances and flavorings more friendly to the environment, but that it is even friendlier to the environment to abstain from producing these substances altogether. This equally applies to biofuels. The second generation biofuels may help to reduce CO_2 emissions. But a worldwide reduction of mobility and lowering of industrial production would undoubtedly cause a larger reduction of CO_2 emissions. This calls for a radically different organization of society – an issue that falls outside the scope of this trend analysis.

Shifting values

In a number of the selected trends of this trend analysis the dilemmas of technological progress, including its possible advantages and ethical concerns, are clearly reflected. Social and ethical objections or concerns are no fixed data but can shift over time. When in 1978 the first test tube baby was born, many responded disapprovingly, arguing that human beings should not make artificial babies and that creating new life was up to God. In 2007 there is no ethical discussion about the acceptability of IVF treatment; at most there is discussion on whether its cost should be part of basic health insurance. In this sense any description of ethical dilemmas merely reflects views at a given moment. Some of the ethical and social objections will evaporate in time, while others will emerge or persist for a long time.

The Eurobarometer study shows that European citizens grow more optimistic about the possibilities of biotechnology for making life more pleasant.[67] In the Netherlands this optimism has been on the rise uninterruptedly since 1993. Its further increase will reverberate in respect to the level of acceptance of biotechnological applications among citizens, consumers, or patients. The acceptance of genetically modified food and agriculture appears to be lagging for the time being, even though the consumer's acceptance and intention to buy seem to have gone up in the past years if the food product is accompanied by a health-enhancing claim. It remains to be seen whether these survey results will be confirmed when these products are available to consumers.

Government policy

The success of any innovation depends on its acceptance by citizens and consumers. Occasionally biotechnology touches concerns of life directly, thus sometimes eliciting ethical questions, fears, and discontent. The introduction of such a socially contested technological innovation proved no easy matter. The government was sometimes following in the wake of technological developments, which gave rise to social unrest and resistance. In the 1970s worried scientists themselves were the ones to sound the bell on possible risks for humans and the environment associated with genetic modification. Initially the government merely responded, only formulating policies a posteriori. As it turned out, public unrest had already reached such level that now, thirty years later, the dust has not settled yet. The government has tried to win the citizens and consumers' confidence through strict measures and authorization systems, guaranteeing safety and facilitating technological progress. It succeeded only in part.

The (Dutch) government seems aware of the mistakes that were made in the past and is now adopting a proactive approach. It is increasingly engaging in 'risk-governance'. More than in the past, the government has attention for an integrated approach of risks, promises, and trends, as is also reflected in the formal assignment of this trend analysis itself. In addition, it has an array of options at its disposal for channeling possible socially contested technological innovations. Thereby the government makes use of these options by involving both scientists and other parties in the decision processes, by having additional scientific research performed, as on specific risks, and by promoting public debate at an early stage. Today, research funding is not only set aside for innovation, but also for study of risks and public debate. Moreover, a wider spectrum of interests is embraced than just those of politics or consumers.

This new policy may still meet with resistance as well. Activist groups may view the attention for the social perception and the government-funded research as sop or 'social lubricant'. Some researchers may experience the new policy merely as useless draining off of their own research budgets to social-ethical issues.

It seems that the right approach regarding major social concerns is to involve all interested parties early on and to formulate shared or collective goals as ways to achieve agreement on the proper direction of specific developments. Although this certainly involves time-consuming processes, the social debate on genetic modification has taught us that trench warfare between proponents and opponents leads to an even longer impasse with major drawbacks for all parties. The government's newly adopted course of action appears a most suitable approach for preventing problems from the past from happening again.

Appendix 1:
Assignment letter Trend analysis

VROM

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Directie Stoffen, Afvalstoffen, Straling
Straling, Nucleaire en Bioveiligheid

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Trendmatige analyse van biotechnologische ontwikkelingen

Datum	Kenmerk	Afschrift aan
21 JUNI 2005	SAS/2005123070	Voorzitter van de Tweede Kamer der Staten Generaal

Geachte heer Zoeteman,

Bij deze wil ik u nogmaals bedanken voor uw inspanningen bij het totstandkomen van de Trendanalyse Biotechnologie 2004. In januari 2005 is het kabinetsstandpunt op de Trendanalyse naar de Tweede Kamer verstuurd[1]. Daarmee is de trendmatige analyse van biotechnologische ontwikkelingen voor 2004 afgerond.

In de aanbiedingsbrief bij het kabinetsstandpunt op de trendanalyse is onder andere stilgestaan bij de volgende trendmatige analyse. Daarbij is aangekondigd dat uw organisatie ook voor die trendanalyse om medewerking zal worden gevraagd. Bij deze wil ik u mede namens de minister van Landbouw, Natuur en Voedselkwaliteit en de staatssecretaris van Volksgezondheid, Welzijn en Sport verzoeken om uw medewerking bij de opstelling van de volgende Trendanalyse biotechnologie. Deze trendmatige analyse zou in 2007 gereed dienen te zijn.

De volgende trendanalyse zou, gelet op de tijd die beschikbaar is voor het opstellen ervan, de volgende onderdelen kunnen bevatten:

- een uitgewerkte analyse van nationale en internationale biotechnologische trends, waarbij in het bijzonder aandacht is voor die trends die de deelgebieden van de biotechnologie overstijgen (overkoepelend overzicht)
- aandacht voor verschuiving van de beleving van waarden in de maatschappij
- aandacht voor kansen èn risico's van biotechnologie voor de maatschappij, in het bijzonder op het gebied van de volksgezondheid, het milieu, de landbouw, de industrie en de economie. Daarbij vraag ik u met nadruk om ook stil te staan bij de mate waarin de ontwikkelingen een bijdrage kunnen leveren aan het oplossen van grote maatschappelijke vraagstukken die in Nederland spelen, daarbij de mondiale context niet uit het oog verliezend.

Bij het opstellen van het kabinetsstandpunt op de Trendanalyse biotechnologie 2004 is rekening gehouden met de mening van burgers en belanghebbenden. Hiertoe zijn burgerpanels gehouden en zijn

[1] Kamerstukken II, vergaderjaar 2004 – 2005, 27 428, nr 57

belanghebbende organisaties om hun mening over de Trendanalyse gevraagd. Ik wil de opstellers van de volgende trendanalyse graag in de gelegenheid stellen die zelf te presenteren aan burgers en belanghebbende organisaties. Een nader uit te werken mogelijkheid hiertoe zou een met mijn departement gezamenlijk georganiseerde workshop kunnen zijn. Vervolgens zal ik met de meest betrokken bewindspersonen van de andere departementen de trendanalyse voorzien van een standpunt en doorsturen naar de Tweede Kamer.

Naast uw organisatie heb ik de Commissie Biotechnologie bij Dieren en de Gezondheidsraad om hun medewerking verzocht. Daartoe heb ik de voorzitters van deze organisaties een brief van vergelijkbare strekking gestuurd. U wil ik verzoeken om het initiatief te nemen tot het opzetten van een overlegstructuur tussen de voorzitters van de betrokken organisaties. Graag laat ik het aan die organisaties zelf over of zij zichzelf voldoende toegerust vinden om bovenbeschreven trendmatige analyse op te stellen, of dat betrokkenheid van aanvullende organisaties benodigd is.

Ik dank u bij voorbaat van harte voor uw inzet om de trendmatige analyse van biotechnologische ontwikkelingen tot een succes te maken.

Hoogachtend,
de Staatssecretaris van Volkshuisvesting,
Ruimtelijke Ordening en Milieubeheer,

drs. P. L. B. A. van Geel

Appendix 2:
Composition Project Commission and Steering Committee

Project Commission

Chairperson

Prof. Dr. N. Leschot	Academic Medical Center Amsterdam

Members

Prof. Dr. Ir. W.E. Bijker	Maastricht University
Prof. Dr. F. Brom	Rathenau Institute / Wageningen University
Prof. Dr. W. van Delden	University of Groningen (emeritus)
Prof. Dr. H. Dons	Bioseeds B.V. / Wageningen University
Dr. J.M. Fentener van Vlissingen	Erasmus MC Rotterdam
Prof. Dr. J.H.J. Hoeijmakers	Erasmus MC Rotterdam
Prof. Dr. M.B. Katan	VU University Amsterdam
Dr. W.R.F. Notten	TNO
Dr. B.P.H. Peeters	CIDC-Lelystad
Ir. H. de Vriend	Lis Consult
Prof. Dr. D.L. Willems	University of Amsterdam
Prof. Dr. A.G.J. van der Zee	University of Groningen

Advisors

Ir. S.J. Beukema	CBD
Dr. G.H.M. ten Velden	Dutch Health Council

Secretary

Dr. Ir. F. van der Wilk	COGEM

Steering Committee

Chairperson

Prof. Dr. Ir. B.C.J. Zoeteman	Chair COGEM

Members

Ir. S.J. Beukema	Secretary CBD
Prof. Dr. J.A. Knottnerus	Chair Dutch Health Council
Prof. Dr. E. Schroten	Chair CBD
Dr. A. Wijbenga	General secretary Dutch Health Council
Dr. Ir. F. van der Wilk	Secretary COGEM (secretary)

Appendix 3:
List of stakeholder responses

As stakeholders were approached: companies, employer organizations, scientific institutes and organizations, professional bodies, patient and consumer organizations, and NGO's, engaged with biothechnology.

Written responses at the start of the activities

In April 2006 approximately thirty-five organizations were approached with the request to send in a list of relevant topics or trends. The following organizations responded:

Platform for Biosafety Officers (BVF Platform)
Dutch forum for Biotechnology and Genetics (FBG)
Goede Waar en co (Good consumer products and Co)
The Humanist Institute for Cooperation with Developing Countries (Hivos)
Humane society (Dutch society for the prevention of cruelty to animals)
Netherlands Biotechnology Society (NBV)
Nefarma
Netherlands Genomics Initiative (NGI)
Netherlands Society for laboratory animal zoology (NPV)
Netherlands Biotech Industry Association (NIABA)
Dutch Society of Medical Microbiology (NVMM)
Plantum NL
Royal Netherlands Academy of Arts and Sciences (KNAW)
Royal Netherlands Chemical Society (KNCV)
Netherlands Study Center for Technology Trends (STT)
The Confederation of Netherlands Industry and Employers (VNO-NCW)
The Dutch Genetic Alliance (VSOP)

Participants in workshop on 30 March 2007

A draft version of this trend analysis was discussed with stakeholders on 30 March 2007. The following representatives of organizations were present:

Ir. J.B.F.C. van den Assum	Ministry of LNV
Drs. J.A. van den Bandt-Stel	VNO-NCW
Prof. Dr. Ir. W.E. Bijker	University Maastricht
Prof. Dr. E. Borst	NFK
Dr. D.A. Bleijs	Bureau GGO
Prof. Dr. F.W.A. Brom	Rathenau Institute
Dr. P.W.M. van Dijck	DSM R&D (DSM Anti-infectives BV)
Dr. J.M. Fentener van Vlissingen	Erasmus MC
Dr. D.C.M. Glandorf	Bureau GGO
Dr. M. van der Graaff	Nefarma
Dr. Ir. P.A.M. Hogervorst	Ministry of VROM
Ir. A.M. van den Hurk	Plantum NL
Drs. R.T.A. Janssen	Niaba
Drs. J.W. van der Kamp	TNO / Niaba

Prof. Dr. O.P. Kuipers	University of Groningen
Prof. Dr. N.J. Leschot	Academic Medical Center Amsterdam
Mr. A. van Limborgh	Ministry of VROM
Prof. Dr. ir. L.C. van Loon	BVF Platform
Mrs. M. Meijer	Oxfam Novib
Dr. Ir. G.M. Munnichs	Rathenau Institute
Dr. C. Oosterwijk	VSOP
Mr. B. Plooyer	Dutch Society for Laboratory Animal Science
Drs. T.A.M. van de Sande	DGIS Coherente Eenheid
Ing. J.M.J. Scheer	BVF Platform
Dr. M.J. Stukart	KNAW
Dr. Mr. J.H.A.A. Uitzetter	Ministry of Economic Affairs
Dr. J.S. Verbeek	LUMC
Mrs. S. Voogd	Oxfam Novib
Ir. H. de Vriend	Lis consult
Drs. M.D.J. van Well	Netherlands Study Center for Technology Trends
Drs. J.B. van den Wijngaard	Ministry of VWS

Reactions received based on workshop

Email Werkplaats Biopolitiek, dated 3 April 2007
Collective letter Niaba, VNO-NCW, Plantum NL & Nefarma, dated 10 April 2007
Letter BVF Platform, dated 16 April 2007

Appendix 4:
Trend analysis biotechnology 2004

The following eight trends were singled out as principal in 2004 because of their anticipated influence on Dutch society:

- Uncertainty about the future for persons on account of better genetic diagnosis of diseases whereby there is no one-to-one relation between presence of a gene and contracting the disease.
- Decreased national policy room for barring GMO imports and guarantee co-existence of non-GM agricultural products resulting from globalization of science and economy.
- Ongoing developments in other regions that can only be influenced by proactive policy and international dialogue.
- Larger differences of opinion between proponents and opponents of the use of embryonic stem cells as more knowledge about the clinical feasibility of new stem cell therapy becomes available.
- Unknown ecological risks through deliberate introduction of GMOs in the field in fighting diseases and pests and the protection of local animal species.
- Threat to food safety by deployment of pharma crops.
- Pressure to limit public transparency (‘openbaarheid van bestuur’) through more radical activism from opponents of authorized testing of GMOs.
- Increasing demand for screening in IVF embryos for several serious disorders.

Furthermore, various other trends were described in 2004, which are grouped below based on their focus:

Biotechnological trends geared toward realizing social goals

- There is a trend toward deliberate introduction into the environment of GMOs replacing or strongly reducing populations that transmit infectious diseases (cf. malaria). A careful weighing between the ecological risks and the usefulness for public health is of eminent importance.
- In the distant future a supply of animal organs could become available that through genetic modification and other operations can be successfully transplanted in human patients. This confronts government with the question whether the moratorium on xenotransplantation should continue to apply in all cases.
- Aside from better use of the existing bulk pharmaceuticals, certain tailor made medicines will be developed. In some (but not all) cases this will lead to more expensive medicine. This in turn will lead to the need of new considerations about the system of compensating the healthcare costs.
- Data on predisposition become available in ever larger degrees of detail. If for serious hereditary diseases the prognostic value is high, this can lead to tensions on the insurability of diseases and on admission or exclusion by insurance companies.
- The introduction of pre-implantation genetic diagnostics makes it possible to prevent serious disorders. The option for parents to select other desired features of the embryo is very limited.
- Gene doping in humans is not effective as of yet and introduction of gene doping by athletes is not anticipated for the near future.
- Pharma crops will be put on the world market shortly, also if this is not supported in Europe. This way of producing pharmaceuticals can have considerable advantages for future patients. Risks of food chain contamination through food or feed products are quite realistic. Food safety and the threat of social unrest are at stake.

- Application of GMOs in a local ecosystem will occur more often and can inadvertently have unwanted effects elsewhere. The current international agreements are not sufficient to overcome or regulate these effects.
- In the near future products, obtained through genetic modification in animals which are currently viewed as unethical, will be offered for approval on the Dutch market. In fact some modifications seem to benefit animals, while others offer a clear benefit to consumers. The issue will crop up whether such imports must be stopped or whether the planned import ban can be selectively lifted.
- In developing countries specific biotechnological applications will be pursued, which may put pressure on, for instance, the EU to provide sufficient room for imports of such applications from these countries.
- An increasing number of applications of applications of genetic modification aimed at indulgence will be introduced on the world market. This will evoke a debate on the options to slow down these developments elsewhere and on how to effectively regulate the imports and domestic use of these organisms.
- The growing risk of abuse of knowledge of potential relevance for bioterrorism calls for reflection on the issue of which scientific data should be published and which not. The debate on the dividing line between freedom of science, effective control mechanisms, and national security will resurface.

Public questions regarding trends linked to the nature of biotechnology

- The justification of the deployment of stem cells and genetically modified stem cells of humans and animals in different developmental stages will constantly give rise to critical voices due to an increasing range of applications. This debate could be diminished if major and widely valued breakthroughs are achieved.
- The disappearance of the view that the use of laboratory animals will diminish may fuel the debate on this issue. Yet the importance of experimental laboratory animal research in the development of new therapies will also increase, and therefore its social acceptance is likely to go up as well.
- Because genetic modification is becoming undetectable, this intervention will be increasingly hidden from the current possibilities for control. Policy efforts should try to identify other points of action to steer developments in the right direction, such as regulating institutions and researchers instead of their interventions.
- The use of genetic modification to produce organisms with sequences from their own species raises the question as to whether the existing rules need to be modified to allow for this.

Trends in the public context affecting the debate on biotechnological developments

- Globalization diminishes the national policy space for barring undesirable developments at the border. It is becoming increasingly difficult to influence nationally undesirable developments and the pressure to allow GM products produced elsewhere is increasing.
- The cultivation of GM crops will sharply increase outside of Europe. Characteristics that provide advantages for the consumer and the processing industry will be incorporated. Questions such as coexistence and the role of government will become more urgent.
- Biotechnological developments that are contrary to the Dutch vision will continue to take place elsewhere. One response to this could be to develop a proactive strategy to influence developments in other countries as much as possible in the direction preferred by the Netherlands, for example by starting a dialogue with national governments and other parties at an early stage in order to reach collective standpoints, which can also be upheld in relation to the WTO.

- Current biotechnological innovation in the Netherlands is trailing developments abroad. This may force the Dutch government to reconsider its policy regarding innovation and regulation.
- In time public acceptance of still controversial applications of biotechnology is expected to grow. This can be accompanied by more aggressive actions from small groups of conscientious objectors. The government will be confronted with the issue of how to deal with these uncompromising opponents.
- The problem of the destruction of field trails will give rise to the issue whether public transparency offsets the damage caused by activists.

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